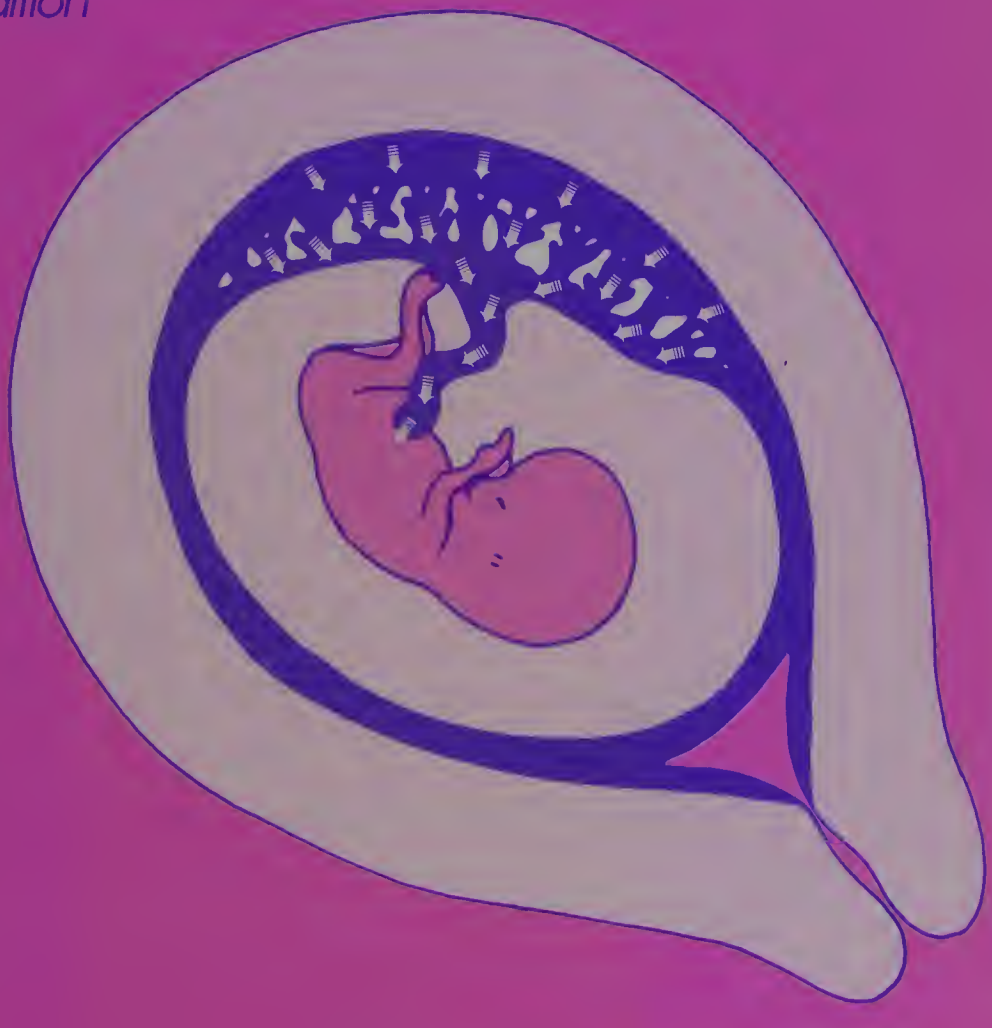
PREGNANCY, DIABETES AND BIRTH

A Management Guide

Second Edition



Dorothy Reycroft Hollingsworth

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A MANAGEMENT GUIDE

SECOND EDITION

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Dorothy Reycroft Hollingsworth, M.D.

Professor of Reproductive Medicine and Medicine
University of California, San Diego
La Jolla, California

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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To Bill Hollingsworth, my loyal, patient friend and husband of 40 years; our three children, Beth Lee Hollingsworth Tripp, Ann Folger Hollingsworth, Susan Reycroft Hollingsworth Vermont; and our four grandchildren, Scott and Jennifer Tripp, Brian and David Vermont.

Foreword

All of us who have attended the circus or watched a variety show on television have been fascinated by the skills of the jugglers. Their masterful hand-eye coordination and timing allow them to keep a variety of objects of varied size and weight spinning through the air. The care of the patient whose pregnancy is complicated by diabetes mellitus often reminds me of these juggling acts. Like a troupe of jugglers, the members of the health care team must coordinate their efforts smoothly so the ball is never dropped. The internist or diabetologist, obstetrician or maternal-fetal specialist, pediatrician or neonatologist, teaching nurse, dietician, social worker, the patient herself, and her partner must adroitly juggle the critical components of the health care program to achieve a successful pregnancy. Like the Indian clubs, hoops, and balls used by the juggler, these items vary greatly and include diet, insulin, exercise, blood glucose monitoring, antepartum fetal assessment, and neonatal care. Like the jugglers who practice their act before the performance, we have learned that care of the woman with diabetes must begin prior to conception. Only in this way can we expect the best outcome. Finally, like the juggler who attempts to defy gravity, we must focus on the one element that can bring the pregnancy complicated by diabetes mellitus crashing to the ground–poor glucose control.

The second edition of *Pregnancy, Diabetes and Birth* by Dr. Dorothy Hollingsworth provides an outstanding guide for all of us who now perform in the center ring or aspire to join the show. Much has changed since the first edition of this textbook in 1984, including our understanding of the genetics of diabetes mellitus, information on the causation of major congenital anomalies in pregnancies complicated by insulin-dependent diabetes mellitus, strategies for the detection and care of the patient with gestational diabetes mellitus, and techniques for antepartum assessment of fetal condition. All of these subjects and more are covered expertly by Dr. Hollingsworth and her colleagues, Denise M. Ney, Ph.D., and Thomas R. Moore, M.D.

Sadly, some of those who performed most brilliantly and contributed so much to our understanding of the pregnancy complicated by diabetes mellitus have passed away since the first edition of this textbook. These include Dr. Norbert Freinkel, who wrote the foreword for the first edition of this textbook and stood as a vanguard with the development of concepts such as "accelerated starvation," "facilitated anabolism," and "fuel-mediated teratogenesis"; Dr. Priscilla White, one of the first to use insulin in the treatment of the pregnancy complicated by diabetes mellitus and to emphasize the contribution of maternal vasculopathy to poor pregnancy outcome; and Dr. Ronald Kalkhoff, whose studies on obesity and lipid metabolism added much to our understanding of gestational diabetes mellitus. This textbook also stands as a tribute to these physicians.

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Preface to the Second Edition and A Personal Note

Many years ago, at 18 years old and a college sophomore, I was asked to be head counselor at Dr. Elliot P. Joslin's camp for diabetic children in North Oxford, Massachusetts. Dr. Joslin was a thin, energetic, sparrow-like man with twinkling blue eyes and a special warmth that was apparent immediately to children. He loved all of them.

Each Sunday, campers and counselors would visit his old farmhouse, which was nearby, sit in rocking chairs on the front porch, and watch the children dash through the rows of his ample fields of corn. This extraordinary man, a New England Yankee through and through, had a quick, bright mind, simple tastes, and boundless curiosity. He left an indelible mark on my future choice of career and style of medical practice.

When I recently read the first edition of Joslin's book, "Treatment of Diabetes Mellitus," which was published in 1916, 6 years before the discovery of insulin, it was enlightening to re-examine his excellent care of pregnant diabetic women and his quite accurate predictions of the future direction of clinical research. He was the first American to describe the management of diabetes in pregnancy at his famous Joslin Clinic at 81 Bay State Road in Boston; we owe him an enormous debt.

Two decades and three children later, after a circuitous educational path, I became an internist, endocrinologist, and diabetologist. The role of a specialist in diabetes varies enormously among different age groups of patients and diverse geographic settings. In no branch of medicine is caring for patients with still poorly understood "womb to tomb" disorders of carbohydrate metabolism more exciting, challenging, and, at times, utterly frustrating than in reproductive medicine. This is the only specialty in diabetology that has a present at the end.

This book has evolved slowly over a period of 12 years while a program was being developed for the management of pregnant women with diabetes at the University of California, San Diego. It reflects the rapidly changing concepts in our understanding of diabetes as a heterogenous syndrome. It considers old and new methods for the delivery of insulin, monitoring of blood glucose control, and current concepts in prenatal and neonatal care.

The theme of the book is based upon the idea that pregnancies complicated by chronic medical problems, such as diabetes, should be as free of stress and complications as possible for patients and their families, the fetus, and the physicians and assistants who are providing their care. This approach requires a coordinated team using simple management principles and individualization of treatment. A great deal of thought has gone into the problem of providing the highest quality of care for women in a variety of health care settings. Our hope is that the guidelines presented in the book will be useful in both private offices and hospital clinics. One purpose has been to simplify the treatment of pregnant diabetic women and to seek ways in which they can be helped to learn about diabetes and to participate in their own care.

In the interim since the first edition in 1984, there is improved, but still inadequate access to prenatal care for diabetic (and many other) women. Advances in the fields of biology, genetics, immunology, and clinical care of diabetic individuals have been enormous. The search for genes for each type of diabetes is moving apace, and use of programmable implantable pumps (PIMS) and β-cell transplantation techniques are on the near horizon.

In reproductive medicine, there has been a complete shift in focus to the concept of **preconception counseling.** We cannot solve the

most difficult problems in diabetic pregnancies (malformations and perinatal complications) unless the traditional specialties of medicine and obstetrics and patients themselves become knowledgeable about the importance of prenatal care well in advance of pregnancy. Because this has become the most important issue for diabetic women who wish to have children, this much-expanded revision of the book deals with the topic in an extensive new introductory section.

Dr. Denise Ney has written a comprehensive, informative chapter on nutrition in normal and diabetic women with guidelines for pregnant patients with different types of carbohydrate intolerance including the difficult subject of nutrition in pregnancy in secondary diabetes that is relevant to the increasing numbers of young women of reproductive age who have cystic fibrosis.

The perinatology sections have been completely rewritten and expanded by Dr. Thomas Moore, a new contributor. They reflect the latest information in this rapidly expanding field. The section on infants of diabetic mothers has been enlarged and describes contemporary progress in neonatology. A significant gap in our knowledge is lack of information from well-designed prospective studies (linking perinatology, neonatology, pediatrics, and adolescent medicine) of long-term outcome of children of all types of diabetic mothers.

For both patients and physicians, it is difficult to deal with chronic medical problems that do not go away. It is our hope that this new edition will help as a guide for relatively simple management approaches to diabetic pregnancies so that these women will no longer be at higher risk for obstetric problems than nondiabetic women. There is no more rewarding medical experience than the smooth perinatal course of a pregnant diabetic woman and the birth of her perfect child.

Dorothy Reycroft Hollingsworth, M.D.
La Jolla, California
September, 1990

Acknowledgments

The development of a new approach for the management of pregnant women with various types of carbohydrate intolerance began during a sabbatical year with Dr. Samuel S. C. Yen at the University of California, San Diego (UCSD) in 1976. My subsequent move to UCSD, Dr. Yen's support, and imaginative and creative ideas have provided an exciting environment for the development of a university program for patient care and clinical and laboratory investigation.

I am deeply indebted to Michelle Williamson, medical illustrator, at the University of California, San Diego (UCSD) Office of Learning Resources who redesigned all the tables and re-drew all the figures for this edition.

Thanks are also due to my secretary, Paula Holder, and Del Alsobrook, word processing specialist, who helped immeasurably in coordinating the completely revised second edition.

The book would not have been possible without the encouragement and assistance of the excellent staff at Williams & Wilkins: Mr. Charles Mitchell saw the book through to final completion and was of invaluable help in coordinating its publication. Our copy editor, Shelley Potler, transformed a difficult second edition revision into a polished manuscript. During both editions, our admiration for Raymond E. Reter, Production Coordinator, was boundless. We shall be forever grateful for his tireless efforts.

It would not have been possible to develop an obstetric program for diabetic women without the special enthusiasm and creativity that abound at UCSD. Excellent assistance with patient care was provided by our diabetes nurse educator, Honoré Murphy, the perinatal fellows and residents in obstetrics.

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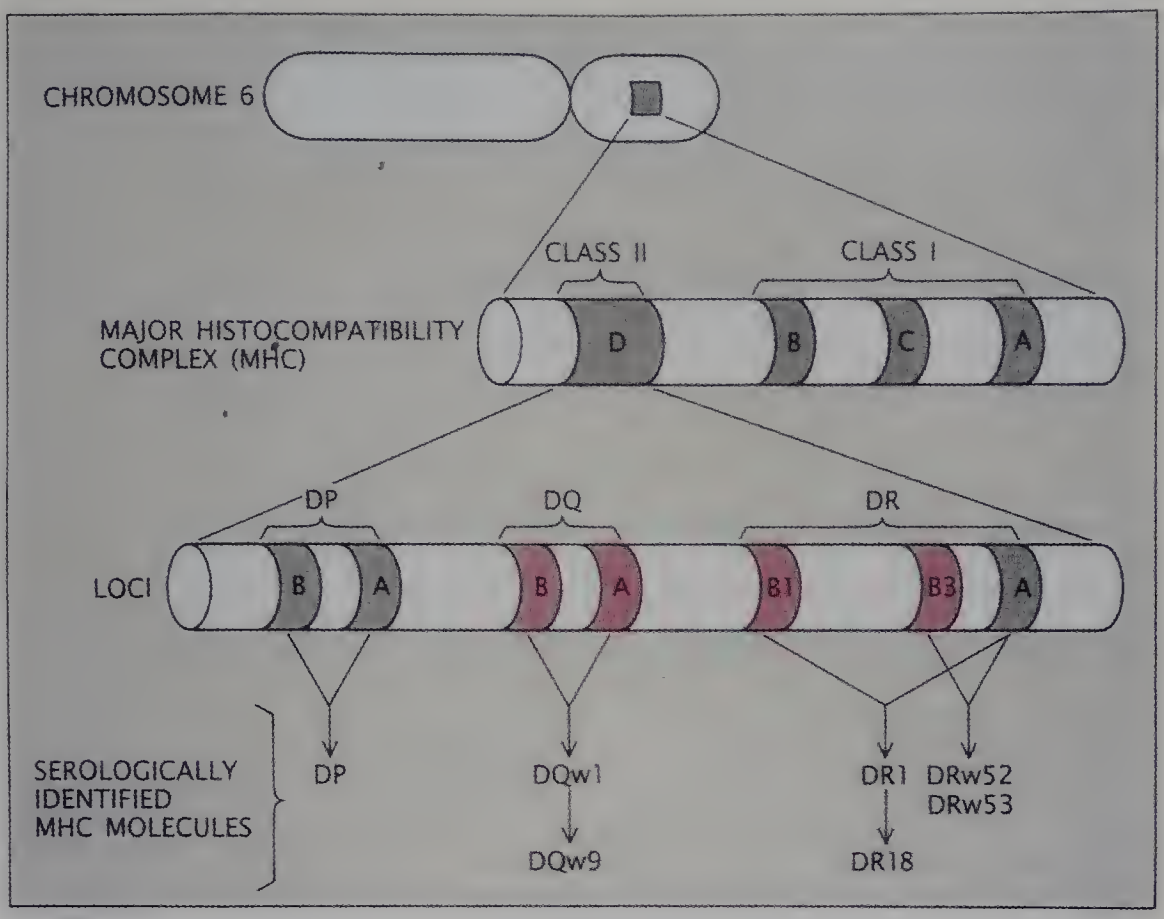
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CLASS I
MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)
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B
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DQ
DR
LOCI
B
A
B
A
B1
B3
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DQw1
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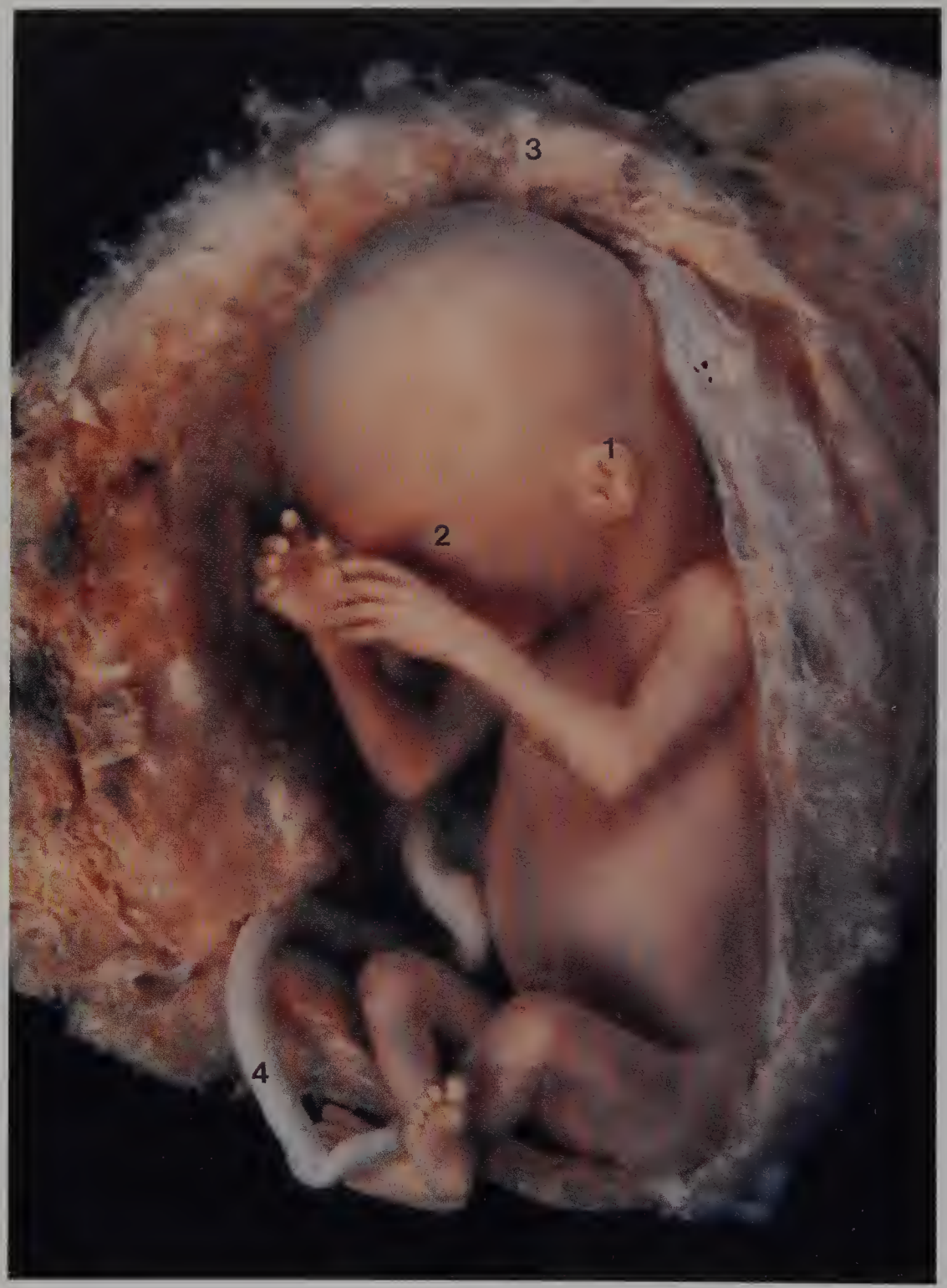
DR1
DRw52
DRw53
DR18

Figure 1.2.



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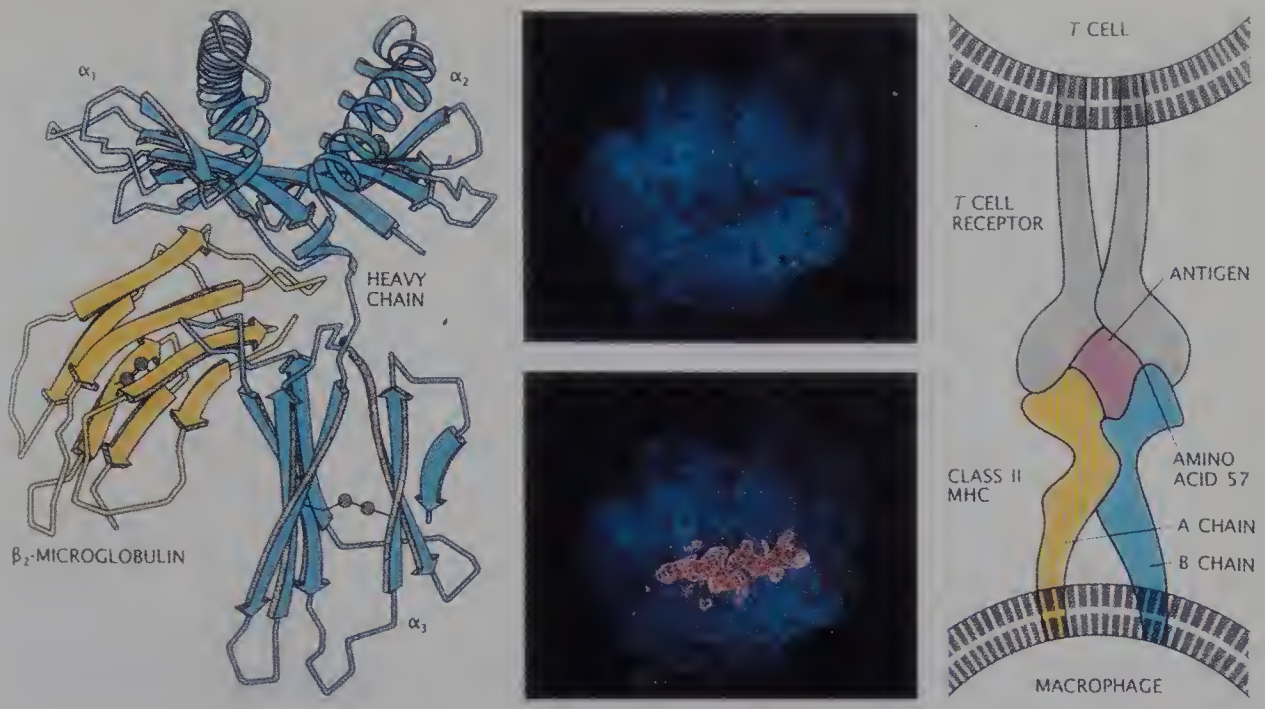
α1
α2
HEAVY CHAIN
β2-MICROGLOBULIN
α3
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T CELL RECEPTOR
ANTIGEN
CLASS II MHC
AMINO ACID 57
A CHAIN
B CHAIN
MACROPHAGE

Figure 8.2.

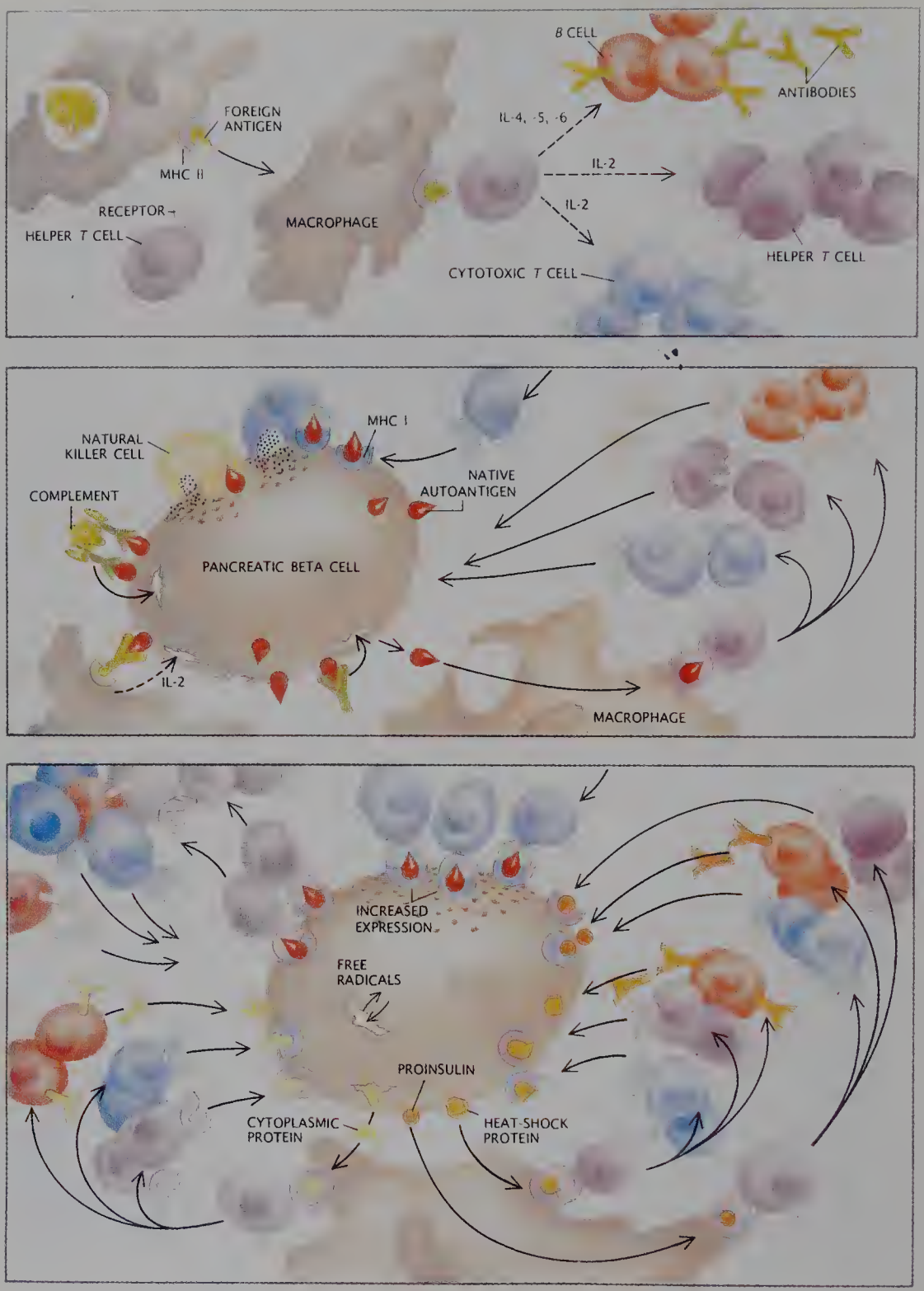
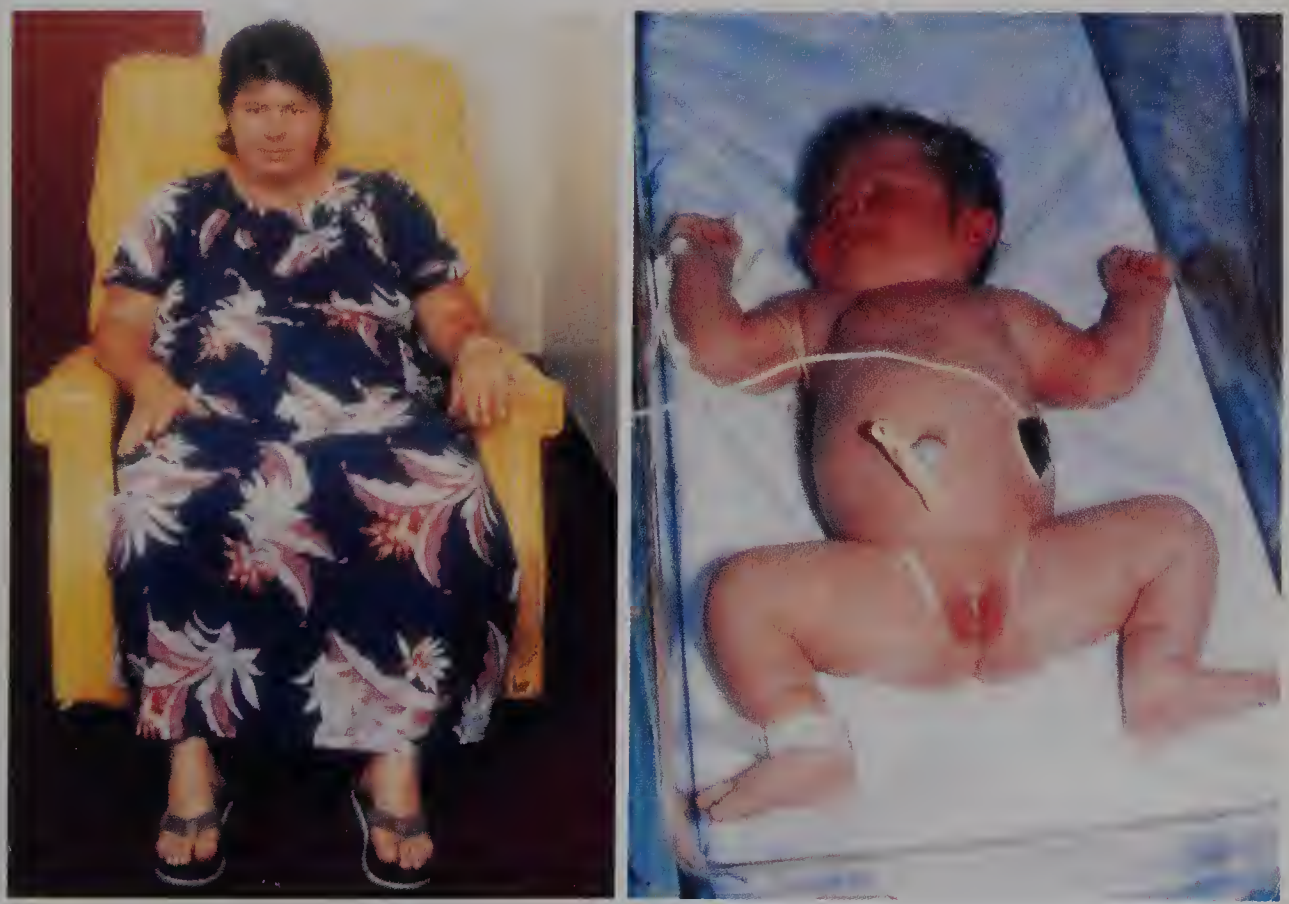

B CELL
ANTIBODIES
FOREIGN ANTIGEN
MHC II
IL-4, -5, -6
IL-2
IL-2
RECEPTOR
HELPER T CELL
MACROPHAGE
HELPER T CELL
CYTOTOXIC T CELL
MHC I
NATURAL KILLER CELL
NATIVE AUTOANTIGEN
COMPLEMENT
PANCREATIC BETA CELL
IL-2
MACROPHAGE
INCREASED EXPRESSION
FREE RADICALS
PROINSULIN
CYTOPLASMIC PROTEIN
HEAT-SHOCK PROTEIN

Figure 8.3.

Figure 8.5.



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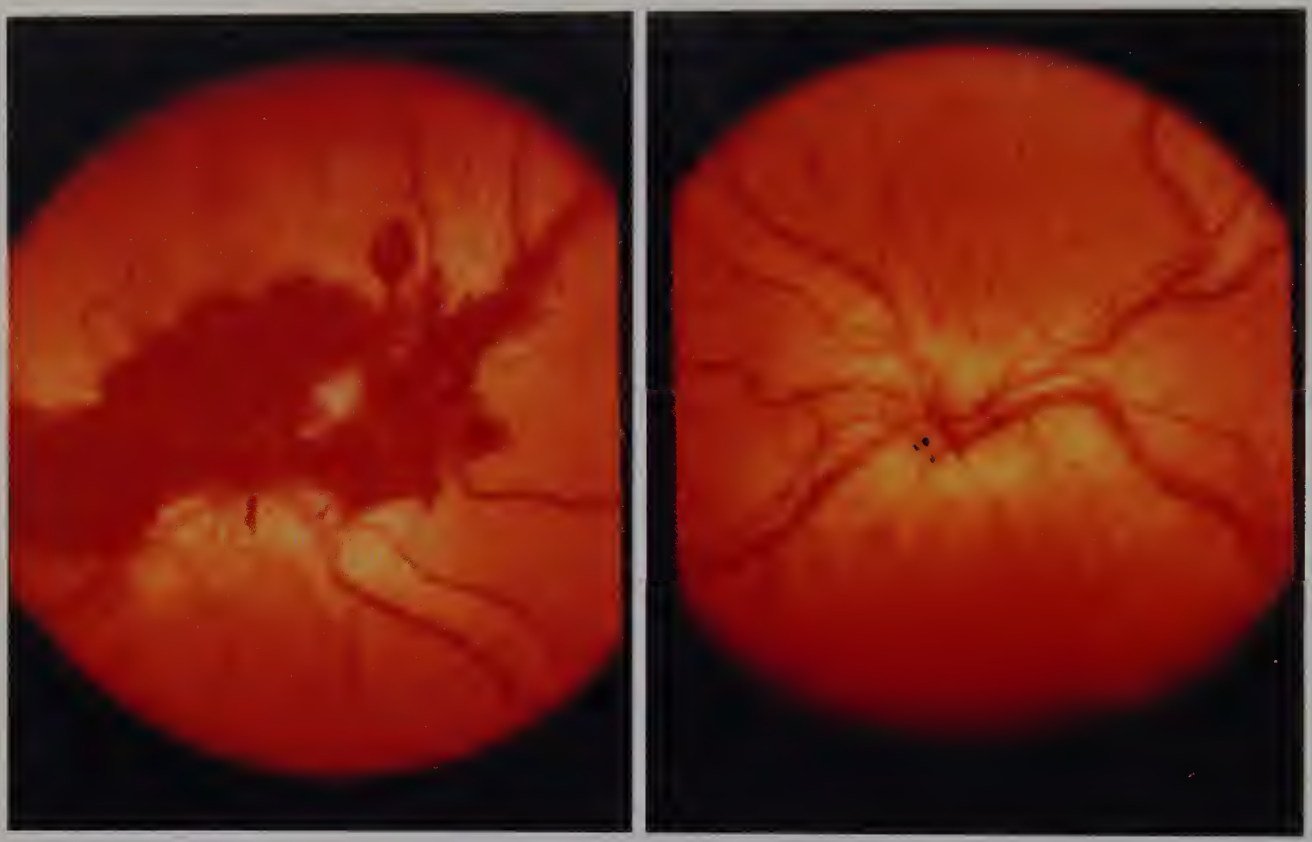

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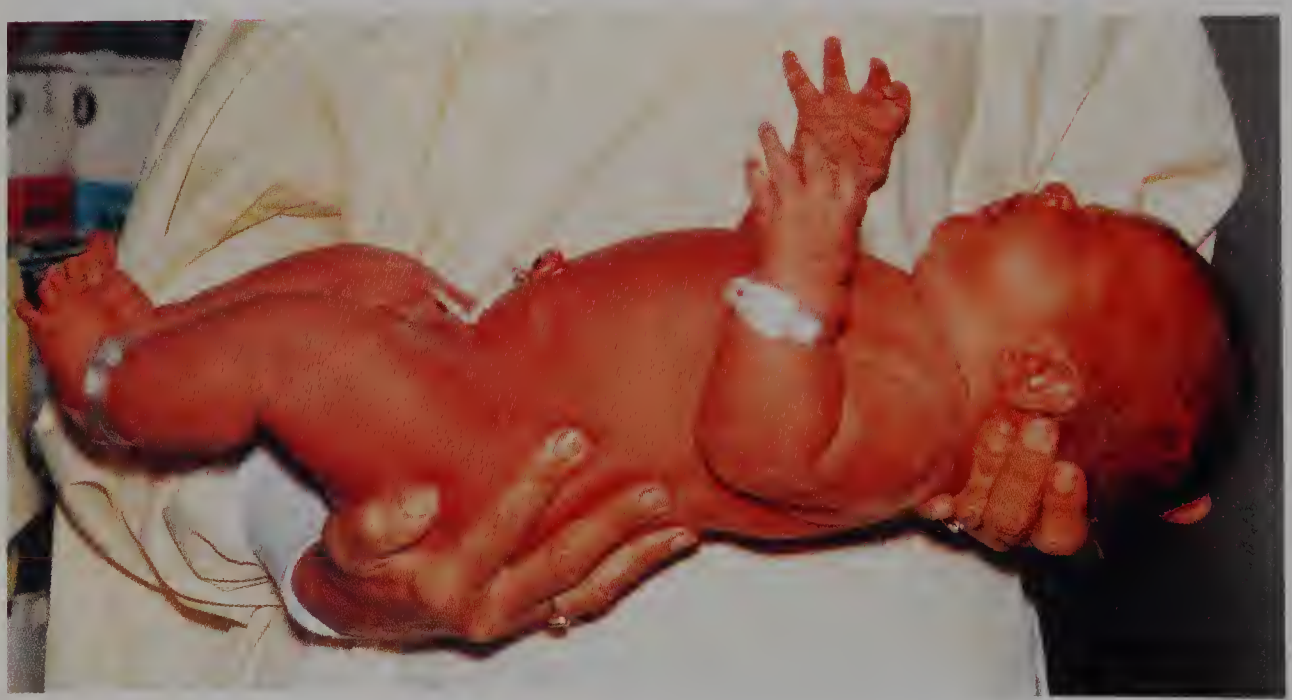

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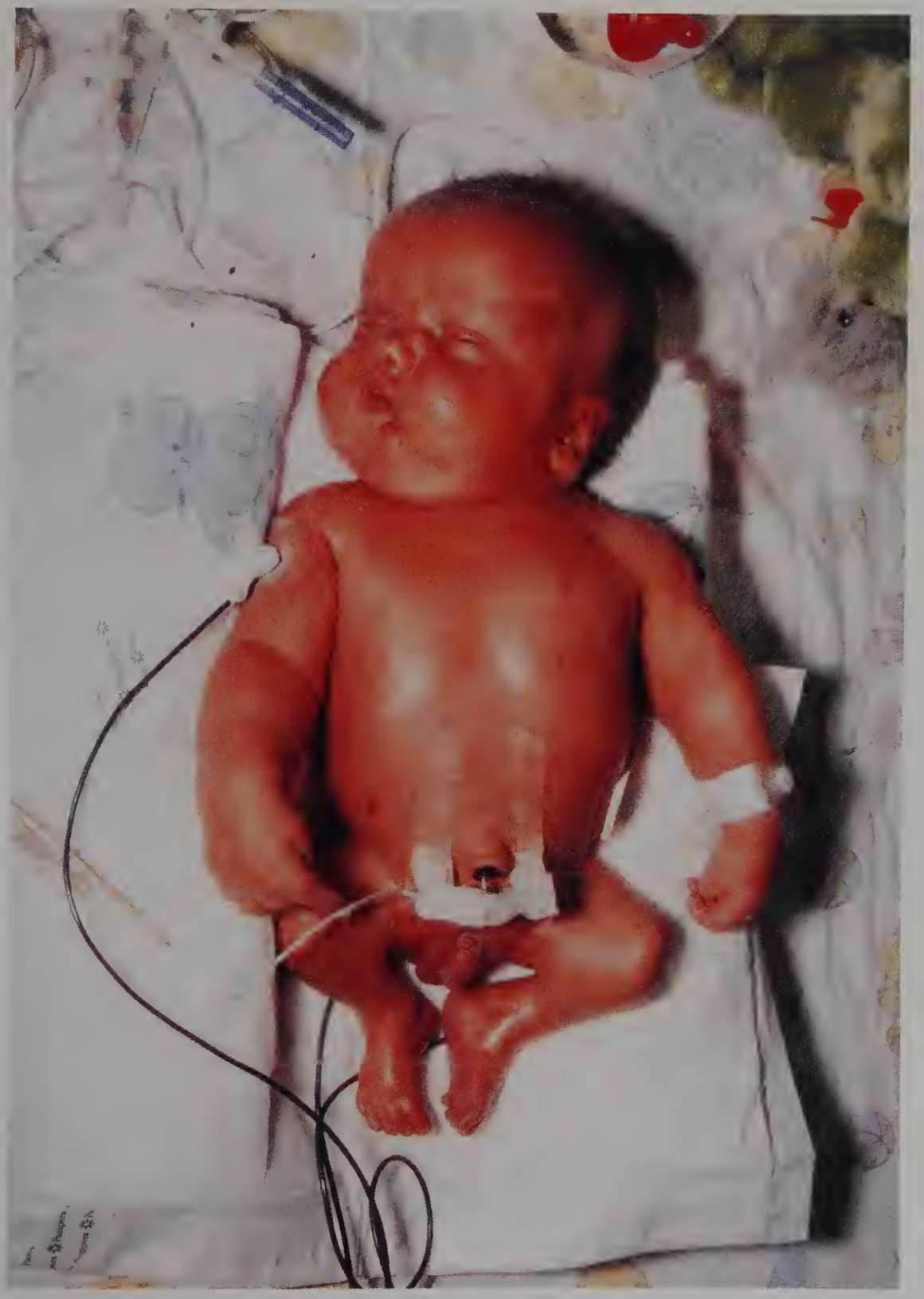


Figure 27.7.

Introduction

Pregnancy complicated by carbohydrate intolerance is the single most common risk factor for women in all reproductive age groups. Diabetes during gestation has serious implications for the maternal-fetal pair. Because diabetes mellitus is not a single disease, but a genetically and clinically heterogeneous group of disorders that share carbohydrate intolerance in common, it is important to define and classify the metabolic syndrome as accurately as possible. This has particular relevance during pregnancy because metabolic alternations are superimposed upon a variety of forms of carbohydrate intolerance that require highly individualized management programs.

This book is designed to be a simple guide for the management of pregnant diabetic women. Diabetic patients are classified according to the guidelines of the National Diabetes Data Group (1) (Table I.1). This classification, which has been adapted for pregnancy, permits a more physiologic approach to individual patients and makes their care easier for the perinatal team of physicians, midwives, nurses, nutritionists, and social workers (2). Figure I.1 illustrates four types of pregnant diabetic women.

The primary goal of the book is to provide a simple, effective plan for the management of diabetic pregnancies and to expand the concept of a perinatal care team. Advances in perinatal care should make pregnancy a less stressful experience for the families of these patients and provide a more normal intrauterine environment for the infants of diabetic mothers.

European reviewers of the first edition suggested that laboratory values should be presented in both conventional and Systeme International (SI) units for the multinational group of obstetricians and diabetologists who have found the book useful. Most laboratories and textbooks do not publish normal pregnancy values along with their usual laboratory reference standards. We have tried to provide these for easier interpretation of tests commonly performed in pregnant diabetic women. For convenience, common reference values, SI units, and conversion factors are presented in the introduction in Tables I.2 and I.3 for both non pregnant and pregnant women.

We hope this new edition reflects the many advances and improvements that have occurred by 1991 in management of diabetic pregnant women and their babies.

Table I.1. Classification of Glucose Intolerance in Pregnant Women[a]

Nomenclature	Old Names	Clinical Characteristics During Pregnancy
Type I (IDDM)—Insulin-dependent diabetes mellitus	Juvenile diabetes (JD) Juvenile-onset diabetes (JOD) Ketosis-prone diabetes Brittle diabetes	Ketosis-prone; insulin deficient due to islet cell loss; often associated with specific HLA types with predisposition to viral insulitis or autoimmune (*islet cell antibody*) phenomena; occurs at any age; common in youth; these women are usually of normal weight but may be obese
Type II (NIDDM)—Noninsulin-dependent diabetes mellitus Nonboese Obese Maturity-onset diabetes of youth (MODY)	Adult-onset diabetes (AOD) Maturity-onset diabetes (MOD) Ketosis-resistant diabetes Stable diabetes	Ketosis resistant; more frequent in adults but ocurs at any age; majority are overweight; may be seen in family aggregates as an autosomal dominant genetic trait; ALWAYS REQUIRE INSULIN FOR HYPERGLYCEMIA DURING PREGNANCY; previous history of 'borderline diabetes', impaired glucose tolerance, or treatment with oral hypoglycemic agents. HBA_{1C} elevated ≤20 weeks' gestation[b]
Type III[c]—Gestational carbohydrate intolerance (GCI) Nonobese Obese	**Gestational diabetes (GDM)**	Screening Tests: ALL PREGNANT WOMEN; 50-g oral glucose load is given randomly (need not be fasting) at 24-28 weeks' gestation; a plasma glucose value 1 h later ≥ 140 mg/dl (7.8 mmol/L) is an indication for a 3-h OGTT with 100 g of glucose
Type IV—Secondary diabetes	Conditons and syndromes associated with imparied glucose tolerance	Cystic fibrosis; endocrine disorders such as acromegaly, hyperprolactinemia, Cushing syndrome, insulin receptor abnormalities, or aberrant forms of insulin, drugs, or chemical agents, renal dialysis, organ transplantations, certain genetic syndromes

[a]Hollingsworth, 1981; Revised, 1988, and 1991. Adapted from the National Diabetes Data Group (NDDG) 1979 and World Health Organization (WHO) 1985 Criteria.

[b]Laboratory methods and normal values vary. Women with gestational carbohydrate intolerance (GDM) have normal HbA1C concentrations during the first half of pregnancy.

[c]All pregnant women at higher risk for gestational carbohydrate intolerance **should be screened at the first prenatal visit.** Risk factors are glycosuria, family history of diabetes in a first degree relative, history of an unexplained fetal demise or unexplained stillbirth in a previous pregnancy, previous heavy-for-date, baby, obesity: body mass index (kg/M^2) >30, maternal age >35 years or parity of five or more.

1. **Diagnosis of gestational diabetes based on NDDG criteria with a 100-g glucose load. Two or more of the following plasma glucose values be met or exceeded: Fasting: 105 mg/dl (5.8 mol/L); 1-h: 190 mg/dl (10.5 mmol/L); 2-h: 165 mg/dl (9.1 mmol/L); 3-h: 145 mg/dl (8.0 mmol/L).**
2. **Diagnosis based on 1985 WHO criteria (pregnant or nonpregnant) for impaired glucose tolerance following a 75 g glucose challenge; venous plasma: fasting: <140 mg/dl (<7.8 mol/L); 2-h: 140–200 mg/dl (7.8–1.1 mmol/L). Diabetes: fasting ≥140 mg/dl (7.8 mmol/L; 2-h: ≥200 mg/dl (11.1 mol/L).**

Figure I.1. Four types of pregnant patients with carbohydrate intolerance. *Top left:* Normal weight young woman who developed insulin-dependent diabetes mellitus (IDDM) as a child. *Top right:* Obese 34-year-old woman who developed non-insulin-dependent diabetes mellitus (NIDDM) at age 12. Her mother, maternal grandmother, maternal twin aunts, and brother all have NIDDM. Reversible carbohydrate intolerance evoked by pregnancy (GDM); this may occur in both obese *(bottom left)* or thin *(bottom right)* women.

Table I.2.
Conventional and Système International (SI) Units for Measurements in serum, Whole Blood, and Plasma[a]

Measurement	Typical Reference Intervals		
	Common Units	Factor Common → SI	SI Units
Acetone (serum)			
Qualitative	Negative		Negative
Quantitative	0.3–2.0 mg/dl	172	51.6–344 μmol/L
Amylase (serum)	60–160 Somogyi units/dl	1.85	111–296 U/L
Base excess			
(♂ whole blood)	−2.4 ± 2.3 mEq/L	1	−2.4–2.3 mmol/L
Base total (serum)	145–160 mEq/L	1	145–160 mmol/L
Bicarbonate (plasma)	21–28 mM	1	21–28 mmol/L
Bilirubin (serum)			
Direct (conjugated)	up to 0.3 mg/dl	17.1	up to 5.1 μmol/L
Indirect (unconjugated)	0.1–1.0 mg/dl		1.7–17.1 μmol/L
Total	0.1–1.2 mg/dl		1.7–20.5 μmol/L
Newborns total	1–12 mg/dl		17.1–205 μmol/L
Blood gases (whole blood)			
pH	7.38–7.44 (arterial)	1	7.38–7.44
	7.36–7.41 (venous)		7.36–7.41
PCO_2	35–40 mm Hg (arterial)	0.133	4.6–5.32 kPa
	40–45 mm Hg (venous)		5.32–5.99 kPa
PO_2	95–100 mm Hg (arterial)	0.133	12.64–13.30 kPa
Calcium (serum)			
Ionized (i Ca)	4.4–4.9 mg/dl	0.25	1.0–1.2 mmol/L
or	2.0–2.4 mEq/L		
	30–58% of total	0.01	0.3–0.58 of total
Total (serum)	9.2–11.0 mg/dl	0.25	2.3–2.8 mmol/L
Carbon dioxide (CO_2 content)			
Whole blood (arterial)	19–24 mM	1	19–24 mmol/L
Plasma or serum (arterial)	21–28 mM	1	21–28 mmol/L
Plasma or serum (venous)	24–30 mM	1	24–30 mmol/L
Chloride (serum)	95–103 mEq/L	1	95–103 mmol/L
Coagulation values			
Nonpregnant			
Fibrinogen (Factor I)			
Plasma	200–400 mg/dl	0.01	2.00–4.00
Pregnant	**400–500 mg/dl**	**7–10**	**4.0–5.0 g/L**
Factor VII	**Rises to 150–200% beginning late in the second trimester (as measured in a one-stage clotting assay).**		
Factor VIII and Von Willebrand factor levels rise to 200–300% of a normal pooled plasma standard (100%)			
Prothrombin (Factor II), Factors V and XII	**Unchanged**		
Factor X levels	**Rise minimally (125% range)**		
Factors XI and XIII	**Slight decline**		
Platelet count	**Holds steady (mean value about 200,000 mm^3)**		
Bleeding and clotting time	**Unchanged**		
Specific prothrombin levels do not rise			
Protein C antigen levels increase modestly (mean about 135%)			
Protein S total and free protein S levels fall significantly; mean free protein S falls from a value of 8.3 mg/L in normal controls to a value of 3.7 mg/L at delivery			
Antithrombin III levels do not change (a fall in ATIII activity is thought to be a warning of impending pre-eclampsia)			

Table I.2
(*continued*)

Measurement	Typical Reference Intervals: Common Units	Factor Common → SI	SI Units
Fibrinolytic activity is depressed in the later months of pregnancy as measured by the prolongation of the euglobulin lysis time and dilute whole blood clot lysis time; this presumably reflects entrance of placental plasminogen activation inhibitor PAI-2 into the maternal circulation			
Complete blood count			
Hematocrit (female)			
Nonpregnant	37–48%		
Pregnant	**↓ to 32.5–41% in 2nd and early 3rd trimester with rise to prepregnant value at term**		
Hemoglobin (whole blood)	**13–15 g/dl (female)**	**10**	**1.86–2.48 mmol/L**
Pregnant nadir 30–34 weeks	**↓ to 10–13 g/dl in 2nd to early 3rd trimester with rise to prepregnant value at term**		
Leukocyte count	**4300–10,800 mm^3**		**4.3–10.8 × 10^9/L**
Nonpregnant			
Pregnant	**6000–16000 mm^3**		**6.0–16.0 × 10^9/L**
(2nd and 3rd trimesters)	**(mean 10,500)**		
Erythrocyte count	**4.2–5.9 million/mm^3**		**4.2–5.9 × 10^{12}/L**
Mean corpuscular hemoglobin (MCH)	**27–32 pg/RBC**		**1.7–2.0 pg/cell**
Mean corpuscular hemoglobin concentration (MCHC)	**32–36%**		**0.32–0.36**
Mean corpuscular volume (MCV)	**86–98 μm^3/cell**		**86–98 fl**
Cortisol (plasma)			
Nonpregnant			
8:00 AM to 10:00 AM	5–23 μg/dl	27.6	138–635 nmol/L
4:00 PM to 6:00 PM	3–13 μg/dl		83–359 nmol/L
Pregnant	**Increase 2.5 times from 1st trimester to term; overlap with nonpregnant values for Cushing syndrome; diurnal variation is preserved**		
Corticosteroid binding globulin (CBG)			
Nonpregnant	33 mg/dl		
Pregnant (6 months)	**70 mg/dl**		
Cortisol free	μg/day		nmol/day
(urine, 24-h)	10–100		27–276
Pregnant	**Increases about double during pregnancy; overlap with nonpregnant values for Cushing syndrome**		
C-Peptide (plasma)			
Nonpregnant (fasting)	≤4 ng/ml	0.331	≤4 μg/L
Pregnant (3rd trimester	**2.6–5.7 ng/ml**		**2.6–5.7 μg/L**
Creatinine (serum or plasma)	mg/dl	88.4	μmol/L
Non-pregnant	0.6–1.2		53–106
Pregnant	**0.5–0.6**		**44.2–53**
Children < 2 yr	**0.3–0.6**		**27–54**
Creatinine clearance (serum or plasma and urine)			
Nonpregnant	87–107 ml/min	0.0167	1.45–1.79 ml/s
Pregnant	**increases about 50%**		

Table I.2
(*continued*)

Measurement	Typical Reference Intervals					
	Common Units		Factor Common → SI	SI Units		
Erythrocyte sedimentation rate (ESR) Female						
Nonpregnant	0–20 mm/h					
Pregnant	**↑ to about 25 mm/h (Personal Communication, Helen M. Ranney, M.D.)**					
Ferritin (serum)	12–150 ng/ml			12–150 μg/L		
Folate (serum)	>2.3 ng/ml (RIA)			>5.2 nmol/L		
Glucose tolerance test	mg/dl			mmol/L		
(serum or plasma)	Time	Normal	Diabetic	0.056	Normal	Diabetic
Nonpregnant	O	70–105	>140		3.9–5.8	≥7.8
(GTT) oral	1-h	120–170	≥200		6.7–9.4	≥11
	1.5-h	100–140	≥200		5.6–7.8	≥11
	2-h	70–120	≥140		3.9–6.7	≥7.8
	Time	**mg/dl**			**mmol/L**	
Pregnant	**0**	**≥105**			**5.8**	
(100-g loading	**1 h**	**190**			**10.5**	
test)						
For diagnosis of	**2 h**	**165**	**2 Abnormal**		**9.1**	**2 Abnormal**
GDM	**3 h**	**145**	**values**		**8.0**	**values**
α-Hydroxybutyrate dehydrogenase (serum)	140–350 U/ml			96.1	140–350 kU/L	
Insulin (plasma) fasting						
Nonpregnant (RIA)	4–24 μIU/ml			0.0417	0.17–1.0 μg/L	
Pregnant (RIA)	**23 ± 9 μIU/ml**				**0.96 ± 0.38**	
Iron, total (serum)	60–150 μg/dl			0.179	11–27 μmol/L	
Iron binding capacity (serum)	200–400 μg/dl			0.179	56–64 μmol/L	
Iron saturation (serum)	20–50%			0.01	Fraction of total iron binding	
Ketone bodies (serum)	Negative				Negative	
Lactate (whole blood, heparin, as lactic acid)	Venous 4.5–19.8 mg/dl				0.5–2.2 mmol/L	
	Arterial 4.5–14.4 mg/dl				0.5–1.6 mmol/L	
Lactic acid dehydrogenase (LDH) (serum)	25–175 IU/L				25–175 IU/L	
Lipids (serum)						
Nonpregnant						
Cholesterol	150–250 mg/dl			0.026	3.9–6.5 mmol/L	
Triglycerides	10–190 mg/dl			0.109	1.09–20.71 mmol/L	
Phospholipids	130–380 mg/dl			0.01	1.50–380 g/L	
Fatty acids (free)	9.0–15 mM/l			1	9.0–15.0 mmol/L	
Pregnant						
Cholesterol				**0.026**		
2nd trimester	**251 ± 8**				**6.5 ± 0.2**	
3rd trimester	**259 ± 13**				**6.7 ± 0.3**	
3 months postpartum	**204 ± 10**				**5.3 ± 0.3**	
Triglyceride				**0.109**		
2nd trimester	**185 ± 22**				**20.2 ± 2.4**	
3rd trimester	**224 ± 24**				**24.4 ± 2.6**	
3 months postpartum	**82 ± 5**				**8.9 ± 0.5**	
Osmolality (serum)	280–295 mOsm/kg			1	280–295 mmol/L	
Pregnant	**270–280 mOsm/kg**				**270–280 mmol/L**	

Table I.2
(*continued*)

Measurement	Typical Reference Intervals: Common Units	Factor Common → SI	SI Units
pH			
Whole blood (arterial)	7.38–7.44	1	7.38–7.44
Whole blood (venous)	7.36–7.41		7.36–7.41
Serum or plasma (venous)	7.35–7.45		7.35–7.45
Phosphatase alkaline (serum)			
Nonpregnant	20–90 IU/L at 30°C	1	20–90 UL at 30°C
Pregnant (term)	**2–4 times nonpregnant values**		
Phosphorus, inorganic (serum)	2.3–4.7 mg/dl	0.323	0.78–1.52 mmol/L
Potassium (plasma)	3.8–5.0 mEq/L	1	3.8–5.0 mmol/L
Prolactin (serum)			
Nonpregnant	1–25 ng/ml	1	1–25 μg/L
Pregnant (34–36 weeks)	**220–400 ng/ml**		**220–400 μg/L**
Proteins (serum)	g/dl		g/L
Total	6.0–7.8	10	60–78
Albumin	3.2–4.5		32–45
Globulin	2.3–3.5		23–35
SGOT (AST, aspartate amino transaminase) (serum)	10–45 IU/L		10–45 IU/L
SGPT (ALT, alanine amino transaminase) (serum)	10–45 IU/L		10–45 IU/L
Sodium (plasma)	136–142 mEq/L	1	136–142 mmol/L
Thyroid hormones (serum)			
Nonpregnant			
T4 (RIA)	5.5–12.5 μg/dl	13	76–163 nmol/L
T3 (RIA)	70–190 ng/dl		1.85–3.0 nmol/L
Free T4 (total)	0.9–2.3 ng/dl		12–30 pmol/L
T3 resin uptake (%)	25–38 relative % uptake	0.01	Relative uptake fraction 0.25–0.38
Thyroxin binding globulin (TBG)	10–26 μg/dl	10	100–260 μg/L
Pregnant (serum)			
T_4 (RIA)	**8.0–14.5 μg/dl**	**13**	**104–188 nmol/L**
T_3 (RIA)	**150–220 ng/dl**		**2.3–3.4 nmol/L**
Free T_4	**0.9–2.3 ng/dl**		**12–30 pmol/L**
T_3 resin uptake (%)	**15–25**	**0.01**	**0.15–0.02**
Thyroxin binding globulin (TBG)	**↑ to twice normal**		
TSH (serum) "sensitive" method			
Nonpregnant	0.5–3.5 μU/ml	1.0	0.5–3.5 μU/ml
Pregnant	**Not increased**		
Urea nitrogen (serum)	mg/dl		mmol/L
Nonpregnant	8–23	0.357	2.9–8.2
Pregnant	**8–9**		**2.9–3.2**
Uric acid (serum)		0.059	0.16–0.43
Nonpregnant	2.7–7.3		
Pregnant (to 24 weeks)	**2.0–3.0**		**0.12–0.18**
Zinc (serum)	50–150 μg/dl	0.153	7.65–22.95 μmol/L

[a]Adapted from standard tables for normal laboratory values published in various clinical guides for laboratory tests. Most values for pregnancy are from Gabbe SG, Niebyl JR, Simpson JI Livingstone, 1986; and UCSD research laboratories. Hematologic and coagulation test results were provided by Samuel I. Rapaport, M.D., UCSD.

Table I.3.
Conventional and Système International (SI) Units for Measurements in Urine[a]

Measurement	Typical Reference Intervals		
	Common Units	Factor Common → SI	SI Units
Albumin			
Qualitative (random)	Negative		Negative
Quantitative (24-h)	15–150 mg/24 h	1	0.015–0.150 g/24 h
Calcium			
Quantitative (24-h) average diet	100–240 mg/24 h	0.025	2.5–6.25 mmol/24 h
Chloride (24-h)	140–250 mEq/24 h	1	140–250 mmol/24 h
Creatinine (24-h)	14–22 mg/kg/24 h	0.0088	0.12–0.19 mmol/kg/24 h
	0.8–1.8 g/24 h	8.8	7.0–15.8 mmol/24 h
Osmolality (random)	500–800 mOsm/kg water	1	500–800 mmol/kg
Potassium (24 h)	40–80 mEq/24 h	1	40–80 mmol/24 h
Protein (24-h)	40–150 mg/24 h	1	40–150 mg/24 h
Sodium (24-h)	75–200 mEq/24 h	1	75–200 mmol/24 h

Adapted from standard tables for normal laboratory values published in various clinical guides for laboratory tests. Most values for pregnancy are from Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill-Livingstone, Hematologic and coagulation test results were provided by Samuel I. Rapaport, M.D., UCSD.

References

1. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28: 1039-1057.

2. Hollingsworth DR, Moore TR. Diabetes in pregnancy. In: Creasy R, Resnik R (eds). Maternal fetal medicine: principles and practice. Philadelphia: WB Saunders, 1989:925-988.

SECTION I

Preconception and Early Postconception Counseling

Dorothy R. Hollingsworth

The concept of preconception planning for pregnancy by diabetic women is a relatively recent idea (1, 2). Coustan states that counseling women with diabetes who plan to conceive is the single most important intervention now available to reduce demonstrably the likelihood of spontaneous abortion and birth defects (3). In the routine implementation of this important aspect of preventive medicine, the United States lags far behind Europe and the United Kingdom (Table 1.1). In our less structured health care system, many adolescent and young adult diabetic women with onset of insulin-dependent diabetes (IDDM; Type I) in childhood no longer have medical supervision and are rather casual about diabetic control and nutrition. When planned or unplanned pregnancy occurs, they present frequently with high concentrations of glycosylated hemoglobin and little or no knowledge of recent advances in diabetology and obstetrics. About 10% of diabetic women have IDDM; others, usually older, heavier, and with a strong family history of diabetes, may become aware for the first time during routine prenatal care and screening procedures that they have asymptomatic non-insulin-dependent (NIDDM; Type II) diabetes. About 90% of all diabetic adult women have NIDDM and many are in the reproductive age group (15–45 years).

Until recently, most obstetricians have had to focus on prenatal care and diabetic control too late in pregnancy (after 7.5–8 weeks' gestation) to prevent serious congenital malformations. Although major improvements have occurred in the management of diabetic pregnancies with a decline in perinatal infant mortality from 65% in the preinsulin era to 2–3% in major medical centers in the late 1980s (Fig. 1.1), this improvement has not been matched in most clinical settings by a reduction in congenital malformations. Birth defects incompatible with life remain the major cause of death in infants of diabetic mothers (IDM). This topic is discussed in greater detail later in this chapter.

Two reasons account for improved outcomes in IDM. First, better control of maternal hyperglycemia has made an enormous difference. However, of equal or even greater importance, has been the development in the mid-1970s of the specialty of perinatology within obstetrics

Table 1.1.
Preconception Counseling for a Diabetic Pregnancy in Europe and America

Country	Women Who Receive Preconception Counseling (%)
Denmark	75
United Kingdom	50
United States	<0.5

and neonatology as a subspecialty of pediatrics. Both factors have resulted in a much higher margin of safety for these pregnancies that was not possible before recent technological improvements in medical and obstetric care of diabetic women.

This chapter addresses the three most frequent questions asked by diabetic women and their physicians:

1. What is known about the heritability of diabetes?
2. What sort of malformations do IDM have and what causes them?
3. Will retinal and renal complications worsen during pregnancy and will they shorten my life expectancy and increase the risk of blindness?

The obstetrician, diabetologist, nurse educator, and genetic counselor all have important roles in providing advice to diabetic women before and throughout pregnancy. Discussions before a planned conception should be presented in several sessions, over 3–6 months or even longer. They should include both the diabetic woman and her partner.

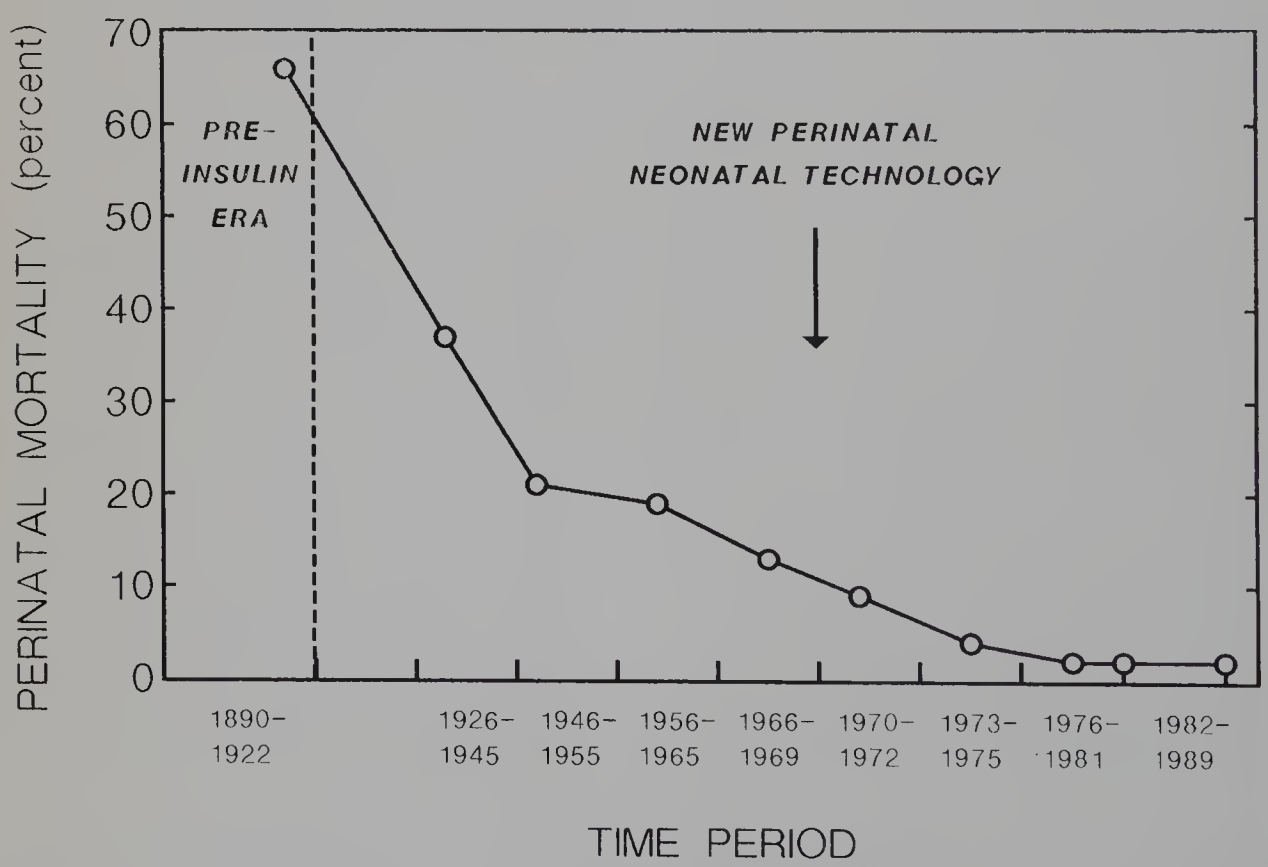


Figure 1.1. The change in perinatal infant mortality from the preinsulin era until 1989. Note that marked improvement had occurred by 1955, which was accelerated by the development of perinatal and neonatal technological advances in the 1970s.

CHAPTER 1

Genetics of Diabetes

Diabetes is recognized as a syndrome and not a single disease. Heterogeneity within the four groups of diabetic pregnant women is well recognized (Introduction; Table 1.1). Many individual women do not fit easily within the two major groupings of insulin-dependent diabetes mellitus (IDDM, Type I) and non-insulin-dependent, but "insulin-requiring" during pregnancy (NIDDM, Type II) diabetes. The problem of classification is even more difficult in women with gestational carbohydrate intolerance (gestational diabetes; GDM) described in detail in Chapter 7. No genetic markers have been identified for the inheritance of IDDM or NIDDM. For the individual pregnant woman, we cannot predict reliably the later risk of diabetes for her baby.

A great deal of genetic information is available, however, and the discussion that follows may serve as a useful guideline for counselors while our knowledge of genetics, immunology, and molecular biology expands. It is reassuring to be able to tell diabetic families that there is no increase in birth defects in progeny of diabetic fathers, babies born to prediabetic women, or those who develop gestationally evoked carbohydrate intolerance during the latter half of pregnancy. However, women in poor metabolic control at conception and during the first trimester have a significantly increased risk of spontaneous abortions and fetal malformations (4–6).

Insulin-dependent Diabetes Mellitus (IDDM; Type I)

At present, we are unable to identify with certainty individuals who are genetically susceptible to IDDM but who do not yet have the disease. Thus, genetic counseling must rely on current knowledge of HLA-associated inherited susceptibility, the rapid advances in molecular genetics of the HLA complex, and studies of polymorphism of the insulin gene. Several excellent recent reviews of genetics, immunology, and epidemiology of IDDM are available that discuss these topics in detail (7–16).

IDDM is most likely a chronic autoimmune disease of pancreatic B cells in genetically susceptible individuals. Major histocompatibility complex (HLA) haplotypes strongly influence susceptibility to diabetes in families with IDDM. Histocompatibility antigens are cell surface proteins that provide the tissue of each individual with a unique biologic label. A major component of genetic susceptibility for IDDM has been identified as a variation of a gene or genes located near or within the HLA complex on the short arm of chromosome 6.

Haplotypes are inherited for the most part in simple Mendelian fashion. The HLA region associated with IDDM lies within the D region or class II region of the HLA genes. Figure 1.2 illustrates the HLA gene complex and antigens coded for by a series of genes on chromosome 6 (10). The genes at each locus on the two homologous chromosomes are not always identical and a large number of alternate genes (alleles) may be present in a population. A primary association of IDDM with HLA-DR3 and HLA-DR4 has been reported by many investigators. In Maclaren's experience, only 5% of children and young adults with IDDM lack one or both of these antigens, while 40% have both antigens (DR3/DR4 heterozygotes) (17). Identification of DR3 and DR4 alleles is not an indication of the presence of IDDM. Although nearly everyone with the disease has one or both alleles, most persons with the alleles do not have the disease and specific diabetes susceptibility genes or markers have not been identified. The DR associations now also in-

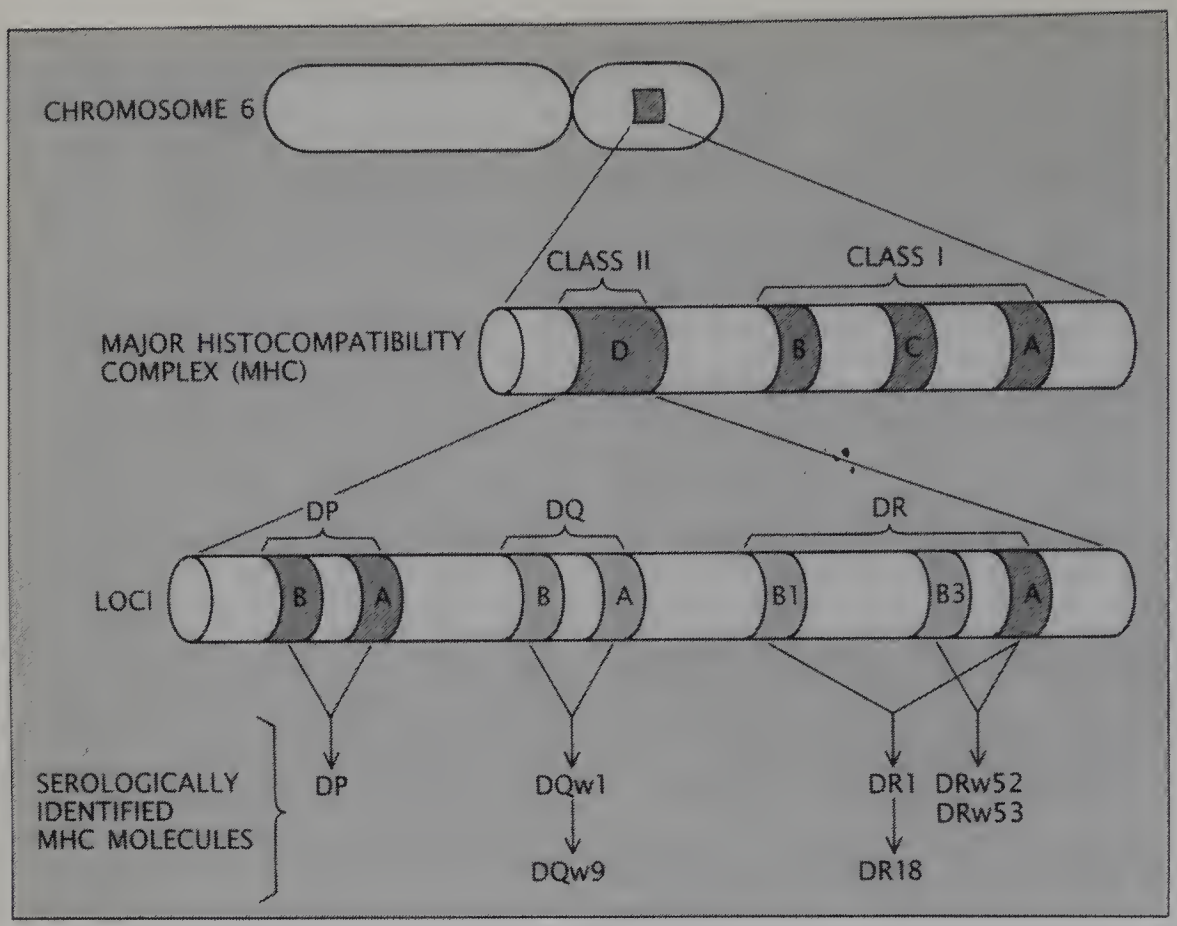


Figure 1.2. IDDM is associated with genes in the major histocompatibility complex (MHC) on **chromosome 6.** The suspect genes lie in the **D region,** which is comprised of three loci: **DP, DQ, and DR.** All three encode so-called class II MHC molecules, each consisting of two amino acid chains (**A** and **B**). Several of the genes for the chains are polymorphic (having or occurring in several distinct forms) or variable (shown in color figure on page xxi). Thus, an assortment of molecular types occurs (these are numbered). **The genes encoding DR1, 3, and 4 are common in IDDM.** They probably do not confer susceptibility directly, but the **DQ genes** usually inherited in conjunction with them probably do. **In contrast, genes that yield aspartic acid at the 57th position of the DQβ chain tend to be protective** while genes giving rise to other amino acids in that slot increase susceptibility. With permission from Atkinson MA, Maclaren NK: What causes diabetes? Scientif Am 1990:62-71. Copyright 1990 by Scientific American, Inc. All rights reserved.

clude DR1 as well as DR3 and DR4 for susceptibility and DR5 as well as DR2 for protection. About 95% of IDDM patients possess either HLA-DR3 or HLA-DR4 compared to 45–54% of the normal population.

MHC class II antigen serological and restriction fragment length polymorphism (RFLP) studies have indicated that HLA-DQβ genes, which are in linkage disequilibrium with HLA-DR are more strongly associated with IDDM than the DR genes (9). An extremely strong association has been reported between IDDM and a short segment of the HLA-DQβ chain gene (9, 11, 15). Using DNA amplified by the polymerase chain reaction and tested with DQβ allele-specific oligonucleotide probes, Morel and associates (16) have reported that the presence of an amino acid other than aspartic acid at position 57 of the HLA-DQβ chain (referred to as non-Asp positivity) in the homozygous state is associated with a relative risk of 107 for the development of IDDM. This is a major advance in the identification of a genetic marker for susceptibility to IDDM. In Japanese IDDM women, however, aspartic acid at position 57 of DQβ does not protect against IDDM; a clear difference in this population compared with Caucasians (10).

Asp 57-negative haplotypes do not always confer susceptibility and, conversely, some Asp 57-positive haplotypes seem to be disease associated. Khalil and colleagues (8), based on

extensive dot blot hybridization studies, have introduced the possibility that a DQα chain bearing an arginine in position 52 also confers susceptibility to IDDM. In their model, they anticipate that both residues DQβ Asp 57 and DQα Arg 52 are critical for modulation of susceptibility, presumably via viral-antigenic peptide and/or autoantigen presentation.

Figure 1.3, adapted from Rotter and Rimoin (18), shows risk to siblings of IDDM based on the number of shared histocompatibility haplotypes. Hitchcock and colleagues (19) have calculated absolute risks for IDDM for Caucasian individuals of various HLA phenotypes and genotypes based on an IDDM prevalence rate of 1 in 500 (Table 1.2). At present, our estimates of genetic transmission of IDDM focus on susceptibility, not inheritance of disease. Little is known of environmental influences, such as nutrition or exposure to viruses or toxins that convert susceptibility into disease (18). Risks for IDDM vary considerably in different geographic locations and among various racial groups. Thus, worldwide genetic counseling in the future will be determined by epidemiologic and population genetic studies now underway along with scientific advances in molecular biology.

Tillil and Köbberling (20) have examined age-corrected genetic risk estimates for first degree relatives of 554 German IDDM patients. They calculated the lifetime recurrence risk to age 80 years in three successive generations. The overall risk for siblings was 6.6 ± 1.1% and for children 4.9 ± 1.7%. The similar risks for siblings and children argue against a simple autosomal recessive trait. Regardless of age of onset, offspring of male probands always had a higher risk than offspring of female probands. Among all probands, fathers were significantly more often affected with IDDM (about twice) than mothers (4.1 ± 0.9 vs. 1.7 ± 0.6%, respectively). The risk for further siblings of the proband was signifi-

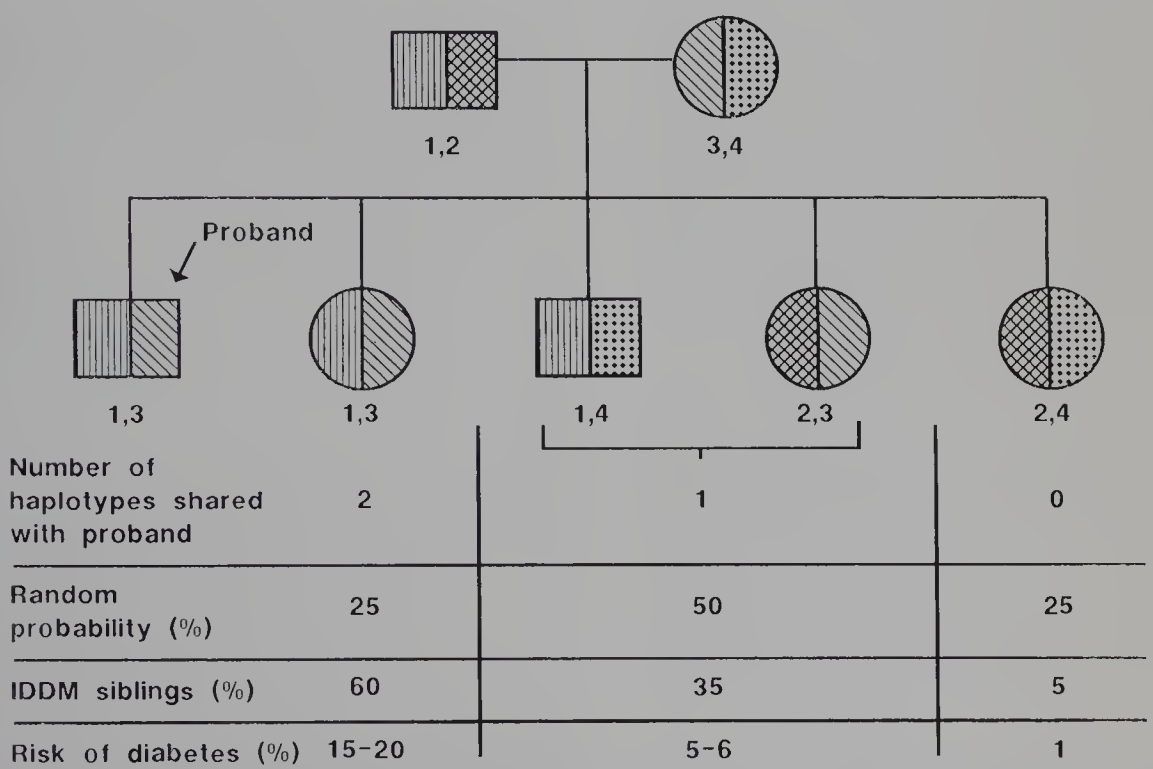


Figure 1.3. Major histocompatibility complex (HLA) haplotypes strongly influence susceptibility to diabetes in families with insulin-dependent disease (Type 1), presumably because the "susceptibility gene" (or genes) lies within or close to the HLA complex. If an individual is diabetic, a sibling with the same two haplotypes (here arbitrarily labeled 1 and 3) has a 15–20% chance of developing the disease. Siblings with only one susceptible haplotype are at a smaller but still substantial risk of 5–6%; those with neither haplotype are at risk of 1% compared with the 0.2% risk for members of the general population. With permission from Rotter JI, Rimoin DL: The genetics of diabetes. Hosp Pract 1987; 22:79-88.

Table 1.2.
Absolute Risks for IDDM for Caucasian Persons of Various HLA Phenotypes and Genotypes (based on an IDDM prevalence rate of 1 in 500)[a]

HLA Phenotype		HLA Genotype	
DR1	1 in 1000	DR3/DR3	1 in 125
DR2	1 in 2500	DR3/DRX	1 in 500
DR3	1 in 185	DR4/DR4	1 in 147
DR4	1 in 208	DR4/DRX	1 in 476
DR5	1 in 2500	DR3/DR4	1 in 42
DR6	1 in 1428	DRX/DRX	1 in 5565
DR7	1 in 1255		
DR8	1 in 555		
DR9	1 in 345		

[a]With permission from Hitchcock, et al. Autoimmunity in insulin-dependent diabetes mellitus: its detection and prevention. In Cruise JM, Lewis RE Jr. (eds): Genetic Basis of Autoimmune Disease. Basel: Karger, 1988; pp 144–167.

cantly increased in the presence of an IDDM parent (25.2 ± 10.3% vs. 5.8 ± 1.0% for the remaining probands). This study indicated a nonrandom clustering of IDDM in families. A younger age at onset was not associated with an increased risk to siblings.

Clinical heterogeneity occurs within the general classification of IDDM. In the natural history of the disorder, it is apparent that this is often not a disease of sudden, explosive onset, even in children. Approximately 25% of patients with IDDM do not develop symptoms until midlife or later. The common and slow onset of IDDM can pose a difficult problem in understanding the pathophysiology of pregnant diabetic women. In sum, IDDM occurs following the rapid or gradual destruction of pancreatic β cells. Various lines of evidence suggest that the etiology and clinical expression of the disorder are heterogeneous. Inheritance of IDDM is polygenic and associated with class II HLA-DR3 and HLA-DR4 histocompatibility antigens near or within the HLA complex on the short arm of chromosome 6. Alleles of HLA-DQβ ASP-57 and HLA-DQα ARG-52 may determine both disease susceptibility and resistance.

Non-insulin-dependent Diabetes Mellitus (NIDDM)

NIDDM is the most common form of diabetes throughout the world. Approximately 1 million women of reproductive age (15–45 years) in the United States have confirmed or probable NIDDM (21). This syndrome is also heterogeneous. It is characterized by abnormalities of insulin secretion and action and associated with insulin resistance. In a few individuals, defects in the synthesis of the insulin molecule (aberrant insulin diabetes) or other rare genetic abnormalities have been described (22). There are no genetic markers for NIDDM; however, strong genetic associations are clearer than in IDDM as evidenced by the almost 100% concordance rate among monozygotic twins compared to only 50% in IDDM (23). Although known to run in families, NIDDM does not fit a classical Mendelian pattern. Environmental factors play an important role in the pathogenesis of NIDDM. This is best illustrated by the demonstration of a marked rise in incidence of the disorder following the adoption of a western life-style. Two excellent recent reviews of the pathogenesis of NIDDM provide a good summary for a practical background to provide genetic counseling (24, 25). Family studies of empiric risk figures for first degree relatives of individuals with NIDDM show increased clustering with 38% affected siblings and one third of offspring exhibiting the disorder or "impairment" of glucose tolerance (26).

During genetic counseling, women with NIDDM should be cautioned about possible first trimester teratogenic effects of oral hypoglycemic agents and urged to discontinue their use before planned or accidental pregnancies (27). Women who have had impaired glucose tolerance during a previous pregnancy (ges-

tational diabetes) or during a periodic screening test should be urged to follow a diabetic diet and attempt to attain a normal body weight before another pregnancy. All women with NIDDM should be advised that they will require multiple daily injections of insulin throughout pregnancy.

Maturity-onset diabetes of the young (MODY) is an important subtype of NIDDM. It occurs during childhood or adolescence. A large number of multigeneration pedigrees have been been studied that have demonstrated an autosomal dominant inheritance with penetrance at a young age. Fajan's classic review provides a complete prospective view over the past 30 years of this interesting disorder (28). No associations have been found between specific HLA antigens and MODY in Caucasian, Afro-American, and Asian pedigrees. In addition, linkage studies of the insulin gene, the insulin receptor gene, the erythrocyte/Hep G2 glucose transporter locus, and the apolipoprotein B locus have shown no association with MODY. This form of NIDDM is not rare and should be suspected when a non-insulin-dependent form of diabetes occurs in children, adolescents, and young adults with a strong positive family history of the disorder over three or four generations. Our youngest pregnant woman with MODY was a 25-year-old nurse who had had NIDDM since age 12.

In sum, NIDDM is not rare in pregnant women and is the most common form of diabetes seen in clinics in the southwestern United States with a large population of Amerindians, Mexicans, and Mexican-Americans. The pathogenesis is characterized by a delayed first stage insulin response to feeding and insulin resistance (see also Chapter 7). All pregnant women with NIDDM will require insulin and should be warned of possible adverse effects on the fetus of oral hypoglycemic agents.

Secondary Diabetes

Cystic Fibrosis

Women with cystic fibrosis (CF) are fertile; the disorder occurs in about 1 of every 2000 Caucasian births. Few parents of children with cystic fibrosis were referred for genetic counseling until the discovery of DNA polymorphisms closely linked to the CF locus. The identification of the cystic fibrosis gene has been a genetic milestone of major importance (29–32). Chromosomal walking and jumping and complementary DNA hybridization were used to isolate DNA sequences encompassing more than 500,000 base pairs from the cystic fibrosis region on the long arm of human chromosome 7. Approximately 70% of the mutations in cystic fibrosis patients correspond to a specific deletion of three base pairs, which results in the loss of a phenylalanine residue at amino acid position 508 of the putative product of the cystic fibrosis gene. This remarkable achievement was accomplished when three laboratories racing toward the same goal decided to join forces and share information (29).

The identification of the CF gene (named cystic fibrosis transmembrane conductance regulator, CFTR) permits prenatal diagnosis by direct analysis of the mutation (33). If unaffected heterozygous carriers of the mutant gene can be identified, disease prevention becomes possible.

At present, only a proportion of the mutant chromosomes for CF can be detected. Table 1.3 shows the potential for detection of couples at risk with the use of population-based screening for carriers. With the availability of mutation analysis, Lemna et al. (34) feel that such testing of the spouse can be encouraged if one parent has a close relative with CF and is found to be a carrier on the basis of mutation or linkage analysis. If both parents are definite carriers, there is a 1 in 4 risk that the child will be affected, and prenatal diagnosis is possible (Fig. 1.4).

Table 1.3.
Potential for the Detection of Couples at Risk with the Use of Population-based Screening for Carriers[a]

% of Cystic Fibrosis Mutations Detectable	Detection of Carrier Status (%)		
	Both Parents	One Parent	Neither Parent
70	49.0	42.0	9.0
75	56.3	37.5	6.2
80	64.0	32.0	4.0
85	72.3	25.5	2.2
90	81.0	18.0	1.0
95	90.3	9.5	0.2

[a]With permission from Lemna et al. Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N Engl J Med 1990; 322:291–296.

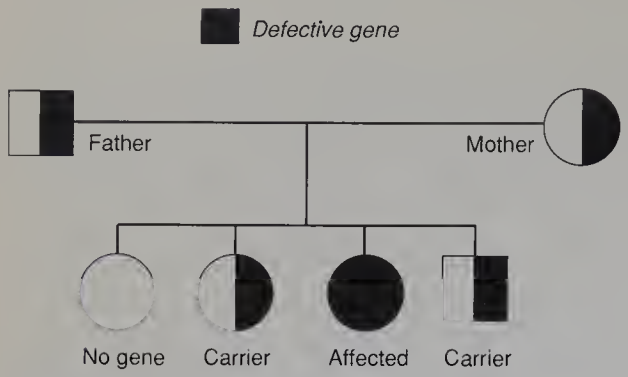


Figure 1.4. In this family, the mother and father are both carriers of the defective gene for cystic fibrosis. There is a 1 in 4 risk that a child will be affected.

Opinions differ as to whether heterozygote screening should begin immediately (1990). Some delay may be appropriate because additional mutations will probably be identified soon and time is needed so that genetic counselors can be trained and individuals being tested can be counseled to understand the results (34, 35).

Routine screening for GDM has detected women with CF with secondary diabetes (Type IV). The diagnosis should be borne in mind when there is a family history of CF or in women who present with unusual pulmonary or gastrointestinal symptoms.

CHAPTER

2

Prevention of Malformations in Infants of Diabetic Mothers

DIABETIC CONTROL BEFORE CONCEPTION

All women with IDDM or NIDDM should be urged to have preconception counseling and become aware of the role that good control of diabetes plays in the prevention of congenital malformations. Counselors generally request that both the patient and her partner participate. Many couples are confused, anxious, or frightened about the prospect of a pregnancy. Some diabetic women have been told that they should never become pregnant because it would endanger their health or shorten their lives; others have had a recommendation for sterilization. Thus, the first goal of a counselor is to allay unreasonable or unfounded anxieties and present factual information.

Each couple requires an individualized approach with ample opportunity for discussion and questions. The importance of diabetic control *before conception* is stressed and each woman is advised to have a comprehensive medical assessment (Table 2.1), instruction in home blood glucose monitoring, a retinal examination, renal evaluation, and nutrition counseling. Frequent supervisory appointments every few weeks at a diabetes center or by a diabetologist are essential to achieve and maintain diabetic control. It usually takes 2-4 months to reach a normal HbA1c concentration along with changes in nutrition and activity that are compatible with the patient's life-style, occupation, and quality of life.

MALFORMATIONS IN INFANTS OF DIABETIC MOTHERS

Congenital malformations have been reported to occur about three times as often in infants of diabetic mothers (IDM) as in "normals" (4.8% vs. 1.65%) (36). They represent the most common cause of death in newborn IDM. The etiology of malformations is most likely multifactorial in origin (37).

Several studies have shown a marked decrease in malformations when prepregnancy and early postconception control was achieved (38, 39). Fuhrmann and associates (40), in a prospective study of intensified metabolic control, reported a rate of birth defects similar to that of the general population and considerably lower than that among insulin-dependent diabetes mellitus (IDDM) patients who did not seek care until 6 or more weeks after conception.

Damm and Mølsted-Pedersen (41) have reported their findings in 1858 newborn IDM between 1967 and 1986 at Rigshospital, Copenhagen. The malformation rate was remarkably constant from 1967–1981, but a major decrease was found in the period 1982–1986 vs. the 1977–1981 period (2.7% vs. 7.4%, $p<0.05$). A correlation between the severity of maternal disease by White classification and by malformations was no longer apparent. In fact, in their latest 5-year period, no major congenital malformation was seen in offspring of mothers with White class F diabetes. Accordingly, the argument for abortion or sterilization of women with class F diabetes has been weakened if not invalidated. These results differ from those of Miodovnik and colleagues who did find an association between maternal vasculopathy and congenital malformations (42). Damm and Mølsted-Pedersen argue that vasculopathy alone does not increase the risk of malformations; the risk previously reported can be reduced by prepregnancy management. In Copenhagen, 75% of diabetic pregnancies

Table 2.1.
Medical Assessment of Diabetic Women Before Conception[a]

Procedure	Tests	Recommendations
History, family history, review of systems	Selected individuals. ICA, IAb, HLA typing, fasting and postprandial C-peptide determinations[b]	Continue contraception until diabetic control is optimal (Normal HbA1c)
Complete physical examination—positive findings		
Hypertension	ECG, cardiac and renal evaluation	Medication to control elevated blood pressure
Retinopathy	Retinal examination	Ophthalmology consultation
Goiter (common in IDDM)	T_4, TSH, thyroid MSA	Depend on thyroid diagnosis, size of goiter, and thyroid function tests
Neuropathy	—	Complete neurologic examination
Obesity (more common in NIDDM)		Weight reduction, exercise
Diabetes assessment— Glycemic control and complications	HbA_{1c} concentration, CBC	Home blood glucose monitoring, adjust insulin and other medications
		Nephrology consultation if renal function is abnormal
Nutrition	Fasting plasma lipoprotein profile	Dietary history and counseling
		Adjust for occupational, cultural, and ethnic considerations
Assess occupation and recreational exercise		Adjust management of diabetes
Type and timing of insulin injections or oral hypoglycemic agents[c]		MSI vs. CSII
		Discontinue oral hypoglycemic drugs

[a]Abbreviations used: IDDM, insulin-dependent diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; ICA, islet cell antibodies; IAb, insulin antibodies; HLA, human leukocyte antigen haplotypes; ECG, electrocardiogram; T_4: thyroxine; MSA, microsomal antibodies; TSH, thyroid-stimulating hormone; MSI, multiple subcutaneous injection; CSII, continuous subcutaneous insulin infusion.
[b]These are not routine tests and will be recommended rarely at present by genetic counselors and diabetologists.
[c]Patients with NIDDM on oral hypoglycemic agents are cautioned not to become pregnant because of teratogenic potential in first trimester.

are planned and, in these pregnancies, only 1% of infants had congenital malformations. In the offspring of 1715 nondiabetic women, major congenital malformations were found in 1.7% (Table 2.2). From 1982–1986, the rate of fatal malformations had been reduced in diabetic women to 1.2% (3 of 258 infants).

The Danish study has clearly demonstrated the marked decrease in malformations in planned versus unplanned diabetic pregnancies (1.0% vs. 8.2%; Table 2.3). Interestingly, the mean HbA1c value measured before the 12th completed gestational week was around 2 SD above the upper limit of the reference interval and no significant differences were found between planned and unplanned pregnancies. Malformations were seen despite normal HbA1c values and there was no correlation between HbA1c and congenital malformations.

Mills and co-workers (43) have published the first data from the prospective United States Diabetes in Early Pregnancy Study (DIEP) being conducted in five universities (Cornell, Harvard, Northwestern, Pittsburgh/Northeast Ohio, and the University of Washington). Again, no correlation was apparent between HbA1c concentration and mean blood glucose level in early pregnancy and the frequency of malformations. Diabetic women who entered

Table 2.2.
Congenital Malformations in Newborn Infants of Diabetic Mothers

	White class A				White classes B and C				White classes B to F			
	Congenital Malformations (%)				Congenital Malformations (%)				Congenital Malformations (%)			
Period	n	Major	Minor	Total	n	Major	Minor	Total	n	Major	Minor	Total
1967–1971	68	2.9	0	2.9	138	5.8	1.4	7.2	265	8.3	2.6	10.9
1972–1976	158	3.2	1.9	5.1	127	7.1	0	7.1	281	8.2	1.1	9.3
1977–1981	267	1.9	0.4	2.2	141	4.3	2.1	6.4	272	7.4	1.1	8.5
1982–1986[a]	**289**	**1.7**	**0.3**	**2.1**	**133**	**3.0**	**0.8**	**3.8**	**258**	**2.7[a,b,c]**	**1.6**	**4.3[a,b,c]**

[a]In 1985, 1715 infants were born to nondiabetic mothers; there were 1.7% major, 1.1% minor, and 2.8% total congenital malformations. None of the differences was statistically significant ($p > .005$).
[b]$p < 0.01$, compared with 1967 to 1981.
[c]$p < 0.05$, compared with 1977 to 1981.
With permission of Damm and Mølsted-Pedersen (41).

the study early had only a "moderate degree" of metabolic control; the 50th percentile for mean glucose values in the 5th through 8th weeks of gestation was approximately 200 mg/dl (11.1 mmol/L), and 90% of subjects had a mean glucose value between 140 and 235 mg/dl (7.8 and 13.0 mmol/L, respectively). These levels are much higher than those of normal nondiabetic women. Major malformations occurred in 4.9% of IDM compared with 9% of those offspring of a group of diabetic women who enrolled in the study after the 21st day following conception and 2.1% in offspring of nondiabetic women. Coustan (3), Damm and Mølsted-Pedersen (41), and Freinkel (44) have all suggested the possibility that metabolites other than glucose might be associated with congenital malformations.

In the DIEP study, fewer congenital malformations occurred when diabetic women were admitted to the hospital before the 21st day after conception. These observations notwithstanding, and the inability to correlate absolute HbA1c levels as a predictor of fetal abnormality in individual cases, do not undermine the validity of the general association between high blood glucose in early pregnancy and an increased risk of fetal malformations (45).

Diabetic embryopathy appears to be multifactorial (46). The late Dr. Freinkel proposed the hypothesis that all the aberrant fuels and fuel-related components of the diabetic state (e.g., high glucose; ketones; somatomedin inhibitor(s); osmolality) have dysmorphogenic potential which he called "fuel mediated organ teratogenesis" (Fig. 2.1) (47, 48). Further, all tissues in the conceptus appear to be at risk.

Table 2.3.
Maternal HbA1c in Early Pregnancy and Major Malformations in Newborn Infants of Insulin-dependent Diabetic Mothers in Planned and Unplanned Pregnancies

		Planned Pregnancies					Unplanned Pregnancies				
		Congenital Malformations			HbA1c		Congenital Malformations			HbA1c	
Period	Total No. of infants	N	n	%	n	Mean ± SD (%)	N	n	%	n	Mean ± SD (%)
1974–1976	173	86[a]	5	5.8			87	10	11.4		
1982–1986	258	197[b,c]	2	1.0[d]	64	7.1 ± 1.2	61	5	8.2	21	7.3 ± 1.5

[a]Including one pair of twins.
[b]Including four pairs of twins.
[c]$p < 0.001$, compared with 1974 to 1976.
[d]$p < 0.01$, compared with unplanned pregnancy.
With permission of Damm and Mølsted-Pedersen (41).

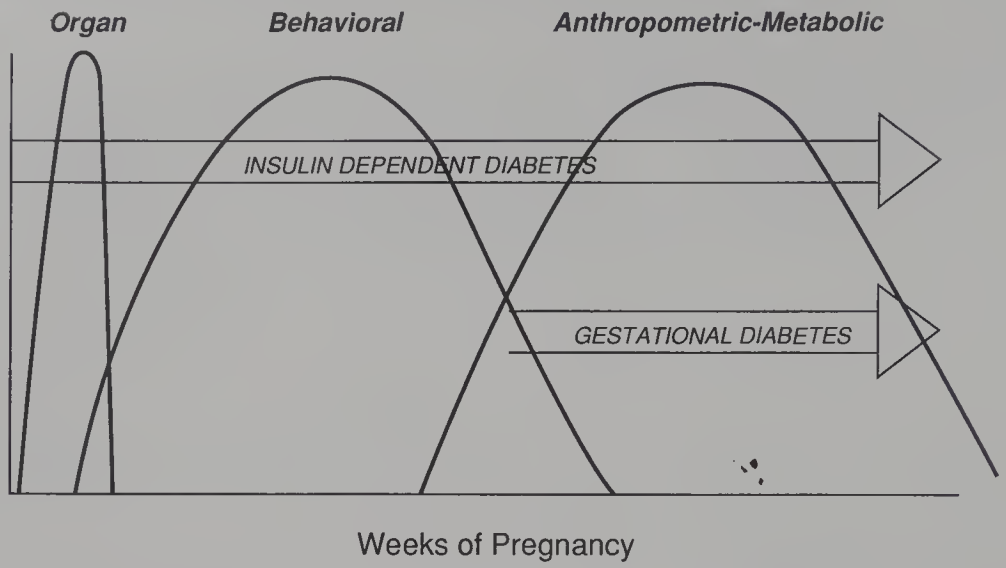


Figure 2.1. Fuel-mediated teratogenesis, the modification of phenotypic gene expression in newly forming cells by ambient fuels and fuel-related products during intrauterine development. Potential long-range effects upon the offspring depend upon the period in gestation during which maternal fuels and fuel-related products are awry and the cells that are undergoing terminal differentiation at that time. When that period coincides with organogenesis in the embryo, the potentiality for "fuel-mediated organ teratogenesis" occurs. With permission from Freinkel N. Review. Diabetic embryopathy and fuel-mediated organ teratogenesis: Lessons from animal models. Horm Metabol Res 1988; 20:463-475 and Georg Thieme Verlag, Stuttgart.

Dose-response relationships for individual metabolic teratogens may be influenced by additive and synergistic interactions so that integrated possibilities cannot be assessed fully by measurements confined to a single fuel or to a fuel-related component. He offered the additional explanation that, in the context of day to day variability in diabetes "control" of the poorly regulated mother and the relatively longer duration of organogenesis, these multifactorial possibilities may account for the multiple birth defects that can occur in individual offspring and the seemingly nonspecific pattern of diabetic embryopathy.

There is probably some genetic susceptibility to teratogens. In animals and humans, insulin therapy diminishes the dysmorphogenic effects of the abnormal "diabetic state." However, a disquieting observation in several animal models for diabetes has been that *hypoglycemia* may be teratogenic during the phase of organogenesis in which the postimplantation rodent embryo is wholly dependent upon glycolysis (e.g., a period in development corresponding to day 16–18 to day 24–25 of human pregnancy) (47). Developmental events in the postimplantation conceptus are shown on Table 2.4. These considerations have prompted the provisional clinical recommendation that *near normalization* rather than *full normalization* of maternal metabolism may be the most prudent therapeutic target for the intensification of diabetes management during the first 4 weeks of pregnancy (43).

The congenital malformations seen in IDM, their ratio of incidences, and the weeks following gestational ovulation in which they occur are shown in Table 2.5. These are graphically illustrated in Figures 2.2 and 2.3. Ferencz and colleagues (51) have reported the relationship of maternal diabetes and cardiovascular mal-

Table 2.4.
Developmental Events in the Postimplantation Conceptus[a]

Total Gestation (Days)	Rat 21–22	Mouse 18–20	Human 267
Implantation	5–6	7	6–7
Primitive streak	9	8	16–18
Neural plate	9.5	8	18–20
First somite	10	8.3	20–21
First branchial arch	10	8.3	20
First heartbeat	10.2		22
Anterior neuropore closed	10.5	9	24–25
10 somites	10.5	8.6	25–26
Upper limb bud	10.5	9.3	27–28
Posterior neuropore closed	11.3	9.5	26–27
Three branchial arches	11.5	9.6	26

[a]Adapted with permission from Wilson (1973) and Shepard (1980) as published by Freinkel (48).

Table 2.5.
Congenital Malformations in Infants of Diabetic Mothers[a]

Anomaly	Ratio of Incidences[b]	Gestational Ovulation (weeks)
Sacral dysgenesis	252	3
Spina bifida, hydrocephalus, or other CNS defect	2	4
Anencephalus	3	
Heart anomalies[c]	4	
Transposition of great vessels		5
Ventricular septal defect		6
Antrial septal defect		
Anal/rectal atresia	3	6
Renal anomalies	5	
Agenesis	6	5
Cystic kidney	4	5
Ureter duplex	23	5
Situs inversus	84	4

[a]Modified from Mills JL, Baker L, Goldman AS. Malformation in infants of diabetic mothers occurs before the seventh gestational week. Diabetes 1979; 28:292–293.
[b]This ratio is derived from Kučera's equation (1971): Ratio = [(number of cases of this anomaly in the diabetic group)/(total diabetic group)]/[(number of cases of this anomaly in the control group)/(total control group)].
[c]Congenital heart lesions with the worst prognosis are (*a*) complex transposition of the great vessels, (*b*) single ventricle, (*c*) hypoplastic left heart, and (*d*) tricuspid atresia.

formations in the population-based case-control investigation of the Baltimore-Washington Infant Study. The strongest associations with overt maternal diabetes were found with double outlet right ventricle and truncus arteriosus. These are malformations dependent on neural-crest cell-derived ectomesenchymal tissues (18–20 days of gestation in humans); precisely the cotruncal abnormalities that result from experimental ablation of the neural crest in chick embryos. No significant diagnosis-specific associations were found with gestationally evoked diabetes (GDM).

In sum, what message should every diabetic woman in the reproductive age group receive? Each should be informed carefully, but in forthright terms, from *menarche and adolescence onward* that overall poor metabolic control of diabetes is a serious risk for malformations in her infants. Arrangements should be made for good longitudinal care for all diabetic women and their progeny. Women who are already pregnant and found to have an elevated HbA1c concentration can be told that early diagnosis of many fetal problems is now possible so that parents can be more fully informed about considerations for interruption of pregnancy and treatments available for specific malformations.

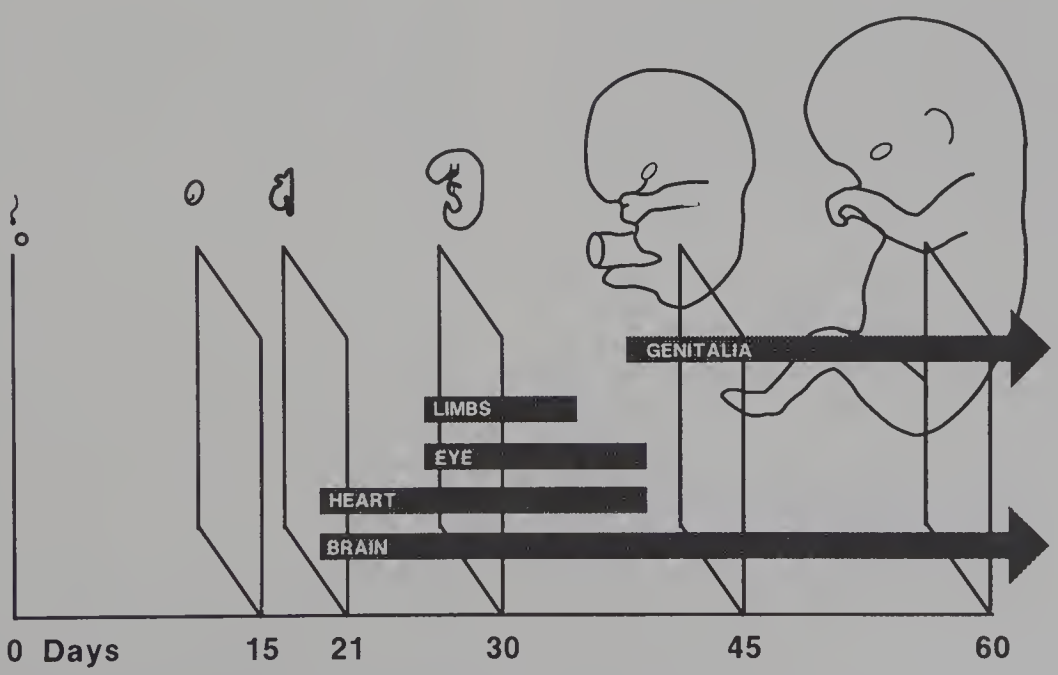


Figure 2.2. Critical timing in days of interference with embryonic development and organogenesis. Redrawn from Tuchman-Duplessis (50) with permission.

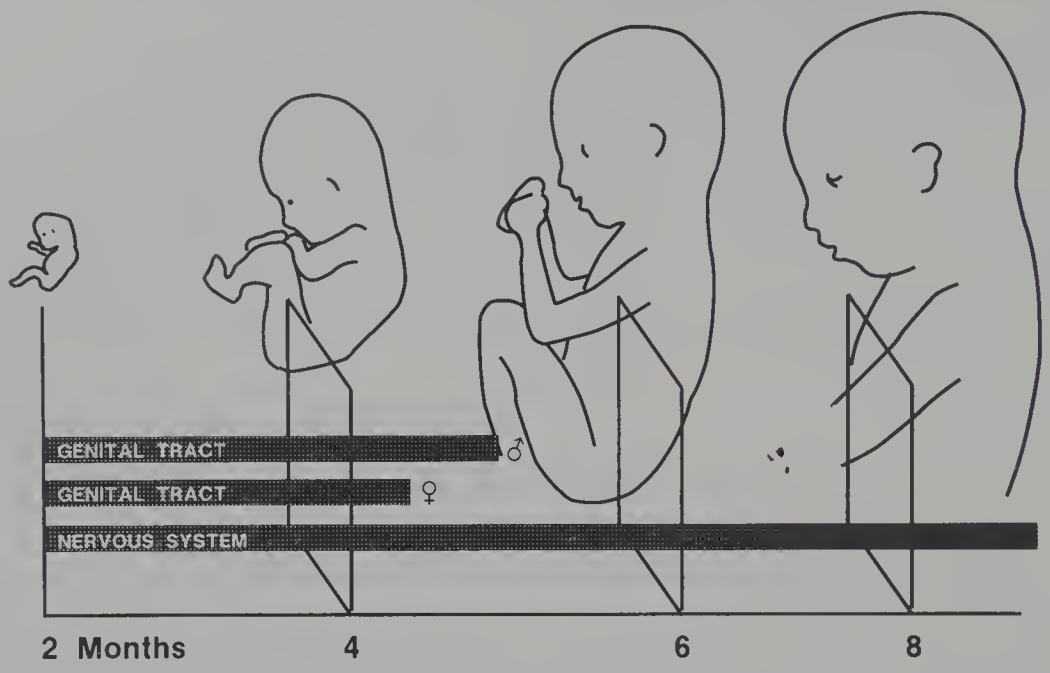


Figure 2.3. The critical periods of interference with the development of genital tract and nervous system. Redrawn from Tuchman-Duplessis (50) with permission.

Procedures for the detection of fetal anomalies include *(a)* maternal serum levels of α-fetoprotein at 14–16 weeks' gestation and *(b)* high resolution ultrasonography and real-time two-dimensional and M-mode echocardiography at 20–22 weeks' gestation. These procedures have enabled prospective diagnosis of neurodevelopmental defects and cardiac malformations, such as transposition of the great vessels, ventricular and atrial septal defects, tricuspid atresia, Ebstein's anomaly, double outlet right ventricle, coarctation of the aorta, and hypoplastic left heart syndrome. These complications can be anticipated and medical care planned for in a special care nursery.

The syndrome of diabetic metabolic embryopathy also includes possible postnatal neurologic developmental defects secondary to severe maternal ketosis or hypoglycemia and unknown additional etiological factors. The long-term effects of fetal hyperglycemia and hyperinsulinemia in utero along with an abnormal supply of all classes of nutrients are unknown (52).

In the United States, the incidence of congenital malformations in IDM whose mothers are not cared for in medical centers with expertise in diabetes is unacceptably high. The major difficulties for diabetic women are *lack of access to (a) diabetes education, (b) preconception counseling, and (c) inexpensive prenatal care.*

CHAPTER

3

Maternal Complications of Diabetes and Risks of Pregnancy

Women with diabetes who have evidence of retinopathy or nephropathy are concerned justifiably about the effect of a pregnancy on the progression of these complications. Their primary worry is the possibility of potentially adverse effects upon the length and quality of their life and their ability to raise a child. Considerable progress has been made in both our understanding and treatment of microangiopathy; frequently, updated information is a critical component of counseling for both nonpregnant and pregnant diabetic women.

RETINOPATHY

Insulin-dependent Diabetes Mellitus (IDDM)

Not all patients with IDDM develop retinal microvascular complications; the pathogenesis of diabetic retinopathy is poorly understood. Rosenstock and Raskin, in a 1988 review, point out that some patients with long-term IDDM never develop severe complications regardless of their glycemic control (53). Two major etiologic hypotheses for development of retinopathy address the respective roles of genetics and control of hyperglycemia. Other proposed retinopathy associations include immunologic differences among patients, insulin-like growth factors, growth hormone excess, and unidentified hormones that might stimulate angiogenesis.

Although diabetic retinopathy is the most common chronic complication associated with diabetes, population-based epidemiologic data in the United States in pregnant women have been quite limited. Klein and colleagues have recently reviewed the Wisconsin epidemiologic study of diabetic retinopathy (WESDR) (54). They found the incidence of proliferative retinopathy to be 0% in IDDM in persons with fewer than 3 years since onset; 28% in individuals with 13–14 years of diabetes. Thereafter, a lower incidence (14–17%) was found. In the Wisconsin study, severity of retinopathy in IDDM was correlated with longer duration of diabetes, older age at examination, higher concentrations of glycosylated hemoglobin, higher diastolic blood pressure, gross proteinuria, and being male. Krolewski and associates (55) have reported a similar incidence of proliferative retinopathy after 15–19 years of IDDM.

Non-insulin-dependent Diabetes Mellitus (NIDDM)

It is not possible to provide preconception counseling in NIDDM concerning pregnancy risks for onset or worsening of retinopathy because no prospective or retrospective studies have been done in this large group of women. Many pregnant NIDDM women do fall into risk categories for retinopathy, such as concomitant hypertension and/or poor glycemic control. However, confirmation of the diagnosis of retinal vascular disease in NIDDM during prenatal care is unusual. This may relate to negative or poor initial physical examinations of the eyes, fewer requests for ophthalmologic studies, and the recommendation not to do fluorescein studies during gestation. In addition, pregnant women with NIDDM are likely to have had the disorder for a relatively short duration of time compared with pregnant IDDM women.

Ballard and colleagues (56) have conducted a population-based study of retinopathy in Rochester, Minnesota. Risk factors for this

complication in NIDDM were an initial fasting blood glucose level of more than 200 mg/dl (11.1 mmol/L), marked obesity, and earlier age at onset. Treatment with insulin was not a risk factor.

In the Wisconsin study mentioned previously (54), patients in the older group (over 30 years) and not taking insulin and with presumptive NIDDM had the lowest frequency and least severe retinopathy. In addition, macular edema when present was less likely to be accompanied by proliferative retinopathy (19%) than in IDDM women who were more than 30 years of age (65%).

In Mexican-Americans, NIDDM pregnancies over the age of 40 years are not unusual and these women are at risk for retinopathy. In newly diagnosed NIDDM patients, without the risk factors described previously, there is a 10-year cumulative risk of retinopathy of less than 10% compared with 40% for women with IDDM at high risk.

Genetics

Dornan and colleagues (57) have related the prevalence of retinopathy in IDDM to HLA-DR4 haplotypes and poor diabetic control. Others (58–61) have concluded that HLA genetic factors, insulin-binding capacity, and autoimmunity are unrelated to the pathogenesis of microvascular disease and that circulating immune complexes may well be secondary to widespread tissue damage in diabetes of long duration (61).

Control of Hyperglycemia

Poor control of blood glucose levels has long been proposed as the cause of microvascular complications. It has been difficult to prove the association because only recently with self-monitoring techniques and periodic measurements of HbA1c concentrations has it been possible to assess the degree of blood glucose control with greater reliability. The ongoing Diabetes Control and Complications Trial (DCCT) (62) sponsored by the National Institutes of Health should provide important information for future preconception counseling of IDDM. The results of previous trials in Europe and the United States designed to evaluate the relationship of diabetes control to microvascular complications have been summarized by Rosenstock and Raskin (53). Hyperglycemia is clearly associated with retinopathy in most studies but multiple risk factors contribute to the pathogenesis of the complication.

In their recent review of the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), Klein and co-workers point out that no medical intervention has been proven to prevent the incidence or progression of this complication (54). Prevention of visual loss relies on early detection of retinopathy and timely treatment of proliferative retinopathy with panretinal photocoagulation and clinically significant macular edema with focal and/or grid photocoagulation. Vitrectomy may restore some vision in some eyes with traction retinal detachment or vitreous hemorrhage. Fluorescein angiography permits the detection of retinopathy, on average, 4 years earlier than with ophthalmoscopy. The median interval between the onset of retinopathy, as indicated by a few microaneurysms and background retinopathy, is about 5 years.

Pregnancy

Does pregnancy precipitate or worsen retinopathy and increase the risk of blindness? To a large extent, this depends upon retinal complications and appropriate treatment along with good blood glucose control before conception. Table 3.1 provides guidelines for eye care for nonpregnant and pregnant women with diabetes (63). The impact of pregnancy on retinal changes in IDDM has been described in both retrospective and prospective studies. Early reports (before 1970) cautioned that the risk for progression of retinopathy during gestation was high; diabetic women with this complication were advised not to become pregnant or to elect abortion should conception occur.

Prospective studies since 1980 have provided a more balanced and optimistic view. Horvat and colleagues (64) in a 12-year prospective study followed 107 women with latent diabetes and 172 women with clinical diabetes. In the already diabetic women, background retinopathy was present in 40 (23%), who had an average duration of diabetes of 13.5 years. Vision remained stable in all but four women (10%) who progressed to proliferative retinopathy. Only one woman developed new vessels in one eye during pregnancy. The three others had proliferative changes noted following pregnancy. Eleven women in their study had proliferative retinopathy with one case devel-

Table 3.1.
Eye Care Guidelines for Women With Diabetes Who Anticipate Becoming or Are Pregnant[a]

General examination	1. In referring patients for routine eye evaluation, the physician should be guided by the expertise and qualifications of the eye doctor to perform the examinations described 2. All patients should be informed that: a. Sight-threatening eye disease is a common complication of diabetes mellitus and is often present even with good vision; b. Early detection and appropriate treatment of diabetic eye disease reduces the risk of visual loss. 3. Baseline ophthalmologic examinations of all IDDM and NIDDM women 3–5 years after the onset of diabetes or at puberty (whichever occurs first); the examination should include: a. History of visual symptoms; b. Measurement of visual acuity and intraocular pressure; c. ophthalmoscopic examination through dilated pupils. 4. After the initial eye examination, it is suggested that women with diabetes mellitus should receive the above ophthalmic exams annually unless more frequent exams are indicated by the presence of abnormalities
Special examinations **Prepregnancy**	1. Women with both insulin-dependent (IDDM, Type I) and noninsulin-dependent (NIDDM, Type II) who are planning pregnancy within 12 months should be examined by an ophthalmologist
Pregnancy	1. Baseline examination for retinopathy by an ophthalmologist as soon as conception is confirmed 2. All diabetic women with IDDM or NIDDM should be under the care of an ophthalmologist for: a. Unexplained visual symptoms; b. Deterioration in visual acuity; c. Increased intraocular pressure; d. Any retinal abnormality; e. Any other occular pathology that threatens vision. 3. Pregnant women should be under the care of a retinal specialist or other ophthalmologist experienced in the management of diabetic retinopathy, when the following conditions are identified: a. Preproliferative retinopathy (multiple cotton-wool spots, multiple intraretinal hemorrhages, intraretinal microvascular abnormalities, venous beading); b. Proliferative retinopathy (retinal neovascularization, preretinal or vitreous hemorrhage, fibrosis, traction retinal detachment); c. Macular edema (hard lipid exudates and/or retinal thickening inside the temporal vascular arcades). 4. Laser photocoagulation therapy reduces the risk of visual loss and is generally effective in preventing blindness in patients with high-risk proliferative retinopathy and/or clinically significant macular edema; vitrectomy can restore vision in certain patients with recent traction retinal detachment or vitreous hemorrhage; laser therapy and vitrectomy should be performed by a retinal specialist or other ophthalmologist experienced in these procedures in people with diabetes; these procedures may or may not be recommended during pregnancy 5. Pregnant women with functionally decreased visual acuity postpartum should undergo low-vision evaluation and rehabilitation

[a]Adapted from Hollingsworth DR, Moore TR (64) and a position statement developed by the committee on professional practice and approved by the Executive Committee of the Board of Directors of the American Diabetes Association, 8 June 1988. Diabetes Care 1988; 11:745–746.

oping de novo during pregnancy (average duration of diabetes was 21 years). In the Horvat study (64), retinopathy fluctuated during the index and subsequent pregnancies; not infrequently, changes occurred in both directions at one time with one part of the eye getting better, another part becoming worse. In this report, the severity of retinopathy at onset of pregnancy was important in predicting severity at the end of or following gestation.

Moloney and Drury (65), in a prospective study of 53 pregnant IDDM patients who had retinal photography every 6 weeks and at 6 months postpartum, found that 33 (62%) had retinopathy at first examination and eight (15%) developed it for the first time during gestation. Four women had neovascularization for the first time with further deterioration with advancing pregnancy. However, by 6 months after delivery, background changes had regressed to control levels and neovascularization showed some regression. Increased doses of insulin (tighter control) and hydramnios were risk factors for retinal hemorrhage. Low fasting blood glucose values and intensive insulin therapy were associated significantly with soft exudates and streak blob hemorrhages that usually resolved in 6 weeks. No effect of pregnancy was demonstrated in women who had diabetes less than 2 years.

In other reports, Phelps and co-workers (66) and Laatikinen and colleagues (67) were also able to correlate worsening retinopathy with degree of hyperglycemia at first prenatal visit and magnitude of improvement in glycemic control. In Serup's prospective Copenhagen study from 1979–1986, of 145 IDDM cases, three ophthalmologic examinations were performed during pregnancy and three in the year following delivery (68). Half of the women who already had retinopathy had some deterioration during pregnancy, but all had regression to some extent following delivery. A few women with background retinopathy at onset of gestation developed proliferative retinopathy that commonly disappeared in the postpartum period. They had no severe changes with respect to vitreous hemorrhages or severe proliferative changes and in only one case was postpartum photocoagulation necessary to arrest retinal proliferative changes at the optic disc.

In the most recent (1990) Wisconsin study reported by Klein and colleagues (69), 171 pregnant women in the first half of pregnancy were recruited from 1982–1986 and compared with 298 nonpregnant insulin-taking women. Blood pressure, blood glucose values, HbA1c concentrations, and stereoscopic color fundus photographs were obtained. No other observations were made during gestation. Fundus photographs were repeated at 9.4 ± 6.6 weeks postpartum and at a similar time period in controls. Thirty-eight pregnant (22%) and 57 nonpregnant (19%) women failed to return for the second examination. There were gradable fundus photographs at both visits in 78% of the pregnant and 80% of the nonpregnant subjects. In this epidemiologic study with no longitudinal examinations of women during pregnancy, elevated glycosylated hemoglobin at first examination was confirmed as a risk factor for retinopathy in both pregnant and nonpregnant women. There were marked differences in metabolic control that reflected current obstetric emphasis of "tight control" in pregnant women but no such management in control subjects. Thus, the frequently reported worsening of retinopathy with intensive insulin therapy and lack of observations during pregnancy make it impossible to conclude that pregnancy alone worsens retinopathy. Other studies of rapid tightening of blood glucose control by multiple daily doses of insulin or use of an insulin pump in nonpregnant individuals have demonstrated progression of retinopathy (70–75).

In sum, all recent studies underline the critical importance of preconception counseling for prevention of worsening retinopathy during pregnancy. Poor diabetic control at conception and untreated retinopathy are preventable risks. Parity is not a risk factor for retinopathy, when analyzed apart from duration of diabetes. Photocoagulation of retinal lesions before conception seems to be more protective than having the procedure performed during pregnancy. Should pregnant women with severe disc neovascularization or with marked progression of retinopathy despite first trimester photocoagulation therapy be advised to have an abortion? At present, there is no evidence that termination of pregnancy would improve substantially the ultimate visual outcome. Pregnant IDDM women with severe retinopathy and potential loss of vision in one or both eyes and their partners are faced with difficult personal considerations. They require

the most up-to-date information and consultation with centers enrolling patients in diabetic retinopathy and vitrectomy studies (DRVS) (2).

Management of diabetic retinopathy during pregnancy and fundus photographs of typical retinal lesions are described in Section 6, Chapter 17.

NEPHROPATHY

Nephropathy (76) of variable degrees of severity is common in women with IDDM. Does pregnancy accelerate this complication and pose additional risks for the mother and fetus?

Insulin-dependent Diabetes Mellitus (IDDM)

Figure 3.1 (77) illustrates the development of albuminuria and clinical nephropathy over time in IDDM patients. The presence of more than 300 mg of albuminuria (Ualb V) in 24 hours indicates incipient diabetic nephropathy and a risk for later development of clinical nephropathy (77–80).

During preconception counseling, all IDDM patients should have an assessment of renal function. Recommendations for this evaluation, both before conception and at the first prenatal visit, are described in Section 6, Chapter 17.

Diabetic nephropathy occurs in 40–45% of IDDM patients. Why more than half of these at-risk women escape without this complication is unclear. Although hyperglycemia is a necessary condition, it is not a sufficient factor to explain patient susceptibility. A Diabetes Control and Complications Trial (DCCT; N = 1441) is in progress in the United States until 1993 (81). This is one of the complications being investigated.

Seaquist and colleagues (82) have reported a familial clustering of diabetic kidney disease with evidence for genetic susceptibility to diabetic nephropathy. Other contributory factors that have been suggested are hypertension, urinary tract infections, smoking, high dietary protein intake, and the presence of other cardiovascular disease risk factors. With modern treatment of diabetic women that includes control of hyperglycemia and hypertension and alert diagnosis and treatment of urinary tract infections, the outlook for a successful pregnancy outcome is excellent. Nephropathy as a complication of pregnancy is discussed in Section 6, Chapter 17.

In the past, antedating major advances in perinatology and neonatology, many physicians strongly discouraged pregnancy in women with diabetic renal disease, especially when there was evidence of impaired renal function and hypertension (83). A more opti-

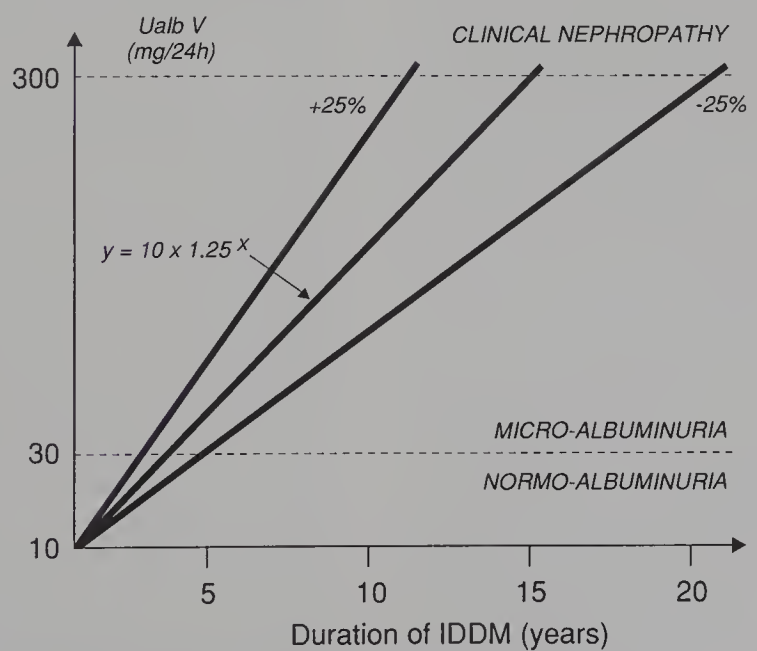


Figure 3.1. Development of proteinuria and clinical nephropathy in IDDM. There is a gradual increase in the excretion of urinary albumin over time in IDDM with microalbuminuria. With permission from Deckert et al. Clinical assessment and prognosis of complications of diabetes. Transplant Proc 1986; 18:1636–1638.

mistic view has been presented by Lindheimer and Katz (84). Hayslett and Reece (85) suggest that if patients with the most severe forms of nephropathy are excluded (poorly controlled first trimester hypertension despite medical therapy, serum creatinine level > 1.5 mg/dl, proteinuria > 3.0 g/24 h in the first trimester), both maternal and fetal outcomes are quite good. This more favorable prognosis, however, requires intensive obstetric and medical monitoring at a tertiary care hospital using an ambulatory care team approach (85).

In the most severe forms of diabetic nephropathy (see criteria previously listed), each woman should have individualized and coordinated management by a diabetologist, a renal medicine specialist, and a perinatologist (76). Women on chronic hemo- or peritoneal dialysis are often anovulatory or amenorrheic. When conception occurs, early spontaneous abortions are common. At best, only 20–25% of pregnancies result in viable infants. Many successful pregnancies are in women with some residual renal function or in those who needed to start dialysis only after pregnancy occurred. No maternal deaths have been recorded in women on dialysis. However, preeclampsia occurs frequently and requires antihypertensive medications. When giving advice about fertility and contraception to young women on dialysis, the nephrologist should discuss realistic expectations of what pregnancy and its management would entail. Women with successful kidney transplants are relieved of their uremia and usually regain near-normal fertility. They must be counseled carefully regarding contraception, because pregnancy in the early months of a transplant could be very deleterious. The choice of contraceptive must balance the unreliability of barrier methods against the possible potentiation of hypertension or thrombogenesis from the use of oral contraceptives. Women who have received a transplant are usually advised to delay any attempt at pregnancy until 2 years after transplantation because failures from acute rejection and other causes are less frequent after this time interval. Criteria for allograft stability sufficient to allow pregnancy have been generally agreed upon (86, 87) and include: stable renal function (serum creatinine less than 2 mg/dl); no proteinuria; no significant hypertension; no evidence of allograft rejection; no evidence of hydronephrosis on intravenous pyelography or ultrasonography; and drug dosages of not more than 15 mg/day of prednisone or prednisolone and 2 mg/kg/day of azathioprine. These medications must not be discontinued, except for life-threatening complications. Most knowledge of pregnancy in renal transplantation has been obtained with the use of azathioprine (Imuran) and it is unclear how much will remain true in the cyclosporine era. Kidney allograft survival data are better with cyclosporine (Sandimmune), but because of nephrotoxicity and reduced compensatory hypertrophy, most cyclosporine-treated patients have serum creatinine levels between approximately 1.2 and 3.0 mg/dl, compared with a range of about 0.8–2.0 with azathioprine (89). Whether the usual relationship between higher serum creatinine values and worse gestational outcomes will decrease reproductive success in cyclosporine-treated patients is not yet known.

Results of pregnancy in azathioprine-treated renal transplant recipients have been extensively documented. Davison (87) has reviewed cumulative data based on 1569 pregnancies in 1009 women. Therapeutic abortions were performed in 22% (for unwanted pregnancy, uncertain maternal prognosis, or maternal medical problems); 16% aborted spontaneously (the same incidence as in normal women). Of the 60% of pregnancies that extended beyond the first trimester, 92% resulted in a viable infant. Preeclampsia occurred in 30%, preterm delivery in about 50%, and intrauterine growth retardation in 20%. Patients with the worst renal function had the most problems in pregnancy.

Normal vaginal delivery is not impaired by the pelvic position of the transplanted kidney in 95% of cases. Neonatal problems that can be anticipated include respiratory distress, leukopenia, thrombocytopenia, adrenal insufficiency, and infection. Most infants recover well from these complications, although growth retardation from congenital cytomegalovirus infection is a serious exception. Despite anxieties about the side effects of immunosuppressive drugs, congenital anomalies are otherwise not a problem and the children have appeared to develop normally.

There is no evidence that survival or function of a transplanted kidney is lessened by pregnancy. Renal allograft rejection episodes

occur in about 9% of pregnancies, which is similar to the rate expected in nonpregnant patients. There may be difficulty distinguishing acute rejection from preeclampsia and renal magnetic resonance imaging or renal biopsy may be needed. Acute antirejection medications can be given if indicated, although there is not much known about their effect on the fetus.

Urinary tract infections are common in women with renal allografts and must be treated before conception and monitored closely thereafter. Antibiotic suppression can be continued during pregnancy, although the choice of medication presents some difficulties. This choice should be made by a transplant surgeon or nephrologist. Nitrofurantoin preparations (e.g., Macrodantin) are not recommended when the glomerular filtration rate (GFR) is less than 50 ml/min (which is the case for many transplant patients) because of side effects. Ampicillin may be used but predisposes to resistant organisms and it may not be effective for long. Trimethoprim combinations (Septra, Bactrim) are widely used for nonpregnant women but are less favored in pregnancy and should be used extremely cautiously in cyclosporine-treated patients because of the possibility of synergistic nephrotoxicity. Sulfonamides on their own may be useful in some cases (e.g., Gantrisin). There is no evidence that recipients of live-related grafts do any better than cadaver-kidney recipients in pregnancy.

In summary, renal transplantation diabetic patients should wait 2 years post transplantation but ideally not more than 5 years, before becoming pregnant. If renal function is good and hypertension or other renal problems are not present, pregnancy is likely to be successful despite the increased frequency of prematurity, reduced fetal growth, and preeclampsia. Close monitoring and surveillance of the pregnancy and of renal allograft function are necessary throughout gestation.

In the United Sates, abortion for chronic renal disease is not mandated or insisted upon by primary physicians (diabetologist, nephrologist, and perinatologist). Informed reproductive decisions are considered to be the responsibility of the patient and her partner. Many young diabetic women with evidence of renal (and retinal) microvascular disease are determined to have a baby and their partners and extended family may support this wish. Most often, however, these are not decisions made before conception. In our experience, such patients usually present to prenatal clinics already pregnant and they have often already made firm personal decisions to continue or to interrupt the pregnancy.

Non-insulin-dependent Diabetes Mellitus (NIDDM)

There are marked differences in age at onset and peak incidence of diabetic nephropathy in NIDDM patients compared to IDDM patients (Table 3.2). In a study of 5059 Pima Indians, no cases of diabetic nephropathy were observed in women aged 5–34 years and there was an incidence of only 3.3 cases per 1000 person-years at risk in those aged 35–44 years (89). Thus, in a well-documented epidemiologic study of women with a high prevalence of NIDDM, diabetic nephropathy was extremely rare during the child-bearing years.

There have been no reports of the natural history of nephropathy in pregnant women with NIDDM despite the prevalence of the disorder in relatively young women of many population groups. Fabre and associates (90) have assessed and quantified the course of renal involvement in nonpregnant women with NIDDM. All 510 of their subjects were diagnosed after age 40 years. The major finding was that abnormal protein excretion occurred sooner after diagnosis in NIDDM than in IDDM and as frequently. However, the clinical characteristics, severity, and outcome of nephropathy differed to a major and surprising extent. There was excessive urinary excretion of high molecular weight proteins (> 100,000); hypertension and cardiovascular complications were common. Even when diabetic control was considered satisfactory, 48% of patients in this study of older women had proteinuria of greater than 150 mg/24 h. The proportion with nephrotic syndrome was no more than 1.8% compared with 45% in IDDM women age 20–50 years at death. In NIDDM patients, adequate GFR was maintained even though proteinuria had been documented for many years. There was only one death from renal insufficiency despite the large number of patients with both long-standing and poorly controlled diabetes.

The long-term prognosis of nephropathy in

Table 3.2.
Diabetes and Nephropathy

Clinical Features (% of all diabetics)	IDDM (90% of all diabetics)	NIDDM[a] (10% of all diabetics)		
		Person-years at Risk	Women (yrs)	Cases[a]
Age	30–34 ± 8 yr	845	5–34	0
		906	35–44	3.3
		1263	45–54	12.0
Incidence	Peak: 10–16 yr after onset IDDM	Incidence:[a]		
		5–34	0	
		35–44	3.3	
		Peak:		
		55–64		
Prevalence	40–45%	15–40%		
		10-yr duration		
Relationship to diabetic control	Control trials are in progress	Influenced to a lesser extent by metabolic control than IDDM		
	Poor glycemic control is a necessary but not sufficient condition to cause albuminuria			

[a]Cases per 1000 person-years at risk (89).

NIDDM is relatively good, unlike that of IDDM. Women with this complication at a young age are almost always asymptomatic; the diagnosis is frequently made in prenatal clinics during routine screening procedures for gestational diabetes. We rarely receive a request for preconception counseling by a woman with NIDDM or her physician. Should efforts be successful in reaching this group or if a patient returns with a subsequent pregnancy, she should be advised to control hyperglycemia, hyperlipidemia, and hypertension in addition to achieving or maintaining normal weight. Urinary tract infections should receive prompt and effective treatment. Selby and colleagues (91) have reviewed the natural history and epidemiology of diabetic nephropathy in IDDM and NIDDM women.

In our experience, renal complications in pregnant women with NIDDM have not been a problem. Expensive monitoring by repeated determinations of creatinine clearance is not necessary or cost effective unless hypertension or preeclampsia are present. This is probably explained by the fact that pregnant women with NIDDM, although often older than those with IDDM, are generally under age 40 years at conception.

The complication of nephropathy emphasizes the importance of distinguishing between pregnant women with IDDM vs. those with NIDDM. The White (1965) pregnancy classification categories for women with renal, myocardial, and retinal complications and older studies of outcome of diabetic pregnancy do not apply to women with NIDDM and GDM.

References for Section I

1. Steel JM, Johnstone FD, Smith AF, Duncan LJP. Five years' experience of a "prepregnancy" clinic for insulin-dependent diabetics. Br Med J 1982;285:353-356.
2. Hollingsworth DR. Diabetes. In: Hollingsworth DR, Resnik R (eds). Medical counseling before pregnancy. New York: Churchill Livingstone, 1988:271-316.
3. Coustan DR. Editorial. Pregnancy in diabetic women. N Engl J Med 1988;319:1663-1665.
4. Miodovnik M, Mimouni F, Siddiqi TA, Khoury J, Berk MA. Spontaneous abortions in repeat diabetic pregnancies: a relationship with glycemic control. Obstet Gynecol 1990;75:75-78.
5. Sutherland HW, Pritchard CW. Increased incidence of spontaneous abortion in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1986;155:135-138.
6. Mills JL, Simpson JL, Driscoll SG, et al. and the National Institute of Child Health and Human Development—Diabetes in Early Pregnancy Study. N Engl J Med 1988;319:1617-1623.
7. Atkinson MA, Maclaren NK. What causes diabetes? Scientif Am 1990;263:62-71.
8. Khalil I, d'Auriol L, Gobet M, et al. A combination of HLA-DQβ Asp 57-negative and HLA-DQα ARG 52 confers susceptibility to insulin-dependent diabetes mellitus. J Clin Invest 1990;85:1315-1319.
9. Todd JA, Bell JI, McDevitt HO. HLA-DQβ gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 1987;329:599-604.
10. Yamagata K, Nakajima H, Hanafusa T, et al. Aspartic acid at position DQβ chain does not protect against Type I (insulin-dependent) diabetes mellitus in Japanese subjects. Diabetologia 1989;32:762-764.
11. Ginsberg-Fellner F. Epidemiology, genetics and immunology. In: Reece EA, Coustan DR (eds). Diabetes mellitus in pregnancy. Principles and practice. New York: Churchill Livingstone, 1988:17-45.
12. Barbosa J, Rich SS. Genetics of insulin-dependent diabetes. In: Immunogenetics of endocrine disorders. New York: Alan R. Liss, 1988: 163-202.
13. Segall M, Bach FH. HLA and diabetes from a T-cell perspective. Diabetes Metab Rev 1987;3(3):803-818.
14. Nerup J, Mandrup-Poulsen T, Mølvig J. The HLA-IDDM Association: Implications for etiology and pathogenesis of IDDM. Diabetes Metab Rev 1987;3:779-802.
15. Nepom BS, Palmer J, Kim SJ, Hansen JA, Holbeck SL, Nepom GT. Specific genomic markers for the HLA-DQ subregion discriminate between DR4+ insulin-dependent diabetes mellitus and DR4+ juvenile rheumatoid arthritis. J Exp Med 1986;164:345-350.
16. Morel PA, Dorman JS, Todd JA, McDevitt HO, Trucco M. Aspartic acid at position 57 of the HLA-DQβ chain protects against Type I diabetes: A family study. Proc Natl Acad Sci 1988;85:8111-8115.
17. Maclaren NK. How when and why to predict IDDM. Diabetes 1988;37:1591-1594.
18. Rotter JI. The modes of inheritance of insulin dependent diabetes mellitus. Am J Hum Genet 1981;33:835-851.
19. Hitchcock CL, Riley WJ, Maclaren NK. Autoimmunity in insulin-dependent diabetes mellitus: its detection and prevention. In: Cruise JM, Lewis RE Jr. (eds). Genetic basis of autoimmune disease. Basel: Karger, 1988:144-167.
20. Tillil H, Köbberling J. Age-corrected empirical genetic risk estimates for first degree relatives of IDDM patients. Diabetes 1987;36:93-99.
21. Harris M. NIH NDDG Surveys. Personal Communication, 1990.
22. Vadheim CM, Rotter JI. Genetics of diabetes mellitus. In: Draznin B, Melmed S, Le Roith D (eds). Molecular and cellular biology of diabetes mellitus. Vol 1. New York: Alan R. Liss, 1989:139-148.
23. Barnett AH, Eff C, Leslie RDG, Pyke DA. Diabetes in identical twins. A study of 200 pairs. Diabetologia 1981;20:87-93.
24. Grill V, Efendić S (eds). Pathogenesis of non-insulin dependent diabetes mellitus. New York: Raven Press, 1988.
25. Leary JL, Weir GC. Non-insulin-dependent diabetes mellitus: Current concepts and pathogenesis. In: Draznin B, Melmed S, Le Roith D (eds). Molecular and cellular biology of diabetes mellitus. Vol 1. New York: Alan R. Liss, 1989:149-158.
26. Köbberling J, Tillil H. Empirical risk figures for first degree relatives of non insulin dependent diabetics. In: The genetics of diabetes mellitus. Proceedings of the Serono Symposia. London: Academic Press, 47:1982;201.
27. Piacquadio K, Hollingsworth D, Murphy H. Fetal malformations following first trimester use

of oral hypoglycemic agents. Diabetes 1990; 39(Suppl 1):123A.
28. Fajans SJ. Maturity-onset diabetes of the young (MODY). Diabetes Metab Rev 1989;5(7):579-606.
29. Koshland DE. The cystic fibrosis gene story. Science 1989;245:1029.
30. Rommens JM, Iannuzzi MC, Kerem B-s, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 1989;245:1059-1065.
31. Riordan JR, Rommens JM, Kerem B-s, Alon N, Rozmahel R, Grzelczak A, et al: Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 1989;245:1066-1073.
32. Kerem B-s, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: Genetic analysis. Science 1989;245:1073-1080.
33. Anonymous. Cystic fibrosis: prospects for screening and therapy. [Editorial] Lancet 1990:335:79-80.
34. Lemna WK, Feldman GL, Kerem B-s, et al. Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N Engl J Med 1990;322:291-296.
35. Special Report. Statement from the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene. N Engl J Med 1990;323:70-71.
36. Kučera V. Rate and type of congenital anomalies among offspring of diabetic women. J Reprod Med 1971;7:61-70.
37. Eriksson UJ, Karlsson M-G, Styrud J. Mechanisms of congenital malformations in diabetic pregnancy. Biol Neonate 1987;51:113-118.
38. Leslie RDG, Pyke DA, John PN, White JM. Haemoglobin A1 in diabetic pregnancy. Lancet 1978;2:958-959.
39. Miller E, Hare JW, Cloherty JP, et al. Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med 1981;301:1331-1334.
40. Fuhrmann K, Reiher H, Semmler K, Glockner E. The effect of intensified insulin therapy before and during pregnancy on the malformation rate in offspring of diabetic mothers. Exp Clin Endocrinol 1984;83:173-177.
41. Damm P, Mølsted-Pedersen L. Significant decrease in congenital malformations in newborn infants of an unselected population of diabetic women. Am J Obstet Gynecol 1989;161:1163-1167.
42. Miodovnik M, Mimouni F, Dignan PSJ, et al. Major malformations in infants of IDDM women. Diabetes Care 1988;11:713-718.
43. Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. N Engl J Med 1988;318:671-676.
44. Freinkel N, Lewis NJ, Akazawa S, Roth SI, Gorman I. The honeybee syndrome--implications of the teratogenicity of mannose in rat-embryo culture. N Engl J Med 1984;310:223-230.
45. Leading article. Congenital malformations in infants of diabetic mothers. Lancet 1988;1:1313-1315.
46. Sadler TW, Hunter ES III, Wynn RE, Phillips LS. Evidence for multifactorial origin of diabetes-induced embryopathies. Diabetes 1989; 38:70-74.
47. Freinkel N. Review. Diabetic embryopathy and fuel-mediated organ teratogenesis: Lessons from animal models. Horm Metabol Res 1988;20:463-475.
48. Freinkel N. The Banting Lecture 1980: of pregnancy and progeny. Diabetes 1980;29:1023-1035.
49. Mills JL, Baker L, Goldman AS. Malformation in infants of diabetic mothers occurs before the seventh gestational week. Diabetes 1979; 28:292-293.
50. Tuchman-Duplessis H. Reactions of the foetus to drugs taken by the mother. In: Wolstenholme GEW, O'Connor M (eds). Foetal autonomy. London: Churchill, 1969:245.
51. Ferencz C, Rubin JD, Mc Carter RJ, Clark EB. Maternal diabetes and cardiovascular malformations: predominance of doublet outlet right ventricle and truncus arteriosus. Teratology 1990;41:319-326.
52. Eriksson UJ, Lewis NJ, Freinkel N. Growth retardation during organogenesis in embryos of experimentally diabetic rats. Diabetes 1984; 33:281-284.
53. Rosenstock J, Raskin P. Diabetes and its complications. Blood glucose control vs. genetic susceptibility. Diabetes Metabol Rev 1988;5:417-435.
54. Klein R, Klein BEK, Moss SE. The Wisconsin epidemiological study of diabetic retinopathy: A review. Diabetes Metabol Rev 1989;5:559-570.
55. Krolewski AF, Warram JF, Rand LI, Christlieb AR, Busick J, Kahr CR. Risk of proliferative diabetic retinopathy in juvenile onset Type I diabetes: A 40-year follow-up study. Diabetes Care 1986;9:443-452.
56. Ballard DJ, Melton LJ, Dwyer MS, et al. Risk factors for diabetic retinopathy: A population based study in Rochester, Minnesota. Diabetes Care 1986;9:334-342.
57. Dornan TL, Ting A, McPherson CK, et al. Genetic susceptibility to the development of retinopathy in insulin-dependent diabetics. Diabetes 1982;31:226-231.
58. Christy M, Nerup J, Platz P, Thomsen M, Ryder LP, Svejgaard A. A review of HLA antigens in longstanding IDDM with and without severe retinopathy. Horm Metab Res 1981;11 (suppl):73-77.
59. Johnston PB, Kidd M, Middleton D, et al. Analysis of HLA antigen association with proliferative diabetic retinopathy. Br J Ophthalmol 1982;66:277-279.
60. Gray RS, Starley IR, Rainbow S, et al. Antigens and other risk factors in the development of ret-

inopathy in Type I diabetes. Br J Ophthalmol 1982;66:280-285.
61. Bodansky HJ, Wolfe E, Cudworth AG, et al. Genetic and immunologic factors in microvascular disease in Type I insulin-dependent diabetes. Diabetes 1982;31:70-74, 1982.
62. The DCCT Research Group. Diabetes control and complications trial (DCCT): Design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530-545.
63. Position Statement Developed By The Committee on Professional Practice and approved by the Executive Committee of the Board of Directors of the American Diabetes Association, 8 June 1988. Eye Care Guidelines. Diabetes Care 1988;11:745-746.
64. Horvat M, Maclean H, Goldberg L, Crock GW. Diabetic retinopathy in pregnancy. Br J Ophthalmol 1980;64:398-403.
65. Moloney JBM, Drury MI. The effect of pregnancy on the natural course of diabetic retinopathy. Am J Ophthalmol 1982;93:745-756.
66. Phelps RL, Sakol P, Metzger BE, Jampol LE, Freinkel N. Changes in diabetic retinopathy during pregnancy, correlations with regulation of hyperglycemia. Arch Ophthalmol 1986; 104:1806-1810.
67. Laatikainen L, Teramo K, Hieta-Heikurainen H, Koivisto V, Pelkonen R. A controlled study of the influence of continuous insulin infusion treatment on diabetic retinopathy during pregnancy. Acta Med Scand 1987;221:367-376.
68. Serup L. Influence of pregnancy on diabetic retinopathy. Acta Endocrinol (Copenh) 1986; 277:122-124.
69. Klein BEK, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. Diabetes Care 1990;13:34-40.
70. Lorenzi M, Goldbaum MH, Spencer EM, Cheney C. Improved diabetic control and retinopathy. N Engl J Med 1983;308:1600.
71. Van Ballegooie E, Hooymans JMH, Timmerman Z, et al. Rapid deterioration of retinopathy during treatment with continuous subcutaneous infusion. Diabetes Care 1984;7:236-242.
72. The Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. N Engl J Med 1984;311:365-372.
73. Dandona P, Bolger JP, Boag F, Fonesca J, Abrams JD. Rapid development and progression of proliferative retinopathy after strict diabetic control. Br Med J 1985;290:895-896.
74. Brinchmann-Hansen O, Dahl-Jørgensen K, Hanssen KF, Sandvik L. Effects of intensified insulin treatment on various lesions of diabetic retinopathy. Am J Ophthalmol 1985;100:644-653.
75. Lauritzen T, Frost-Larsen K, Larsen HW, Dekert T. Two year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes 1985; 34(suppl 3):74-79.
76. Ward DM. Hypertension, renal diseases and kidney transplantation. In: Hollingsworth DR, Resnik R (eds). Medical counseling before pregnancy. New York: Churchill Livingstone, 1988:357-383.
77. Deckert T, Feldt-Rasmussen B, Bonch-Johnsen K, Kverneland A, Thomson OF. Clinical assessment and prognosis of complications of diabetes. Transplant Proc 1986;18:1636-38.
78. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin dependent diabetes mellitus. Lancet 1982;1:1430-1432.
79. Mathiesen ER, Oxenbøll R, Johansen K, Svendsen PA, Deckert T. Incipient nephropathy in Type I (insulin-dependent) diabetes. Diabetologia 1984;26:406-410.
80. Mogensen CE, Christiansen CK. Predicting diabetic nephropathy in insulin dependent patients. N Engl J Med 1984;311:89-93.
81. DCCT Research Group. Diabetes Control and Complications Trial (DCCT). Update. Diabetes Care 1990;13:427-433.
82. Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. N Engl J Med 1989;320:1161-1165.
83. Grenfell A, Brudenell JM, Doddridge MC, Watkins PJ. Pregnancy in diabetic women who have proteinuria. Q J Med 1986; New series 59.228:379-386.
84. Lindheimer MD, Katz AI. Kidney disease. In: Lindheimer MD, Katz AI(eds). Kidney Function and Disease in Pregnancy. Philadelphia: Lea & Febiger, 1977:106-187.
85. Hayslett J, Reece EA. Effect of diabetic nephropathy on pregnancy. Am J Kidney Dis 1987; 9:344-349.
86. Marushak A, Weber T, Bock J, et al. Pregnancy following kidney transplantation. Acta Obstet Gynecol Scand 1986;65:557-559.
87. Davison JM. Renal transplantation in pregnancy. Am J Kidney Dis 1987;9:374-380.
88. Halasz NA, Gamboa EA, Ward DM, Steiner RW, Bronsther OL. Kidney transplantation in the cyclosporine era. Arch Surg 1987;122:1001-1004.
89. Nelson RG, Newman JM, Knowler WC, et al. Incidence of end-stage renal disease in Type 2 (non-insulin-dependent diabetes mellitus) in Pima Indians. Diabetologia 1988;31:730-736.
90. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT. The kidney in maturity onset diabetes mellitus. A clinical study of 510 patients. Kidney Int 1982;21:730-738.
91. Selby JV, Fitzsimmons SC, Newman JM, Katz PP, Sepe S, Showstack J. State of the art/review. The natural history and epidemiology of diabetic nephropathy. Implications for prevention and control. JAMA 1990;263:1954-1960.
92. White P. Pregnancy and diabetes. Medical aspects. Med Clin North Am 1965;49:1015-1024.

SECTION

II

Maternal Metabolic Adjustments in Normal and Diabetic Pregnancies

Dorothy R. Hollingsworth

Normal and diabetic pregnancies are unusual experiments of nature that involve complex metabolic alterations in the maternal, placental, and fetal compartments. Freinkel and Metzger (1, 2) described pregnancy as a tissue culture experience in which the conceptus develops de novo with the composition of the tissue culture medium determined by the vagaries of maternal fuels that gain access to the fetus. This interesting concept has profound implications for the fetus, the newborn infant, and, perhaps, for the child and adult who have had an abnormal biochemical environment in utero.

CHAPTER

4

Key Role of the Placenta

NORMAL PREGNANCY

In normal women, pregnancy evokes remarkable alterations in metabolic homeostasis to favor an advantageous environment for fetal embryogenesis, growth, maturation, and survival. To achieve a proper metabolic milieu for a constantly feeding fetus and an intermittently fasting and feeding mother, a well-integrated metabolic shift must occur. Fetal needs take precedence and demand an uninterrupted supply of fuel.

Early Gestation

In the first few weeks of pregnancy, maternal carbohydrate metabolism is affected by a rise in maternal levels of estrogen and progesterone that stimulates pancreatic β-cell hyperplasia and insulin secretion (4–7). At the same time, there is an increase in tissue storage of glycogen, a decrease in the production of hepatic glucose, an increase in peripheral utilization of glucose, and a decrease in maternal fasting levels of plasma glucose. The overall metabolic change is anabolic (Table 4.1).

As pregnancy progresses, pancreatic islet cell hypertrophy continues and there is an increased insulin response to glucose or meal stimulation. Thus, normal adaptation to pregnancy results in relative fasting hypoglycemia, and marked sensitivity to food deprivation (2).

As shown in Table 4.2, normal pregnancy is characterized by maternal fat storage in the early months followed later by fat mobilization concurrent with accelerated utilization of glucose and amino acids by the fetus. Late in pregnancy, concentrations of free fatty acids and lipoprotein lipids are both increased.

During pregnancy, a huge new endocrine organ develops de novo—the placenta. There is no biologic equivalent to this multipurpose gland that synthesizes hypothalamic and pituitary-like peptides, steroid duplications, pregnancy-associated proteins and growth hormones. Its functions are clearly metabolic, endocrine, autocrine, and paracrine. And of course, it must fulfill its role as an umbilical lifeline to the developing embryo and fetus. The genetic and hereditary component of each new individual's future life span is decided at conception. Our most important and earliest environmental heritage is our first nurturing milieu, the maternal-placental-fetal trio (Fig. 4.1). When the intrauterine environment is disturbed or perturbed, the consequences to the

Table 4.1.
Carbohydrate Metabolism in Early Pregnancy (to 20 Weeks)

Hormonal Change	Effect	Metabolic Change
	↑ Tissue glycogen storage	
↑ Estrogen and progesterone	↓ Hepatic glucose production	Anabolic
	↑ Peripheral glucose utilization	Due to ↑ sex steroids + Hyperinsulinemia
↑ β-Cell hyperplasia and insulin secretion	↓ Fasting plasma glucose	

Table 4.2.
Fat Metabolism in Pregnancy

Hormonal Change	Effect	Metabolic Change
Early		
↑ Estrogen ↑ Progesterone ↑ Insulin	↑ Fat synthesis ↑ Fat cell hypertrophy Inhibition of lipolysis	→ Anabolic fat storage
Late		
↑ hCS	Lipolysis	→ Catabolic fat mobilization

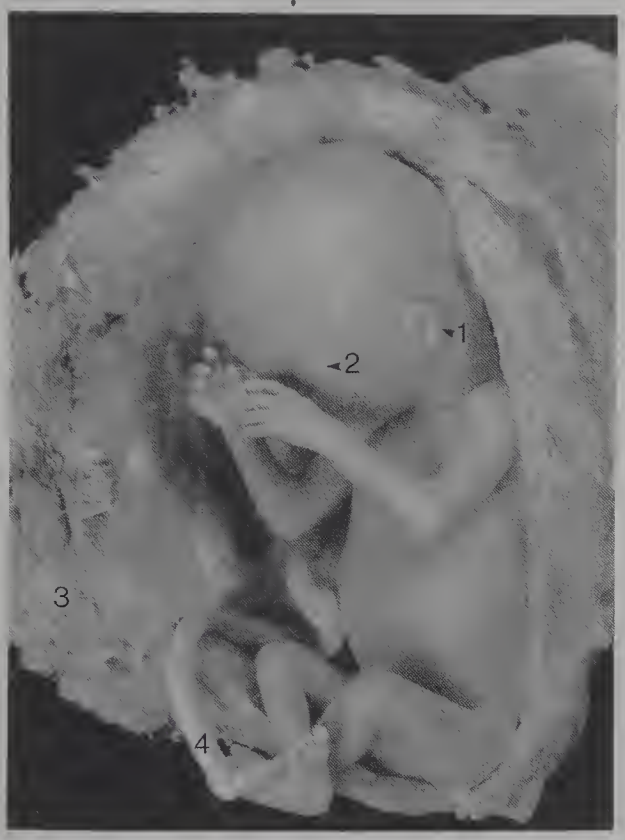


Figure 4.1. Twelve-week-old male fetus and membranes measuring 85 mm from crown to rump. *1*, ear; *2*, eye; *3*, placenta; *4*, umbilical cord. With permission from Margaret A. England, Senior Lecturer in Anatomy, University of Leicester, U.K. and Wolf Medical Publications Ltd.

fetus can be far reaching and life long—if it survives at all.

The common maternal medical problem of carbohydrate intolerance, whether it be a transient pregnancy-evoked hyperglycemia (1–3% of all pregnancies), diabetes (insulin-dependent diabetes mellitus [IDDM] or non-insulin-dependent diabetes mellitus [NIDDM]), antedating pregnancy, cystic fibrosis, or accentuated reversible hyperlipidemia of gestation (3), there is an important metabolic impact on the fetus. The longer-term implications of having an abnormal diet in utero and other problems that occur in these pregnancies are being addressed by multidisciplinary research investigations.

Late Gestation

During the latter half of pregnancy (Table 4.3), carbohydrate metabolism is stressed by rising levels of human chorionic somatomammotropin (hCS) from the placenta (Fig. 4.2), prolactin (decidual and possibly of pituitary origin), cortisol, and glucagon. These hormonal changes contribute to decreased glucose tolerance, insulin resistance, decreased stores of hepatic glycogen, and an increase in production of hepatic glucose. The physiologic effect

Table 4.3.
Carbohydrate Metabolism in Late Pregnancy (20–40 Weeks)

Hormonal Change	Effect	Metabolic Change
	"Diabetogenic"	
↑ hCS	↓ Glucose tolerance	Facilitated anabolism during feeding
↑ Prolactin	Insulin resistance	Accelerated starvation during fasting
↑ Bound and free cortisol	↓ Hepatic glycogen stores	↓
	↑ Hepatic glucose production	Ensure glucose and amino acids to fetus

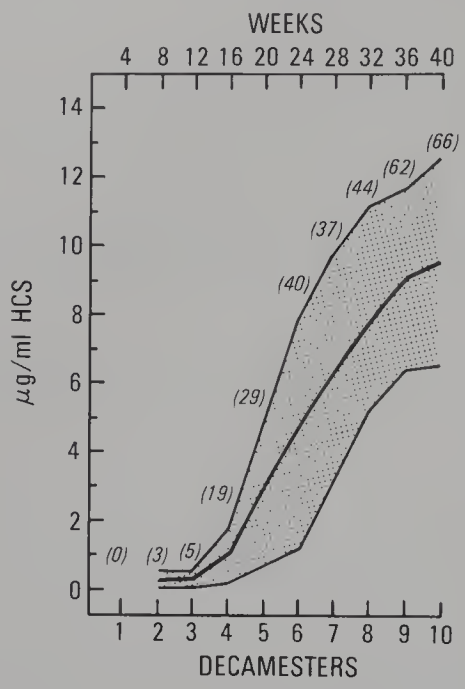


Figure 4.2. Increase in human chorionic somatomammotropin (hCS, previously called human placental lactogen (HPL)) levels (mean 2 SD) by decamester in normal pregnant women.

is to ensure a constant supply of glucose, lipids, and amino acids to the fetus (8).

Freinkel (9) was the first to describe these combined effects as maternal "accelerated starvation" when food is unavailable and "facilitated anabolism" with food ingestion. Other 24-h metabolic studies by Phelps and colleagues (10) have shown alterations in the concentrations of every major class of nutrient in late gestation. Figure 4.3 shows the marked changes in plasma glucose and insulin levels in normal women at the 3rd trimester. Figure 4.4 depicts the marked decrease in maternal levels of alanine and leucine around the 24-h clock and Figure 4.5 shows the significantly higher maternal levels of free fatty acids and triglyceride in late pregnancy.

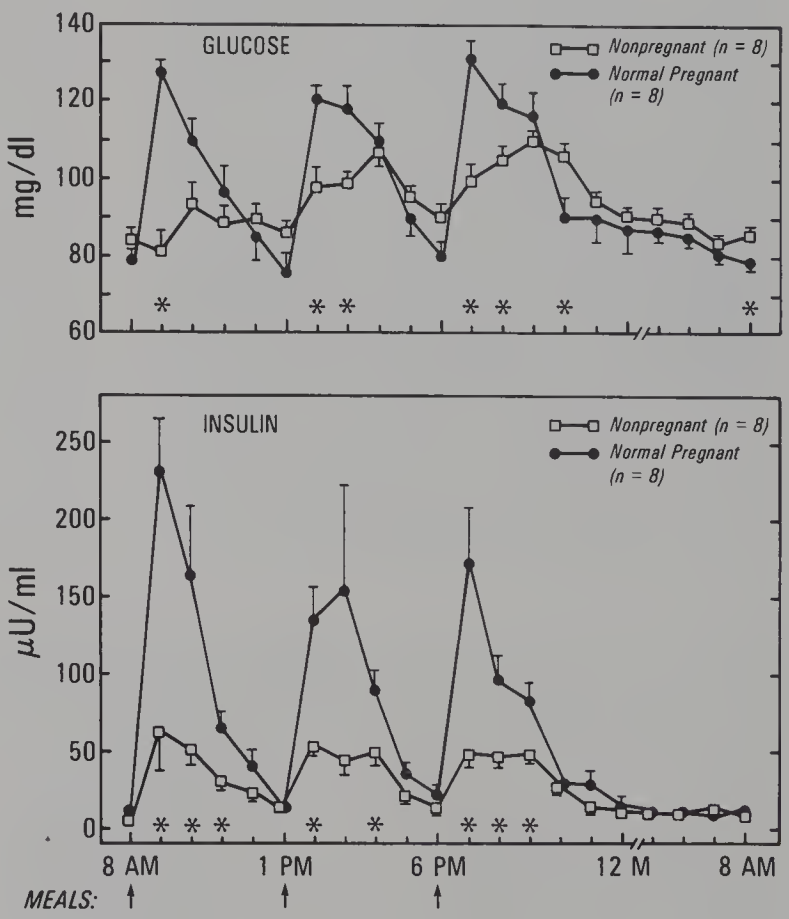


Figure 4.3. The effect of normal late pregnancy on the diurnal changes in plasma glucose and insulin concentration. *Asterisks* indicate values during pregnancy that are significantly elevated. (●—●), Normal pregnant women; (□—□), normal nonpregnant women. With permission from Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 1981; 140:730-736.

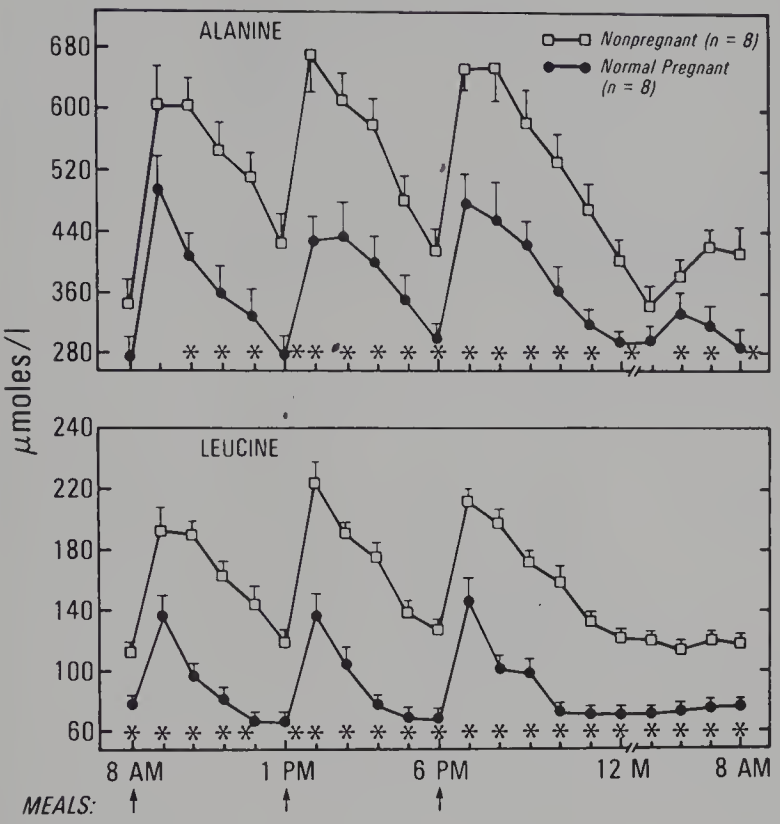


Figure 4.4. The effect of normal late pregnancy on diurnal and meal-stimulated levels of alanine and leucine. Note the significantly lower values in the pregnant women. With permission from Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol and individual amino acids in late normal pregnancy Am J Obstet Gynecol 1981; 140:730-736.

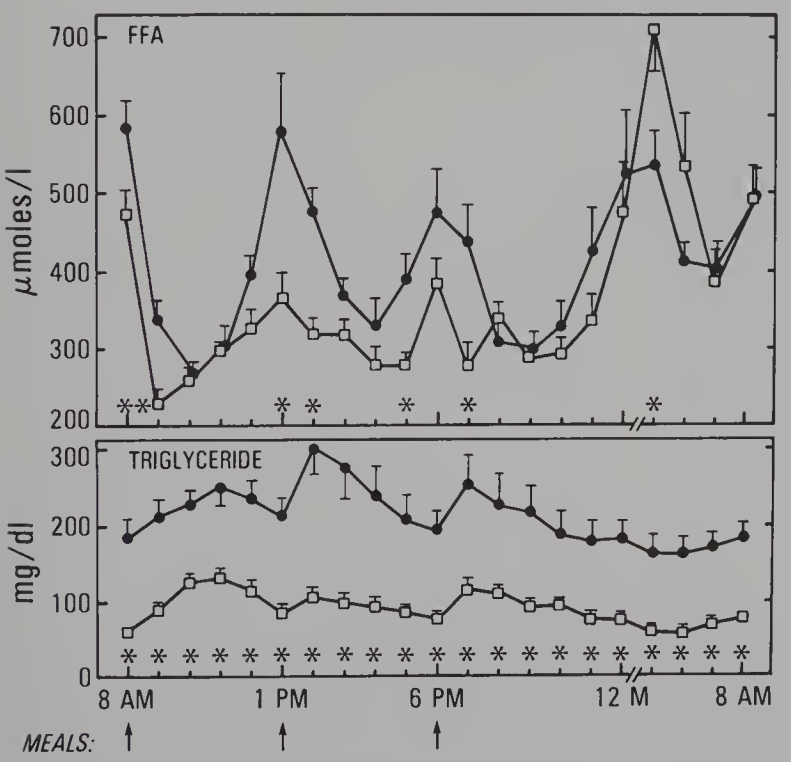


Figure 4.5. The effect of normal late pregnancy on the diurnal changes and meal-stimulated levels of plasma-free fatty acids and triglyceride. ●, normal pregnant women; □, normal, nonpregnant women. With permission from Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 1981; 140:730-736.

CHAPTER

5

The Maternal-Placental-Fetal Unit

PLACENTAL TRANSFER OF NUTRIENTS AND INSULIN

Glucose

The placenta modulates the transfer of nutrients to the fetus, which is totally dependent upon metabolic fuels from the maternal circulation. Figure 5.1 is a schematic representation of the maternal to fetal transfer of glucose, amino acids, and fat. Battaglia and Meschia have published a comprehensive review of fetal nutrition (11).

Glucose is transported across the placenta to the fetus by saturation-dependent carriers (12, 13). Several studies have focused on the factors that control fetal uptake and utilization of glucose. The quantity of glucose delivered into the umbilical circulation is less than the quantity taken up from the uterine circulation because the placenta also utilizes glucose as a metabolic fuel. Bozzetti and colleagues (14) have investigated the relationship between maternal and fetal glucose concentrations in pregnant women at different gestational ages. At 17–21 weeks, fetal blood was obtained during fetoscopy; from 32–36 weeks, from umbilical cord serum samples, and at 34–37 weeks from fetal blood samples during cesarean sections. They demonstrated a significant linear relationship between maternal and fetal glucose determinations at mid- and late gestation. At midgestation, fetal glucose concentration is **independent** and may exceed maternal glucose concentrations when maternal glucose levels are more than 80 mg/dl (4.4 mmol/L). At concentrations above this value, the relationship between maternal and fetal concentrations differed significantly. At equal maternal concentrations, there were **higher** glucose concentrations in the midtrimester fetus. In late gestation, as the maternal glucose concentration increases, there is an increase in the maternal arterial-umbilical arterial glucose concentration difference and the umbilical glucose/oxygen quotient that reflects increased glucose utilization by the fetus. Of interest, there were no significant differences between appropriately grown and small-for-gestational age fetuses with respect to these relationships. From the standpoint of nutritional requirements of pregnancy, the uptake of metabolic substrates by the pregnant uterus is more important than fetal uptake alone (11). The placental-to-fetal glucose transfer rate depends upon: *(a)* the glucose concentration gradient; and *(b)* the area available for transfer. Thus, any factors that alter these two variables influence normal, excessive, or diminished glucose transport to the fetus. For example, conditions that impair fetal growth result in a reduced glucose rate while those that cause large placentas (insulin-dependent diabetes mellitus [IDDM], non-insulin-dependent diabetes mellitus [NIDDM], and some gestationally evoked diabetes [GDM]) result in a larger transfer of glucose.

Battaglia and Meschia (11) discuss the important question of the possible role that maternal and fetal insulin concentrations might play in the regulation of placental glucose uptake and transport. The placenta is richly endowed with receptors for insulin on the maternal surface of the trophoblast (15). Reports of studies of insulin infusion into either maternal or fetal blood have not shown a significant change in the rate of placental glucose uptake as long as maternal and fetal glucose concentrations are kept constant by means of a glucose clamp technique (16). Of course, this is not the in vivo circumstance in diabetic pregnancies where there may be a large magnitude

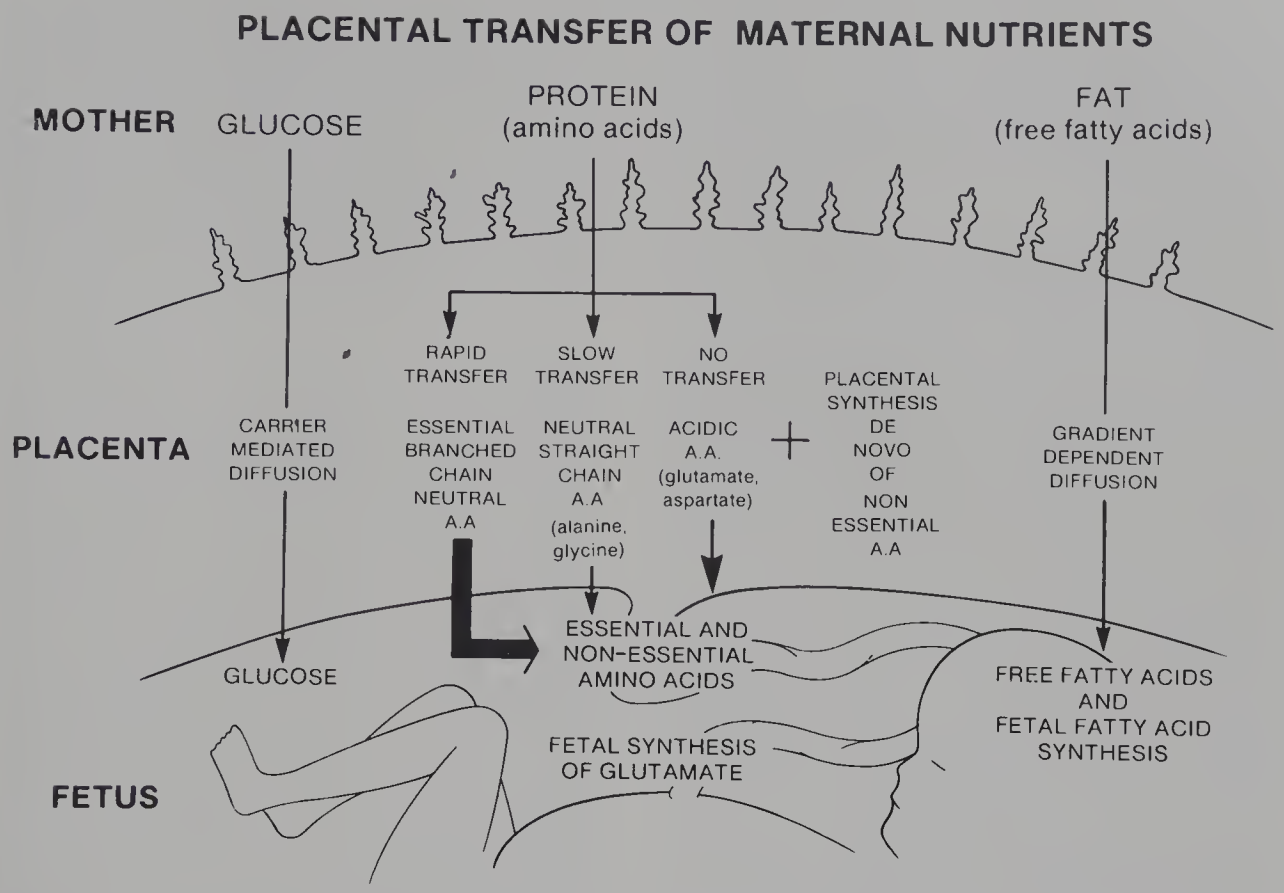


Figure 5.1. The transport of maternal fuels to the placental and fetal compartments. The placenta serves as a modulator for the total parenteral alimentation of the fetus. See text for description.

of glucose excursions around the 24-h metabolic clock. Once glucose is transferred to the fetus, however, the utilization role is regulated by fetal insulin (17, 18).

Amino Acids

Essential amino acids are rapidly transferred from the mother to the fetus by energy-dependent active transport mechanisms; fetal plasma levels exceed maternal concentrations (19). The question of how protein synthesis within the placenta and amino acid transport across the placenta are linked has not been resolved (11).

Cetin and colleagues (20) have used the technique of cordocentesis to obtain human fetal blood for analysis of amino acid concentrations in normal and growth-retarded fetuses in 11 pregnancies in which the mother was having the procedure for fetal karyotyping, the presence or absence of thalassemia minor, or toxoplasmosis. Amino acid levels were also measured at cesarean section in 14 normal term infants and in 12 small-for-gestational age (SGA) fetuses. In normal fetuses, fetal/maternal total molar concentration ratios of amino acids did not change significantly between the second and third trimesters. SGA fetuses had significantly lower concentrations of total α-aminonitrogen due mainly to a reduction of branched chain amino acids—valine, leucine, and isoleucine—and of lysine and serine. Maternal arterial concentrations of phenylalanine, arginine, histidine, and alanine were elevated in SGA pregnancies. It has not been established whether the selective reduction of some amino acids in SGA fetuses is causally related to the condition or an interesting but unexplained association with intrauterine growth retardation.

Lipids

Free fatty acids (FFA) readily cross the placenta in amounts exceeding those necessary to fulfill lipid storage requirements. Although the placentas of all species investigated appear to be virtually impermeable to esterified lipids, FFA derived from maternal triglyceride (TG) have been shown to cross the placenta in rabbits and in humans (21–24). There is con-

siderable storage of triglyceride within the placenta and hydrolysis of very low-density lipoprotein (VLDL). FFA transported to the fetus are rapidly taken up and esterified by the fetal liver and released into the circulation as VLDL (Fig. 5.2).

In the fetal rat, mouse, and guinea pig liver, the rates of transfer and enzymes of fatty acid synthesis are affected by changes in the nature of the maternal diet. Thus, the fetus is dependent upon a supply of long-chain unsaturated fatty acids from the maternal circulation and the lipid composition of the fetal liver, particularly for unsaturated fatty acids, is dependent upon maternal dietary intake.

In a review of placental metabolism and transport of lipid, Coleman (25) states that both the developing fetus and the placenta require fatty acids for the synthesis of complex lipids necessary for the biogenesis of plasma membranes, intracellular membranes, and organelles; triacylglycerol stores; and secreted products such as lipoproteins, bile, and pulmonary surfactant. Although fetal tissues can readily synthesize fatty acids, considerable evidence exists in nonruminants that as much as 50% of the fatty acid requirements of the fetus are maternally derived. The placenta may be even more dependent than the fetus on the maternal contribution because the placenta synthesizes fatty acids poorly. The major sources of fatty acid provided to the fetus and placenta have not been identified with certainty. The mechanism of transport of maternal FFAs and lipoprotein-carried lipid has not been investigated on a molecular level. Future studies with cultured trophoblasts should be useful in providing answers to many questions concerning placental lipid metabolism and the role of the placenta in transporting lipid to the fetus.

Insulin

There has been considerable controversy and debate since 1911 concerning possible placental transfer of insulin (26). In 1961, Josimovich and Knobil (27) injected I^{131} insulin into pregnant rhesus monkeys in a procedure that permitted sampling of maternal blood, umbilical venous, and arterial blood. When I^{131}-labeled insulin was injected into the maternal circulation, it was detected in umbilical venous plasma within 5 minutes. A marked umbilical arterial-venous difference was observed that suggested rapid degradation of the labeled hormone by the fetus. They concluded that insulin could cross the primate placenta and in both directions.

A year later, Buse and co-workers (28) studied 28 pregnant women, aged 14–41 years, who were given a single intravenous injection of I^{131} insulin at 7–274 minutes before delivery. They concluded from their experiments that the human placenta is relatively impermeable to insulin I^{131}, but that it actively traps and

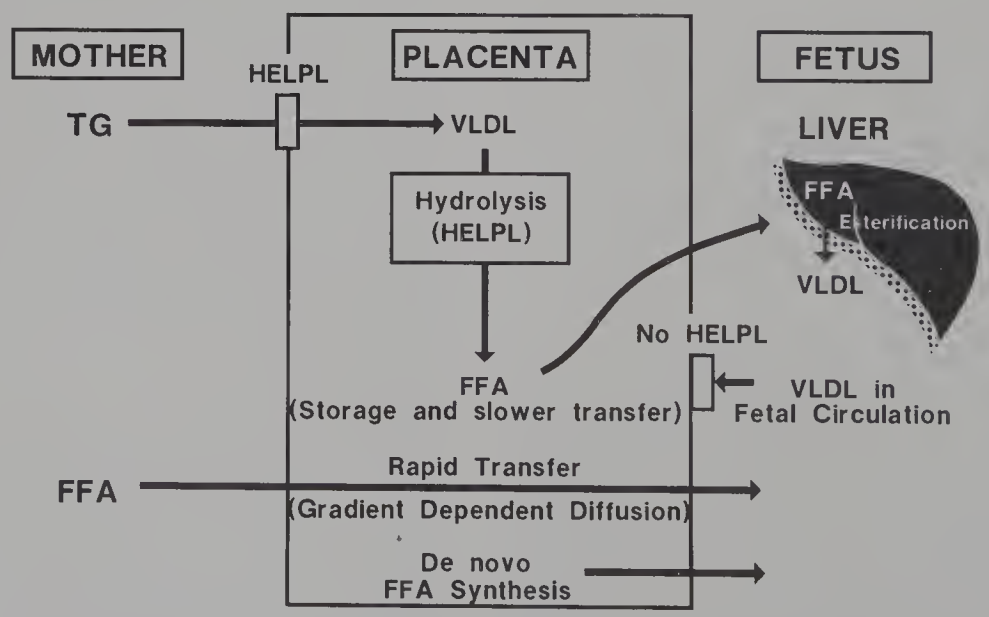


Figure 5.2. Mechanisms by which maternal FFAs and triglycerides give rise to FFAs in the fetal circulation. Abbreviations: TG = triglyceride; FFA = free fatty acids; HELPL = heparin elutable lipoprotein lipase; VLDL = very-low-density lipoproteins.

degrades the hormone. Their experiments did not completely exclude the possibility that small amounts of insulin I^{131} or its trichloroacetic acid (TCA)-precepitable breakdown products may have crossed the placental barrier during the period of observation. The low levels of TCA-precepitable radioactivity found in fetal blood did not permit further characterization of this material.

In experiments in 1965, Gitlin and associates (29) gave I^{131}-labeled insulin to nine pregnant women having cesarean sections at 36–40 weeks' gestation. The mothers were delivered 16–68 minutes after the intravenous administration of a 0.15 μg/kg of body weight dose of I^{131}. In their study, the data suggested that insulin readily traverses the human placenta and that the amount transferred from mother to fetus is equivalent to 33% of the insulin utilized by the normal fetus at term. Again, the placenta appeared to be equally permeable in both directions.

The foregoing experiments encouraged Keller and Krohmer (30) to perform perfusion experiments on the isolated human placenta in an artificial milieu unaffected by fetal or maternal metabolic activity. In this study of seven placentas in an artificial milieu, they reported that insulin traverses the placenta from the fetal to maternal system but not in the opposite direction.

Adam and colleagues (31) reported different findings at 16–20 weeks' gestation when they performed metabolic studies in 23 pregnant women, aged 16–41 years, who were having abortions (1969). In eight pregnant women who were also having planned sterilizations, insulin I^{131} was infused continuously into a maternal peripheral arm vein during the abortion procedure. No insulin transfer from mother to fetus was documented at this early age of gestation.

Kalhan and co-workers (32) have provided further evidence against placental transfer of insulin in studies in which they infused I^{125} insulin into normal women and demonstrated no significant transplacental transfer In a similar study in pregnant diabetic women, including three with high titers of insulin antibodies, the same investigators failed to find evidence of maternal to fetal transfer of insulin.

The placental transfer of animal insulin was first identified with the use of specific antisera that made it possible to distinguish animal from human insulin (33). In the newborn infants of two diabetic mothers treated with insulin, the insulin concentrations in umbilical plasma were 5020 and 25,100 pmol/L, of which 10% and 25%, respectively, were of animal origin.

In a recent report (1990), Menon and colleagues (34) have clearly demonstrated that, in some women with IDDM, considerable amounts of antibody-bound insulin are transferred from mother to fetus during pregnancy. Moreover, the extent of transfer correlates with maternal concentration of anti-insulin antibody. The most interesting finding in this study was the high correlation between concentrations of animal insulin in cord serum and fetal macrosomia. This latter finding appeared to indicate that the transferred antibody-bound insulin had biologic activity and supported the hypothesis that maternal antibody formation to insulin is a determinant of fetal outcome, e.g., macrosomia. Sperling and Devaskar (35) emphasize that evidence now indicates that insulin in the fetal circulation is of fetal origin except when it is antibody bound **independent** of maternal glucose levels. Macrosomic infants have always been a metabolic puzzle. The work described in these clinical studies reopens the whole question of possible circumstances in which maternal transfer of insulin might contribute significantly to fetal growth.

The importance of the maternal-fetal metabolic relationship for nutrients and insulin in normal, diabetic, and problem pregnancies has become essential for our understanding of fetal, infant, and lifelong outcomes in under- and overgrown fetuses. At present, we have no intelligent way to make decisions for the modification of maternal dietary prescriptions or medications such as insulin, antihypertensive and, tocolytic agents to ensure ideal fetal growth and development. Prospective research studies that employ the technique of cordocentesis should be enlightening.

The overall effect of the metabolic changes during pregnancy is diabetogenic and characterized by resistance to insulin. The mechanism for development of insulin resistance in normal pregnant women is complex and is associated with increasing maternal serum levels of hCS, prolactin, progesterone, estrogens, and free cortisol that result in enhanced pan-

creatic secretion of insulin. Although the precise mechanism of altered sensitivity to insulin is unknown, Puavilai and colleagues (36) have suggested that the impairment of insulin action in normal pregnant women is at a site distal to the insulin receptor, e.g., a postreceptor defect. In diabetic women, particularly those with marked obesity, other mechanisms at the level of the insulin receptor may also be important.

CHAPTER

6

Maternal Plasma Concentrations of Hormones and Lipids in Normal and Diabetic Pregnancies

The striking changes in maternal plasma levels of glucose and insulin in normal pregnant women were illustrated earlier in Figure 4.3. In this chapter, metabolic profiles around the 24-h clock for C-peptide, glucagon, cortisol, and prolactin concentrations are compared in longitudinal observations during late pregnancy and 3 months postpartum (control) in normal women, IDDM (Type I) patients, and NIDDM (Type II) women. Fasting plasma lipid levels are also compared in normal and diabetic women.

C-PEPTIDE

Insulin is formed in pancreatic β cells by enzymatic splitting of a precursor molecule, proinsulin, which is cleaved into insulin and a connecting peptide (CP; Fig. 6.1). The molar ratio of CP to insulin equals 1 in the β-cell granules and portal circulation, but is significantly higher in the peripheral circulation because of the slower degradation of CP. Measurement of CP levels hourly around the 24-h metabolic clock during pregnancy has been a useful method for the assessment of β-cell reserve.

Figure 6.2 depicts 24-h excursions of CP in normal women and Type I (IDDM) and Type II (NIDDM) diabetic subjects at a control period (3 months postpartum) and at 2nd and 3rd trimesters. Normal pregnant women have a progressive rise in serum levels of CP to the 3rd trimester. Significantly lower levels of CP were observed in Type I diabetes versus controls (postpartum, $p < 0.02$; 2nd trimester, $p < 0.007$; 3rd trimester, $p < 0.004$) and these patients had an insignificant response to meal stimulation. Type II patients were remarkable in that they had higher baseline CP values than normal patients, a delayed response to meal stimulation, and higher total CP concentration (area under the 24-h curve) than normal subjects.

The measurement of CP around the clock or during a 2-h mixed meal tolerance test is useful in the differentiation of women who are mildly or severely insulin deficient from those with hyperinsulinemia and target cell resistance to the hormone.

GLUCAGON

Glucagon diurnal profiles in late 3rd trimester were not significantly different in normal and NIDDM (Type II) women (Fig. 6.3). Postpartum, however, plasma levels in NIDDM patients remained higher than both normal subjects and women with IDDM (Type I).

In IDDM women, there was no increase in glucagon levels during pregnancy and postpartum values were comparable to those of normal women. NIDDM (Type II) women had persistently higher glucagon measurements than IDDM (Type I diabetes) regardless of whether or not they were pregnant.

CORTISOL

Free and protein-bound serum cortisol values rise in all pregnant women unless they have hypoadrenalism (Fig. 6.4). They maintain the usual 24-h pattern, diabetic or not, with preservation of a nocturnal elevation that reaches a peak at 0600 hours. Women with IDDM (Type I) have lower nocturnal values

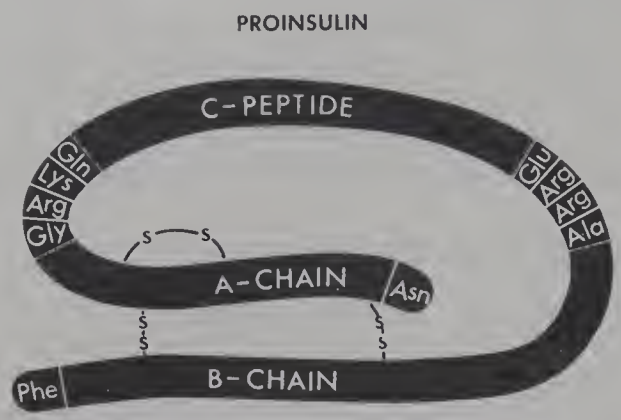


Figure 6.1. Schematic drawing of the proinsulin molecule showing the A- and B-chains of insulin and the connecting C-peptide.

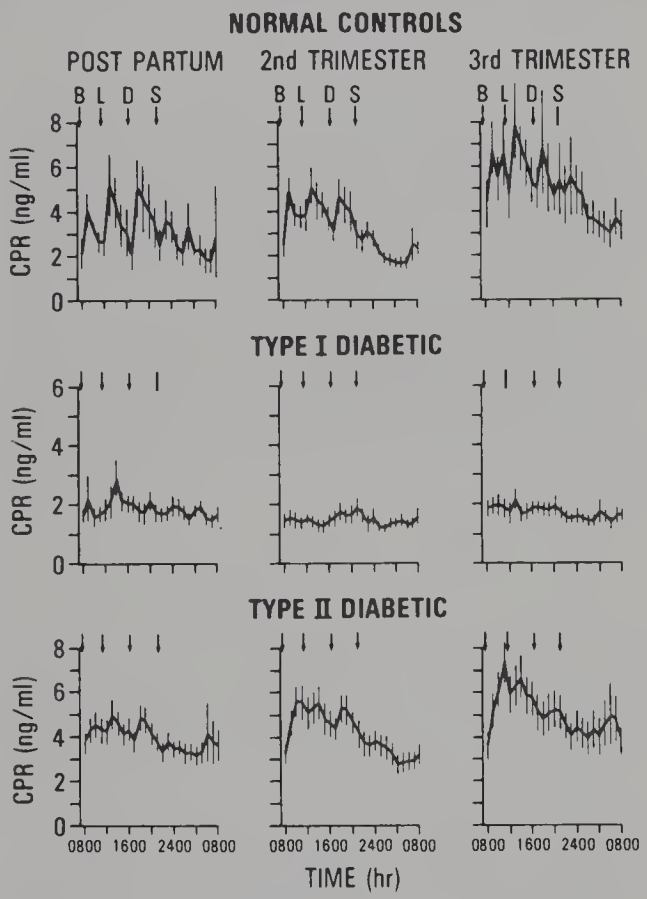


Figure 6.2. Hourly measurements of C-peptide immunoreactivity (CPR) in four normal pregnant women *(top panel)*, six patients with Type I diabetes *(middle panel)*, and six subjects with Type II diabetes *(bottom panel)*. Control values (3 months postpartum) are shown in the *left column*, 2nd trimester (24-27 weeks) in the *center column*, and late 3rd trimester (34-37 weeks) in the *right column*. *B*, *L*, *D*, and *S* indicate breakfast, lunch, dinner, and snacks. See text for description. With permission from Hollingsworth DR. Alterations of maternal metabolism in normal and diabetic pregnancies. Differences in insulin-dependent, non-insulin dependent and gestational diabetes. Am J Obstet Gynecol 1983;146:417-428.

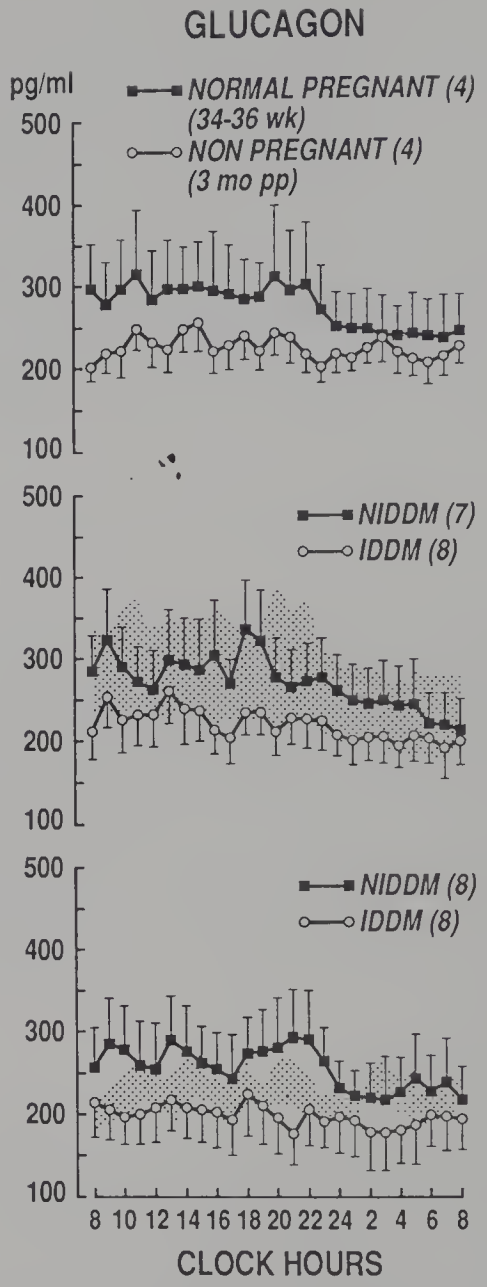


Figure 6.3. Hourly measurements of plasma glucagon levels ± SEM at 34-37 weeks' gestation (■-■) or 3 months postpartum (O-O). *Top panel*, normal women have higher levels during pregnancy than postpartum. *Middle panel*, glucagon levels are compared at late 3rd trimester in pregnant NIDDM versus IDDM patients. *Dotted areas in background* represent values in normal pregnant women. IDDM women have lower measurements than either normal or NIDDM women. *Bottom panel*, at 3 months postpartum, NIDDM women have higher than normal glucacon concentrations around the 24-h clock while IDDM values remain low and unchanged from pregnancy.

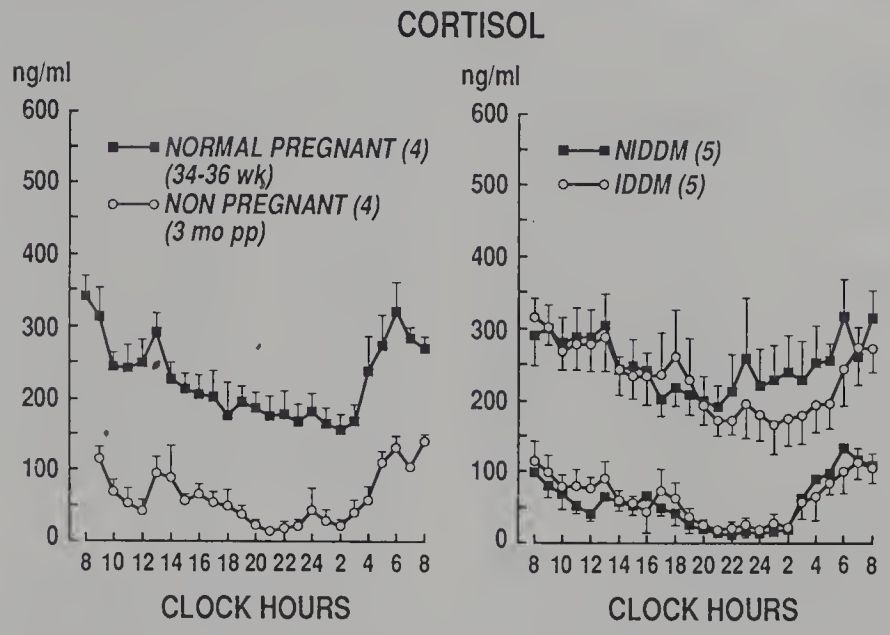


Figure 6.4. Cortisol 24-h profiles in pregnant and nonpregnant normal women, as well as NIDDM and IDDM women. *Left,* in late 3rd trimester, normal pregnant women (■-■) have higher levels of plasma cortisol with a normal diurnal rhythm. Lower postpartum measurements are shown in the *open circles* (O-O). *Right,* NIDDM subjects have a normal cortisol pattern late in pregnancy while nocturnal IDDM values are slightly lower (PNS). Postpartum measurements in both groups resembled those of normal women.

and a lower morning peak than NIDDM (Type II) women. Postpartum, no differences were apparent between normal and diabetic women and all three groups had returned to a normal pattern.

PROLACTIN

Prolactin levels rise in both normal and diabetic women beginning shortly after conception. Marked elevations are apparent at late 3rd trimester (Fig. 6.5). In normal women, values range from 200-400 ng/ml. IDDM (Type I) women have somewhat lower levels but preserve a normal sleep-associated peak. In contrast, NIDDM (Type II) women have consistently lower values than normal or IDDM patients in late gestation and do not have a nocturnal spike.

From our observations of hormonal profiles obtained at the peak of maternal metabolic stress of gestation (late 3rd trimester), interesting differences are apparent between insulin-dependent versus non-insulin-dependent women (8).

CHOLESTEROL AND TRIGLYCERIDES

The most striking lipid change during normal and diabetic pregnancies is the increase in plasma triglyceride (TG). During the first trimester of human pregnancy, hypertriglyceridemia results primarily from an increase of very low-density lipoprotein (VLDL) (37). Concentrations of cholesterol and phospholipid also increase during pregnancy. Figure 6.6 depicts differences in total plasma TG and cholesterol levels at 3 months postpartum (control) and in the 2nd and 3rd trimesters in normal women.

Lipid abnormalities are common in diabetes and vary in individual patients because of the heterogeneity of carbohydrate intolerance. Hyperlipidemia results from the interaction of the diabetic syndrome, genetic background of the patient, and the environment. Thus, pregnancy evokes a metabolic stress that exaggerates the heterogeneous characteristics of diabetic women, who may already have lipid abnormalities associated with insulin deficiency, insulin resistance, obesity, or abnormal genetic factors, in addition to varying degrees of hyperglycemia.

Pregnant women with IDDM in relatively good control do not differ from normal women in mean fasting plasma levels of total cholesterol (CHOL) and TG, (VLDL) TG, low-density lipoprotein (LDL) CHOL, high-density lipoprotein (HDL) CHOL, or ratios of TG:CHOL in

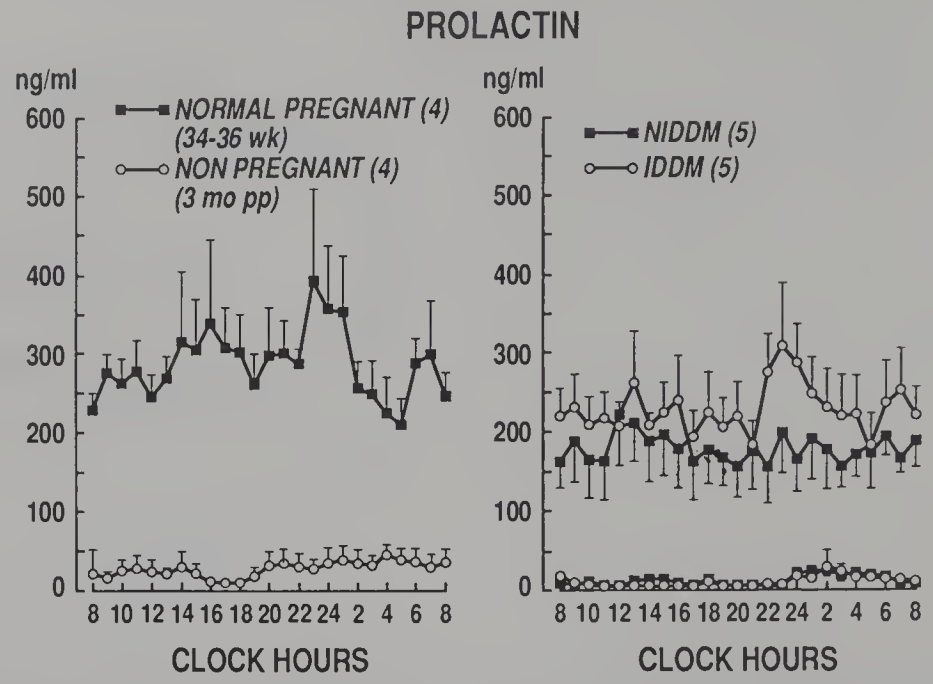


Figure 6.5. *Left,* markedly elevated hourly prolactin concentrations in normal pregnant women at 34-36 weeks' gestation (■-■). The O-O indicate normal postpartum values in nonlactating women. *Right,* IDDM hourly prolactin values (O-O) do not differ from normals while NIDDM women (■-■) have lower concentrations than either normal or IDDM (O-O) women. This difference was not apparent postpartum.

LDL or HDL during mid- or late pregnancy or postpartum (3).

In marked contrast, some pregnant women with NIDDM in comparable diabetic control have significantly higher total fasting TG than normal or IDDM women at 2nd trimester, 3rd trimester, and postpartum. In addition, pregnancy-accentuated hypertriglyceridemia is also apparent in elevated LDL TG:CHOL and HDL TG:CHOL ratios. The differences between IDDM and NIDDM women are not correlated with prepregnancy weight, weight gain during gestation, or diabetic control.

A lower mean level of HDL CHOL in NIDDM throughout pregnancy and 3 months postpartum that was not related to degree of glucose intolerance has also been observed (Fig. 6.7).

In summary, normal pregnancy is charac-

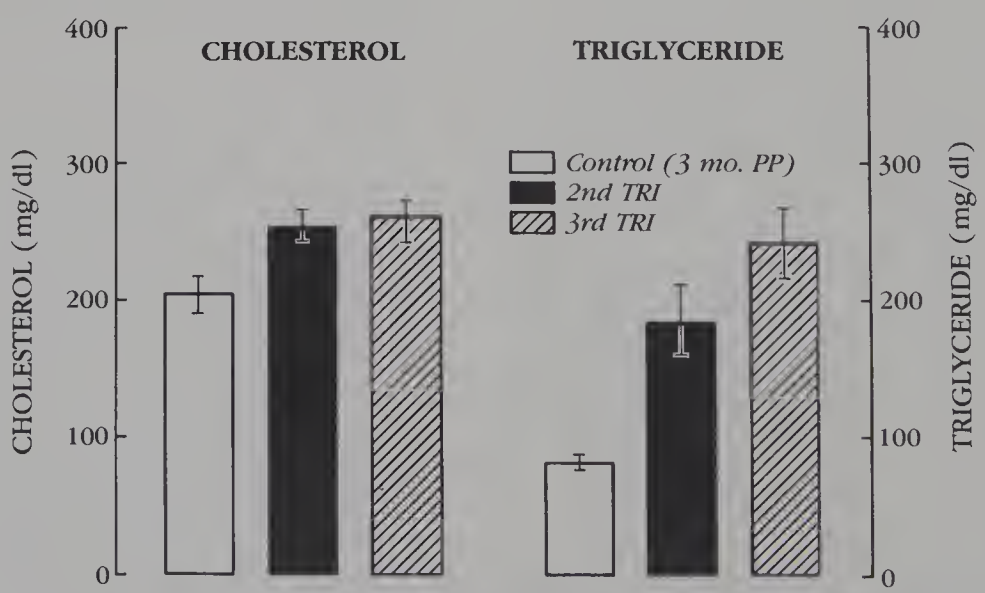


Figure 6.6. Fasting levels of total plasma cholesterol and triglyceride (SD) in normal weight women in the 2nd trimester, 3rd trimester, and 3 months postpartum.

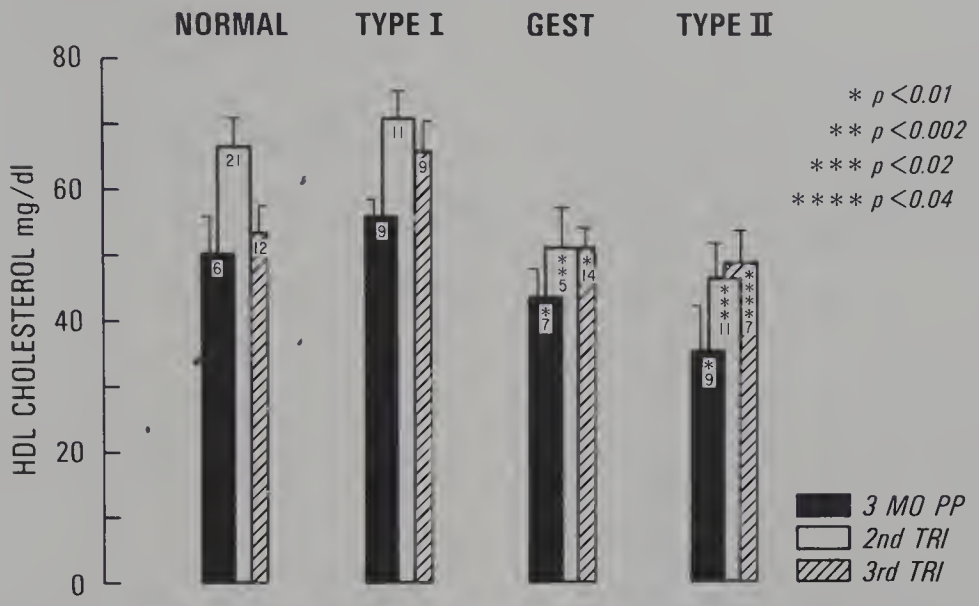


Figure 6.7. Fasting plasma HDL-cholesterol levels at 3 months postpartum (control) and in the 2nd and 3rd trimesters in normal pregnant women *(NORMAL)*, IDDM *(TYPE I)*, gestational *(GEST)* and NIDDM *(TYPE II)* diabetes. In well-controlled Type I patients, there were no significant differences from normal subjects. Women with GDM and NIDDM had significantly lower HDL-cholesterol values both during pregnancy and postpartum.

terized by profound metabolic changes that are modulated by a new endocrine organ, the placenta. Gestation is diabetogenic and accompanied by modest insulin resistance, selective hypoaminoacidemia (particularly alanine and leucine), and endogenous hypercholesterolemia and hypertriglyceridemia. Women with IDDM and NIDDM diverge as distinctly different entities during the metabolic stress of pregnancy.

References for Section II

1. Freinkel N, Metzger BE. Pregnancy as a tissue culture experience: the critical implications of maternal metabolism for fetal development. In: Pregnancy, metabolism, diabetes and the fetus. CIBA Foundation Symposium 63 (new series). Amsterdam: Excerpta Medica 1979: pp 23–28.
2. Freinkel N. Banting Lecture 1980: Of pregnancy and progeny. Diabetes 1980;29:1023–1035.
3. Hollingsworth DR, Grundy S. Pregnancy associated hypertriglyceridemia in normal and diabetic women: differences in insulin-dependent, non-insulin dependent and gestational diabetes. Diabetes 1982;31:1092–1097.
4. Kalkhoff RK, Jacobson M, Lemper D. Progesterone, pregnancy and the augmented plasma insulin response. J Clin Endocrinol Metab 1970;31:24–28.
5. Costrini NV, Kalkhoff RK. Relative effects of pregnancy, estradiol and progesterone on plasma insulin and pancreatic islet insulin secretion. J Clin Invest 1971;50:992–999.
6. Aerts L, Van Assche FA, Faure A, Sutter-Dub MT. Effects of treatment with progesterone and oestradiol-17β on the endocrine pancreas, in ovariectomized rats: ultrastructural variations in the β-cells. J Endocrinol 1980;84:317–320.
7. Kalkhoff RK. Metabolic effects of progesterone. Am J Obstet Gynecol 1982;142:735–738.
8. Hollingsworth DR. Alterations of maternal metabolism in normal and diabetic pregnancies. Differences in insulin-dependent, non-insulin dependent and gestational diabetes. Am J Obstet Gynecol 1983;146:417–428.
9. Freinkel N. Effects of the conceptus on maternal metabolism. In: Leibel BS, Wrenshall GA (eds). Amsterdam: Excerpta Medica 1964: pp 679–691.
10. Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 1981;140:730–736.
11. Battaglia FC, Meschia G. Fetal nutrition. Ann Rev Nutr 1988;8:43–61.
12. Simmons MA, Battaglia FC, Meschia G. Placental transfer of glucose. J Dev Physiol 1979;1:221–243.
13. Hauguel S, Desmaizieres V, Challier JC. Glucose uptake, utilization and transfer by the human placenta as functions of maternal glucose concentration. Pediatr Res 1986;20:269–273.
14. Bozzetti P, Ferrari MM, Marconi AM, et al. The relationship of maternal and fetal glucose concentrations in the human from midgestation until term. Metabolism 1988;37:358–363.
15. Deal CL, Guyda HJ. Insulin receptors of human term placental cells and choriocarcinoma (JEG-3) cells: characteristics and regulation. Endocrinology 1983;112:1512–1523.
16. Challier JC, Hauguel S, Desmaizieres V. Effect of insulin on glucose uptake and metabolism in the human placenta. J Clin Endocrinol Metab 1986;62:803–807.
17. Philipps AF, Rosenkrantz TS, Porte PJ, Raye JR. The effects of chronic fetal hyperglycemia on substrate uptake by the ovine fetus and conceptus. Pediatr Res 1985;19:659–666.
18. Urbach J, Mor L, Ronen N, Brandes JM. Does insulin affect placental glucose metabolism and transfer? Am J Obstet Gynecol 1989;161:953–959.
19. Holtzman IR, Lemons JA, Meschia G, Battaglia FC. Uterine uptake of amino acids and placental glutamine and glutamate balance in the pregnant ewe. J Dev Physiol 1979;11:137–149.
20. Cetin I, Corbetta C, Sereni LP. Umbilical amino acid concentrations in normal and growth-retarded fetuses sampled in utero by cordocentesis. Am J Obstet Gynecol 1990;162:253–261.
21. Elphick MC, Hudson DG, Hull D. Transfer of fatty acids across the rabbit placenta. J Physiol 1975;252:29–42.
22. Elphick MC, Filshie GM, Hull D. The passage of fat emulsion across the human placenta. Brit J Obstet Gynaecol 1978;85:610–618.
23. Thomas CR, Lowy C, St Hillaire RJ, Brunzell JD. Studies on the placental hydrolysis and transfer of lipids to the fetal guinea pig. In: Miller RK, Thiede HA (eds). Fetal nutrition, metabolism and immunology. The role of the placenta. New York:Plenum, Vol 1, 1984: pp 135–148.
24. Knopp RH, Warth MR, Charles D, Childs M, Li JR, Manbuchi H, Van Allen MI. Lipoprotein metabolism in pregnancy, fat transport to the fetus and the effects of diabetes. Biol Neonate 1986;50:297–317.
25. Coleman RA. Placental metabolism and transport of lipid. Fed Proc 1986;45:2519–2523.
26. Carlson AJ, Drennan FM. The control of pancreatic diabetes in pregnancy by the passage of the internal secretion of the pancreas of the fetus to the blood of the mother. Am J Physiol 1911;28:391–395.

27. Josimovich JB, Knobil E. Placental transfer of I^{131}-insulin in the rhesus monkey. Am J Physiol 1961;200:471–476.
28. Buse M, Roberts WJ, Buse J. The role of the human placenta in the transfer and metabolism of insulin. J Clin Invest 1962;41:29–41.
29. Gitlin D, Kumate J, Morales C. On the transport of insulin across the human placenta. Pediatrics 1965;35:65–69.
30. Keller JM, Krohmer JS. Insulin transfer in the isolated human placenta. Obstet Gynecol 1968;32:77–80.
31. Adam PA, Teramo K, Raiha N, Gitlin D, Schwartz R. Human fetal insulin metabolism early in gestation. Response to acute elevation of the fetal glucose concentration and placental transfer of human insulin-I^{131}. Diabetes 1969;18:409–416.
32. Kalhan SC, Schwartz R, Adam PAJ. Placental barrier to human insulin I^{125} in insulin-dependent diabetic mothers. J Clin Endocrinol Metab 1975;40:139–142.
33. Bauman WA, Yalow RS. Transplacental passage of insulin complexed to antibody. Proc Natl Acad Sci USA 1981;78:4588–4590.
34. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khouri JC. Transplacental passage of insulin in pregnant women with insulin dependent diabetes mellitus. N Engl J Med 1990;323:309–315.
35. Sperling MA, Devaskar S. Insulin action. In: Drazin B, Melmed S, LeRoith D (eds). Molecular and cellular biology of diabetes mellitus. Vol 2, New York:Alan R. Liss Inc. 1989: pp 203–217.
36. Puavilai G, Drobny EC, Domont LA, Baumann G. Insulin receptors and insulin resistance in human pregnancy: evidence for a post receptor defect in insulin action. J Clin Endocrinol Metab 1982;54:247–253.
37. Warth MR, Arky RA, Knopp RH. Lipid metabolism in pregnancy. III. Altered lipid composition in intermediate, very low, low and high-density lipoprotein fractions. J Clin Endocrinol Metab 1975;41:649–655.

SECTION

III

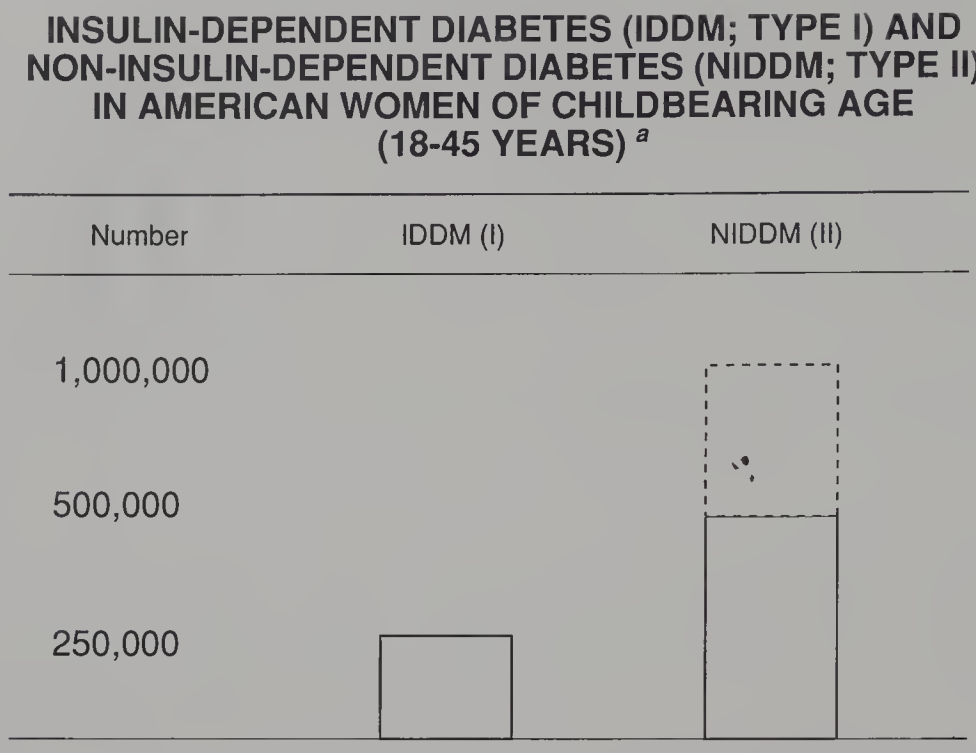
Effect of Pregnancy on Different Types of Diabetes

Dorothy R. Hollingsworth

In Table I.1 of the introduction (1), a revision is presented of our classification of diabetes in pregnancy, first published in 1981 (2). The accompanying color photographs (Fig I.1 in the introduction) illustrate typical women with insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) and lean and obese women with gestational diabetes (GDM).

Our reasons for abandoning the popular White obstetric classification of diabetes first published in 1949 (3), before it was possible to measure insulin levels in serum or plasma by radioimmunoassay, and several subsequent revisions (4) are three-fold. First, pregnancy is but a brief interlude in the lives of diabetic women or those who develop GDM. Their disorders of carbohydrate metabolism need to be viewed in the broader perspective of diabetes defined by the National Institutes of Health (NIH), National Diabetes Data Group (NDDG) (5), or, in the case of women with GDM, reclassified definitively postpartum, according to World Health Organization (WHO) criteria (6, 7) as *(a)* diabetes no longer present (normal), *(b)* impaired, or *(c)* diabetes present. Second, the large body of knowledge emerging in the 1980s in genetics, autoimmune disorders, and molecular biology requires that we begin to understand and manage each pregnant diabetic woman in our clinics according to the most up-to-date knowledge of her genetic background and pathophysiology. Third, in the most recent and better designed studies of diabetic pregnancies, there is no evidence that pregnancy complications are correlated with obstetric White classification. Moreover, this approach to pregnant diabetic women has prevented us from gaining any knowledge at all of the risk of malformations, retinal and renal complications, outcome measures of pregnancy labor and delivery, problems in newborn infants, and long-term outcome of children of NIDDM women. Throughout the world, most diabetic women of childbearing age have NIDDM.

In the United States, it is estimated that there are about 1,000,000 women of childbearing age with NIDDM, compared with 250,000 with IDDM (Fig. 7.1) (8). To keep pace



[a] *Personal Communication from Maureen Harris Ph.D. National Diabetes Data Group (NDDG), NIDDK, NIH, Bethesda, Maryland. Figures derived from survey data (8)*

Figure 7.1. Number of women of childbearing age (18–45 years) in the United States with IDDM and NIDDM. The *dotted box* in the NIDDM column indicates probable or possible undiagnosed women in this age group with NIDDM. The figures are from survey data collected by Harris (8).

with modern biology, potential contributions in the field of reproductive medicine will necessitate well-designed prospective clinical studies that add to the unfolding story of the genetics and course of all types and subtypes of diabetes in pregnant women.

CHAPTER

7

Gestational Carbohydrate Intolerance (GCI); Gestational Diabetes Mellitus

The metabolic stress of pregnancy may result in reversible carbohydrate intolerance. This problem is estimated to occur in 1–3% of all pregnancies. Table 7.1 describes women who are at particular risk for GDM.

GDM is usually detected in the second half of pregnancy when placental synthesis of peptide and steroid hormones reaches a peak. Women who are found to have markedly abnormal oral glucose tolerance tests early in pregnancy (with fasting plasma glucose levels of ≥105 mg/dl [5.5 mmol/L] and/or one or more values >200 mg/dl [>11 mmol/L] following an oral glucose challenge) and elevated HbA1c concentrations are more likely to have NIDDM rather than GDM even though hyperglycemia was detected for the first time during pregnancy. Barden and Knowles (9) and Harris (10) have reviewed the problems and clinical correlations of the diagnosis of diabetes during pregnancy.

Heterogeneity of GDM

Women who develop *reversible* glucose intolerance during pregnancy do not represent a single metabolic problem. Although many of these patients are obese and have a strong family history of diabetes, others are of normal weight or thin before conception and may have no history of carbohydrate intolerance in their families. The 400-kcal breakfast mixed meal tolerance test (MTT) described later in this section permits a better metabolic definition of such patients.

Metabolic differences among patients with GDM are most apparent when obese subjects are compared with those who are normal or slightly overweight. Figure 7.2 depicts CP values during a breakfast MTT performed at 25 weeks' gestation in a massively obese woman (weight: 245 lb, 11kg; body mass index [BMI] = 43) versus those of a slightly overweight patient (weight: 140 lb, 64 kg; BMI = 28). Both women had similar degrees of glucose intolerance (mean 24-h plasma glucose values: obese, 102 mg/dl (5.6 mmol/L); slightly overweight, 113 mg/dl) (6.2 mmol/L). Normal mean 24-h glucose value at 25 weeks' gestation is 87 mg/dl ± 1.7 SEM (4.8 mmol/L ± 0.09). The thinner patient had relative insulin deficiency while the very obese woman was hyperinsulinemic and insulin resistant. These two women with quite different metabolic problems share the diagnosis "gestational diabetes" in our current diagnostic classification of diabetic pregnancies.

In both obese and thin groups of patients with mild *reversible* glucose intolerance, mean HbA1c concentrations do not differ significantly from normal. Although most women with reversible glucose intolerance during pregnancy have normal HbA1c concentrations before 20 weeks of gestation and plasma glucose values that do not exceed 200 mg/dl (11 mmol/L) at any point during a 3-h oral glucose tolerance test with a 100-g glucose load, this is not always true.

Patient G. T., a normal-weight young woman (Fig. 7.3), arrived at the hospital for the first time at 42 weeks' gestation with the chief complaint of no fetal movement. A 5300-g stillborn infant was delivered following induction of labor. A HbA1c concentration obtained on the first day postpartum was 9.8%.

Table 7.1.
Pregnant Women at Risk for Gestational Diabetes

1. Previous history of gestational diabetes or positive family history of diabetes
2. Glycosuria or symptoms of diabetes
3. Fasting plasma glucose ≥105 mg/dl (5.8 mmol/L) or 2-h postprandial plasma glucose level of ≥120 mg/dl (6.6 mmol/L)
4. Obesity (>150 lb or body mass index (kg/m^2) of ≥27 before pregnancy)
5. Previous infant >9 lb (4100 g)
6. Previous unexplained intrauterine fetal demise
7. Development of polyhydramnios and/or macrosomic fetus

Figure 7.3. A 24-year-old slightly overweight woman who has had reversible carbohydrate intolerance in two successive pregnancies. See text for description.

An oral GTT with a 75-g load of glucose was normal at 3 months postpartum.

One year later, the patient returned to the hospital for prenatal care at 29 weeks' gestation. At this time, her 3-h GTT was markedly abnormal (plasma glucose values: fasting, 115 mg/dl (6.3 mmol/L); 1 h, 169 mg/dl (9.3 mmol/L) 2 h, 237 mg/dl (13.1 mmol/L), 3 h 171 mg/dl (9.5 mmol/L). An hourly 24-h plasma glucose profile revealed a mean 24-h glucose of 132 mg/dl (7.3 mmol/L) with a 24-h urinary loss of glucose of 8.2 g and a HbA1c level of 7.6%. A daily dose of 28 units of rapid-acting regular/crystaline insulin in divided doses before each meal was required to maintain normal levels of plasma glucose. At term, HbA1c was 7.4%. A normal 3200-g infant was born by spontaneous vaginal delivery. Glucose tolerance was again normal after delivery and pancreatic islet cell antibody studies were negative.

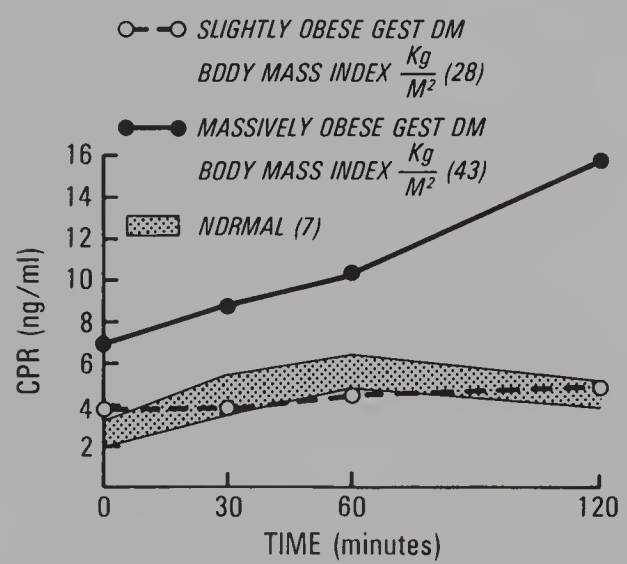


Figure 7.2. Serum C-peptide responses in two women with GDM following a 400-kcal mixed meal. Note the markedly elevated C-peptide values in the massively obese subject and the slow and inadequate insulin response in a slightly obese patient.

Screening for Gestational Diabetes as Part of Prenatal Care

Pregnancy represents a special situation for detection of carbohydrate intolerance in contrast to mass population screening programs that have now been abandoned as unrewarding. GDM is associated with higher maternal morbidity and an increased risk of perinatal morbidity and mortality for infants. Selective screening of women known to be at risk for

diabetes fails to detect many women of normal weight who develop GDM.

Improved infant perinatal mortality and morbidity rates have followed higher detection rates and more aggressive treatment of mild carbohydrate intolerance in pregnant women. In addition, failing the carbohydrate stress test of pregnancy alerts patients and their physicians to the increased risk for these women to develop overt diabetes in later life. Thus, preventive health measures, such as improved nutrition, weight control, and a regular exercise program can be instituted during pregnancy and continued postpartum. Routine screening of *all* pregnant women for gestational carbohydrate intolerance is recommended (11).

Criteria for Diagnosis of GDM

Care must be taken not to overdiagnose maternal diabetes; it is preferable to describe women with abnormal screening tests as having "impaired glucose tolerance during pregnancy" or "gestational carbohydrate intolerance" (GCI) rather than using the term *diabetes* since final definition depends upon reevaluation 6–12 weeks postpartum. Worldwide, there is no unanimity of opinion concerning criteria for the diagnosis of GDM. Several approaches will be mentioned in the discussion that follows.

Table 7.2 outlines the several types of tests in general use for detection of GDM. In the United States, the most common screening test is the administration of a 50-g glucose cola drink (Glucola) load with a single plasma glucose determination drawn at 1 h. Patients need not be fasting and women with risk factors (Table 7.1) for diabetes can easily be screened at or before the first clinic visit.

In women who have positive 1-h Glucola test, a 3-h oral glucose tolerance test is performed (Table 7.3). The diagnosis of GDM is made according to the criteria of O'Sullivan and Mahan (11). The procedure followed in our clinic is outlined in Table 7.4.

In patients with a positive history of risk factors for diabetes, we recommend that a HbA1c concentration be obtained at the same time to detect early the presence of previously unrecognized NIDDM.

Table 7.2.
Tests for Carbohydrate Intolerance During Pregnancy

1. Simple screening tests, abnormal values
   A. Fasting plasma glucose ≥105 mg/dl (5.8 mmol/L) or serum glucose of ≥90 mg/dl (5.0 mmol/L)
   B. Random 2-h or more postprandial plasma glucose ≥120 mg/dl (6.6 mmol/L)
2. Recommended loading tests for screening
   A. 50-g glucose load given orally at random (need not be fasting); abnormal: 1-h plasma glucose ≥140 mg/dl (7.8 mmol/L)
   B. 3-h oral glucose tolerance test with 100-g glucose (Table 7.3) (11)
3. 75-g oral glucose tolerance test (12)
4. Breakfast mixed-meal tolerance test (13–15)

Differences in Lean and Obese GDM

In the NDDG criteria for NIDDM, there is a further subdivision for lean and obese individuals. We have been impressed that lean GDM women (BMI < 27 kg/m^2) have marked

Table 7.3.
Diagnosis of Gestational Diabetes[a]

	Venous Plasma or Serum		Venous Plasma or Serum		Capillary whole blood	
	(mg/dl)	(mmol/L)[a]	(mg/dl)	(mmol/L)[b]	(mg/dl)	(mmol/L)[c]
Fasting	105	5.8	95	5.3	114	6.3
1 h	190	10.6	180	10.0	211	11.7
2 h	165	9.2	155	8.6	183	10.0
3 h	145	8.1	140	7.8	157	8.7

[a]Two or more oral glucose tolerance test (OGGT with 100 g of glucose); values must be met or exceeded. National Diabetes Data Group. Diabetes 1979; 28:1039.
[b]Data from Carpenter and Coustan. Am J Obstet Gynecol 1982; 144:768.
[c]Data from Weiner et al. Am J Obstet Gynecol 1987; 156:1085. This study was performed with the Accuchek II meter.

Table 7.4.
Detection and Diagnosis of Impaired Glucose Tolerance or Gestational Carbohydrate Intolerance (GCI); Gestational Diabetes (GDM) During Pregnancy[a]

First prenatal visit Evaluation for diabetes mellitus	Positive History: previous gestational diabetes, history of large babies, family history of diabetes, glycosuria, symptoms of diabetes or fasting plasma glucose ≥105 mg/dl (5.8 mmol/L) or 2-h postprandial plasma glucose ≥120 mg/dl (6.6 mmol/L); perform a 50-g oral glucose screening test; if 1-h glucose is ≥140 mg/dl (7.8 mmol/L), a 3-h (100-g) oral glucose tolerance test criteria of National Diabetes Data Group (NDDG) (5) is indicated and an HbA1c test
All women with negative history Glucose load screening test at 24-28 weeks gestation	50-g glucose load given at random; abnormal: 1-h plasma glucose ≥140 mg/dl (7.8 mmol/L)
Women with positive screening test: 3-h glucose tolerance test with 100 g of glucose	Abnormal: two or more elevated values by NDDG criteria (Table 7.3)
Women with a positive screening test and normal 3-h glucose tolerance test or a single abnormal value	Repeat 50-g glucose load at 32 weeks or if patient has hydramnios or a macrosomic fetus on ultrasonographic examination; if positive, repeat 3-h glucose tolerance test

[a]These are the procedures currently followed in the United States and differ from screening procedures used in the UK, Europe, and other parts of the world. A unified approach awaits better genetic definition of the diabetic syndrome.

metabolic differences when compared with obese GDM subjects (BMI ≥ 27). In a study of hourly measurements of blood glucose and insulin concentrations around the 24-h clock, we found virtually no difference in blood glucose levels in these two groups of women (Fig. 7.4). Plasma insulin levels, however, were quite different, indicating a greater degree in insulin resistance in obese compared with lean GDM patients. In a more extensive study of 38 lean and 45 obese GDM women, placental weights and infant birth weights were both higher in the obese GDM group but the differences did not reach statistical significance (Table 7.5) (16).

A major obstetric concern for women with GDM is the possibility of a macrosomic fetus, shoulder dystocia, or birth injury. Thus, size at birth is an important variable in GDM pregnancies. Are there differences in infants of lean versus obese GDM mothers and how do they compare with babies of normal lean and obese women?

We have addressed this question by collecting anthropometric measurements in 199 *normal* newborn boys and girls born in San Diego (sea level) (Fig. 7.5) (17). These data differ from those of others reported in the literature in that all infants included in the study had mothers with a normal BMI, a normal 1-h blood glucose concentration (≤ 140 mg/dl; 7.8 mmol/L) following a 50-g glucose cola drink and no complications during pregnancy. All measurements were obtained in the first 48 h after birth.

A comparison of measurements of infants of normal lean mothers with those of *lean GDM mothers* showed that the latter were heavier and longer than normal infants with increased waist-to-hip ratios and wider triceps and subscapular skinfolds (Table 7.6). Measurements obtained in infants of 12 obese normal women were compared with those of *obese GDM mothers* (Table 7.7). Infants of obese women were heavier than those of lean normal women. They differed from infants of obese GDM mothers who had increased measurements of the subscapular skinfold. A disparity in skin fold measurements was also apparent when infants of lean GDM were compared with those of obese GDM mothers (Table 7.8). Thus, in infants of both lean and obese GDM mothers with

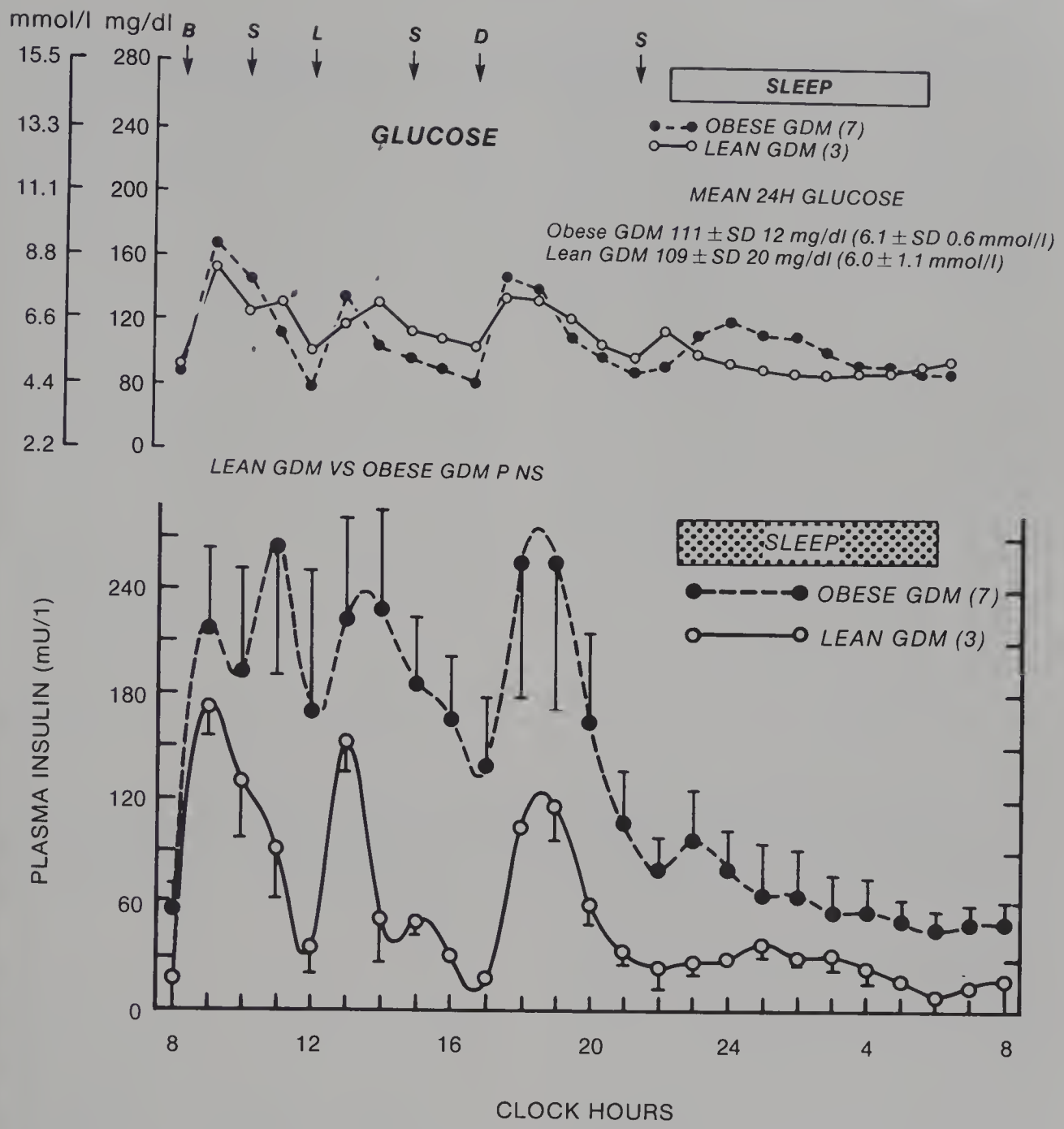


Figure 7.4. *Top,* plasma glucose determinations were measured hourly around the 24-h metabolic clock in seven obese GDM women and three lean GDM women. Mean 24-h blood glucose values were nearly identical. *Bottom,* plasma insulin levels in the same women differed markedly with hyperinsulinemia and insulin resistance apparent in obese GDM.

similar mean birth weights to those of infants of normal-weight mothers, there was evidence at birth of a significant difference in fat patterning in utero; there was a greater accumulation of truncal fat in infants of both lean and obese GDM mothers. Relative central obesity can and does cause dystocia in mothers of normal-weight infants of diabetic mothers (IDM). The long-term implications of abnormal fat patterning in utero are unknown.

Table 7.5.
Characteristics of Lean and Obese Women with Gestational Diabetes[a]

Group	Age (yr)	Wt (kg)	BMI (kg/M^2)	Weight gain in pregnancy (kg)	HbA1 (at term) (%)	Placental wt (g)	Infant birth wt (g)	Gestational age (weeks)
Gestational Diabetes								
Lean[b] (38)	31 ± 7	56 ± 7	23 ± 3 (36)	14 ± 6 (32)	6.4 ± 0.8	530 ± 100 (34)	3574 ± 570	40 ± 1
Obese (45)	31 ± 5	93 ± 17	36 ± 5 (34)	14 ± 10 (34)	6.9 ± 1	570 ± 105 (32)	3812 ± 535	40 ± 1
p	NS	0.0	0.0	NS	.02	NS	NS	NS
Normal								
Lean (23)	26 ± 4	57 ± 8	22 ± 3	16 ± 5 (10)	5.8 ± 0.5 (16)	542 ± 114 (10)	3368 ± 60 (199)	40 ± 0.1
Obese (17)	28 ± 6	93 ± 18*	35 ± 5*	11 ± 5 (12)	6.0 ± 0.9 (9)	611 ± 164 (13)	3813 ± 588 (16)	40 ± 1
p	NS	0.0	0.0	0.02	NS	NS	0.0	NS

[a]All values are presented as mean ± standard deviation; [b] () = Number of subjects.

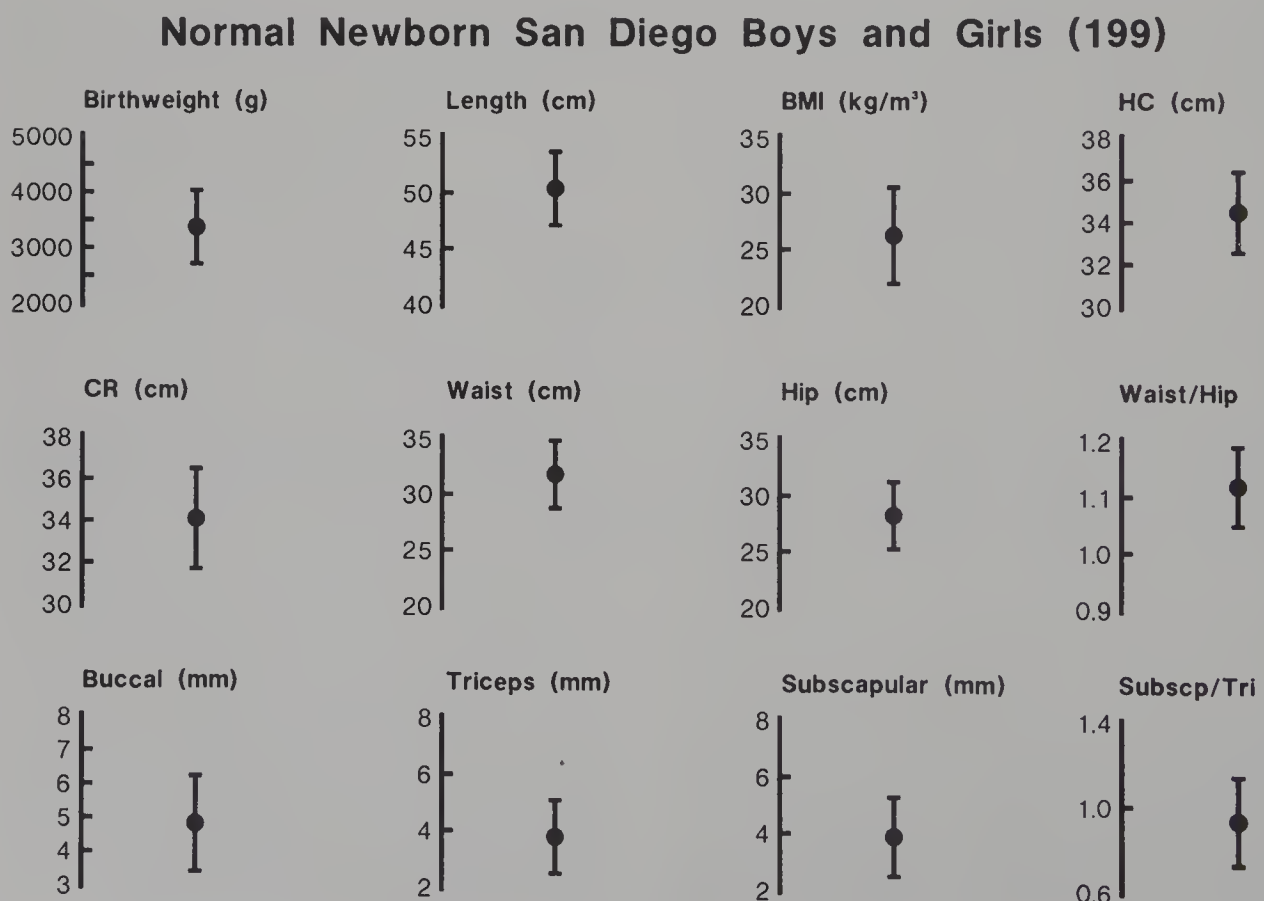


Figure 7.5. Measurements ± 2 SD in 199 newborn San Diego infants (sea level).

Table 7.6.
Measurements of Infants of Lean Normal and Lean GDM Mothers

Variable	Lean Normal (199)	Lean GDM (32)	P
IBW (g)	3368 ± 60	3574 ± 570	0.0
IBL (cm)	50 ± 0.5	51 ± 2	0.0
W/H × 100	112 ± .00	114 ± 2	0.0
	Skinfolds		
Buccal (mm)	4.8 ± 1	4.6 ± 1	NS
Triceps (mm)	3.8 ± 0.2	4.1 ± 0.6	0.0
Subscap (mm)	3.9 ± 0.2	4.4 ± 0.9	0.0

Table 7.7.
Measurements of Infants of Obese Normal and Obese GDM Mothers

Variable	Obese Normal (12)	Obese GDM (38)	P
IBW (g)	3813 ± 588	3812 ± 535	NS
IBL (cm)	52 ± 2	52 ± 2	NS
W/H × 100	111 ± 2	113 ± 4	NS
	Skinfolds		
Buccal (mm)	5.0 ± 1	5.5 ± 1	NS
Triceps (mm)	4.5 ± 1	4.5 ± 1	NS
Subscap (mm)	4.8 ± 1	5.5 ± 1	.03

Table 7.8.
Measurements of Infants of Lean and Obese GDM

Variable	Lean GDM (32)	Obese GDM (38)	P
IBW (g)	3574 ± 570	3812 ± 535	NS
IBL (cm)	51 ± 2	52 ± 2	.04
BMI (kg/m^3)	26 ± 2	30 ± 4	.04
Waist (cm)	32 ± 2	33 ± 2	.03
Hip (cm)	28 ± 2	30 ± 2	.03
W/H × 100	114 ± 2	113 ± 4	NS
	Skinfolds		
Buccal (mm)	4.6 ± 1	5.5 ± 1	.01
Triceps (mm)	4.1 ± 0.6	4.5 ± 1	NS
Subscap (mm)	4.4 ± 0.9	5.5 ± 1	.01
TSF	13.1 ± 2	15 ± 3	.03

THE 400-KILOCALORIE MIXED MEAL TOLERANCE TEST (MTT)

The 3-h oral 100-g glucose tolerance test for gestational diabetes is an unpleasant experience for pregnant women. Some are unable to follow the instructions to have a diet of 150–300 g of carbohydrate for the 3 days preceding the test. Others experience nausea after ingestion of such a high glucose load and promptly vomit. The idea of a more physiologic breakfast meal tolerance test (MTT) is appealing and has had a number of clinical trials (13-16, 18, 19).

The MTT is well tolerated by patients and a breakfast test has been standardized in Aberdeen, Scotland where a quality-controlled, standardized mixed formula test meal representing an average United Kingdom breakfast was obtained from Boots Pharmaceutical Company (18). Sutherland and colleagues (19) tested 101 unselected women with both an MTT and a 75-g oral glucose load (WHO criteria). The one mother with an infant with a birth weight above the 90th percentile had normal blood glucose values during both tests. The 2-h 75-g OGTT failed to identify any of the three women with possible diabetogenic fetopathy. Sutherland and colleagues suggest there is mounting evidence to justify a radical reappraisal of approaches to evaluate maternal metabolism and carbohydrate tolerance in human pregnancy (19).

The MTT can be administered easily in an outpatient clinic. Table 7.9 shows the composition of the breakfast meal and normal values ± SD for plasma glucose, C-peptide, and insulin in six normal women. The test is performed as follows: After a 10-h overnight fast, baseline blood samples are drawn for plasma lipids, HbA1c concentration, glucose, insulin and C-peptide levels. The patient eats the 400-kcal breakfast in 10 min. At 30, 60, and 120 min after the start of feeding, glucose and hormone determinations are repeated. Figure 7.6 shows mean ± SD plasma levels of glucose and insulin in seven normal women during a MTT performed at the 2nd trimester and repeated in the same individuals before delivery. Note the slightly higher glucose values at the 2nd trimester test when compared with the late pregnancy test. Although normal pregnant women had a rather narrow range of fasting levels of plasma insulin, they differed markedly in response to the test meal as is apparent

Table 7.9.
400-Calorie Mixed Meal (Breakfast) Tolerance Test

Test Meal Exchange	Food	Amount	Carbohydrate (g)	Protein (g)	Fat (g)	kcal	Dietary Fiber (g)
1 Fruit	Grape juice	3.0 oz	15.8	0.4		65	
1 Bread	White bread	25 g	11.9	2.2	0.8	64	0.68
1 Meat	Egg	50 g	0.35	6.4	5.8	79	
1 Fat	Margarine	4 g			4.0	36	
1 Milk	Whole milk	8 oz	11.0	8.0	9.0	157	
Total			39.05	17	19.6	400	0.68
Percent			39	17	44	100	<1.0

Test: normal values in 6 normal pregnant women at 3rd trimester (34–37 weeks)

Time (min)	Plasma glucose, mg/dl, ±SD	(mmol/L)	C-peptide (ng/dl, ±SD)	Insulin (μU/ml, ±SD)
0	75 ± 8	(4.2)	2.6 ± 1.5	23 ± 9
Test meal				
30	103 ± 13	(5.7)	5.7 ± 3.5	135 ± 61
60	100 ± 12	(5.5)	5.7 ± 3.5	117 ± 48
120	87 ± 8	(4.8)	5.4 ± 4.1	83 ± 49

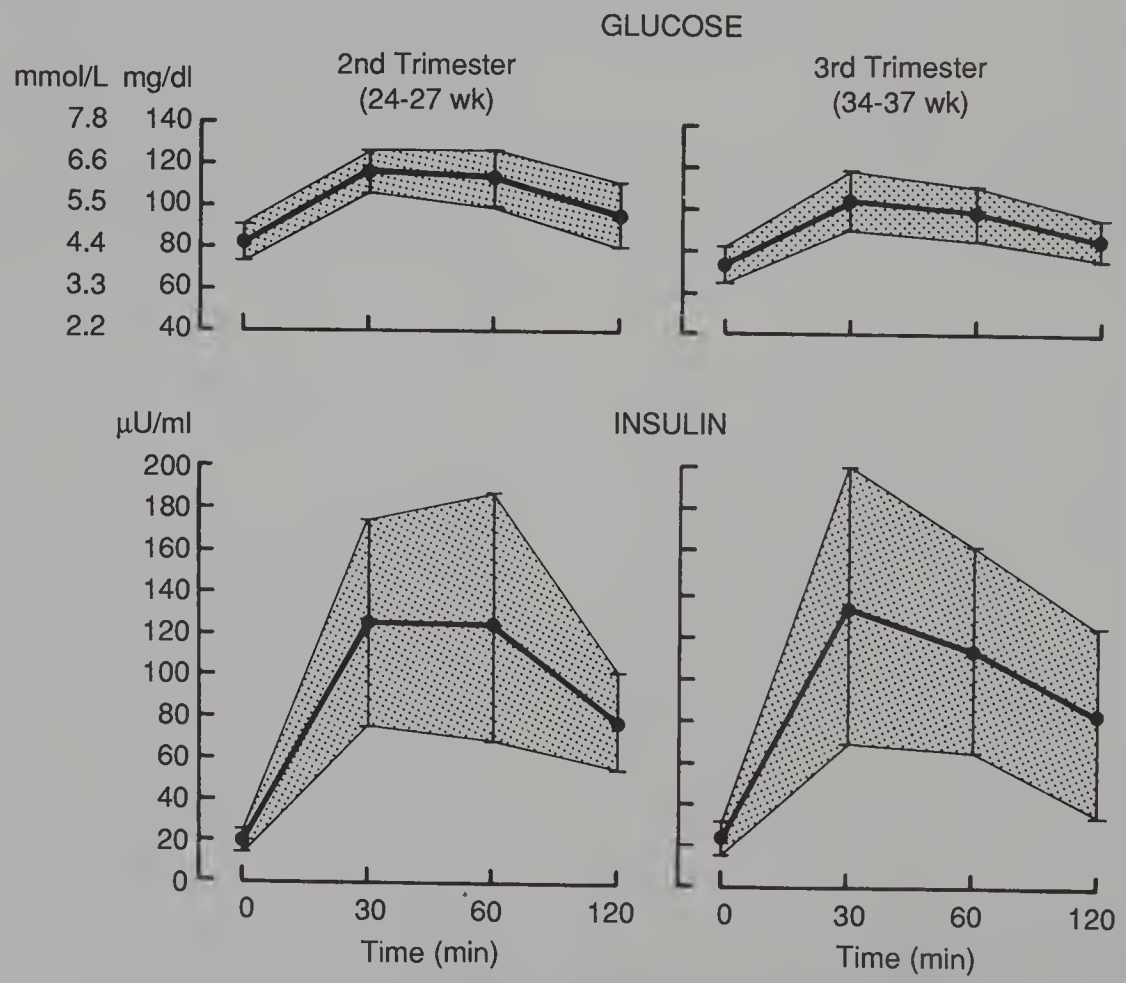


Figure 7.6. Fasting and meal-stimulated plasma glucose and insulin values in seven normal pregnant women during a 2-h 400-kcal MTT at 2nd and 3rd trimesters. See text for description. Mean glucose values are ±2 SD; mean insulin values are ±1 SD.

in the wide standard deviation at 30, 60, and 120 min. Normal values for the MTT obtained in 23 lean and 10 obese normal women are shown in Table 7.10.

Because some diabetic women have abnormal fasting plasma cholesterol (CHOL), triglyceride (TG), and lipoprotein values and both normal and diabetic women may develop gestational hypertriglyceridemia (20), it is useful to do a screening test for abnormal lipid levels at the fasting period. In selected women, plasma glucagon responses to the test meal, an HbA1c concentration, and serum titers of pancreatic islet cell antibodies may provide additional information of interest.

MTT tests in obese GDM women are characterized by significantly higher levels of glucose and insulin at all points during the test (Figs. 7.7 and 7.8). Insulin measurements were particularly informative because they clearly demonstrated hyperinsulinemia and insulin resistance when compared with both normal and lean women with GDM ($p < 0.001$) or obese normals ($p < 0.03$).

In addition, MTTs are of special help in IDDM women to determine whether there is still residual β-cell function and in lean and obese NIDDM women to evaluate whether individual patients have a decreased, normal, or delayed and elevated insulin response to the physiologic challenge of a normal meal. At present, in the absence of genetic markers for all types of diabetes, we suggest that GDM may be an expression of early genetic and environmental interaction that can unmask susceptibility to either IDDM (of slowly evolving type) or NIDDM. A physiologic breakfast MTT provides a better metabolic description of individual patients or groups of women with GDM than an unphysiologic, unpleasant, large glucose loading test with measurements limited to changes in plasma concentrations of glucose. Moreover, among diabetic women, we need to detect those with elevated levels of plasma lipoproteins so that we can provide better advice for preventive health measures and choice of contraceptives.

In conclusion, the remarkable metabolic changes that occur in normal pregnancy provide a very real stress for women with decreased or "relatively decreased" insulin reserve. Pregnancy is the best test we have for

Table 7.10.
Breakfast Meal Tolerance Test in 23 Lean and 10 Obese Normal Pregnant Women[a]

Time (min)	*Glucose* mg/dl (mmol/L)	Insulin μU/ml	C-peptide ng/ml	Glucagon pg/ml	hCS μg/dl	CHOL mg/dl	TG mg/dl
0	75 ± 7	17 ± 9	2.3 ± 1	158 ± 67	4.6 ± 1.4	259 ± 46	244 ± 82
L	(4.2)						
O	80 ± 6	26 ± 19	5.1 ± 3	179 ± 80	4.9 ± 1.4	256 ± 24	229 ± 72
	(4.4)						
30							
L	111 ± 13	102 ± 45	6.5 ± 4	161 ± 73	4.4 ± 1.1		
	(6.2)						
O	112 ± 8	123 ± 63	10.5 ± 6	188 ± 77	4.5 ± 1.7		
	(6.2)						
60							
L	106 ± 12	90 ± 42	6.7 ± 4	152 ± 58	4.7 ± 1.4		
	(5.9)						
O	108 ± 15	109 ± 45	11.0 ± 4	187 ± 74	4.3 ± 1.6		
	(6.0)						
120							
L	84 ± 8	51 ± 36	6.1 ± 4	170 ± 79	4.8 ± 1.6		
	(4.7)						
O	92 ± 6	56 ± 20	9.5 ± 5	187 ± 72	4.8 ± 1.6		
	(5.1)						

[a]All values are presented as mean ± standard deviation; abbreviations: hCS: human chorionic somatomammotropin (hPL; human placental lactogen); CHOL: cholesterol; TG: triglyceride; L: lean (BMI ≤24; N = 23); O: obese (BMI ≥27; N = 10).

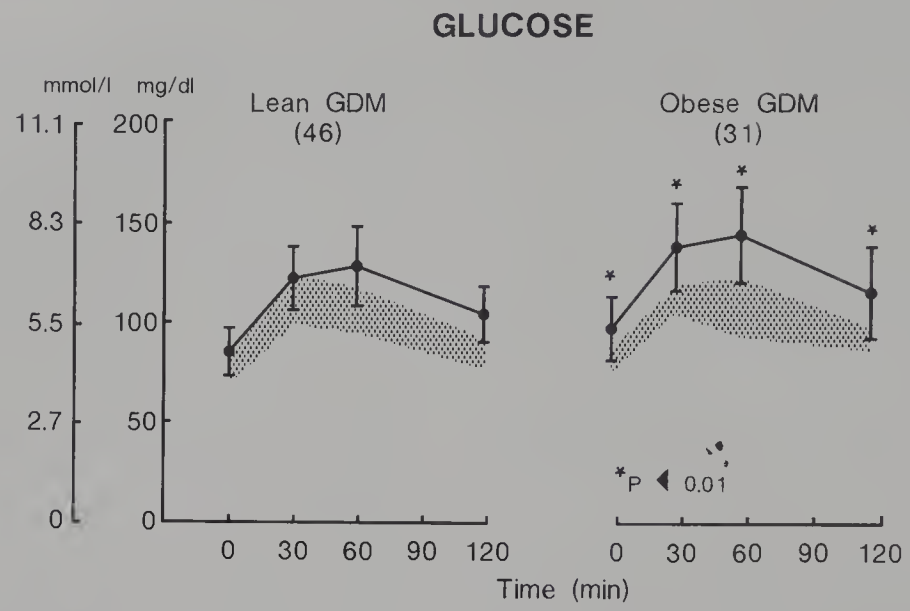


Figure 7.7. Fasting and meal-stimulated plasma glucose concentrations in 46 lean and 31 obese GDM women. Obese GDM women have significantly higher values at each point during the test. The *stippled areas* in this figure and in Figure 7.8 indicate values in normal, lean, and obese pregnant women.

diabetes and may provide the first hint of a genetic environmental interaction that indicates a "susceptibility" for later development of diabetes. There are various tests used throughout the world to diagnose GDM. It seems clear on the basis of clinical observations that it is a heterogeneous syndrome with the two largest subgroups being lean and obese women. Dietary management of GDM is discussed in Section 4, Chapter 14 as well as general treatment and labor and delivery. Postpartum reassessment and educational suggestions for follow-up are also described in Chapter 14.

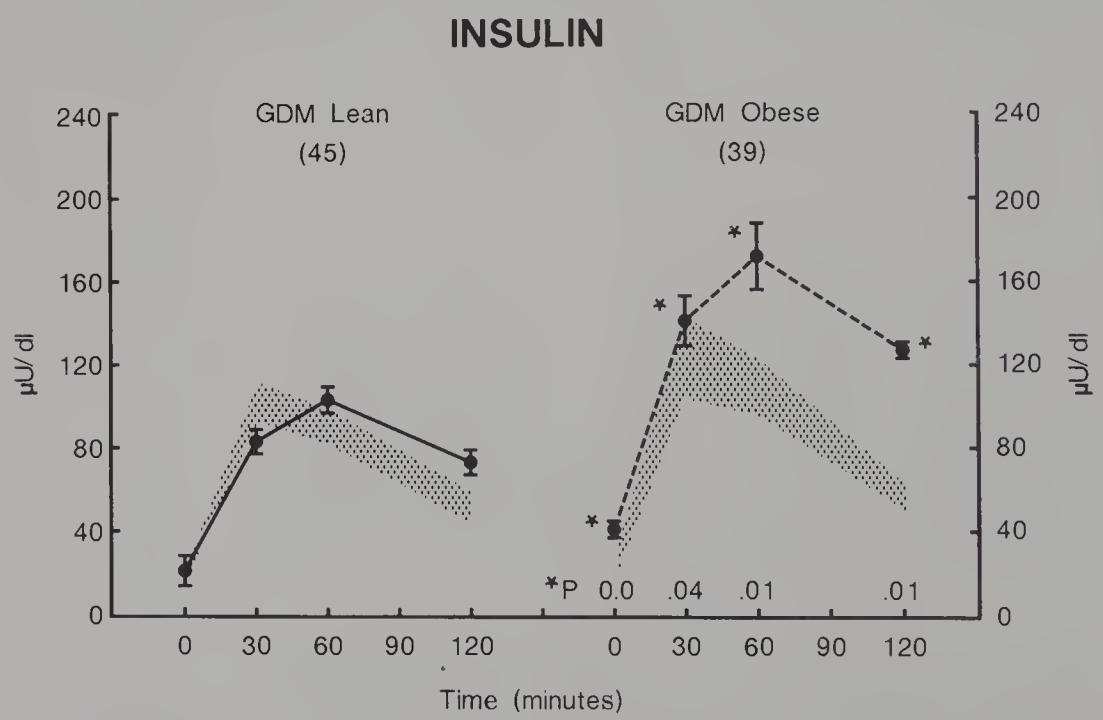


Figure 7.8. Measurements of plasma insulin values during a meal-stimulation test in 46 lean and 39 obese GDM women. Obese GDM women have significantly higher fasting and subsequent values at each point during the test and higher total integrated insulin units under the 2-h curve than normal women.

CHAPTER

8

Insulin-Dependent Diabetes Mellitus (IDDM, Type I)

Pregnancy has a profound effect on women with IDDM because they have a marked or relatively severe decrease in pancreatic β-cell function. The original onset of the disorder may be explosive, especially in children or adolescents, and is often manifested suddenly with diabetic ketoacidosis, an infectious disease, or a surgical procedure, such as an appendectomy. In recent years, it has become apparent that this type of onset is more often the exception than the rule. Current knowledge supports the concept that an environmental insult (? viral or other) evokes an autoimmune response in genetically "susceptible" individuals. Islet cell antibodies (ICA) may occur even before the disease becomes clinically apparent. Over time, as the β-cell mass declines, the first metabolic indication of a problem is an abnormal (delayed) insulin response to glucose. When about 80% of β cells are destroyed, the oral glucose tolerance test becomes abnormal; symptoms and a diagnosis of IDDM occur when virtually all β cells (90%) are lost. This life-long spectrum of an autoimmune genetic disorder is not unlike that of the similar pattern observed in autoimmune Graves' disease or Hashimoto chronic thyroiditis. The onset of IDDM has been documented in affected individuals from the newborn period to age 93 years.

PATHOGENESIS OF IDDM

Many of the exciting advances in our understanding of this disease have occurred during the decade of the 1980s. This section is not meant to be a recapitulation of the review in Section I, Chapter 1 (references 7-21). Rather, it is envisioned as a complementary discussion to serve as a bridge between recent advances in research in diabetes and as a background for the clinical care of pregnant women with IDDM.

Why do β-cells die? Figure 8.1 graphically displays the clinical course that follows β-cell loss (21). As described in Section I, genes in the major histocompatibility complex (MHC) on chromosome 6 have been associated with IDDM. The suspect genes lie in the D region of the MHC (Section I, Fig. 1.2) (22).

In 1987, Todd and associates (23) identified a region of DQ molecules that increases susceptibility to diabetes. In individuals who inherit the genes for DQ proteins 1 through 6, they reported that susceptibility for IDDM is usually determined by the 57th amino acid on the DQB chain. When this position is occupied by aspartic acid, which is negatively charged, the likelihood of developing diabetes is low, but noncharged amino acids, such as valine or serine, at the same position (as occurs in the DQw 3.2 protein) raises the risk. The presence of aspartic acid at position 57, however, is not protective for everyone.

An explanation of why a lack of aspartic acid at position 57 of the class II DQB chain can contribute to the pathogenesis of diabetes requires analysis of the structure of MHC molecules. Figure 8.2 shows a model of analyses of the structure of MHC molecules. Atkinson and Riley (22) have proposed a three-part hypothesis to explain how pancreatic β cells might be attacked, become impaired or destroyed, and respond to continuing attack. Figure 8.3 is an artist's view of how this sequence might proceed.

Within the general category of IDDM, it has

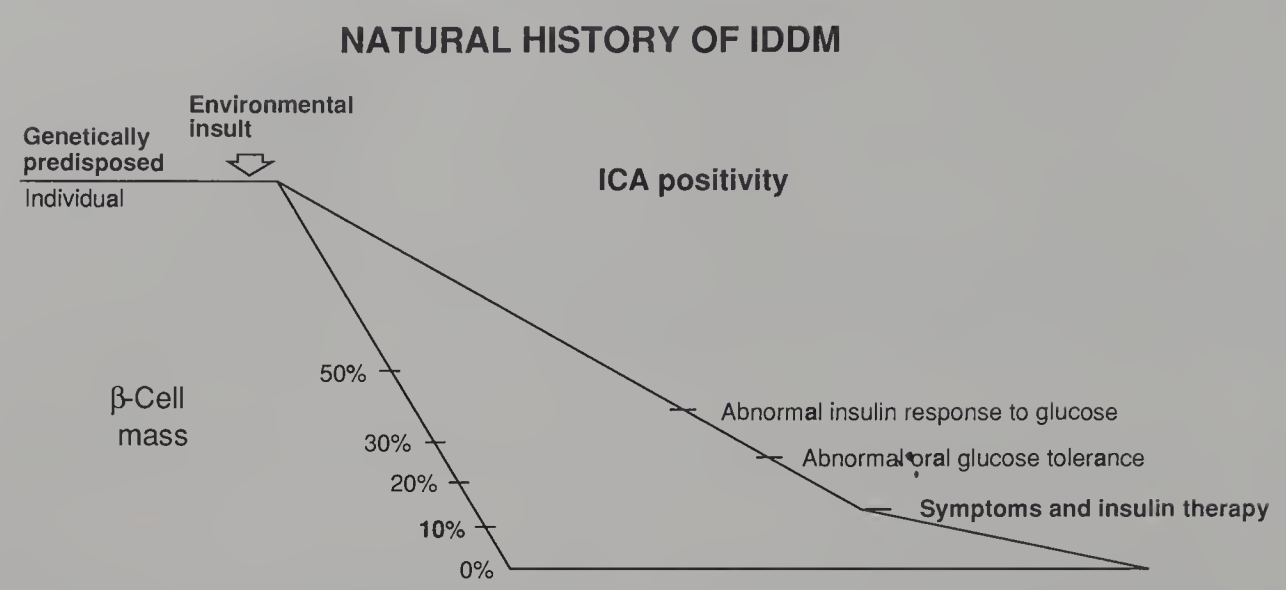


Figure 8.1. In the natural history of IDDM, there is a "prediabetic" phase of variable length of time. The disorder occurs in genetically predisposed individuals with a superimposed autoimmune process reflected by a positive islet cell antibody (ICA) titer. When β-cell mass diminishes to about 10%, symptoms of polyuria, polydipsia, and polyphagia occur and treatment with insulin becomes imperative. With permission from Hitchcock CL, Riley WJ, Maclaren NK. Autoimmmunity in insulin-dependent diabetes mellitus: Its detection and prevention. In: Cruse JM, Lewis RE (eds). Genetic basis of autoimmune disease. New York: Karger 1988: pp 144-167.

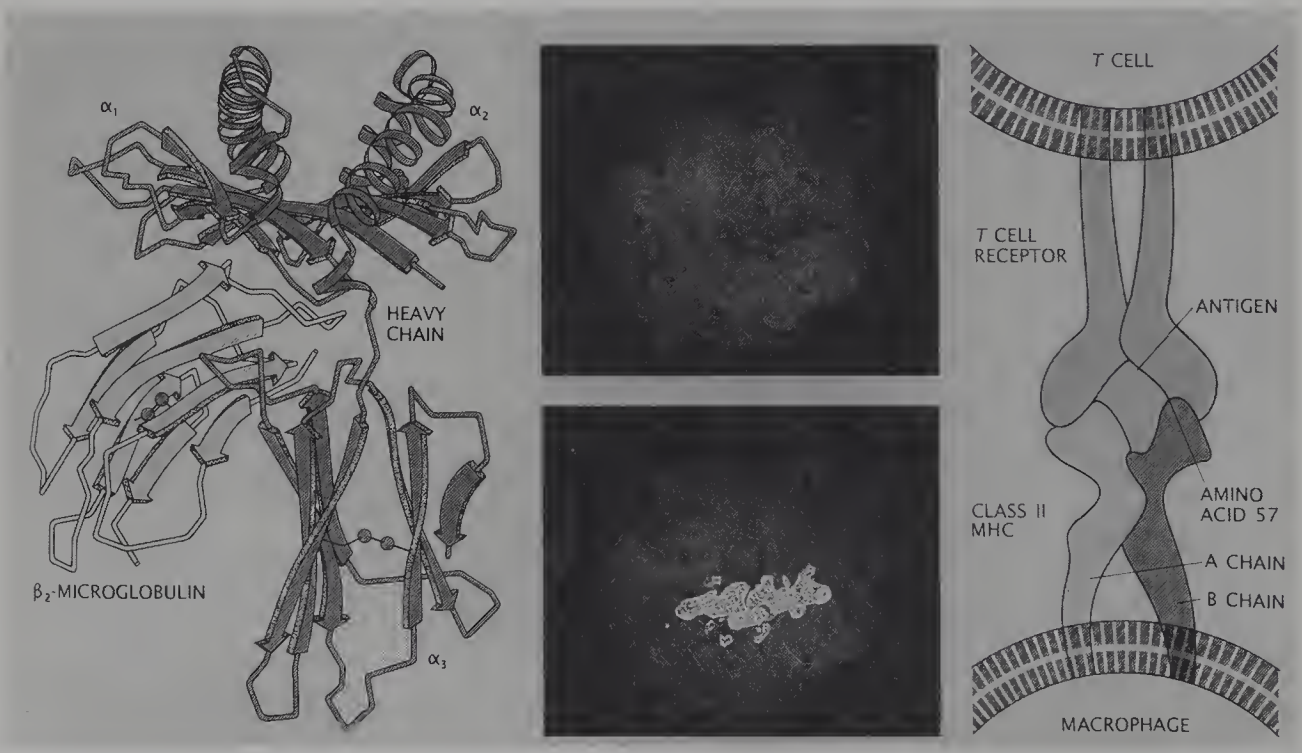


Figure 8.2. *Left,* in this panel is shown a class I molecule. It consists of a heavy chain (*blue* in color figure, see page) and a small reversibly bound polypeptide, β_2-microglobulin (*yellow* in color figure, see page). The first two domains of the α chain (*top*) form a cleft to bind antigen. *Center,* in the *top of this panel,* the empty cleft is viewed from above; the *center bottom photograph.* shows the cleft occupied by antigen (*pink* in the color figure, see page). *Right,* class II molecules on macrophages present antigens to helper T cells. The 57th amino acid on the a chain (*blue* in color figure, see page) is thought to lie on the surface of the class II binding cleft. With permission from Atkinson MA, Maclaren NK. What causes diabetes? Scientific American 1990;263:62-71.

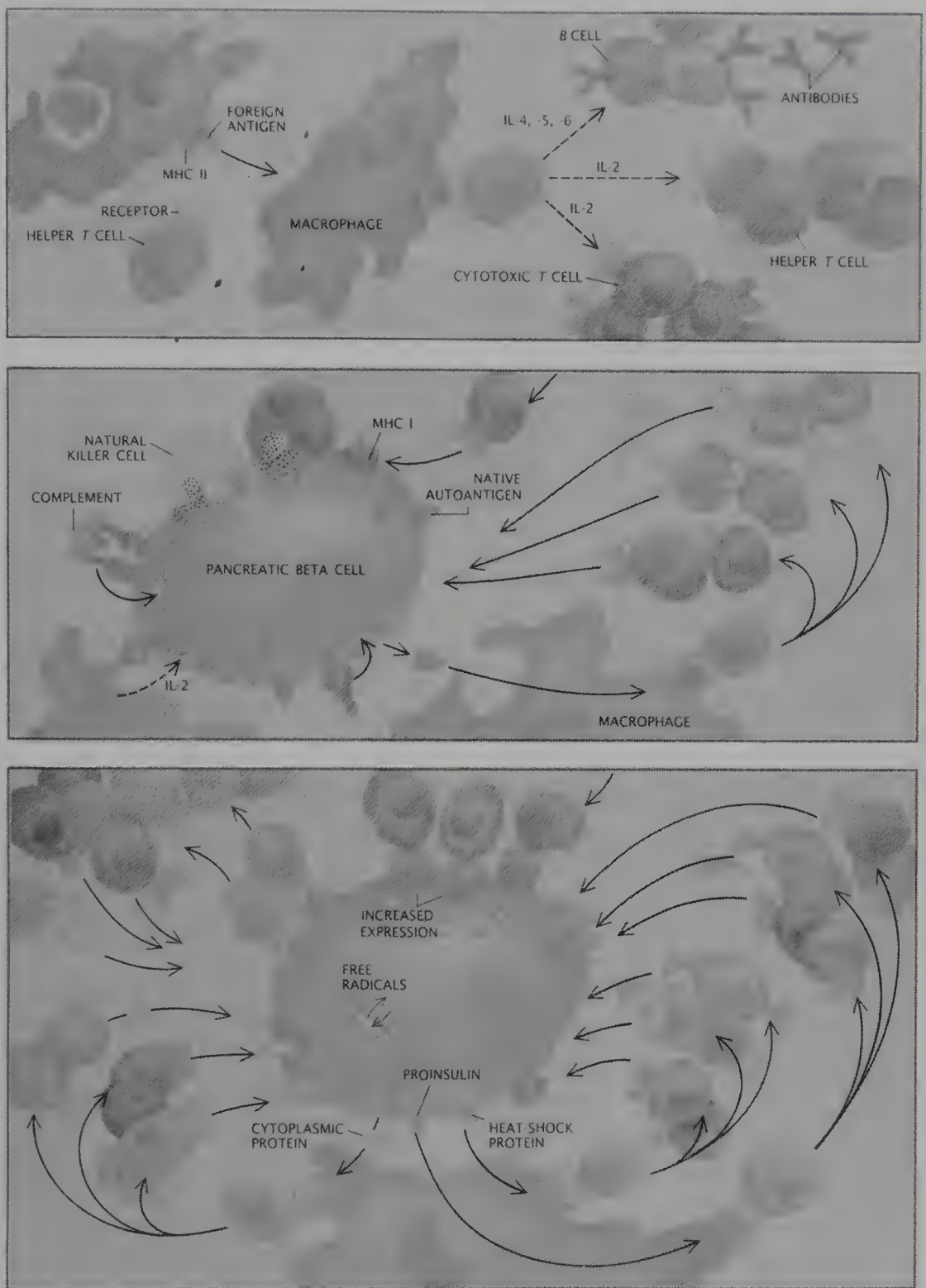


Figure 8.3. *Top,* the initiating event is a vigorous immune response against a foreign antigen (*green* in color figure, see page) that closely resembles a normal component of β cells. Macrophages ingest an invader somewhere in the body and present the mimic antigen (in tight association with a class II MHC molecule) to helper T cells (*violet* in color figure, see page). The helper T cells, in turn, secrete peptides (interleukins) that promote activity by other helper cells and antibody producing β-cells and cytotoxic T cells (*blue* in color figure, see page). *Center,* in the pancreas, the sensitized cytotoxic T cells (*blue* in color figure, see page) easily recognize the natural "twin" (*red* in color figure, see page) of the foreign antigen, actually an "autoantigen" on β cells wherever the twin is bound by class I MHC molecules, which are ubiquitous. Antibodies bind the β cells as well and, thus, impair them directly or by eliciting help from other components of the immune systems, such as the toxic proteins that are collectively known as complement (*chartreuse* in color figure, see page). Macrophages become involved and stimulate helper T cells to amplify the cell-mediated

Table 8.1.
Heterogeneity Within IDDM: DR3 Compared With DR4[a]

Characteristic	DR3	DR4
Production of insulin antibodies	Low or absent	High response
Islet cell antibodies	Persistent	Disappear shortly after diagnosis
Antipancreatic cell-mediated immunity	Increased	Not increased
Thyroid and other autoimune endocrine diseases	Frequent	Less frequent
Onset	Any age	Young age
Seasonal variation in onset	None	Yes
Residual β-cell function, short-term after diagnosis	High	No
Can present as NIDDM	Yes	Less frequent
Association with proliferative retinopathy	Not increased	? Increased
Gene preferentially transmitted by mothers	Yes	No

[a]Table adapted from Rotter and Rimoin (31) and published with permission.

been possible to observe two subsets of patients who have different clinical characteristics. Rotter and Rimoin have compared individuals with HLA phenotypes DR3 and DR4 (Table 8.1).

In pregnant IDDM, the above chain of events that led to insulin-dependent diabetes has almost always long since passed. These women now have a lifelong metabolic disorder that requires daily replacement of the hormone insulin that they are unable to synthesize in adequate amounts to maintain normal blood glucose concentrations.

Many IDDM women do become pregnant, frequently after a prolonged period of poor control. They often experience a gap in medical care when they emerge from pediatric settings but delay the selection of a new family physician or internist. Their care tends to be less closely supervised when they become independent from their families and bored or impatient with living with a chronic lifelong disease. Although most IDDM develop the disease as children, adolescents, or young adults, the onset of the disorder is also recognized in middle-aged or older adults.

In IDDM patients who are in fair or good control at conception, the first sign of pregnancy is often the sudden development of ketonuria without apparent reason. Diabetic control tends to become erratic, often punctuated by episodes of hypoglycemia followed by rebound hyperglycemia. In addition, even mild nausea and vomiting associated with changes in food intake and activity produce marked changes in the requirement for insulin. During the first weeks of gestation, insulin doses often have to be decreased or changes

destruction. *Bottom,* further attack follows as the β cells become more and more damaged. The cells overproduce class I MHC molecules (thus promoting more activity by cytotoxic T cells). They also display class II molecules. Such display by cells not a part of the immune system should induce the system to suppress autoimmunity but in prediabetics the opposite occurs; the display stimulates more helper T-cell activity. As the β cells become ever more damaged, substances normally sequestered within them, such as proinsulin, begin to appear at the surface of the cell. They arouse new waves of attack that in the end overcome the β cells. With permission from Atkinson MA, Maclaren NK. What causes diabetes? Scientific American 1990;263:62-71.

must be made in the time of administration. Dietary alterations are necessary and have to be carefully individualized.

RISKS FOR WOMEN WITH IDDM

Women with IDDM usually request prenatal care shortly after conception or during the first 8–12 weeks of gestation because they frequently develop symptomatic hypoglycemia and/or ketonuria. This change in their customary diabetic control is unpleasant and confusing. Ideally, educational emphasis in the future will focus on preconception counseling and access to prenatal care by 10–30 days' gestation for all diabetic women in the reproductive age group. At present, this approach is undergoing clinical trials in specially designated National Institutes of Health-supported perinatal centers to test the effect of early diabetic control on the outcome of pregnancy.

In many hospitals, special preconception and diabetic perinatal centers are not yet available. Economical and cost-effective ambulatory programs need to be devised to ensure standard high quality care in different clinical settings. On most obstetric services or in private offices, many IDDM patients have not contacted an obstetrician until at least 6–8 weeks' gestation.

An occasional IDDM woman presents to the obstetrician in excellent control and with experience and training in the use of multiple daily insulin injections or a subcutaneous pump for constant insulin infusion. She may have noted a modest decrease in insulin requirement or experienced hypoglycemia a week or two after conception. If the pregnancy was planned, the patient might already have anticipated some increase in lability of blood glucose values, changes in food intake, and insulin requirements. In these carefully supervised patients, medical and obstetric care can be coordinated easily throughout gestation by the combined efforts of the diabetes center and the obstetrician. It is anticipated that this approach will decrease maternal risk for hypoglycemia or spontaneous abortion during 1st trimester.

In contrast, many IDDM patients have already experienced repeated and often severe episodes of hypoglycemia and frequent ketonuria before they are first seen for prenatal care. Their diabetes may be in only fair or poor control, even when they have a monitor to measure blood glucose levels at home. Although some women test their blood glucose levels three to four times daily, many are less consistent on a long-term basis. The obstetrician should assess overall control on the first visit by a careful history and physical examination and an HbA1c determination. In patients who are in poor control (elevated HbA1c concentration), there is an increased likelihood of spontaneous abortion. Vaginal bleeding or spotting is an ominous sign and sonographic examinations are helpful in the assessment of early fetal development and viability. All patients should begin a well-supervised program for diabetic pregnancy as soon as possible (see Sections IV–XIII).

Control of Plasma Glucose Levels Around the 24-H Clock

The first 7–8 weeks of gestation are critical, because it is during this period that the embryologic development of all major organs occurs (see Section I). There is insufficient clinical information available to know whether prompt, intensive establishment of good metabolic control by hospitalization and the use of either an artificial pancreas (Biostator) or constant intravenous insulin infusion would actually decrease the likelihood of fetal loss or teratogenesis. If the pregnancy has progressed beyond 8 weeks and the patient has had previous education concerning diabetes and the use of a blood glucose monitor, good control should be feasible on an outpatient basis. This option requires frequent communication between the patient, physician, dietitian, and nurse clinician. However, embryogenesis is already complete and even excellent control beyond this point will not prevent malformations.

The most difficult pregnant IDDM women are those in whom there has been no regular diabetic care before conception and nothing is remembered about previous education during childhood and adolescence. These women characteristically request an appointment after 8 weeks' gestation and are invariably in poor control with a much higher risk for poor outcome for the pregnancy. An immediate 5- to 7-day hospitalization should be recommended for careful re-education and achievement of good

metabolic control. This therapeutic and preventive medicine approach helps establish good patient rapport with the diabetic care team and reduces the need for frequent hospitalizations throughout pregnancy.

Figure 8.4 shows a 24-h plasma glucose profile of a 25-year-old woman who had IDDM since age 13. Her chief complaint was episodes of hypoglycemia on her usual insulin dose of 50 U of intermediate-acting (NPH) insulin and 10 U of rapid-acting (regular) insulin in the morning and 5 U of NPH insulin and 5 U of regular insulin before dinner. A 2-h postprandial plasma glucose value at the first prenatal clinic visit was 264 mg/dl (14.6 mmol/L). During the 1st day of hospitalization, she received her customary prepregnancy dose of insulin. On this regimen, marked excursions of plasma glucose levels were documented. The mean 24-h plasma glucose level was 104 mg/dl (5.7 mmol/L) (mean for normal pregnant women, 76 mg/dl ± 3 SD mg/dl; 4.2 mmol/L ± 0.16 SD mmol/L). The HbA1c concentration was 9.5%. During the 24-h study, it was also apparent that, with this treatment regimen, there was a prolonged duration of insulin effect from her large morning dose of intermediate-acting insulin. This information permitted adjustment of her overall daily dose of insulin from 70 to 56 U for 24 h and a redistribution of the proportion of intermediate and short-acting insulin (AM: 30 U NPH, 18 U regular; PM: 4 U NPH, 4 U regular). During the 7-day hospitalization, the patient was instructed in a proper diet for pregnancy and the use of a glucose monitor for determinations of blood glucose values at home.

Although hospitalization of women with IDDM in poor control early in pregnancy may seem costly, it can be justified for the following reasons: *(a)* the physician has an immediate understanding of the patient's diabetic control and problems; *(b)* the patient learns a great deal about the management of her diabetes; and *(c)* an early and excellent doctor-patient relationship develops that makes the subsequent course of the pregnancy far easier and less stressful. In addition, this early and comprehensive evaluation permits an assessment of retinopathy, nephropathy, neuropathy, plasma lipids, and cardiovascular status if this has not been accomplished in the preconception period.

A 24-h profile of blood glucose levels is in-

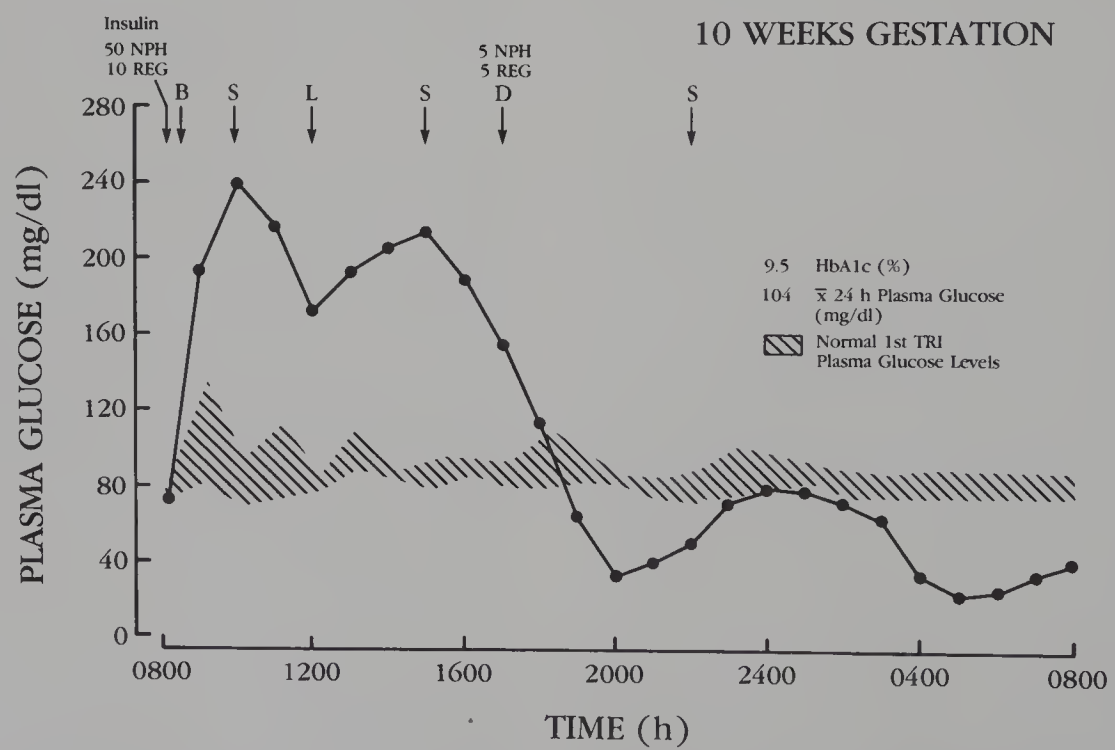


Figure 8.4. Hourly plasma glucose values in an IDDM patient at 10 weeks' gestation with severe episodes of nocturnal hypoglycemia. Noted marked excursion of plasma glucose values with a mean 24-hour glucose value of only 104 mg/dl (5.7 mmol/L) and moderately elevated HbA1c concentration of 9.5%. *Hatched lines* show plasma glucose values in six normal women ± SD during 1st trimester. ↓ indicates meals (*B, S, L, and D:* breakfast, snack, lunch, and dinner).

valuable. In a community hospital, this can easily be accomplished with a glucose meter at the bedside. It is worthwhile to plot the results on a graph because the diurnal excursion is more easily appreciated than by scanning a row of figures.

IDDM Pregnancies with Severe Complications

Actually, most IDDM pregnancies go quite well. Perinatologists and medical diabetologists have become quite skillful at replacement insulin therapy, adapted for each individual pregnant woman, taking into account the metabolic alterations of gestation. Management of IDDM pregnancies requires a great deal of time and each patient should have a designated primary physician (perinatologist and/or diabetologist) who can make and assume responsibility for therapeutic decisions.

The "team approach" in ambulatory clinics varies in different settings, but works best when it is in place in a single clinic location to eliminate extra medical visits and costs for the patient; it also facilitates rapid and meaningful communication among physicians.

For IDDM pregnancies, we have available in hospitals caring for high-risk pregnancies a "margin of safety" that was not possible before the last decade. This includes the assumption of greater responsibility on the part of each patient (discussed more extensively in Section 5), modern technology in ultrasonography, perinatal monitoring procedures, judicious handling of the timing and mode of delivery, and sophisticated neonatal care.

The key coordinating team member for a diabetes in pregnancy clinic is a specially trained, experienced, seasoned, nonjudgmental diabetes nurse-clinician and patient educator. This individual, more than any other, makes all the difference in the ambience, warmth, and excellence of diabetes care during complicated pregnancies. This is a full-time job in those hospitals that have more than an occasional diabetic patient. The nurse-clinician also provides invaluable assistance with scheduling timely appointments for blood tests, evaluation of renal function, ultrasonographic examinations, and consultations with renal, cardiac, and ophthalmologic specialists. Finally, the nurse-clinician coordinates inpatient and outpatient care when hospitalizations are necessary. Additional support personnel include a dietitian who is well versed in diabetes, diabetic pregnancies, and the marked variability in different racial and ethnic diets. Social problems can easily become overwhelming for young parents and families. An expert in social services is needed to achieve early access to and funding for prenatal care as well as assistance with interpersonal and economic problems.

Some women with IDDM arrive in our clinics with severe microvascular complications; they may be already pregnant and determined to have a baby. These are our most trying pregnancies and the case that follows is from our own clinic.

Patient S.B.

Ms. S.B. developed IDDM acutely at 10 years of age. Her treatment during adolescence had been erratic and, at age 19, she had a 1st trimester spontaneous abortion. At age 21, she was hospitalized elsewhere with diabetic ketoacidosis. She first presented to the University of California San Diego (USCD) Medical Center in 1985 at 7 weeks' gestation in good diabetic control with a HbA1 concentration of 7.2% (NL for 1985 method: 5-8%), but with pyelonephritis, double ureters, and far advanced diabetic retinopathy. Her renal problems were discovered at age 16 when she had had IDDM for only 6 years. These problems most likely stemmed from repeated urinary tract infections associated with her genitourinary malformation rather than from diabetes. The details of her clinical and obstetric data are shown on Table 8.2. The prenatal course was stormy and subsequently complicated by preeclampsia that necessitated delivery of a preterm infant by cesarean section.

After delivery, S.B. married the father of the baby and was followed at regular intervals by the UCSD Diabetes Center. In 1987, she called to say she was several weeks pregnant and would like early postconception counseling. Extensive sessions were held over several days and many hours with a perinatologist who had a special interest and vast experience in diabetic pregnancies, as well as with a diabetologist and the chief of the nephrology division. They all explained their most frank views of the high likelihood for the development of maternal and fetal complications. The patient decided upon and arranged for an abortion.

Table 8.2.
Clinical Data in IDDM Patient, S.B., During Two Pregnancies[a]

	1985 (Pregnancy 2)		1987 (Pregnancy 3)		
Variable	First Prenatal visit (wk) 7	Delivery (wk) 34	First Prenatal Visit (wk) 10	Delivery (wk) 38	1990
Age (yr)	26	27	28	29	31
Marital status	S	S	M	M	M
Insulin U/day	30	34	36	50	26
Wt (kg)	142 (65)	169 (77) (General edema)	147 (67)	160 (73)	134 (61)
Retinopathy	Bilateral proliferative retinopathy OD: 150% panretinal coag peripheral cryopexy attenuated retinovitreal neovascularization OS: cataract blind	Hypertensive and diabetic retinopathy OD: transient exudative retinal detachment OS: blind	OD: stable proliferative retinopathy OS: blind	OD: no change OS: blind	OD: stable OS: prosthesis
HCT	28.2	18.0	24.3	29.4	33.7
HbA1c	7.2	5.4	5.3	6.3	7.2
BUN/CR	23/.85	32/1.6	19/1.4	26/1.7	/1.2
Creat cl (ml/min)	94	40	63	55	75
24-h Ur Prot (g)	2.8	5.0	0.46	3.1	0.4

BP	108/62	150/90	116/72 (12 wk)	160/90 (37 wk)	102/60
Pregnancy complications	Preeclampsia Pyelonephritis (double ureters) Neuropathy Anemia		Anemia mild preeclampsia at 38 weeks' gestation		Tubal ligation
Gestational age (wk)	Baby girl 34 (C/S)		Baby girl 38 (C/S) 450		
Placenta (g)	300 with abruption and infarct		Normal		
Wt (g)	2140		2890		
L (cm)	46		48.5		
HC (cm)	32		33.5		
Apgar (1 min/5 min)	6/9		9/9		
Neonatal complications	Premature, respirator distress syndrome Hypoglycemia Hypocalcemia Hyperbilirubinemia		Hypoglycemia Hyperbilirubinemia		
Status of child at age	5 yr: normal		3 yr: normal		

[a]Abbreviations: HCT, hematocrit; BUN/CR, blood urea nitrogen/creatinine; Creat cl, creatinine clearance; Ur Prot, urine protein; BP blood pressure; HC, head circumference; OD, right eye; OS, left eye; C/S, cesarean section.

On the morning of the scheduled abortion, Mrs. S.B. called and said she was simply unable to go through with the procedure; she asked if we all could take care of her again? Her second pregnancy was most instructive. She was placed on macrodantin to prevent or suppress urinary tract infections and followed weekly in the Diabetes in Pregnancy Clinic. No retinal, renal, or neuropathic problems were encountered and her relaxed, cooperative demeanor made control of her diabetes quite easy. At 38 weeks' gestation, she experienced mild preeclampsia with hypertension, proteinuria, and a further increase in her serum creatinine level with a decrease in creatinine clearance to 55 ml/minute. These late complications at term prompted a cesarean section delivery of an appropriate for gestational age infant girl. Both children are fine at 3 and 5 years of age. Mrs. S.B. has had a tubal ligation. Figure 8.5 is a picture of this young family shortly after the birth of the second child. All are well in 1990 and S.B.'s diabetes and microvascular complications are stable.

The above case is not atypical. Adolescent diabetic women can and do mature into stable adults. Nonetheless, their pregnancies often try the ingenuity, patience, and fortitude of the staff of an obstetric diabetes clinic.

EARLY GESTATION AND NIDDM

Since 90% of women with diabetes have NIDDM, it is not surprising that many conceive and represent a large number of pregnancies complicated by carbohydrate intolerance.

Although women from middle and upper income groups with NIDDM may present early for prenatal care, this is unusual in patients with a low income who lack easy access to the health care system. Even for patients with Medicaid coverage or those in health care programs for indigent people, prenatal care for high-risk pregnancies is inordinately delayed. Because these women do not experience 1st trimester hypoglycemia or other symptoms re-

Figure 8.5. Photograph of IDDM patient, S.B., her husband, and two children shortly after delivery of the second baby.

lated to diabetes, they frequently do not come to medical attention before late 2nd trimester. On first evaluation, it is not uncommon to find a random plasma glucose level of >200 mg/dl (11 mmol/L) and a HbA1c concentration of >10%.

In patients with NIDDM, the fetus may have an abnormal intrauterine metabolic environment for a long period of time. The postnatal implications of a disturbed nutritional environment in utero are unknown. Figure 9.4 shows a 24-h plasma glucose profile of a 36-year-old woman with NIDDM who was receiving no insulin on entry into the diabetic prenatal program at 27 weeks' gestation. The mean 24-h plasma glucose value was 178 mg/dl (9.8 mmol/L) and the 24-h urinary loss of glucose was 50 g. The HbA1c concentration was 12.5%. At the first prenatal examination, polyhydramnios and fetal macrosomia were noted. Despite hospitalization and markedly improved control of diatebes (Fig. 9.4), onset of labor occurred at 34 weeks' gestation with subsequent delivery of a macrosomic, polycythemic infant with respiratory distress syndrome. In this pregnancy, the late establishment of good control of diabetes did not prevent complications for the mother or infant.

Improvement in the early control and management of this large group of pregnant diabetic women who are non-insulin-dependent when not pregnant (but require insulin when pregnant) will be accomplished best by patient and physician education. The concept of preconception counseling will be especially valuable for these individuals.

CHAPTER

9

Non-Insulin-Dependent Diabetes (NIDDM, Type II)

Pregnant women with NIDDM are not rare. In the United States, 90% of diabetics have this form of diabetes. Harris (8) estimates that the number of NIDDM women of childbearing age may be at least one million (Fig. 3.1). Table 9.1 describes the clinical features that differentiate NIDDM from IDDM. In our own clinic and in those cities and communities with large Mexican-American, Asian, Pacific Island, or American Indian populations, these women compose the majority of pregnant diabetic individuals (24). Figure 9.1 shows the ethnic composition of the Diabetes in Pregnancy Clinic at the University of California San Diego during a representative 2-year period. All pregnant women with NIDDM require insulin, but none are insulin dependent or prone to ketosis. To achieve and maintain normoglycemia, they require two to four insulin injections each day. Oral hypoglycemic agents are contraindicated in NIDDM pregnancies because of increased risk of teratogenesis (25).

PATHOGENESIS OF NIDDM

In pregnant and nonpregnant women, NIDDM is genetically, pathologically, and physiologically quite distinct from IDDM. In NIDDM, islet cell dysfunction and insulin resistance are both present but their relationship is unknown (26). Harris has presented a comprehensive overview of the prevalence, characteristics, morbidity, mortality, and risk factors for NIDDM in blacks and whites in the United States (27). Among Pima Indians in Arizona, more than 50% of the population has NIDDM. Extensive and ongoing population and metabolic studies in these native Americans have provided additional insights into the pathogenesis of NIDDM. Bogardus and colleagues (28) have reported preliminary data suggesting that, in the Pima, insulin resistance in muscle, aggravated by obesity, appears to be familial and possibly genetically determined. The degree of insulin resistance is proportional to the degree of glycemia among nondiabetics. However, in diabetics with a fasting blood glucose of approximately 300 mg/dl (17 mmol/L) or higher there is no greater insulin resistance than in those with fasting blood glucose values of approximately 150 mg/dl (8.3 mmol/L). These investigators postulate that mild hyperglycemia results from muscle insulin resistance; further increases in hyperglycemia are a result of decreasing insulin secretion resulting from effects on the pancreas of chronic insulin resistance mediated by mild chronic hyperglycemia. Pima Indians are commonly obese, have diabetes during pregnancy 40 times more frequently than reported by O'Sullivan and others (29, 30), and have a high incidence of subsequent maternal diabetes and obese children with early onset NIDDM.

There are a number of genetic abnormalities that can result in an interference with the action of insulin. Figure 9.2 (31) is a schematic description of defects in various points of insulin action. No single gene has been identified with this disorder but, in family studies, empiric risk figures for first degree relatives of individuals with NIDDM show increased clustering with a 38% incidence of affected siblings. The presence of diabetes or impairment of glucose tolerance was reported in one third of offspring (32).

The possible provocative role of greater availability of food with acquired obesity in genetically susceptible individuals appears to

Table 9.1.
Clinical Characteristics That Differentiate Non-Insulin-Dependent Diabetes (NIDDM) from Insulin-Dependent (IDDM) Diabetes Mellitus[a]

Characteristics	NIDDM	IDDM
Obesity at onset	Common, often of central or masculine type	Uncommon
Metabolic ketoacidosis	Ketosis less likely	Prone to ketosis
Age	Predominantly older (>30 yr)	Predominantly young (<30 yr)
Seasonal trend	None	Fall and winter
Insulin levels	Variable	Low to absent
Appearance of symptoms	Variable, usually slow	Acute or subacute
Inflammatory cells in islets	Absent	Present initially
Treatment	Diet control or oral hypoglycemics may be sufficient, although insulin may be required to control hyperglycemia	Insulin is required for life
Family history of diabetes	Common with increased prevalence of NIDDM	Uncommon, but increased prevalence of IDDM
Twin studies	Close to 100% concordance in monozygotic twins	20–50% concordance in monozygotic twins
Association with other autoimmune endocrine diseases and antibodies	No	Yes
Islet cell antibodies	No	Yes
HLA associations	No	Yes
Further subtypes	Maturity Onset Diabetes of the Young, mutant insulins	DR3, DR4 associated

[a]Both types may present initially during pregnancy as gestational carbohydrate intolerance.

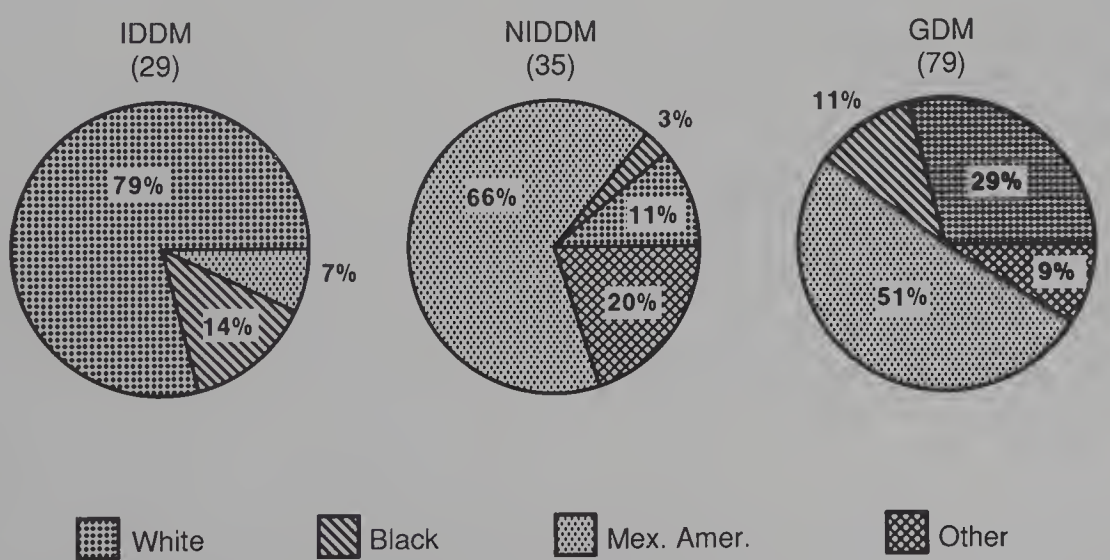


Figure 9.1. Ethnic distribution of 143 diabetic women at the University of California San Diego Diabetes in Pregnancy Clinic from July 1, 1986 to April 1, 1988. Most women (55%) have gestational diabetes and more than half are Mexican-American. The category "Other" includes Asians, Pacific Islanders, Philippinos, and American Indians. Note the predominance of insulin-dependent diabetes (IDDM) in whites. In contrast, the majority of women who have non-insulin-dependent diabetes (NIDDM) or gestational diabetes (GDM) are Mexican-American.

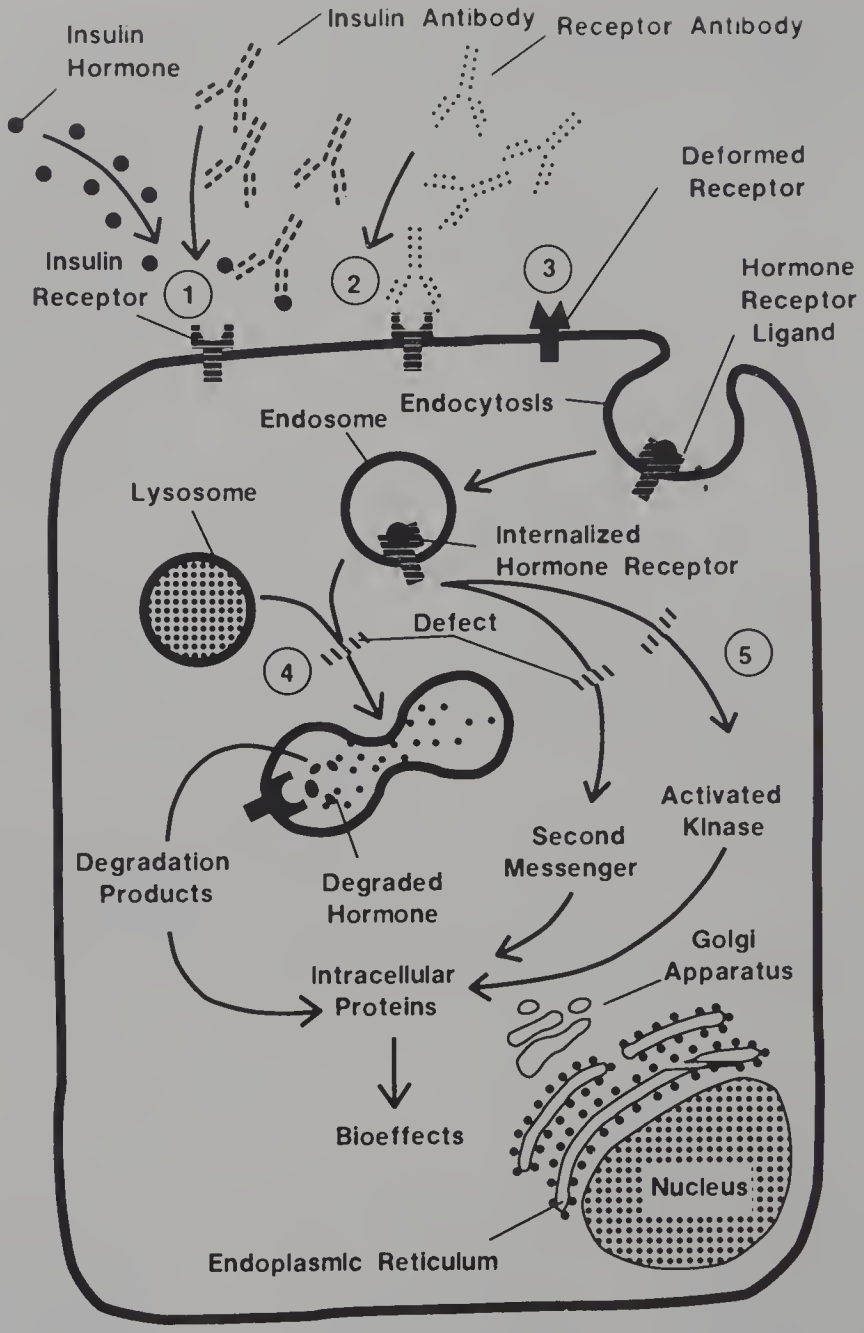


Figure 9.2. Genetic heterogeneity of NIDDM almost certainly implies physiologic heterogeneity though thus far it has proved impossible to associate most known genetic defects with specific physiologic mechanisms. Abnormalities may involve the insulin molecule (aberrant insulin syndrome), formation of antibodies to insulin *(1)*, to insulin receptors on the cell surface *(2)*, or abnormalities of the receptor *(3)*. Within the cell, abnormal postreceptor action may block the intracellular degradation of insulin or one or more processes by which the insulin-receptor complex modulates activities of the cell *(4, 5)*. With permission from Rotter JI, Rimoin DL. The genetics of diabetes. Medical genetics XVIII. Hosp Pract 1987; May:79-88.

be an important association with the expression of NIDDM in all populations studied.

Two excellent recent books review current knowledge of the biochemistry, physiology, and molecular events that regulate synthesis, release, and action of insulin (33, 34). The basic controversy of the relative importance of insulin secretion or insulin resistance as the primary factor in the pathogenesis of NIDDM remains unresolved. This heterogeneous type of diabetes, which occurs in both obese and lean individuals, represents a prime example of the importance of the future need to translate research in molecular biology to the practice of common medical problems, such as diabetes.

Heterogeneity of NIDDM

Pregnant women with NIDDM are also heterogeneous and are separated easily into two main subsets—lean and obese. In both subsets, the diagnosis has often not been made before conception, but there may be a previous history antedating pregnancy of impaired or "borderline" glucose tolerance that was treated with diet, oral hypoglycemic agents, or insulin. Lean NIDDM women characteristically have low-normal levels of circulating insulin and C-peptide around the 24-h clock with an inadequate response to meal stimulation. In contrast, and not always predictable by the body mass index (BMI), obese NIDDM may have low-normal, high-normal, or quite elevated levels of insulin and C-peptide. Their most common pattern is characterized by fasting hyperinsulinemia, a delayed stimulation response following meals and marked hyperinsulinemia with a peak 2 h later. Calculation of insulin area under a 2-h curve during a MTT shows a higher integrated insulin unit value than that of normal pregnant women.

Many NIDDM women, who are well controlled on diet alone, small doses of oral hypoglycemic agents, or total insulin doses of 25 or less units per day often require a striking increase in insulin dose during pregnancy to maintain normal glucose values. In some women, 50-100 U or even 200 U of insulin per day are necessary, given in divided doses. This change is usually interpreted as due to an exaggerated resistance to insulin, compared with their status when not pregnant.

Some very obese NIDDM women exhibit such marked insulin resistance that >200 U of insulin per day are necessary for diabetic control. We have studied one extreme case reported in detail elsewhere (35) of a woman who was treated with a constant subcutaneous insulin infusion (CSII) (Fig. 9.3).

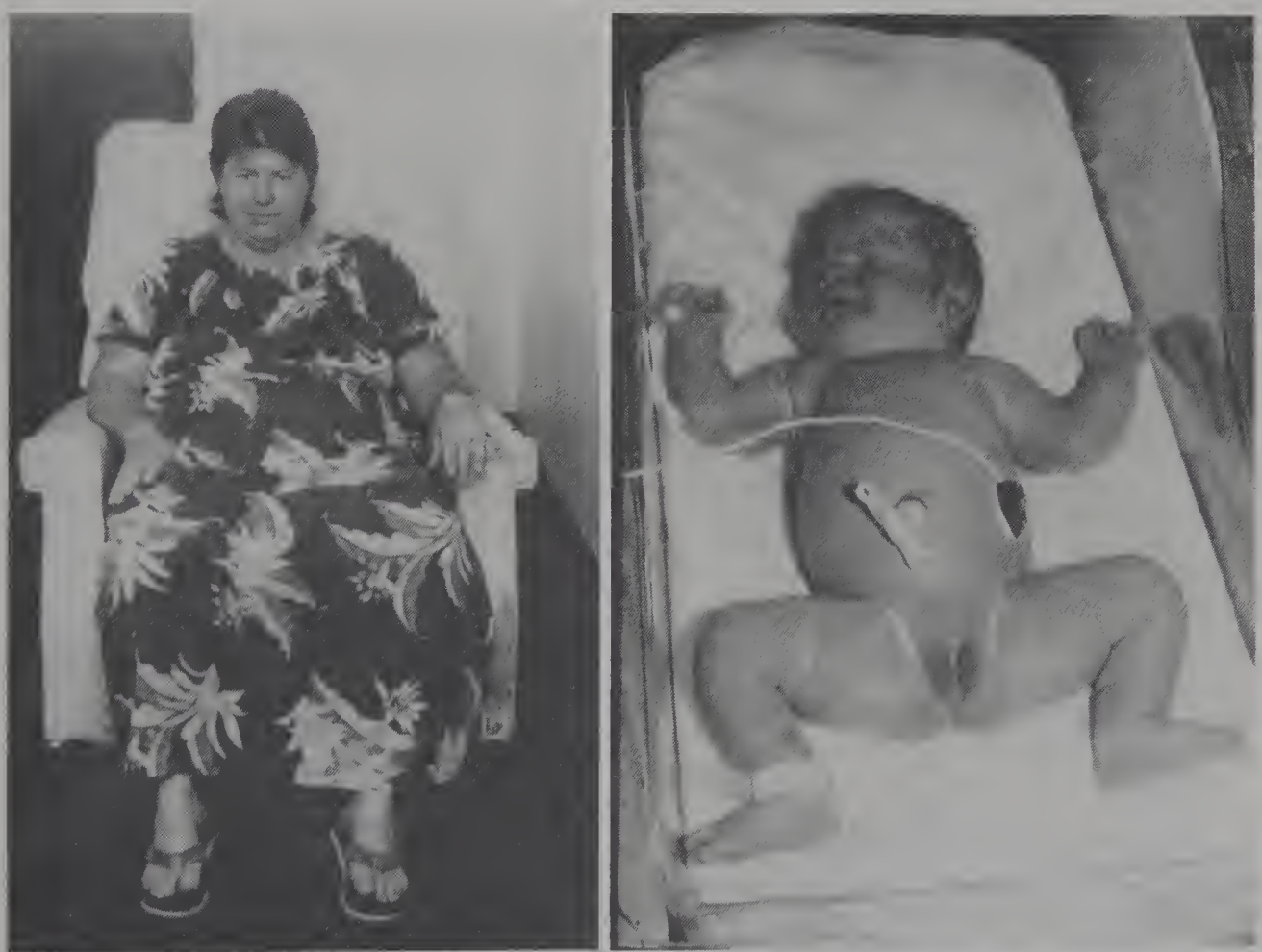


Figure 9.3. *Left,* patient S.A. with NIDDM and severe insulin resistance at 24 weeks' gestation. She was treated with continuous subcutaneous infusion of insulin (CSII) and was euglycemic from 29 weeks' gestation until delivery at term. *Right,* infant of patient S.A. born at 38.5 weeks' gestation (birth weight of 4530 g), with marked truncal obesity, severe hypoglycemia, hyperbilirubinemia, and polycythemia necessitating a partial exchange transfusion.

Patient S.A.

Mrs. S.A. was a 33-year-old, 260-lb (118-kg) white woman with NIDDM. In a previous pregnancy, she had gestational diabetes (reversible postpartum) and delivered a 4570-g infant girl. Two years later, she developed NIDDM and was treated with chlorpropamide twice daily; this was continued through the first few weeks of the current pregnancy. Between pregnancies, she had two spontaneous 1st trimester abortions and a fetal death at 25 weeks' gestation.

The patient was sent to UCSD Medical Center at 20 weeks' gestation because of difficulty in establishing glycemic control with an insulin dose of 150 U/day. Her insulin dose was increased progressively to 250 U/day and her dietary intake was reduced to 1800 kcal/day. Plasma glucose levels remained elevated around the clock (mean 24-h ± SD glucose

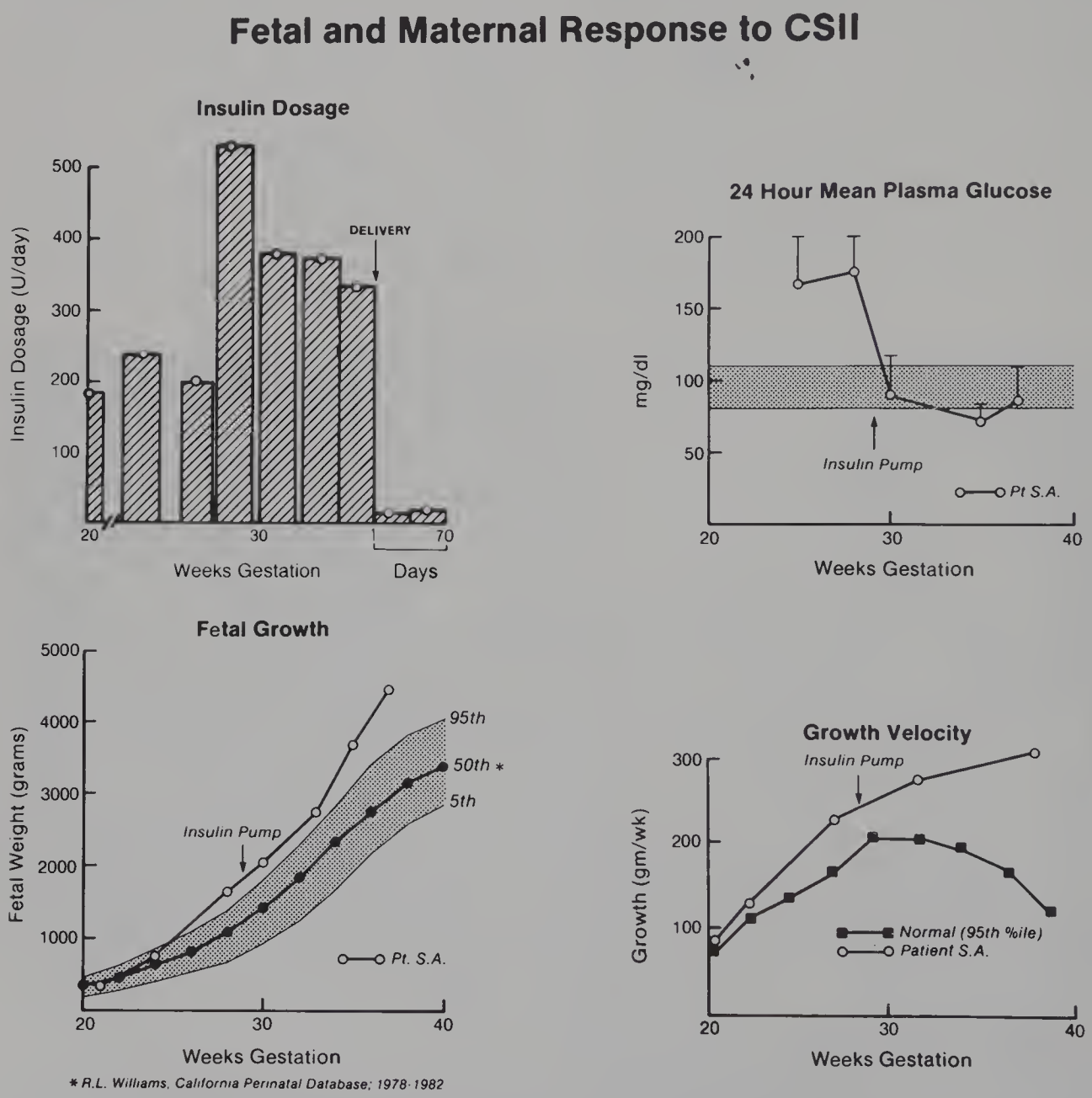


Figure 9.4. *Top left,* insulin doses per 24 h in patient S.A. Continuous subcutaneous insulin infusion (CSII) was initiated at 29 weeks' gestation and continued until term delivery. Note prompt decrease in insulin requirement immediately postpartum. *Top right,* Excellent and rapid control of maternal hyperglycemia by CSII from 29 weeks to term. *Lower left,* fetal weight estimates by ultrasonography. An already macrosomic fetus had accelerated growth and growth velocity *(lower right)* during CSII despite reduced maternal dietary intake to 1800 kcal/day. Total maternal weight gain was only 19 lb (3.6 kg).

value of 168 ± 37 mg/dl [9.3 ± 2.0 mmol/L]; normal 84 ± 2 SD 10 mg/dl [4.6 ± 2 SD 0.5 mmol/L]. Because of failure to achieve acceptable control, a rising HbA1c concentration of from 8.7% to 10.5%, macrosomia, and hydramnios, continuous subcutaneous infusion of insulin (CSII) was initiated. Euglycemia was established in 2 days with a total insulin dose of 500 U in 24 h. She remained on this treatment until cesarean section delivery at 38.5 weeks. Fetal growth actually accelerated in utero despite maternal normoglycemia. The placenta was huge, 870 g (normal 526 ± 38 g), but normal on histological examination. The baby girl (Fig. 9.3) was obese and had hypoglycemia, hyperbilirubinemia, and polycythemia. Maternal insulin dose at delivery was 333 U/day; on day 1 postpartum, she required only 13 U of regular insulin in divided doses given subcutaneously. Figure 9.4 shows maternal mean 24-h glucose levels and fetal growth during CSII. We concluded that: *(a)* already established fetal macrosomia at 29 weeks' gestation is not reversible even with long-term (2 months) maternal euglycemia before term birth; and *(b)* pregnancy-related factors, probably placental, were associated with extreme insulin resistance in this patient with immediate reversal postpartum.

CHAPTER

10

Emotional Support and Summary

EMOTONAL SUPPORT

Because early pregnancy is often associated with emotional as well as metabolic lability, weekly prenatal visits are recommended for women with diabetes. Patients with IDDM should not be requested to be fasting for hospital visits because they are at risk for recognized or unrecognized hypoglycemia. Blood glucose levels can be checked 2 h after breakfast and other values assessed from the patient's records during home monitoring. Arrangements for 24-h telephone communication with the physician and/or nurse-clinician should be made at the first clinic visit.

During this early period, it is helpful to meet with both the husband and wife or other family members. Patients should develop an early feeling of security; their fears can be discussed reasonably and realistic plans can be made for the management of the pregnancy, labor, and delivery. These points are emphasized because it is impossible to establish good diabetic control in a frightened, distraught patient who does not understand her complicated pregnancy and is emotionally unable to help with her metabolic problem.

The concept of a perinatal team for diabetic pregnancies is invaluable because it permits different kinds and levels of support from physicians, specially trained nurses, dietitians, and social workers.

SUMMARY

In this section, pregnancies have been described in women with different types of diabetes. IDDM is an autoimmune genetic disease with β-cell destruction and a hormonal deficiency (insulin). NIDDM is characterized as a disorder of insulin resistance and abnormal pancreatic β-cell function. A distinction is made between lean and obese NIDDM women. Gestational diabetes (GDM) emerges as a heterogeneous syndrome that is defined, detected, described, and treated differently throughout the world. It may represent the first hint, evoked by the severe metabolic stress of pregnancy, of "susceptibility" for any type or subtype of diabetes in later years. Again, lacking genetic markers, it is easiest to define these women as lean or obese, to control their hyperglycemia accordingly, and to redefine their metabolic status postpartum according to WHO criteria.

References for Section III

1. Hollingsworth DR, Moore TR. Diabetes and pregnancy. In:Creasy RK, Resnik R (eds). Maternal-fetal medicine: principles and practice, 2nd ed. Philadelphia: WB Saunders 1989: pp 925–988.
2. Hollingsworth DR, Cousins L. Diabetes in pregnancy: A new perspective. In: Milunsky A, Friedman E, Gluck L (eds). Advances in perinatal medicine. Vol 2. New York: Plenum Press 1981: pp 245–320.
3. White P. Pregnancy complicating diabetes. Am J Med 1949;7:609–616.
4. White P. Diabetes mellitus in pregnancy. Clin Perinatol 1974;1:331–347.
5. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28; 1039–1057.
6. WHO Expert Committee on Diabetes Mellitus. World Health Organization Technical Report. Series 646, 1980.
7. Diabetes Mellitus Report of a WHO Study Group. World Health Organization Technical Report. Series 727, 1985.
8. Harris M. National Institutes of Health (NIH), National Diabetes Data Group (NDDG). Figures derived from survey data. Personal Communication, August 1990.
9. Barden TP, Knowles HC Jr. Diagnosis of diabetes in pregnancy. Clin Obstet Gynecol 1981;24:3–19.
10. Harris M. Gestational diabetes may represent discovery of preexisting glucose intolerance. Diabetes Care 1988;11:402–411.
11. American Diabetes Association Second International Workshop Conference on Gestational Diabetes. Diabetes 1985;34 (suppl 2): 123–126.
12. The Diabetic Pregnancy Study Group of The European Association for the Study of Diabetes. Coordinators: Lind T, Philips PR. A prospective multicenter study to determine the influence of pregnancy upon the 75-g oral glucose tolerance test (OGTT). In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in pregnancy and the newborn. IV. London: Springer-Verlag 1989: pp 209–226.
13. Hollingsworth DR. Types of carbohydrate tolerance in pregnant women. In: Hollingsworth DR (ed). Pregnancy diabetes and birth, 1st ed. Baltimore: Williams & Wilkins 1984: pp 2–16.
14. Paris-Bockel D, Comte F, Jeanmougin P, Keller B, Schlienger JL. The breakfast tolerance test: application to the diagnosis of gestational diabetes (in French). Sem Hop Paris 1983;59:2167–2172.
15. Coustan DR, Widness JA, Carpenter MW, Rotondo L, Pratt DC. The "breakfast tolerance test." Screening for gestational diabetes with a standardized mixed nutrient meal. Am J Obstet Gynecol 1987;157:1113–1117.
16. Hollingsworth DR, Ney D, Fujimoto V, Milewski M, Murphy H. Further observations in lean and obese women with gestational diabetes during a 400 kilocalorie meal tolerance test. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in pregnancy and the newborn. IV. London: Springer-Verlag 1989: pp 245–256.
17. Vaucher Y, Hollingsworth DR. Unpublished data, 1990.
18. Campbell DM, Sutherland HW, Tuttle S. Standardized test meal in human pregnancy. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in pregnancy and the newborn. IV. London: Springer-Verlag 1989: pp 257–266.
19. Sutherland HW, Pearson DWM, Lean MEJ, Campbell DM. Breakfast tolerance test in pregnancy. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in pregnancy and the newborn. IV. London: Springer-Verlag 1989: pp 267–275.
20. Hollingsworth DR, Grundy SM. Pregnancy associated hypertriglyceridemia in normal and diabetic women: Differences in insulin dependent, non insulin dependent and gestational diabetes. Diabetes 1982;31:1092–1097.
21. Hitchcock CL, Riley WJ, Maclaren NK. Autoimmunity in insulin-dependent diabetes mellitus: Its detection and prevention. In: Cruse JM, Lewis RE (eds). Genetic basis of autommune disease. New York: Karger 1988: pp 144–167.
22. Atkinson MA, Maclaren NK. What causes diabetes? Scientific American 1990;263:62–71.
23. Todd JA, Bell JI, McDevitt HO. HLA-DQβ gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 1987;329:599–604.
24. Hollingsworth DR, Vaucher Y, Yamamoto T. Diabetic in pregnancy in Mexican-Americans. Diabetes Care 1991; (Suppl 3).
25. Piacquadio K, Hollingsworth D, Murphy H. Fetal malformations following first trimester use of oral hypoglycemic agents. Diabetes 1990. (Suppl 11A-312A) 39:123A.
26. Unger RH, Foster DW. Diabetes mellitus. In:

Wilson JD, Foster DW (eds). Williams textbook of endocrinology. Philadelphia: WB Saunders 1985: pp 1018–1080.
27. Harris M. Noninsulin-dependent diabetes mellitus in Black and White Americans. Diabet Metab Rev 1990;6:71–90.
28. Bogardus C, Lillioja S, Howard BV, Mott DM, Bennett PH. Cross-sectional and longitudinal studies of carbohydrate metabolism in Pima Indians. In: Grill V, Efendic S (eds). Pathogenesis of non-insulin dependent diabetes mellitus. New York: Raven Press 1988: pp 285–301.
29. Pettit DJ, Knowler WC, Baird HR, Bennett PH. Gestational diabetes: Infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in Pima Indians. Diabetes Care 1980;3:458–464.
30. O'Sullivan JB, Mahan CM, Charles D, Dandrow RV. Medical treatment of the gestational diabetic 1974;43:817–821.
31. Rotter JI, Rimoin DL. The genetics of diabetes. Medical genetics XVIII. Hosp Pract 1987;May: 79–88.
32. Köbberling J, Tillil H. Empirical risk figures for first degree relatives of non-insulin dependent diabetics. In: The genetics of diabetes mellitus. Proceedings of the Serono Symposia. London: Academic Press 1982:47: p 201.
33. Grill V, Efendic S (eds). Pathogenesis of non-insulin dependent diabetes mellitus. New York: Raven Press, 1988.
34. Leary JL, Weir GC. Non-insulin-dependent diabetes mellitus: Current concepts and pathogenesis. In: Draznin B, Melmed S, Le Roith D (eds). Molecular and cellular biology of diabetes mellitus. Vol 1. New York: Alan R. Liss 1989: pp 149–158.
35. Moore TR, Hollingsworth DR, Kolterman O, Nager C. Continuous subcutaneous insulin infusion in an obese pregnant woman with type II diabetes: accelerated fetal growth and neonatal complications. Obstet Gynecol 1987;70:480–485.

SECTION

IV

Treatment of Pregnant Women with Diabetes

Dorothy R. Hollingsworth

CHAPTER

11

General Considerations

The primary goal in the management of diabetic pregnancies is a good outcome with minimal morbidity and no mortality for the mother, the fetus, and the infant. To achieve this goal, the best course for the diabetic woman and her physician to follow requires *(a)* good diabetic control before conception and during pregnancy, the peripartum, and the postpartum periods; *(b)* **prevention** of complications by good prenatal care at frequent intervals; *(c)* early detection and prompt treatment of minor and major medical problems; *(d)* careful timing and appropriate mode of delivery; and *(e)* a positive reproductive experience for the patient and her family.

The expansion of knowledge in the fields of diabetes and perinatal medicine has been markedly accelerated during the past decade, since the first edition of this book. To facilitate the translation of advances in both the basic sciences and clinical medicine to individual patients it has become both reasonable and practical to establish regional centers for high-risk pregnancies.

This goal has become a reality; many more hospitals in 1990 have facilities for ambulatory care management of high-risk diabetic pregnancies and neonatal tertiary care nurseries for problems of infants of diabetic mothers.

For diabetic women with heterogeneous metabolic disorders of carbohydrate metabolism that are exaggerated by the normal physiologic changes of pregnancy, a team approach that utilizes the skills of physicians, nurses, nutritionists, and social workers provides an excellent method for coordinated care. In addition, in regional centers, experts in ophthalmology, renal disease, neurology, cardiology, anesthesiology, and neonatology are readily available.

However, many pregnant diabetic women and particularly the large number with gestational diabetes do not have easy access to geographically widely separated regional centers for diabetes and other preinatal problems. This chapter is a summary of current information on the three modalities used to treat diabetes during pregnancy, e.g., insulin, diet and exercise (Fig. 11.1). It is meant to serve as a general guideline for physicians and paramedical personnel who have primary responsibility for the care of pregnant diabetic women in diverse settings for prenatal care.

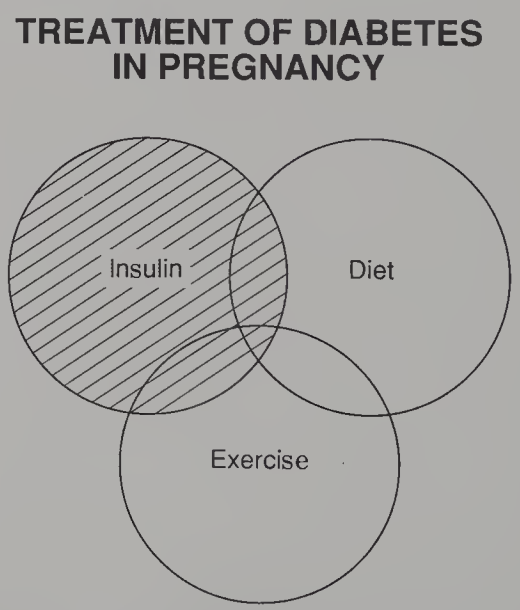


Figure 11.1. Diagrammatic representation of the three modalities of treatment in diabetic pregnancies. Insulin is emphasized because it modulates metabolic responses to both nutrition and exercise.

CHAPTER

12

Insulin: An Essential Pharmacologic Agent and Potentially Dangerous Drug

In IDDM, the goal of physiologic replacement of insulin remains elusive (1). Although earlier, less pure insulins extracted from cows and pigs, which had a high potential for antiinsulin antibody formation in the recipient, are no longer in common use, it is still difficult to titer exactly an ideal dose of this hormone for each patient. This is especially true in pregnant women. Because this is the only drug we have to control diabetes during gestation, it is prudent to become familiar with different types of insulin, their duration of action, and modes and sites of administration. By far, the most common problems in diabetic prenatal clinics are the frequent rotation of physicians and paramedical personnel and the irresistible urge to prescribe excessive doses of insulin.

In normal adult nondiabetic individuals, insulin is secreted into the portal system in the basal state at a rate of approximately 1 U/h. The total daily secretion of insulin is approximately 40 U (2–4). Thus, in IDDM, this might be considered a general insulin replacement requirement. The intake of food triggers a nicely balanced release of 5–10 U of insulin from the β cell, depending upon the type and amount of food ingested. Pregnant IDDM women require about a third more insulin each day, approximately 15–20 U/day during the 2nd and 3rd trimesters. These estimates are based upon the increased insulin requirements of normal pregnant women (5–7).

INSULIN PREPARATIONS AND THEIR PHARMACOKINETICS

The most recent advances in the manufacture of insulin have been the now limitless potential to produce human insulin by recombinant-DNA technology and the development of genetically engineered insulin analogues. Animal insulins have improved in quality and monovalent porcine preparations have reduced the frequency of insulin allergy and the production (but not total elimination) of insulin antibodies during treatment.

The physiologic importance of insulin antibodies in diabetic control is unclear (8–10). In several clinical studies, measurements of titers of circulating antibodies have shown *(a)* attenuated responses to regular insulin injected subcutaneously, and *(b)* delays in recovery from hypoglycemia when measurable titers of insulin antibodies were present (11, 12).

Does the presence of variable titers of insulin antibodies have any implications for pregnant women? Bauman and Yalow (13) were the first to report transplacental passage of insulin complexed to antibody. Two years later (1984), Mylvaganam and colleagues (14) demonstrated antibodies to insulin in 92% of 131 insulin-treated pregnant diabetic women. Pregnancy had no effect on the antibody titers, but a change from conventional insulin, in use at that time, to a highly purified porcine insulin resulted in a significant reduction of antibody levels. Insulin antibodies were freely transferred to the fetus but not detectable after the first 8 months of life. They did not report an association of higher maternal insulin antibody titers with percentile birth weights or cord serum measurements of C-peptide, but their presence was associated with indices of neonatal morbidity.

Interest in this topic has been rekindled by the report of Menon and associates (15) that

demonstrated antibody-bound insulin traverses the placenta in insulin-treated IDDM and may have biologic activity. They suggest the possibility that the antibody-insulin complex can stimulate β cells and can be a determinant of fetal macrosomia independent of maternal blood glucose levels. If these observations are extended and confirmed, the present recommendation to use only the least antigenic insulin preparations during pregnancy will have more than theoretical relevance.

Types of Insulin

Table 12.1 shows types of regular/fast-acting insulins recommended for pregnant women. Table 12.2 is a list of intermediate-acting insulins (NPH, lente) and Table 12.3 shows the effect of mixing on **immediate** insulin action of Novo Nordisk preparations (16–19). These tables include the usual published durations of action for different types of insulin. These should not be used as firm, fast, always reliable time spans. Duration of insulin action and more information on mixing of different proportions of rapid-acting insulin and intermediate-acting insulins (NPH and lente) are described later in this chapter.

Duration of Insulin Action

Biosynthetic and semisynthetic insulins are identical in structure and pharmacology to human insulin. The biologic activity and intravenous pharmacokinetics of human insulin are remarkably similar to those of porcine insulin, except that human insulin is slightly less antigenic.

Human insulin is absorbed more quickly than porcine insulin when injected subcutaneously (20, 21). This is important in tightly controlled pregnant IDDM women who should be cautioned to take their morning insulin dose immediately before breakfast. Intermediate-acting human insulin has a shorter duration of action than purified porcine insulin.

Novo-Nordisk Pharmaceutical Company recommends an initial 20% decrease in insulin dose when a shift is made to its products. There are conflicting reports about the observation that human insulin is associated with more inapparent hypoglycemia following intravenous bolus injections (22). In a randomized 2-hour infusion study in 8 healthy young men, Heine and colleagues (22) reported sympathoadrenergic (but not more neuroglycopenic) symptoms. These investigators suggested the explanation that the decreased adrenal response with human insulin (inapparent hypo-

Table 12.1.
Fast-acting Insulins[a]

Characteristics of products: clear, crystalline, neutral pH, and contain no retarding agents
Action: Onset, 0.5 h; maximum effect, 1–4 h; end, 6–8 h

Human Insulin	Source	Buffer	Zinc Content	Preservatives
Novo Nordisk				
Novolin-R®	Fast-acting human insulin (semi-synthetic)	None	Unknown	Phenol
Novolin PenFill®	Made as human insulin injection USP			
Lilly				
Humulin-R	Biosynthetic Human	None	.01–.04 mg/100 U	M-cresol
Purified Pork	**Source**	**Buffer**	**Zinc Content**	**Preservatives**
Novo Nordisk				
Purified Pork	Rapid-acting purified pork	None	Unknown	Phenol
Lilly				
Rapid-acting (regular) Iletin II	Purified pork	None	0.1–0.4 mg/100 U	M-cresol

[a]See text for expanded discussion of duration of action.

Table 12.2.
Intermediate-acting Insulins[a]

Characteristics of products: suspension, neutral pH, zinc as retarding agent

Lente Insulin	Type	Source	Time Course (h)			Zinc Content
			Onset	Max	End	
Novo Nordisk						
Novolin L®	Lente	Lente human insulin zinc suspension (semi-synthetic)	2.5	7–15	22	0.15 mg/100 U
Purified Pork L	Lente®	Purified pork insulin zinc suspension USP				
Lilly						
Iletin II	Lente	Purified pork	1–3	6–12	18–26	.12–.25 mg/100 U

Characteristics of products: suspension, neutral pH, protamine as retarding agent

NPH Insulin	Type	Source	Time Course (h)			Protamine (mg/100 U)
			Onset	Max	End	
Novo Nordisk						
Novolin® N	NPH	Human insulin isophane suspension (semi-synthetic)	1.5	4–12	24	0.35
Novolin® N PenFill	NPH	Human insulin isophane suspension (semi-synthetic)				
Purified Pork N	NPH	Purified pork isophane insulin suspension USP				
Lilly						
Iletin II	NPH	Purified pork	1–2	6–12	18–26	0.30–0.50
Humulin N	NPH	Biosynthetic human	1–2	6–12	18–24[a]	0.30–0.50

[a]See text and references for expanded discussion of duration of action of intermediate-acting insulins.

glycemia) reported by others might be due to the different physiochemical characteristics of human and porcine insulins. Porcine insulin is more lipophilic than human insulin and may have greater penetration of the blood-brain barrier to account for a difference in autonomic responses. In tightly controlled pregnant women who do not experience symptoms of hypoglycemia when blood glucose levels are below 60 mg/dl (3.3 mmol/L), it may be wise to shift to purified pork insulin in some individuals to avoid repeated and severe asymptomatic hypoglycemia.

Table 12.3.
Effect of Mixing on Immediate Insulin Action

Rapid-acting Insulin (Regular)	Intermediate-acting Insulin (NPH or lente)	Loss of Immediate Insulin Action[a]
Velosulin	Insulatard-NPH	0
Rapid-acting	Lente	+
Rapid-acting	NPH	+

[a]0, no loss of action; +, loss of action.

Insulins with rapid action (crystalline zinc; CZI or clear insulin) have a theoretical maximum effect in 2–3 h when administered subcutaneously. The effect is usually dissipated within 4–5 h. **It should be noted, however, that there are marked individual variations in the "usual time course" published by pharmaceutical companies.** This is particularly true in women with long-standing diabetes who have received less pure insulins and developed high titers of insulin antibodies. This situation can make diabetes control especially difficult because the time course of action of rapid-acting insulin can be inordinately prolonged and a source of confusion for the patient and physician.

Figure 12.1 depicts the effective time course of a patient who received a single subcutaneous dose of rapid-acting insulin. The onset

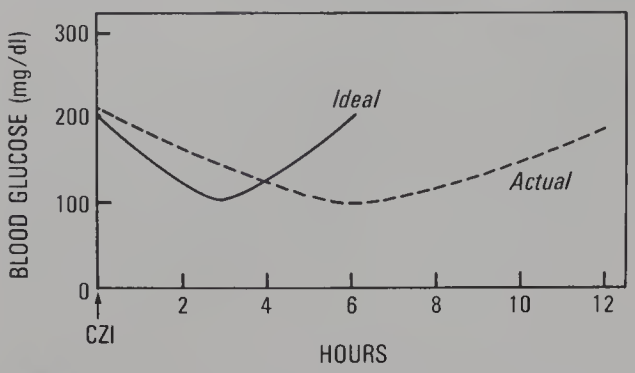


Figure 12.1. Duration of action of rapid-acting insulin. The *solid line* (—) shows the predicted time course that is customarily used for instruction in diabetic clinics. The *dotted line* (---) shows the actual time course in a patient given a single morning dose of rapid-acting insulin. Note the nadir was not reached for 6 h and the total duration of action was 12 h. With permission from Bressler R, Galloway JA. Insulin treatment of diabetes mellitus. Med Clin North Am 1971;55:861–876.

of action was slower and the duration was longer than normal subjects (23).

Rapid-acting insulin may also be administered as an intravenous bolus, which produces a maximum depression of the blood glucose in about 30 min, or by a slow intravenous drip at a rate of 0.5–2.5 U/h, which maintains the level of blood glucose in the euglycemic range. The constant low-dose intravenous infusion of insulin has been especially useful in treating diabetic ketoacidosis, bringing poorly regulated patients into better control, and maintaining euglycemia during labor, delivery, and the immediate postpartum period.

Intermediate-acting insulins (NPH, lente), theoretically produce a maximal effect at about 8 h, which is dissipated by 24 h. **Many patients do not follow this time course,** which has been so ingrained in medical student and postgraduate teaching. Bressler and Galloway (24) have reported three patterns of response that may follow a single daily dose of intermediate-acting (NPH) insulin (Fig. 12.2).

The time course of insulin action is also dependent upon the pharmacology of mixtures of insulin. Because the use of combined injections of rapid-acting and intermediate-acting insulin is common, it is important to note the variations in maximum increase in serum insulin, time of maximum increase, maximum reduction in blood glucose, and time of maximum reduction that result from various combinations.

Galloway and colleagues (25) have evaluated serum insulin concentrations (SIC) and blood glucose response to mixtures of rapid-acting and intermediate-acting insulin in 45 normal males of normal weight who had no antibodies to insulin. They assessed the effects of concentration, depth, and method of administration and found that a higher ratio of rapid-acting:lente was needed to achieve peak SIC than with rapid-acting:NPH combinations (Tables 12.4 and 12.5). The depth and site of injection were also important factors. These findings in normal subjects, which showed

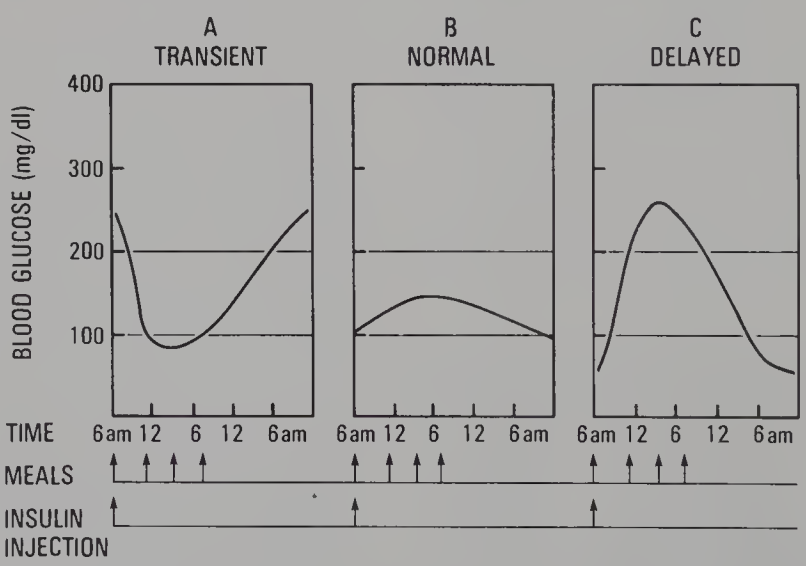


Figure 12.2. This figure shows three different responses of blood glucose concentrations to a single morning injection of intermediate-acting acting NPH insulin. With permission from Bressler R, Galloway JA. Insulin treatment of diabetes mellitus. Med Clin North Am 1971;55:861–876.

Table 12.4.
Summary of Studies to Demonstrate the Influence on Serum Insulin Concentration after the Administration of Insulin[a,b]

Treatment	Maximum Increase in Serum Insulin (μU/ml)	Time of Maximum Increase (h)	Maximum Reduction of Blood Glucose (mg/dl)	Time of Maximum Reduction (h)
NPH	21.8 ± 38.8	4.6 ± 3.2	21.8 ± 9.3	8.5 ± 2.4
NPH:NRI, 1:1	58.5 ± 24.9	2.3 ± 0.8	35.8 ± 12.4	2.2 ± 0.5
NPH:NRI, 2:1	49.6 ± 17.2	3.7 ± 3.9	30.0 ± 9.7	4.4 ± 3.4
NPH:NRI, 3:1	28.6 ± 23.9	2.9 ± 2.9	24.5 ± 9.1	7.1 ± 2.9
NPH:NRI, 1:2	58.7 ± 12.6	1.8 ± 0.5	35.9 ± 10.2	2.6 ± 1.1
NPH:NRI, 1:3	57.6 ± 21.2	1.5 ± 0.4	33.4 ± 11.5	2.4 ± 0.9
NRI	70.5 ± 21.7	1.8 ± 1.1	41.8 ± 12.3	3.2 ± 1.6
Least significant difference[c]	27.8		11.2	2.2

[a]Table used with permission from Galloway et al. Insulin concentration and blood glucose responses after injections of regular insulin, and various insulin mixtures. Diabetes Care 1981; 4:366–376.
[b]Factors include site and method of administration, depth of injection and intra- and intersubject variation. Also included are areas under the SIC curves and, where appropriate, fractional absorption. NPH:NRI is the proportion of intermediate (NPH) to short acting (R) insulin. **Note the values in Tables 12.4 and 12.5 are in normal nondiabetic nonobese males.**
[c]Two means are significantly different at the 0.05 level if they differ by more than this quantity.

marked inter- and intrasubject variations, emphasize the difficulties in the administration of combinations of different preparations of this hormone to pregnant women who have varying degrees of insulin resistance, variable levels of insulin antibodies, and low or absent circulating levels of endogenous insulin in addition to marked differences in body weight.

During pregnancy, insulin is most often prescribed as a mixture of rapid-acting and intermediate-acting (NPH or lente) insulins in the same syringe. Twice daily or more frequent injections are the most common regimen, although many modifications are devised for individual women.

In a mixture of rapid-acting insulin with intermediate-acting insulin (NPH, an isophane insulin suspension), the separate action profiles of the components of mixtures may be retained up to 72 h depending upon the proportions of each insulin type. In mixtures of rapid-acting insulin with lente insulin (an insulin-zinc suspension), there is a modification of the duration profile of the rapid-acting insulin that appears to interact with the excess zinc in the lente preparation often resulting in

Table 12.5.
Means (± SD) of Peaks and Times of Peak Serum Insulin Concentrations and Blood Glucose Responses in Normal Fasting Subjects Given Lente and Regular Insulin (NRI) in Ratios of 1:1–3:1 and 1:2 or 1:3[a]

Treatment	Maximum Increase in Serum Insulin (μU/ml)	Time of Maximum Increase (h)	Maximum Reduction of Blood Glucose (mg/dl)	Time of Maximum Reduction (h)
Lente	31.0 ± 15.8	3.5 ± 2.9	24.1 ± 8.5	6.6 ± 2.9
Lente:NRI, 1:1	41.4 ± 6.7	2.5 ± 0.8	29.9 ± 7.3	4.3 ± 2.1
Lente:NRI, 2:1	44.9 ± 10.9	3.5 ± 2.1	29.9 ± 9.0	5.1 ± 2.2
Lente:NRI, 3:1	35.2 ± 14.8	4.4 ± 3.0	26.3 ± 8.0	5.8 ± 2.7
Lente:NRI, 1:2	63.7 ± 17.2	2.9 ± 2.8	33.0 ± 7.5	2.7 ± 1.3
Lente:NRI, 1:3	63.8 ± 17.3	1.8 ± 0.9	36.0 ± 8.5	2.6 ± 1.3
NRI	72.8 ± 15.6	2.6 ± 3.3	36.1 ± 7.3	2.2 ± 1.0
Least significant difference[b]	15.9		7.2	2.3

[a]Table used with permission from Galloway et al. Insulin concentration and blood glucose responses after injection of regular insulin, and various insulin mixtures. Diabetes Care 1981; 4:366–376.
[b]Two means are significantly different at the 0.05 level if they differ by more than this quantity.

a longer duration. In individual pregnant women, depending on their life-style and eating patterns, this difference could theoretically be associated with hypoglycemia. However, a more recent study by Tunbridge and associates (23) in a double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens, did not find an increase in hypoglycemic events associated with lente insulin. They concluded that lente- and NPH-based twice daily human insulin regimens give indistinguishable metabolic control.

We customarily use intermediate-acting NPH insulin in our clinic unless a patient is already receiving lente insulin, because it is easiest to prescribe as few types of insulin as possible with a staff of rotating students and house officers. Premixed rapid-acting and isophane NPH insulins are available as a 30%/70% mixture. Although a convenience for patients who do not see well or have difficulty in preparing mixtures, the inflexible dose has not been practical in most pregnant women.

During pregnancy, it is not unusual to find patients who are receiving either excessive or insufficient amounts of insulin. Each patient differs from every other patient; each lives and eats in a highly individual fashion and is subject to emotional stresses peculiar only to herself and her family. The dose of exogenous insulin must be carefully determined throughout gestation and readjusted frequently during periods of minor bacterial infection, viral illness, gastrointestinal upset, urinary tract infection, emotional trauma, or other medical complications of pregnancy. This requires that a pregnant diabetic woman be in frequent communication with a physician who knows her well.

INSULIN ADMINISTRATION DURING PREGNANCY

Table 12.6 describes possible methods of delivery of insulin. Until mechanical and technical problems are solved, administration of insulin on a long-term basis during pregnancy is limited to the use of multiple subcutaneous insulin injections (MSI) or a carefully initiated and supervised continuous subcutaneous infusion pump (CSII).

Multiple Subcutaneous Injections (MSI)

Excellent diabetic control can be achieved with intensified conventional therapy with

Table 12.6.
Possible Methods of Insulin Delivery for Pregnant Women with Diabetes

Method	Advantages	Disadvantages
1. Closed-loop systems (glucose serum-controlled insulin infusion system)	Servo-controlled feedback	Nonportable; intravenous delivery limited to 24–48 h
2. Long-term intravenous portable pump with insulin reservoir and electronic control box	Normoglycemic control for 1–3 months	Requires catheter in subclavian vein; mechanical difficulties; precipitation of insulin in pump tubes
3. Implantable insulin infusion devices	Physiologic feedback control of plasma glucose	Present infusion pumps lack a long-term sensor
4. Open-loop continuous subcutaneous insulin infusion (fixed program or demand program)	Independent delivery of basal and premeal insulin doses can be used for long periods (2–8 months) in ambulatory care	Infection, hypoglycemia, or hyperglycemia with ketosis (occasionally fatal); pump malfunction with over- or underinsulinization; psychosocial and compliance problems; labor-intensive; requires 24 h/day diabetes and obstetric staff
5. Multiple subcutaneous injections	Good control of glucose levels in motivated patients; most pregnant women use this method	Over- or underinsulinization

multiple subcutaneous injections of insulin (26, 27). It should be noted, however, that women who lack normal counterregulatory mechanisms in response to hypoglycemia are also at increased risk for insulin-induced coma during regimens that employ multiple subcutaneous injections. Multiple injections of insulin require careful attention to the type and amount of insulin being administered. At least two and often three or more injections per day may be necessary to establish and maintain good control during pregnancy. The differences in management of IDDM versus NIDDM are discussed later in this section.

In women who begin pregnancy or present for prenatal care in extremely poor control, there is probably not a role for use of the artificial β cell (Biostator) or prolonged intravenous or MSI administration to improve control quickly.

The risk of malformations associated with hypoglycemia before embryogenesis is complete (7.5 weeks) may be as high or higher than that of hyperglycemia. Every effort should be made to avoid extremes of both hyper- and hypoglycemia after initial assessment of diabetic control; early hospitalization for diabetes education may be necessary. Gestational control is smoother and easier if achieved gradually over 2–3 weeks.

In patients who are hyperglycemic, but continue to secrete normal or elevated levels of endogenous insulin [many obese women with NIDDM or gestational diabetes (GDM)], the type of insulin and timing of injections may need to be modified during pregnancy to prevent overinsulinization. In **obese** subjects who are resistant to insulin and have difficulty in releasing insulin following meals, a small dose of regular insulin before each meal is a more physiologic approach than the administration of split doses of intermediate and rapid-acting insulin.

Pregnant women most often receive insulin by subcutaneous injections. There is considerable variability of insulin absorption from different sites of injection or even from the same site. Analysis of peak insulin levels and the area under insulin-response curves after repeated injections in a single patient at the same anatomical site and with the same dose and technique show coefficients of variation of 20–30% for both rapid-acting and intermediate-acting insulins (28). The time between injection and peak plasma insulin concentration may vary as much as 50% and, in glucose-clamp studies, the amount of glucose needed to maintain euglycemia may vary by 35% for the same dose of insulin. Thus, in IDDM women with 0 insulin reserve, variable characteristics of insulin absorption can make a real difference in the magnitude of glucose excursions despite close attention to the other aspects of diabetic control.

Bantle and colleagues (29) have reported that the usual clinical practice of rotating sites of insulin injection actually increases day-to-day variations in blood glucose concentrations. This can be reduced if a single site, such as the abdomen, is used for all injections. Subcutaneously injected ^{125}I-labeled rapid-acting insulin has been reported to disappear 86% faster from the abdominal wall than from the leg and 30% faster than from the arm (30). In addition, insulin is absorbed more quickly when it is injected into an extremity that is subsequently exercised (31).

MSI programs are of several types. The easiest to implement is a twice daily regimen with a mixture of intermediate-acting and rapid-acting insulin before breakfast and the evening meal. Some women may need a small dose of rapid-acting insulin before lunch. In nonpregnant IDDM women with a "dawn phenomenon" described later in this chapter, an intermediate-acting insulin is given at bedtime in addition to other dose regimens in the morning and before dinner.

Other physicians and patients work out a basal dose of ultra-lente (long-acting insulin) before either breakfast or dinner and additional rapid-acting insulin before each meal. There has been some reluctance to use ultra-lente insulin in pregnant IDDM women because of possible added risk of hypoglycemia. Our experience is limited to one patient who arrived for prenatal care early in 1st trimester already following an ultra-lente schedule. Because she was doing extremely well and was in good diabetic control, we elected to continue her program and cautiously increase her before-meals rapid-acting insulin doses in increments of 2 units as needed according to home blood glucose monitoring results as pregnancy progressed. She did extremely well with no complications during gestation. She had a repeat cesarean section delivery of a normal weight infant at term.

Continuous Subcutaneous Infusion of Insulin (CSII)

A decade ago, three successful feasibility studies were published that demonstrated normal glucose profiles could be achieved by continuous subcutaneous insulin infusion (CSII) in pregnant IDDM (32–34). Coustan and colleagues (35) conducted a randomized study of 22 IDDM women to CSII or MSI from early pregnancy onward. Both groups of women had frequent outpatient visits and performed home blood glucose monitoring four to six times a day. Women in the two groups achieved excellent diabetic control and good fetal outcomes. Severe hypoglycemia was comparable in both methods of insulin administration. There was probably no inherent advantage in either form of treatment. Rather, excellent results occur when patients are highly motivated, enroll in clinical studies, and receive constant supervision from their physicians and paramedical personnel.

Over the years, interest in treating women with CSII has waned unless they were on an insulin infusion pump before conception. In carefully selected women, remarkable glycemic control is possible. Those who like the method and do not opt out for personal reasons enjoy the freedom a computerized pump with built-in warning features for pump failure provides. They feel in better control of their disease.

An occasional patient develops a neurosis with an hypnotic fascination for repeatedly testing blood glucose levels throughout the day and night. Our diabetes center pump nurse removed one of our medical students from the CSII program when he was discovered to be monitoring his blood glucose levels 17 times a day. The most sophisticated models of CSII pumps are expensive and medical obstetric care of CSII patients is labor-intensive. Fortunately, pregnant IDDM women can be assured they will also do quite well on MSI.

The main complications of CSII are infections at the infusion site, severe hypoglycemia, and more frequent hyperglycemia and ketosis in the presence of unrecognized infections. Pickup and colleagues (36) have reported that in patients with "brittle diabetes" (a rare problem characterized by wide, fast, completely unpredictable excursions in levels of blood glucose that are evidently unrelated to insulin, food intake, or exercise), it is not possible to obtain better control with CSII than by conventional injection therapy.

The technique for CSII is described in Table 12.7 (37). Until treatment is well established, blood glucose levels need to be monitored before and 2 h after each meal, at bedtime, whenever symptoms occur, and around 2:00 or 3:00 AM.

Chantelau and associates (38) have published a follow-up of long-term safety, efficacy and side effects of CSII in 140 nonpregnant

Table 12.7.
Technique for Subcutaneous Insulin Infusion[a]

Delivery cannula and implantation site
Fine gauge (25- or 27-gauge) metal needle with wings attached to a connecting tube (butterfly, Abbott Laboratories) is inserted by patient and secured to skin by wings; accidental withdrawal is rare
Reimplant cannula every 1–3 days at different site in anterior abdominal wall usually at same time insulin syringe is refilled.
Insulin
Short-acting (regular insulin) is used in the pump syringe
Pumps
Several infusion pumps are available in the United States and new models are being developed and marketed
Most pumps deliver insulin from a syringe; they infuse insulin at a basal rate (the volumetric rate is fixed or can be preset) and have the capability to deliver a preprandial boost either manually, electronically, or in a computer program
The basal infusion rate is calculated according to the concentration of insulin in the syringe; the basal rate can be programmed for a lower dose at night
The pump is usually worn in a pouch attached to a belt around the waist or as a shoulder harness.

[a]Adapted from Pickup JC. Continuous subcutaneous insulin infusion. Br Med J 1982; 285:49–50.

IDDM patients from their diabetes center in Dusseldorf. At follow-up after 4.5 ± 0.2 years, only 24 patients had stopped the pump and resumed insulin injection therapy. Most previous long-term reports have presented disappointing results; e.g., frequent complications, failure to maintain improved metabolic control, and a high rate of rejection by patients (39–43).

The Chantelau study was much more optimistic than others. The investigators found a 1% decrease of HbA1c values in their patients to 6.7 ± 0.1% during the long observation period. Inflammation at the catheter site occurred with about the same frequency noted in other studies but episodes of diabetic ketoacidosis (0.14 per patient-year) and disabling hypoglycemia (0.1 per patient-year, including 0.05 incidents of hypoglycemic coma per patient-year) were observed at lower rates than those in any comparable study. An analysis of subgroups of patients suggested that a normal (< 5.6%) HbA1c value at follow-up was associated with an increased incidence of hypoglycemia whereas poor metabolic control (HbA1c > 7.5%) was associated with increased rates of skin complications and hospitalizations for ketoacidosis. In their center, 83% of CSII patients were maintained for a long time with generally excellent results.

A number of deaths have been associated with use of CSII. Teutsch and colleagues (44) have described seven patients who died. All were alone at the time of death and information about circumstances of the deaths was unavailable, save for one man whose pump was operating in a bolus mode. Teutsch and coworkers (45) recommend that patients with suboptimal counterregulatory mechanisms for hypoglycemia be identified before a CSII program is started (46, 47) and be treated with less intensive regimens, e.g., lower therapeutic goals for diabetic control.

All patients on intensive therapy (MSI or CSII) should have a knowledgeable person close at hand (especially at night) and a readily available glucagon kit to assist in treatment of hypoglycemia.

Some patients have found the SLEEP-SENTRY (48), a 45-g wristwatch-like device capable of detecting a fall in skin temperature and a fall in the galvanic skin resistance during sweating, helpful as an alert for nocturnal blood glucose values of < 54 mg/dl (< 3 mmol/L) (Fig. 12.3). In a clinical trial at Steno Memorial Hospital, Gentofte, Denmark (49), the Sleep-Sentry detected significant hypoglycemia in about two thirds of patients. At 3:00 AM, the alarm sounded 22 times in 22 patients; hypoglycemia was present six times giving a diagnostic true positive rate of 0.27 (95% confidence limits of 0.11–0.50). In 35 of 38 cases with no alarm, the blood glucose was at a reassuring level of more than 54 mg/dl (3 mmol/L)), with a diagnostic sensitivity of 0.92 (95% confidence limits 0.79–0.98). Thus, if a pregnant woman on an intensive insulin regimen is not averse to tolerating middle-of-the-night false alarms, this device can be very helpful. We especially recommend it for women alone at night.

In sum, the method of insulin administra-

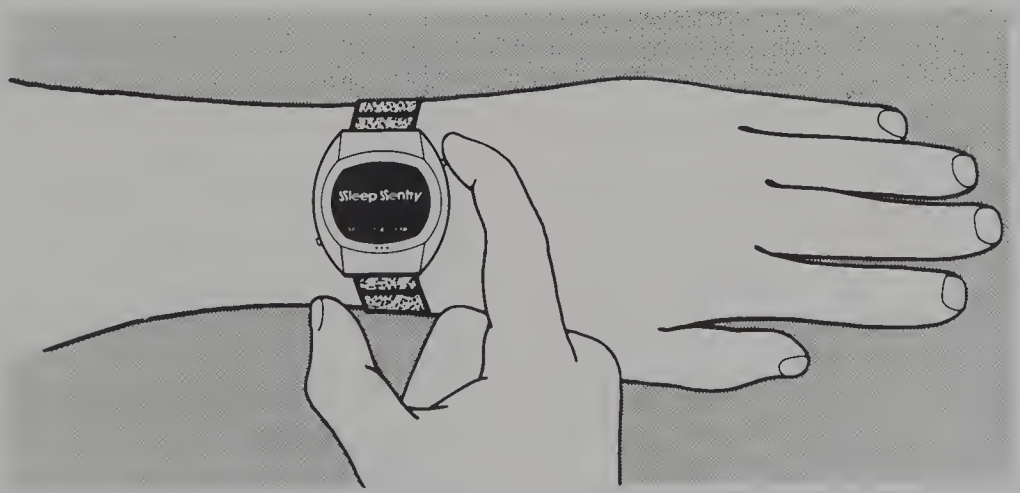


Figure 12.3. Photograph of the Sleep-Sentry, a wristwatch-like device that is often helpful in alerting IDDM patients to episodes of nocturnal hypoglycemia. The Sleep-Sentry is available from Diabetes Supplies, 8181 North Stadium Drive, Suite 202, Houston, Texas 77054.

tion for pregnant women will depend on their individual characteristics and life-styles, the experience of physician and clinic, and the availability of an extended staff with special expertise should CSII be the method of choice. We are still some years away from successful islet cell transplants. Programmable implantable medication systems (PIMS) are, however, undergoing their first clinical trials (50).

Risk Factors for Hypoglycemia in Pregnant IDDM on Intensive Insulin Regimens

IDDM patients who have had symptomatic diabetes mellitus and insulin replacement treatment for more than 2–5 years usually have no functioning β cells, a deficient glucagon response to hypoglycemia, and a higher risk of hypoglycemia. In long-standing IDDM women, the epinephrine response to hypoglycemia and action of other counterregulatory hormones (cortisol and growth hormone) may be abnormal or inadequate. A newly recognized problem has been the demonstration that intensive therapy by either MSI or CSII may be associated with deterioration of responses of counterregulatory hormones to hypoglycemia (51). This is manifested by a decrease in the glycemic threshold for the release of epinephrine. This leads to a lowering of the glycemic threshold at which symptoms of hypoglycemia are recognized—and the type of **inapparent hypoglycemia** so common in pregnant IDDM women. In the ongoing Diabetes Control and Complications Trial (DCCT), nonpregnant patients who were intensively treated had a twofold to threefold increase in the occurrence of severe hypoglycemia, which resulted in a modification of the original research protocol (52).

Glucose counterregulation and its impact on diabetes mellitus is reviewed in detail in the 1988 Lilly Lecture by Gerich (53). The search for a solution to the increasing problem of hypoglycemia as more intensive insulin regimens are implemented is described in the summary of a recent conference. This conference concluded that, fundamentally, pending the prevention or cure of IDDM, we must learn to deliver insulin in a more physiologic fashion or to prevent, correct, or compensate for compromised glucose counterregulation if we are to achieve euglycemia safely in most patients with IDDM (54).

HYPOGLYCEMIA IN DIABETIC PREGNANCIES

From the previous discussion, it is readily apparent that insulin is a potentially dangerous drug. Hypoglycemia is, by far, the most serious and common adverse reaction to the administration of insulin: it can result in substantial morbidity and death. The effect of severe maternal hypoglycemia on the human fetus at all stages of gestation is unknown because it is not possible to assess in utero neurodevelopmental processes.

The effects of hypoglycemia on mammalian embryos undergoing neurulation (3rd to 4th week of human development) have been investigated by Sadler and Hunter (55). This study of mouse embryos maintained in whole embryo cultures investigated growth and malformations when blood glucose levels were 40, 60, 80, and 147 mg/dl (2.2, 3.3, 4.4, and 8.2 mmol/L). The normal blood glucose level in the pregnant mouse is 125 mg/dl (6.9 mmol/L). Their results demonstrated that glucose levels approximately 50% of normal maternal levels were teratogenic but not growth inhibitory; lower glucose concentrations to 30–40% of maternal levels were lethal to the embryo. Furthermore, a 14-h exposure to reduced blood sugar levels in either the first or second half of the culture period produced malformations. From a biochemical standpoint, glucose appears to be an essential energy source during the earliest stages of embryogenesis. Because of these and other studies (56–58) with similar findings of increased risk of fetal teratogenesis in hypoglycemic mothers, a cautionary note has been sounded to obstetricians and diabetologists to avoid this problem in pregnant women by less stringent diabetic control during the first 8 weeks after fertilization of the embryo. It is difficult to tread a fine line of reasonably good control (maternal blood glucose values between 70–150 mgl/dl; 3.8–8.3 mmol/L and no episodes of hypoglycemia), unless there has been good control(without episodes of hyperglycemia with blood glucose values ≥ 70 mg/dl [3.8 mmol/L]), unless there has been good control in the **preconception** period and a normal HbA1c concentration. The risks of hypoglycemia with use of methods for intensified glucose control (MSI and CSII) have been discussed previously.

The Somogyi Phenomenon

In the 1930s, Dr. Michael Somogyi, a biochemist at Jewish Hospital in St. Louis, asked local physicians to send him their worst diabetic patients who seemed impossible to control (59). He subsequently published his landmark studies on a new reagent for measurement of blood glucose concentrations (60, 61). He had become interested in the wide fluctuations of blood glucose levels in difficult-to-control patients and observed that even mild transient hypoglycemia evoked subsequent hyperglycemia (62). Rebound hyperglycemia following hypoglycemia is referred to as the Somogyi phenomenon.

In recent years, the existence of the Somogyi phenomenon has been questioned although morning hyperglycemia is often demonstrated in poorly controlled IDDM. The exact cause is not always apparent and cannot be confidently assumed always to represent a rebound effect of nocturnal hypoglycemia. Somogyi found, in his "impossible to control patients," that a gradual decrement in insulin dose resulted in improved diabetic control and fewer episodes of hypoglycemia. The Somogyi phenomenon has long been familiar to pediatric diabetologists who describe the most common cause of poor diabetic control in children and adolescents as chronic overtreatment with insulin (63). Although this phenomenon can readily be documented in many IDDM, there are, of course, additional explanations for high morning glucose concentrations. Most patients eat a snack after a nocturnal episode of hypoglycemia that may have been undocumented. The increased caloric intake in the absence of an adequate concentration of circulating insulin can cause marked hyperglycemia by breakfast time.

Morning hyperglycemia has been demonstrated in well-controlled IDDM patients on CSII when they were deliberately made mildly hypoglycemic without symptoms at night (64). In this study, fasting glucose levels rose by approximately 27 mg/dl (1.5 mmol/L) and postbreakfast levels by 72 mg/dl (4 mmol/L). These elevations were correlated significantly with those of plasma levels of growth hormone, epinephrine, and cortisol. This rebound in glucose concentrations, although small, reflected a balance between insulin availability (the CSII infusion was continuous) and activation of counterregulation. There was a disproportionate effect on postbreakfast hyperglycemia with postprandial glucose levels three times as high as fasting values.

In some patients, hypoglycemia evokes a state of insulin resistance for as long as 7 h. This effect has been demonstrated in studies during a somatostatin-insulin-glucose-infusion test (65). The extent to which insulin resistance and/or insulinopenia (unrelated to levels of counterregulatory hormones) account for rebound hyperglycemia in clinical practice is unclear at present.

Several diabetologists have proposed that nocturnal hypoglycemia does not commonly result in severe morning hyperglycemia (66–72). Perriello and colleagues (64) have reinterpreted some of the papers that doubt the occurrence of Somogyi phenomena. They noted that one third of the IDDM patients, who had adequate counterregulation and were described in previous publications, did have severe rebound fasting hyperglycemia that was interpreted as evidence supporting a confirmation of the Somogyi phenomenon.

In sum, the explanation of morning hyperglycemia requires careful examination of each patient for possible etiologic factors. In pregnant women, the risk for nocturnal hypoglycemia is exacerbated by a constantly feeding fetus while the mother sleeps. Thus, insulin doses before the evening meal must be scrutinized carefully and blood glucose levels checked periodically at 2:00 to 3:00 AM to detect asymptomatic hypoglycemia. This possibility should always be considered in the differential diagnosis of fasting hyperglycemia in pregnant IDDM. Postprandial hyperglycemia following hypoglycemia in pregnant women may be prolonged 6–9 h or longer. Overtreatment of rebound hyperglycemia with additional insulin precipitates further episodes of hypoglycemia as originally described by Somogyi.

Brittle Diabetes

Brittle diabetes is a poorly defined term used to describe many IDDM patients who are difficult to control. Gill and colleagues call the syndrome "emotive, subjective and imprecise" (73). A practical definition of brittle diabetes that is clinically useful is a description of IDDM women with control so fragile that they are subject to frequent and precipitous fluc-

tuations between hyperglycemia and insulin reactions without other known causes of metabolic instability (74). The syndrome is well recognized in pediatrics as occurring in children whose sensitivity to insulin is such that a dosage change of 10% will result in either ketonemia or reactions (75).

It is possible to define the reason for glycemic instability in many patients labeled brittle and attempts should be made to do so. Tattersall's more contemporary definition (76) refers to these individuals as those whose lives are constantly disrupted by hypo- or hyperglycemia whatever the cause. The usual causes of such instability are shown on Table 12.8 (73). **Pregnancy in diabetic IDDM is a prototype for the coalescence of all possible reasons for fragile control of hyperglycemia.**

Table 12.8.
Causes of Brittle Diabetes—a Complex Syndrome in Pregnant IDDM Women[a]

Therapeutic errors	Inappropriate insulin regimens General Overinsulinization Injection problems Monitoring problems Dietary errors Obsessional attention
Intercurrent illness	Infections Urinary tract infections Dental or foot care problems Cholecystitis, hepatitis Viral or bacterial respiratory infections Progressive renal failure Malabsorption (autonomic gastrointestinal neuropathy)
Psychological problems	Anxiety Personality disorders Psychopathy Obstetric crises Conflicts with family or significant others
Hormonal changes and insulin resistance	Marked maternal physiologic and hormonal changes The placenta as a new autonomous endocrine organ

[a]Adapted from Gill et al. Brittle diabetes—present concepts. Diabetologia 1985; 28:579–589

In obstetric outpatient prenatal diabetic clinics, the first approach to marked lability in blood glucose concentrations should be exclusion of therapeutic errors by taking a careful history from the patient and observing her technique for insulin injection. This solves most problems. Intercurrent illnesses are common and trivial infections, such as a cold or toothache, may be a reason for poor control. Table 12.9 is a list of 10 factors that increase risks of severe hypoglycemia in pregnant IDDM women during intensive insulin therapy with MSI or CSII.

Psychologic problems as a cause of instability of diabetes are discussed later in Section VI. These are the most difficult to ameliorate because they reside in the patient and her life circumstances. A sympathetic staff in the diabetes clinic and optimistic, encouraging support can make an encouraging difference in smoothing the long course to delivery.

Hormonal changes associated with pregnancy and varying degrees of insulin resistance are familiar problems to obstetricians and diabetologists. In most women, an increased requirement for insulin as pregnancy progresses can be met by gradual and small increases (2–4 units) in the dose of insulin.

Table 12.9.
Ten Factors that Increase Risks of Severe Hypoglycemia in Pregnant Women During Intensive Insulin Therapy with MSI or CSII[a]

Previous history of severe hypoglycemia
Hypoglycemia unawareness
Obstetric complications
Concomitant treatment with β-blockers
Past uncooperative behavior in treatment programs
Severe emotional disorders
Drug or alcohol abuse
Adrenal or pituitary insufficiency (multiple endocrine neoplasia [MEN] syndrome)
Learning disabilities
Blindness or other physical handicaps

[a]Abbreviations: MSI; multiple subcutaneous injections, CSII; constant subcutaneous insulin infusion.

Table 12.10.
Strategy for Management of Seemingly Hopeless Brittle Diabetes in Pregnant IDDM Women

Recognize the problem
Start again policy; admit to hospital
"One physician" medical care
Intensive re-education
Meticulous and rapid search for cause
Devise an outpatient strategy with family, significant other, and assigned clinic person

An occasional pregnant IDDM patient with brittle diabetes seems hopeless. Tables 12.10 and 12.11 present a practical approach that may work for a time or need to be repeated at intervals during pregnancy, depending on the pathophysiology of the instability of glycemic control. We have found the approach outlined to be a useful and informative maneuver; **it does require the personal attention of a single obstetrician and diabetologist as well as help from the patient.** Most women respond well to this strategy and a careful explanation of the 24-h profile of the assessment of their control. The difficult problem of coordinating insulin doses with different occupational life-styles and eating patterns is illustrated later in this section in Table 14.10.

The Dawn Phenomenon

The dawn phenomenon is described in nonpregnant IDDM and NIDDM women as an increase in insulin requirement and elevation of blood glucose concentrations between 4:00 AM and 8:00 AM (77). The phenomenon occurs in the absence of preceding hypoglycemia, al-

Table 12.11.
Reestablishment of Diabetic Control During a Brief Hospitalization[a]

Admit to high-risk pregnancy ward on Monday. Continue insulin dose prescription from clinic and prescribed diet; assign a single physician for complete responsibility for patient's care

FIRST MORNING:

1. Fasting, 7:00 AM blood glucose determination by patient with blood glucose meter at bedside; repeat hourly, through 8:00 AM the following morning; plot each value on graph (Table 12.11A)
2. Begin 24-h fractional urine collection for quantitative urinary glucose loss; 24-h urine can be pooled for creatinine clearance determination
3. HbA1c

Meals at 8:00 AM; 12:00 noon, 5:00 PM
Snacks at 10:00 AM; 3:00 PM; 10:00 PM

Diabetes and nutrition reeducation; patient should be fully clothed and *ambulatory* during hospitalization

SECOND MORNING:

1. Obstetrician and diabetologist review 24-h blood glucose profile, quantitative urinary glucose loss at each collection period, and other laboratory data
2. Judicious adjustment of insulin dose

Observe and continue patient education for 48 h on new insulin dose; patient monitors and graphs blood glucose before and 2 h after each meal, at bedtime, and if symptoms of hypoglycemia occur

Discharge Friday PM with minor insulin adjustment if necessary; return to clinic the following week for additional fine tuning of insulin dose

[a]We have found this the quickest, most efficient way to sort out difficult patients. Frequent, sporadic insulin dose changes by multiple physicians without a management plan or diurnal visual graph of a patient's progress prolongs hospitalization and is often unsuccessful.
[b]Maintain clinic dietary prescription and insulin doses in this 24-h profile period. If hypoglycemia occurs, treat as described in text.

Table 12.11A.
24-Hour Assessment of Diabetic Control

24-HOUR ASSESSMENT OF DIABETIC CONTROL

Name: _____

Birthdate: _____

Hospital #: _____

INSULIN: AM _____ PM _____ DATE _____ WEEK OF GESTATION _____

PATIENT VALUES:

Mean 24h Blood Glucose _____ mg/dl _____ mmol/L
Urine Glucose _____ g
HbA_{1C} _____ %

	mg/dl	mmol/L
Chol. (3rd Tri)		
TG (3rd Tri)		
BUN/Creat.		

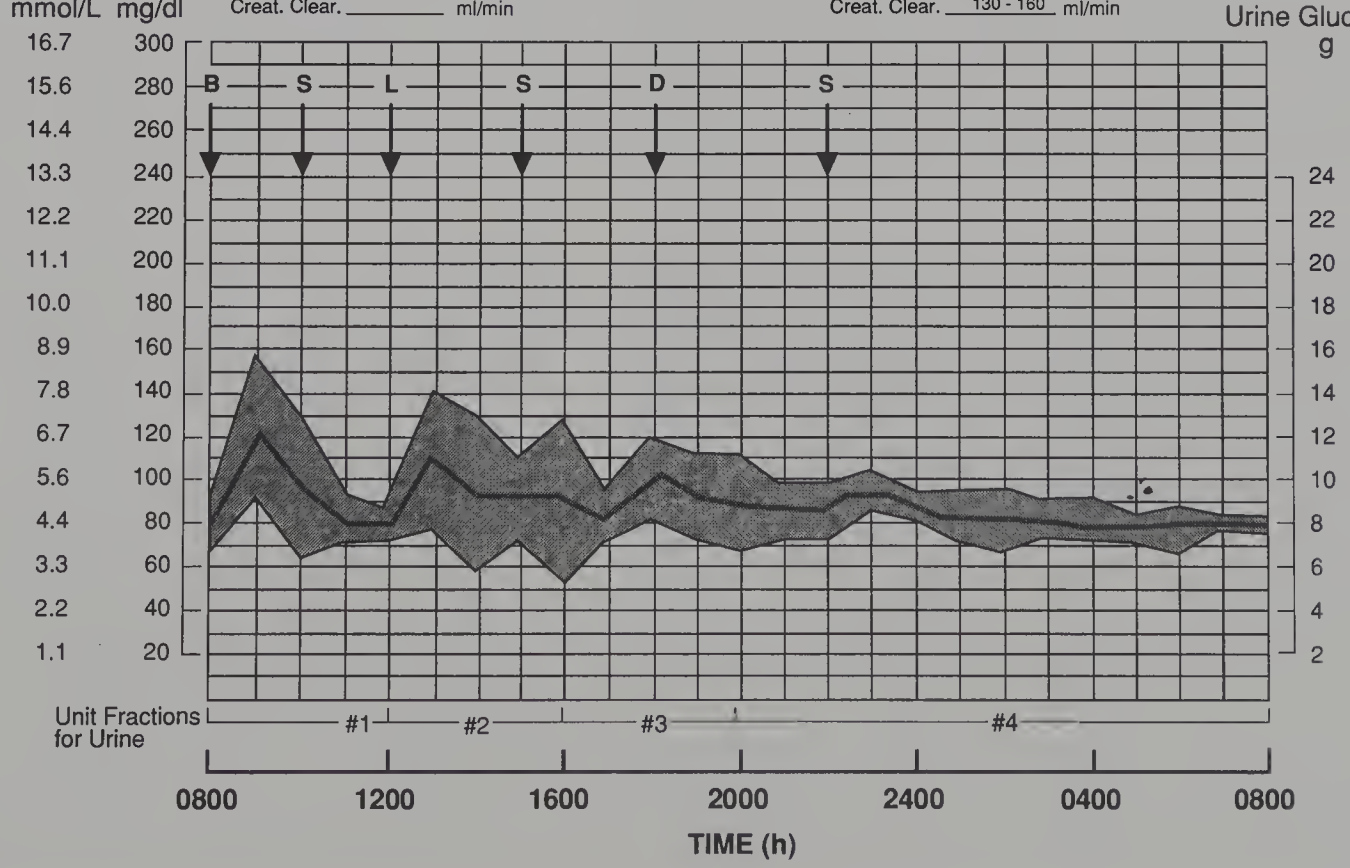
Creat. Clear. _____ ml/min

NORMAL PREGNANCY VALUES:

Mean 24h Blood Glucose 84 ± 2 SD 10 mg/dl 4.7 mmol/L
Urine Glucose < 0.5 g/24 h
HbA_{1C} 5.2 - 6.3 %

	mg/dl	mmol/L
Chol. (3rd Tri)	259 ± 13	6.7 ± 0.3
TG (3rd Tri)	224 ± 24	24 ± 2.6
BUN/Creat.	8-9	0.5-0.6

Creat. Clear. 130 - 160 ml/min



Blood Glucose Grid

though this may not have been recognized or been disregarded as minimal. The pathogenesis of the entity is not well understood. It has been attributed to: *(a)* an increase in insulin clearance, *(b)* a decrease in insulin sensitivity, or *(c)* nocturnal spikes in growth hormone or cortisol. The ongoing controversy of the existence of a dawn phenomenon has not been extended to or investigated in pregnant IDDM women.

We have performed more than 100 24-h glucose and hormonal profiles of pregnant normal and IDDM women at all stages of gestation and never observed a dawn phenomenon. This may be attributed to suppression of maternal plasma pituitary growth hormone levels during gestation or lack of diurnal excursions of placental growth hormone (chorionic somatomammotropin, hCS; human placental lactogen, hPL) in normal, IDDM, and NIDDM patients (78). In management of pregnant diabetic women, the hypothetical existence of this phenomenon to explain morning hyperglycemia should not be used as a rationale to increase evening doses of insulin; rather, other causes should be sought as previously discussed.

We have observed and documented the dawn phenomenon in pregnant, obese NIDDM patients. These women respond well to a bedtime dose of 10–15 units of an intermediate-acting insulin. This has been quite safe because they are not prone to inapparent hypoglycemia.

EEG Abnormalities, Cognitive Changes, and Physical Injuries Following Hypoglycemia

Aside from the risk of death during hypoglycemia, impairment of cognitive function and physical injuries are the most serious effects of iatrogenic hypoglycemia in IDDM patients. Dangerously low asymptomatic plasma glucose levels are a rare problem in pregnant NIDDM women because they do not have impairment of counterregulatory mechanisms even in long-standing disease. In addition, some β-cell function is preserved. In 12 years, we have never observed a serious hypoglycemic reaction (confusion, loss of consciousness) in a pregnant NIDDM woman.

The dangers and mortality associated with severe hypoglycemia in IDDM were first brought to our attention by pediatricians. Abnormal electroencephalographic (EEG) findings following hypoglycemia have been described since 1962 in children in Europe and Israel (79–89).

Haumont and Dorchy (88) investigated EEG examinations in 61 diabetic children and adolescents between the ages of 1 and 22 years. The duration of diabetes ranged from 4 months to 12 years. All neurologic examinations were normal and no family members had a history of epilepsy. All subjects had experienced both mild and severe episodes of hypoglycemia. Retinal examinations with fluorescein were performed in 45 patients. In this study, abnormal EEG patterns were found in 25% of patients (15 of 61) in contrast to 10–15% of nonspecific abnormalities seen in a normal population. The abnormalities were diffuse nonrhythmic slowing in six children, paroxysmal spikes and waves in five, bursts of delta waves in two children, and spikes and sharp waves in one child each. There were no focal abnormalities. EEG abnormalities were higher in patients with poor control. In patients with more than five severe hypoglycemic episodes (loss of consciousness and/or convulsions), 80% had abnormal EEGs. Minor hypoglycemic episodes had no effect on the EEG. Although all patients had had diabetes 12 years or less, the investigators were able to demonstrate incipient retinal angiopathy and correlate its presence with frequent and severe episodes of hypoglycemia and pathologic electrocerebral (EEG) activity.

The above findings were confirmed a decade later (1989) by Soltesz and Ascadi in 70 Hungarian children (89). They reported abnormal EEG tracings in 26% of diabetic children and in only 7% of normal controls. Abnormal findings were associated with a young age, earlier onset of diabetes, and previously severe episodes of hypoglycemia (62%). All diabetic children who had had hypoglycemic convulsions had EEG abnormalities.

Children with onset of IDDM before age 4–5 years are at increased risk for development of mild to moderate neuropsychological impairment (90–97), although the course is not clearly defined. Golden and colleagues (97) have conducted the first longitudinal study of cognitive tests in 23 IDDM children diagnosed before age 5 yr and reported results that suggested that hypoglycemia, even if mild and asymptomatic, may be related to impaired cognitive function.

Ryan and colleagues (98) have studied 11 IDDM children aged 11–18 yr using the insulin-glucose-clamp technique to induce and maintain hypoglycemia. Cognitive tests were performed at baseline (blood glucose 100 mg/dl; 5.5 mmol/L), at the end of a hypoglycemic plateau (blood glucose 55-65 mg/dl; 3.1–3.6 mmol/L), and again after restoration to euglycemia. They demonstrated a significant decline in mental efficiency associated with the **mildly hypoglycemic** blood levels in the study protocol; complete recovery did not occur with restoration of euglycemia. Not all subjects showed cognitive impairment during hypoglycemia and they observed a high degree of intersubject variability.

In normal adults, what is the blood glucose threshold level for early impairment of cognitive function? DeFeo and co-workers (99) examined this question in six normal adult males and six females under conditions of insulin-induced, glucose-controlled plasma glucose decrements or during maintenance of euglycemia. Cognitive function was evaluated every 10-30 minutes by measuring the latency of the P300 wave, which is the most prominent component of auditory event-related potentials. They found: *(a)* a fall in plasma glucose concentration from 83 ± 3 mg/dl to 80 ± 1 mg/dl (4.6 ± 0.17 to 4.4 ± 0.05 mmol/L) for 150 minutes had no effect on P300 wave latency, *(b)* there was a significantly increased latency with blood sugar decrements from 87 ± 3 to 72 ± 1 mg/dl (4.8 ± 0.17 to 4 mmol ± 0.05 mmol/L) for 120 minutes, *(c)* when plasma glucose levels were decreased from 88 ± 2 to 50 ± 1 mg/dl (4.9 ± 0.1 to 2.8 ± 0.05 mmol/L), a marked increase in P wave latency was demonstrated that had a high correlation with plasma glucose concentrations ($r = 0.76$; $P<0.001$). The threshold for hypoglycemic symptoms was 49 ± 2 mg/dl (2.7 ± 0.1 mmol/L). These observations in normal nondiabetic subjects are an important baseline because they show that the threshold of 72 ± 1 mg/dl (4 ± 1 mmol/L) is higher than currently thought for early impairment of cognitive function (neuroglycopenia). Hormonal counterregulation follows the onset of neuroglycopenia and symptomatic hypoglycemia is a **late** indicator of neuroglycopenia.

Blackman and colleagues (100) have provided confirmatory evidence for the above findings in 19 healthy normal subjects. Although they observed individual variation in response to hypoglycemia, they noted that cognitive dysfunction occurred at an average plasma glucose levels of 59.4 and 46.8 mg/dl (3.3 and 2.6 mmol/L). They reported that decision-making rather than sensory or motor processes were predominantly affected as well as auditory and visual P300 reaction time. Again, recovery of cortical dysfunction lagged behind a restoration of plasma glucose levels to normal by 45-75 minutes.

Adults with IDDM, not unexpectedly, show frequent cognitive dysfunction associated with inapparent hypoglycemia (101). Diminished "attention" is the main manifestation of cerebral dysfunction. Poor performance of everyday tasks was apparent at blood glucose concentrations of 54 mg/dl (3 mmol/L), not usually considered to be in a hazardous range. The performance tests indicated that the frontal lobes are more sensitive to hypoglycemia than other cortical regions. These deficits have implications for everyday life; an excess of automobile accidents in IDDM women but not men (102), seizures with musculoskeletal injuries (103), and permanent neuropsychological impairment (104).

This extensive, perhaps too comprehensive, discussion of hypoglycemia and brain function is relevant to pregnant IDDM women because meticulous diabetic control—in the best interest of the fetus—places them at considerable personal risk if they are overinsulinized and experience frequent episodes of apparent or inapparent hypoglycemia. Low blood glucose concentrations negatively influence brain function because of the inability of the brain to utilize oxygen during episodes of hypoglycemia despite normal arterial oxygen tension. This can result in brain damage. Many more episodes of hypoglycemia are recognized since home blood glucose monitoring became part of standard diabetic care during the past decade. We have now recognized in our own clinic a number of IDDM women with impaired cognitive abilities following severe episodes of hypoglycemia during previous pregnancies in our program.

Do episodes of severe maternal hypoglycemia affect the fetus? We are unable to measure neurodevelopmental changes in utero. In hypoglycemic mothers, blood pressure does not change, but maternal pulse rate increases. In six of nine women studied by Stangenberg and

colleagues (105), there was a decrease in fetal heart rate variability during hypoglycemic periods that increased with normalization of maternal blood glucose levels. The authors postulated this could be a direct effect of glycopenia on the fetal heart. There are no prospective studies that specifically address this problem in school-age follow-up studies of children of IDDM women who experienced mild and/or severe episodes of hypoglycemia during their pregnancies.

We have never observed a severe episode of hypoglycemia (mental confusion, seizures, or coma) in a pregnant NIDDM or GDM woman, probably because each has normal counterregulatory responses for low glucose levels and rarely, if ever, experiences inapparent hypoglycemia.

CHAPTER

13

Insulin Treatment of Pregnant GDM, IDDM, and NIDDM Women

There are many ways to devise insulin regimens for pregnant women, not unlike approaches used in treating IDDM in children, adolescents, and adults. The methods we use, described later in this chapter, were selected because they are simple and easy to "fine-tune." The important point is to individualize insulin administration for each patient based on her work, play, eating, and sleep habits. Successful regimens can be implemented even in women with consistent but unusual eating patterns and physical activities. Table 14.10, in the following chapter, illustrates the coordination of insulin administration and dietary adjustments in several nonroutine diabetic pregnancies. For these reasons and to keep things simple, we do not use meters with data banks or algorithms that neither we, nor our pregnant patients in a dynamic ever-changing metabolic state, can interpret.

For working women or those often away from home, it may be an added convenience to carry an "insulin-pen" for injecting insulin doses (Fig. 13.1).

GDM

Women with gestational diabetes (with normal HbA1c concentration before 20 weeks' gestation and reversible hyperglycemia postpartum documented by repeat testing according to WHO criteria) have two metabolic characteristics: *(a)* impaired β-cell recognition of elevated glucose concentrations, and *(b)* a delay in release of insulin. This form of diabetes is relatively mild if strict criteria are used for diagnosis that eliminate most women with asymptomatic, previously undiagnosed NIDDM.

There are two treatment options: *(a)* dietary treatment (discussed later in this section) or *(b)* diet plus insulin. At least half of women with GDM maintain near-normal plasma glucose profiles around the clock when treated by dietary means. However, if they have an elevated fasting plasma glucose (>90 mg/dl; 5.0 mmol/L) or 2-h postprandial glucose levels that exceed 120 mg/dl (6.7 mmol/L) on several days between clinic visits, insulin treatment should be started. In **normal-weight GDM women,** residual β-cell function is present and their problem is insufficient insulin reserve capacity to maintain normoglycemia with meal stimulation. It is most physiologic to give them a small dose of rapid-acting insulin before each meal. Blood glucose levels are monitored before each meal and insulin doses are easily adjusted on a daily or weekly basis.

Obese GDM women present a different problem. In addition to the defects in β-cell function described previously, they may have appreciable insulin resistance secondary to obesity that becomes more intense when pregnant. They respond well to a reduction in caloric intake (see 1990 guidelines later in this section) and preprandial doses of rapid-acting insulin. In some, a 10:00 PM dose of intermediate-acting insulin is necessary to achieve a normal 24-h glucose profile. This can be prescribed safely—if cautiously with the first dose, because they do not have brittle (unstable) diabetes or lack normal hormonal responses to hypoglycemia.

In some centers, there has been enthusiasm for treating all GDM with insulin ("prophylactic insulin") (106, 107). The rationale for this approach is to prevent fetal macrosomia. Roversi and colleagues (106) were the first to

Figure 13.1. Novolin pen™. Simple, portable dial-a-dose insulin delivery system. Pen refill cartridges are available as semi-synthetic rapid-acting human insulin, NPH human (semi-synthetic) insulin isophane suspension, or 70% NPH human insulin isophane suspension with 30% rapid-acting human (semi-synthetic) insulin. Provided by the Novo-Nordisk Company, Princeton, NJ, courtesy of Rex Clements, MD.

report this method of treatment in an uncontrolled series of 225 pregnancies. A maximal tolerated dose of insulin was prescribed using hypoglycemic symptoms to determine the maximum dose. On this regimen, only 2.6% of babies were macrosomic and operative delivery rate (primary cesarean section, vacuum extraction, and forceps application) was 14.5%. Mean plasma glucose values were only 90 mg/dl (5.0 mmol/L) before treatment and 70 mg/dl (3.9 mmol/L) during therapy. No comparison group was studied and there was no follow-up of the infants. In our 24-h metabolic studies, the mean 24-h glucose value in normal pregnant women was 84 ± 2 SD 10 mg/dl (4.7 ± 2 SD 0.5 mmol/L). We would question the rationale for iatrogenically establishing "chronic relative hypoglycemia" in a developing fetus for the sole purpose and dubious success of decreasing its birth weight.

Coustan and Lewis (107), in a randomized trial of prophylactic insulin treatment (20 U NPH and 10 U of regular insulin each morning) in 34 women versus 11 treated with diet, reported 2 of 34 infants in the prophylactic group with a birth weight of > 8.5 lb (3.9 kg) and 4 of 11 infants of this size in the diet group. This was a very small sample size in an uncontrolled study not correlated with maternal preconception BMI in the two groups. **One also has to keep in mind that, in routine prenatal clinics, 8% of normal newborn term infants weigh > 4000 g (108).**

Our approach is similar to that of Goldberg and colleagues (109) who followed 58 women with GDM who monitored their blood glucose levels four times daily and began insulin treatment if fasting whole blood glucose values exceeded 95 mg/dl (5.3 mmol/L) and 1-h postprandial values were above 120 mg/dl (6.7 mmol/L). In the Goldberg study, comparison with an historical control group showed a reduction in the incidence of macrosomia from 24% in the controls to 9% in women on home monitoring. We customarily use the 2-h postbreakfast glucose value for making decisions about the initiation of insulin therapy and subsequent changes in dose.

An optimal approach to treatment of GDM requires a large prospective, well-designed clinical trial that includes long-term longitudinal follow-up of infants of GDM mothers.

IDDM

No two IDDM women follow exactly the same insulin replacement regimen and this is certainly true in pregnancy. Substantial insulin adjustments may be required during pregnancy in women with different work patterns and life-styles. Some women will be most comfortable remaining on or beginning round-

the-clock, rapid-acting insulin administered by a pump. A few patients will wish to try to simulate baseline insulin availability of insulin over 24 h by a single injection of long-acting/ultra-lente insulin given in the morning or at night with supplemental doses of rapid-acting insulin administered before each meal.

The simplest, most common form of insulin replacement in prenatal (or other) clinic settings is to give a morning (before breakfast) dose of a mixture of intermediate-acting/NPH or lente and rapid-acting insulin in a single syringe. This is adjusted carefully to maintain normal glucose levels during morning and afternoon until a second (usually about one third smaller mixture is given before dinner), taking into account the effect of midmorning and midafternoon small snacks. **This regimen constitutes the baseline replacement dose.** Adjustments of insulin components are based on glucose monitoring over a period of several days. It takes about 3 days to reflect a change in baseline insulin requirements and this should be done carefully. Some patients will have smoother control with the addition of 2-4 units of rapid-acting insulin before the noon meal.

Figure 13.2 illustrates the establishment of control of hyperglycemia in an IDDM who presented for prenatal care at 25 weeks' gestation. She was hospitalized for rapid (24-h) assessment and diabetes re-education (Table 12.11) and gradually regulated over the next several weeks in the outpatient clinic. No glucose meter was available; insulin adjusments were made by checking a 2-h postbreakfast glucose value in the clinic each week and evaluating urinary quantitative glucose loss in fractional urines from the 24-h period before the clinic visit. She was hospitalized for 36 h in late 3rd trimester to reassess diabetic control before delivery (Fig. 13.2).

Of course, adjustments have to be made for unexpected events—minor illnesses, forgotten or irregular snacks, missed or late meals, emotional upsets, long waiting times in a hospital clinic. Nevertheless, most IDDM patients quickly learn about these things and can make personal adjustments. Diabetic control is never optimal over Christmas holidays, on vacations, changes of jobs, or during any period when there is a change in usual patterns of living. The worst circumstances are unexpected deaths, divorces or marital problems, accidents, or illnesses in children in the family. For all of these reasons, "reading the numbers on the glucose log each week" is meaningless without a conversation concerning possible reasons for "outliers" in glucose measurements.

The lives of most pregnant diabetic women do not follow a preset algorithm for selecting insulin doses. They, least of all, respond to such a mechanistic approach to their IDDM. In our clinic, we never prescribe a bedtime dose of either rapid-acting or intermediate-acting insulin for IDDM patients for the following reasons: *(a)* during sleep—with a constantly feeding fetus—and a mother who injects before breakfast and dinner doses of an insulin mixture and has a bedtime snack, 24-h glucose profiles (hourly determinations) show a downward drift of maternal blood glucose through the night. This is especially true in women with long-standing diabetes, 0 residual insulin, and previous treatment with impure insulins resulting in high titers of insulin antibodies; *(b)* the risk of apparent or inapparent nocturnal hypoglycemia in IDDM is simply too great. Should such an episode occur—many are detected only with 24-h glucose profiles, the metabolic consequences are not brief; morning and postbreakfast hyperglycemia are the rule and maternal glucose control may be disturbed for an entire day or longer, and *(c)* no metabolic studies conducted by many investigators in diverse settings in the United States or Europe have reported documentation of a dawn effect in **pregnant** IDDM women.

In the interim between weekly clinic visits, the pattern of glucose excursions is observed carefully. Ideally, one physician should follow each patient longitudinally during gestation and get to know her (and her family) well. Fine adjustments in her program are then quite easy, especially when they are coordinated with the nutritionist. This approach can be difficult in large teaching hospitals with physicians at many different levels of training. It works well though if the clinic has a nurse clinician who does not rotate and perinatal fellows and chief OB residents who have at least a 3- to 6-month assignment to the clinic. In private settings or HMOs, all obstetricians in the group should be knowledgeable about the modern care of diabetic women or, alterna-

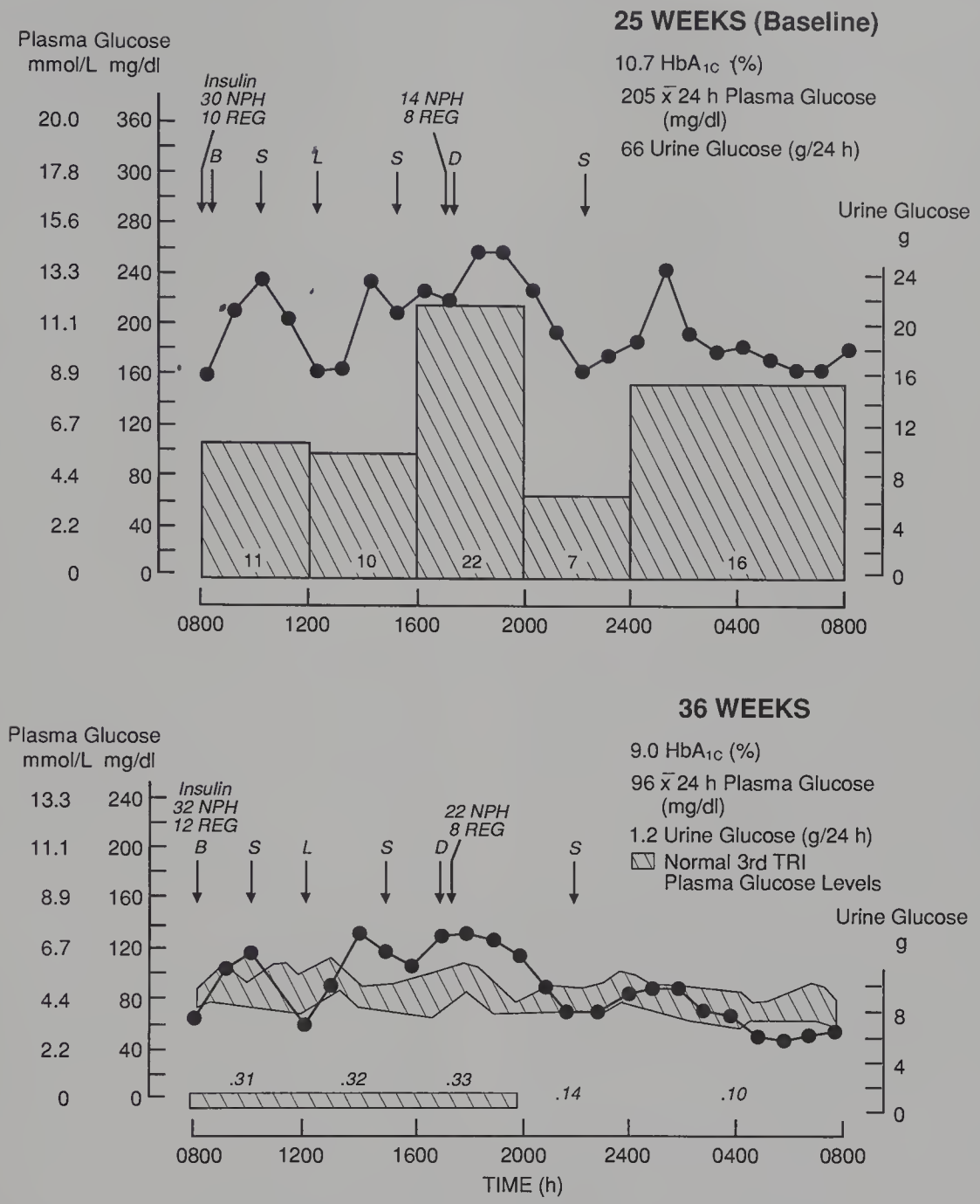


Figure 13.2. These two graphs illustrate 24-h blood and quantitative urinary glucose profiles in a young IDDM on entry into prenatal clinic at 24 weeks'gestation and at late third trimester (36 weeks). *Top:* Every blood glucose determination during the baseline period was abnormal. Mean plasma glucose value was 205 mg/dl (11.4 mmol/L) and HbA1c concentration was 10.7%. Urinary glucose loss was 66 g in 24 h. The assessment was performed on her usual insulin dose of 30 U NPH and 10 U of rapid-acting insulin in the morning and a second predinner dose of 14 U of NPH and 8 U of rapid-acting insulin (total 62 U). *Arrows* indicate times of meals, snacks, and insulin injections in this figure and in Figure 13.3. *Bottom:* At 36 weeks' gestation, the follow-up glucose profile is "near-normal." Mean 24-h glucose has declined to 96 mg/dl (5.3 mmol/L); HbA1c to 9% and urinary loss to 1.2 g in 24 h. Her insulin dose had increased only 12 U/day. The *open hatched area* represents normal plasma glucose values ± SD in six normal pregnant women at 34–37 weeks' gestation.

tively, refer patients who require so much time (in an already busy practice) to a perinatal center that follows many such problem pregnancies.

NIDDM

In many ways, the treatment of pregnant NIDDM women is more difficult and challenging than that of IDDM women because we understand so little about their hepatic and lipid metabolic functions or the genesis of their insulin resistance. NIDDM patients come in two sizes: fat (body mass index; BMI, $kg/m^2 \geq 27$) and thin (BMI < 27).

Thin NIDDM women in 24-h metabolic studies are relatively insulin-deficient but, at this stage, at least, are not ketosis-prone and respond well to twice daily injections of rapid-acting and NPH or lente insulins or preprandial doses of rapid-acting insulin. In prenatal clinics—where it would be both expensive and unnecessary to measure antibodies to insulin, pancreatic islet cell antibodies or HLA tissue types, we can view these patients as perhaps having slowly evolving IDDM without yet having lost 80–90% of their β cells or as having NIDDM and, for one reason or another, are not yet fat. Their subsequent course will unfold over time. Because they have some residual β-cell function and have not had diabetes very long, they are at much less risk for hypoglycemia unless their insulin deficit is excessive. The definition of subgroups of diabetic patients awaits gene markers for each type of disorder.

Several insulin regimens need to be considered for fat, moderately fat, significantly obese ($>$ 200 lb; $>$ 90 kg), and massively obese ($>$ 300 lb; 150 kg) pregnant NIDDM women, many of whom have no difficulty in conceiving. It is rare to see extreme insulin resistance in women who weigh less than 200 lb (90 kg). If the pathophysiology of NIDDM is taken into considération, e.g., faulty or slow β-cell recognition of elevated blood glucose concentrations and a delay in release of insulin, administration of regular insulin before each meal is a reasonable approach that we have found quite successful. There are NIDDM patients, however, who are clearly deficient in insulin overnight and they may demonstrate gradually rising nocturnal glucose levels. We have not investigated this phenomenon further, but as mentioned previously, find a dose of about 10 U of NPH or lente insulin at bedtime smoothes the nocturnal curve. Figure 13.3 illustrates 24-h plasma and urinary glucose profiles in a massively obese, 287-lb (131-kg) pregnant NIDDM woman at 6 and 25 weeks' gestation and 3 months postpartum. Her treatment with rapid-acting insulin before each meal had been started the previous week in the outpatient prenatal clinic.

This case illustrates how much more difficult it is to achieve good diabetic control in massively obese NIDDM women who frequently have no health care supervision before or after pregnancy. Insulin resistance was apparent with less than ideal diabetic control with an increase in insulin dose from 0 units before pregnancy to 112 U/24 h by only 25 weeks' gestation. Pregnancy complications prevented a late 3rd trimester assessment. In this case, the addition of 10–15 U of intermediate-acting NPH insulin would have safely smoothed the nocturnal curve. Patients have not complained about taking three to four insulin injections a day. Pregnancy and the desire for a good outcome provide intense motivation that far exceeds the impetus for optimal glycemic control that diabetic women experience at other periods of their chronic disease.

NIDDM women have a dramatic honeymoon postpartum with a marked fall in insulin requirements. Unfortunately, early hospital discharge is usually with instructions to take no or small doses of insulin. Unless there are definite postpartum arrangements that they may not be able to afford, there is a rapid deterioration of diabetic control (Fig. 13.3, *bottom panel).*

Some obese NIDDM women (usually $>$ 200 lb; 90 kg) who have required no treatment before conception or were controlled by diet alone or oral hypoglycemic agents often have hyperglycemia to such a marked degree during gestation that, by early 3rd trimester ($>$ 26 weeks' gestation), they require $>$ 100 U of insulin a day. An occasional NIDDM patient develops severe, but reversible insulin resistance that requires insulin doses of $>$ 200 U/day. This seems to be a clearly pregnancy-associated (? placental) phenomenon because it disappears immediately upon delivery of the baby and the placenta. To keep the volume of insulin doses

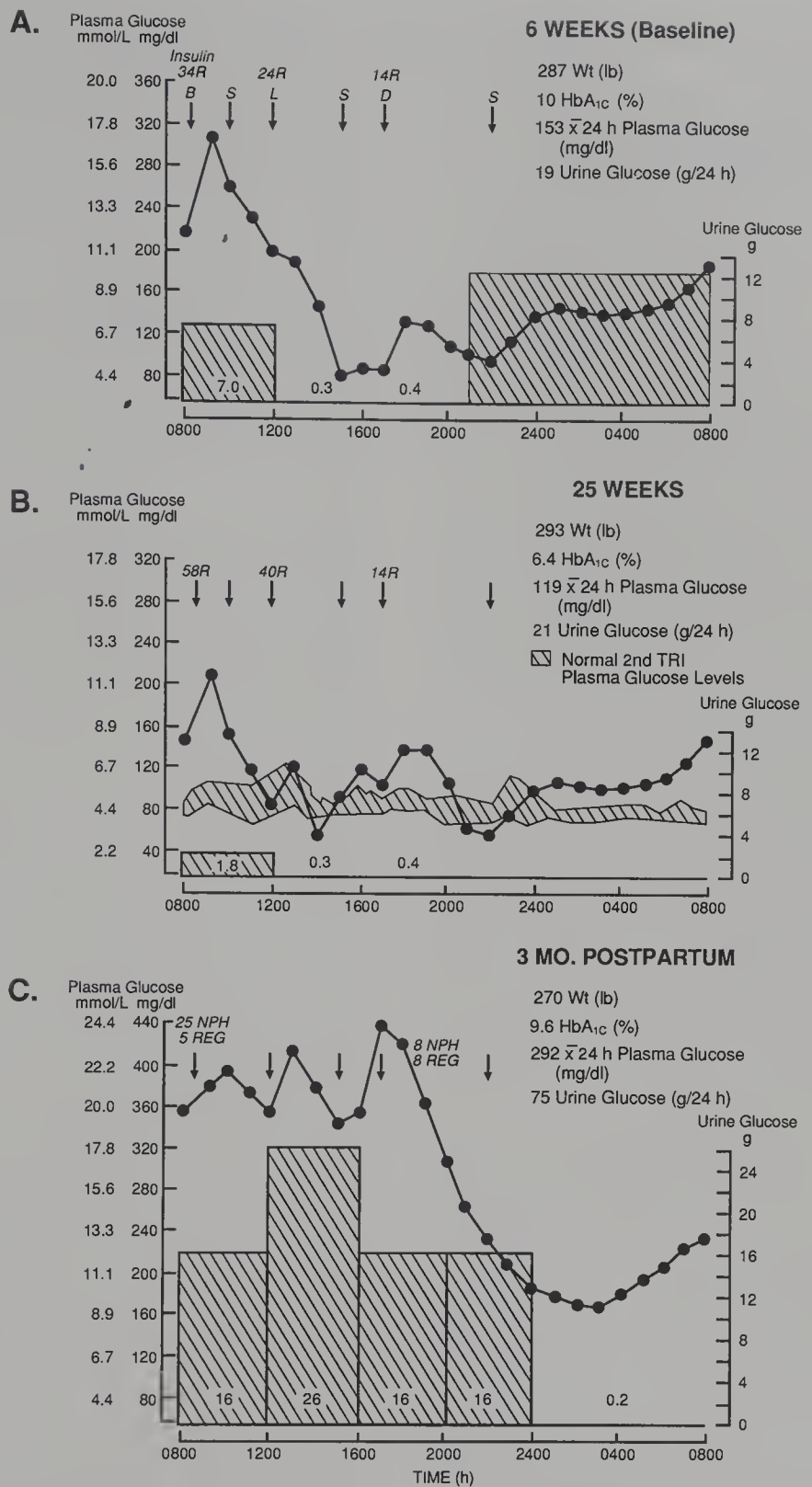


Figure 13.3. Hourly plasma glucose determinations and fractional urinary glucose loss around the 24-h clock in a pregnant NIDDM woman at 6 and 25 weeks' gestation and 3 months postpartum. *Top:* Markedly abnormal 24-h glucose profile with a mean 24-h glucose value of 153 mg/dl (8.5 mmol/L), HbA1c 6.4%, and 24-h urinary glucose loss was 19 g. *Middle:* At 25 weeks' gestation, marked improvement was apparent with a decline in mean 24-h glucose value to 119 mg/dl (6.6 mmol/L), HbA1c 6.4%, and 24-h urinary glucose loss of 2.1 g. The *open hatched area* represents the 2nd trimester 24-h plasma glucose profile in six normal pregnant women. The patient remained underinsulinized despite an increase from 0 U before conception to 112 U/day by 25 weeks' gestation. *Bottom:* By 3 months postpartum, there was no carry-over of intensive diabetes education program and the patient was not under medical supervision. Her diabetes was seriously out of control with mean 24-h plasma glucose of 292 mg/dl (16.2 mmol/L), HbA1c concentration of 9.65, and urinary glucose loss of 75 g in 24 h.

reasonable in women who require excessive amounts, we have used U-500 rapid-acting insulin prepared by The Lilly Company.

The dietary treatment of NIDDM women is described by Ney in the following chapter. This fascinating type of diabetic pregnancy is largely unexplored in humans. It is certainly heterogeneous and greatly modified by the normal hormonal changes that occur during gestation. It is tempting to surmise that the answers reside in the placenta.

In summary, this section is a review of different types of purified or human insulins available for pregnant women and the various ways the hormone can be administered. A major focus has been the increasingly frequent and severe problem of hypoglycemia in IDDM (but not NIDDM or GDM) pregnancies. This complication, usually a result of overinsulinization, carries a risk of morbidity, mortality, and subsequent impairment of cognitive function for the mother. Potential risks of maternal hypoglycemia for the fetus and child are unknown. Methods are described for administration of insulin for individual diabetic women and general guidelines are presented for insulin treatment of IDDM women, who have a problem of hormonal replacement, NIDDM women who have abnormal β-cell function and insulin resistance, and GDM women, who experience a relatively mild, temporary perturbation of glucose tolerance limited to pregnancy.

There are many ways to achieve the therapeutic goal of relative euglycemia during pregnancy; none is a substitute for a normal pancreas and all methods require experience and clinical judgment.

CHAPTER

14

Maternal Nutrition and Diet

Denise M. Ney

Nutrition and diet have been recognized as critical factors in the management of pregnancies complicated by diabetes since the 19th century (110, 111). Provision of adequate nutrition during pregnancy is essential for optimal fetal growth and development. Women with diabetes need special dietary measures, along with insulin, to achieve normal plasma glucose concentrations throughout the 24-h day. In addition, those women who develop carbohydrate intolerance during pregnancy (gestational diabetes; GDM) also require highly individualized dietary advice and, often, the addition of insulin to achieve and sustain normoglycemia. Current dietary practice for women with diabetic pregnancies follows the accepted guidelines for nutrition during normal pregnancy (112, 113) and recommendations for the nutritional management of diabetes (114).

Development of acceptable guidelines for nutritional management of diabetes during pregnancy is complicated by the heterogeneity of various types of diabetes. There is a lack of consensus regarding nutritional advice for pregnant diabetic women. The areas of controversy include the question of optimal caloric intake and meal patterns in lean and obese women, the percentage of calories from dietary carbohydrate, use of non-nutritive food components, such as caffeine and aspartame, and consideration of the possible benefit of high-carbohydrate, high-fiber diets.

In the first part of this chapter, nutrition in normal pregnancy will be reviewed, followed by a discussion of general principles for dietary management of diabetes. The third part will focus on guidelines for individualized nutritional management of women with GDM, IDDM (Type I), and NIDDM (Type II) diabetes. The special nutritional considerations for pregnant women with diabetes secondary to cystic fibrosis are included because of the increasing frequency of this problem.

RECOMMENDATIONS FOR NORMAL WOMEN

Adequate nutrition during pregnancy contributes to a successful pregnancy outcome. Current guidelines for nutrition in pregnancy are summarized in the 1990 Institute of Medicine, National Academy of Sciences publication, "Nutrition During Pregnancy" (112), a review published by the Tenth Study Group of the Royal College of Obstetricians and Gynecologists (1983) (115) and the 1989 version of the Food and Nutrition Board, National Academy of Sciences, National Research Council Recommended Dietary Allowances (RDAs) (113).

1989 Recommended Dietary Allowances (RDAs)

A number of significant changes have been introduced in the latest version of the RDAs. Thus, use of the 1989 RDAs as guidelines for nutrient intake during pregnancy and lactation deserves comment. The RDAs are defined as "the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged by the Food and Nutrition Board to be adequate to meet the known nutrient requirements of practically all healthy persons" (113). They are intended to reflect average intakes over at least 3 days and, for some nutrients such as vitamins A and B_{12}, they reflect average intake over several months. For most nutrients, and in particular for pregnancy and lactation, nutrient requirements are based on limited data.

Unlike the 1980 RDAs, the new recommendations for women during pregnancy and lac-

Table 14.1.
Recommended Dietary Allowances for Nonpregnant Women and for Pregnancy and Lactation, Revised 1989.[a,b]

Category	Age (yr) or Condition	Weight[c] (kg)	Weight[c] (lb)	Height[c] (cm)	Height[c] (in)	Energy[d] (per kg)	Energy[d] (per day)	Protein (g)	Fat-Soluble Vitamins: Vitamin A (μg RE)[e]	Vitamin D (μg)[f]	Vitamin E (mg α-TE)[g]	Vitamin K (μg)
Females	19–24	58	128	164	65	38	2,200	46	800	10	8	60
	25–50	63	138	163	64	36	2,200	50	800	5	8	65
Pregnant							+ 300	60	800	10	10	65
Lactating[i]	1st 6 months						+ 500	65	1,300	10	12	65
	2nd 6 months						+ 500	62	1,200	10	11	65

[a] Adapted from Food and Nutrition Board, National Academy of Sciences-National Research Council. Recommended Dietary Allowances, 10th edition. National Academy Press. Washington, DC, 1989.
[b] The allowances expressed as average daily intakes over time, are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods in order to provide other nutrients for which human requirements have been less well defined.
[c] Weights and heights of Reference Adults are actual medians for the U.S. population of the designated age, as reported by NHANES II. The use of these figures does not imply that the height-to-weight ratios are ideal.

tation are tabulated as absolute figures rather than as additions to the basic allowances (Table 14.1). This change reflects convenience and the precision with which the additional costs of reproduction and lactation are known. Because there are differences in the amount of milk produced during different stages of lactation, separate RDAs are now provided for the first and second 6 months of lactation. The 1989 RDAs also contain important changes in the allowances for protein, folate, calcium, iron, and zinc for nonpregnant women and for pregnancy and lactation. These allowances are discussed later in this section.

Weight and height of reference individuals in different age and sex classes are used to establish the RDAs for many nutrients. Current changes in the RDAs resulted from use of a different method to determine the heights and weights of reference individuals. In the 1980 RDAs, heights and weights of reference individuals were set at an arbitrary ideal. In contrast, the 1989 RDAs use actual median (50th percentile) values for the U.S. population as reported in the second National Health and Nutrition Examination Survey (NHANES II). These weight and height values more accurately reflect the U.S. population; however, they are not necessarily ideal and may lead to overestimation of energy and nutrient needs when applied to individuals. For example, the weight on which energy requirements are based for nonpregnant women, aged 23–50 yr, is 63 kg according to the 1989 RDAs but 55 kg according to the 1980 RDAs. This results in 1989 recommendations for energy of 2200 kcal (range, 1760–2640 kcal) and 1980 recommendations of 2000 kcal (range, 1600–2400 kcal). While the 1989 RDAs may be more valid for evaluating the intake of a population group, they require more interpretation, particularly with regard to energy needs, for individuals who deviate from the median weights used for the reference individuals. This change affects more than just energy allowances because weight is the basis for setting the RDAs for many nutrients.

In summary, the 1989 RDAs for pregnancy reflect nutrient needs of women at median body weight with moderate to light activity level (Table 14.1). The coefficient of variation for energy requirements for adults is 20%. While the RDAs are useful as guidelines, it is important to remember that most women are not "median" body size and have variable activity patterns. Moreover, women from different cultural backgrounds have diverse eating habits and customs. Thus, it is important to develop an individualized diet plan for pregnant women that is both culturally acceptable and nutritionally appropriate.

Energy and Weight Gain

The total energy cost of pregnancy in healthy, well-nourished women is controversial and is the focus of debate among nutritionists. The World Health Organization (WHO) (116) and the U.S. Food and Nutrition Board (113) estimate a total energy cost of 80,000 kcal for a full-term pregnancy during

Water-Soluble Vitamins							Minerals						
Vitamin C (mg)	Thiamin (mg)	Riboflavin (mg)	Niacin[h] (mg NE)	Vitamin B_6 (mg)	Folate (μg)	Vitamin B_{12} (μg)	Calcium (mg)	Phosphorus (mg)	Magnesium (mg)	Iron (mg)	Zinc (mg)	Iodine (μg)	Selenium (μg)
60	1.1	1.3	15	1.6	180	2.0	1,200	1,200	280	15	12	150	55
60	1.1	1.3	15	1.6	180	2.0	800	800	280	15	12	150	55
75	1.5	1.6	17	2.2	400	2.2	1,200	1,200	320	30[j]	15	175	65
95	1.6	1.8	20	2.1	280	2.6	1,200	1,200	355	15[j]	19	200	75
90	1.6	1.7	20	2.1	260	2.6	1,200	1,200	340	15	16	200	75

[d] In the range of light to moderate activity, the coefficient of variation is ± 20%.
[e] Retinol equivalents, 1 retinol equivalent = 1 μg retinol or 6 μg β-carotene.
[f] As cholecalciferol. 10 μg cholecalciferol = 400 IV of vitamin D.
[g] α-Tocopherol equivalents. 1 mg d-α tocopherol = 1 α-TE. Calculation of vitamin E activity of the diet as α-tocopherol equivalents.
[h] 1 NE (niacin equivalent) is equal to 1 mg of niacin or 60 mg of dietary tryptophan.
[i] An additional 300 kcal/day is recommended during the 2nd and 3rd trimesters of pregnancy only.
[j] Daily iron supplements are recommended for pregnancy, but not for lactation.

which the mother gains 12.5 kg and gives birth to a 3.3-kg baby. Various groups have estimated the energy cost of a normal pregnancy to be as low as 45,000 kcal (117) to 68,000 kcal (118) or as high as 111,000 kcal (119). The National Academy of Sciences in its publication, "Nutrition During Pregnancy," states that the total energy cost of pregnancy is now believed to be 55,000 kcal (112). Differences in these estimates of energy expenditure reflect assumptions regarding the composition of weight gain, the usual energy intake of pregnant women, and measurement of the different components of energy expenditure. Current research using whole-body calorimetry to measure energy expenditure in pregnant women has demonstrated a large inter-individual variation in the energy cost of pregnancy (120).

The 1989 RDA for pregnancy recommends an additional 300 kcal/day during the 2nd and 3rd trimesters with a cumulative energy cost of pregnancy of 80,000 kcal. This increase in energy needs reflects greater energy requirements for maintenance due to a larger tissue mass, the energy equivalent of new maternal and fetal tissue, and the cost of synthesizing these new tissues (Fig. 14.1). There is no allowance in the RDA for activity; for example, the additional energy needed to move a heavier body as pregnancy progresses. The assumption is implied that with advancing gestation, energy expenditure for activity will decrease.

Several investigators suggest that WHO and U.S. RDAs overestimate energy needs because they do not take into consideration that pregnant women may have a decreased ther-

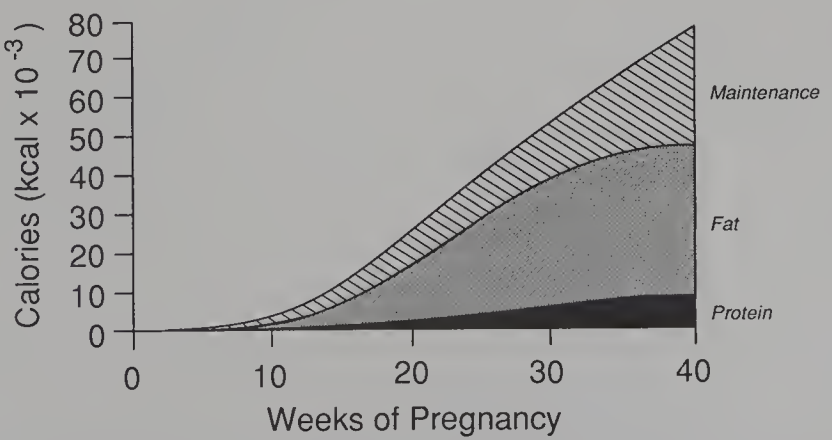


Figure 14.1. The cumulative energy cost of pregnancy and its components. With permission from Hytten FE: Nutritional physiology during pregnancy, p. 1. In Campbell DM, Gillmer MDG (eds). Nutrition in Pregnancy. Proceedings of the Tenth Study Group of the Royal College of Obstetricians and Gynaecologists. September, 1982. Royal College of Obstetricians and Gynaecologists, London, 1983.

Table 14.2.
Average Composition of Pregnancy Weight Gain[a]

Tissue	Weight (lb)	
Fetus	7.5	
Placenta	1.0	Fetal = 13 lb
Amniotic fluid	2.0	
Uterus[b]	2.5	
Breast tissue[b]	3.0	
Blood volume[c]	4.0 (1500 ml)	Maternal = 11–15 lb
Maternal stores	4.0–8.0	
Total		24–28 lb

[a]Adapted from: Maternal nutrition and the course of pregnancy. NAS, 1970.
[b]Weight increase.
[c]Increase in volume (ml).

mogenic response to food, and may utilize energy for activity more efficiently than nonpregnant women. Recent work by King suggests that pregnancy does not reduce the thermogenic response to food (121). She has also reported that, with advancing gestation, pregnant women do not change their pace of walking or efficiency of energy use. This suggests that pregnant women do not utilize energy for activity more efficiently than nonpregnant women and that physically active pregnant women will require greater energy to move their heavier bodies (121). The impact of physical activity on the energy requirements of pregnancy depends on the percentage of time usually spent being physically active. Additional studies are needed to assess the effects of pregnancy, in both lean and obese women, on energy expenditure due to activity, diet-induced thermogenesis, and resting metabolic rate.

Weight Gain

Weight gain during pregnancy reflects growth of both fetal and maternal tissues as outlined in Table 14.2 and Figure 14.1. Since 1970, most reported average total pregnancy weight gains have ranged between 10 and 15 kg (22 and 33 lb) with a range from approximately 7–18 kg (16–40 lb) corresponding to the 15th to 85th percentiles (112). Recommendations for a normal range of maternal weight gain may vary depending on the mother's prepregnant body weight (122) or her prepregnancy body mass index (BMI). BMI is a mathematical expression (BMI = wt/ht^2 = $kg/m^2 \times 100$) of body weight corrected for height. It is commonly used to assess prepregnancy weight for height (112). Recommendations for total weight gain for pregnant women according to prepregnancy BMI are presented in Table 14.3. Tables for estimating BMI are provided in the Appendix.

Table 14.3.
Recommended Total Weight Gain Ranges for Pregnant Women[a] By Pregnancy Body Mass Index (BMI)[b,c]

	Recommended Total Gain		Usual Rate of Gain	
Weight-for-Height Category[d]	kg	lb	1st trimester kg(lb)	2nd and 3rd trimesters kg(lb) per week
Low (BMI < 19.8)	12.5–18.0	28–40	2.3 (5.0)	0.49 (1.07)
Normal (BMI of 19.8–26.0)	11.5–16.0	25–35	1.6 (3.5)	0.44 (0.97)
High[e] (BMI > 26.0–29.0)	7.5–11.5	15–25	0.9 (2.0)	0.30 (0.67)

[a]Young adolescents and black women should strive for gains at the upper end of the recommended range. Short women (<157 cm, or 62 inches) should strive for gains at the lower end of the range.

[b]BMI is calculated using metric units. $BMI = \frac{wt}{ht^2} = \frac{kg}{m^2} \times 100$.

[c]Adapted from Nutrition During Pregnancy. National Academy Press. Washington, DC, 1990.
[d]The ranges for BMI generally correspond to 90, 120, and 135% of the 1959 Metropolitan Life Insurance Company's weight-for-height standards.
[e]The recommended target weight gain for obese women (BMI >29) is at least 6.0 kg (15 lb).

The recommended gestational pattern of weight gain for women who enter pregnancy at normal weight consists of a minimal weight gain of 2–5 lb (1–2.3 kg) during the 1st trimester with a linear rate of weight gain of 0.45–0.52 kg (1 lb) per week during the last 20 weeks of pregnancy (112). The average rate of weight gain during the 2nd trimester of pregnancy may be slightly higher than that during the 3rd trimester. The usual rates of weight gain for women with low, normal, and high prepregnancy BMI are presented in Table 14.3.

Various weight gain charts and tables are available (112) to monitor the rate of weight gain during pregnancy. Current approaches to assess appropriate rate of weight gain in women at the extremes of prepregnant weight for height (i.e., BMI <19.8 or >27) deserve special comment. Rosso (123) developed a weight gain chart that applies different assumptions of weight gain patterns for underweight and overweight women (Fig. 14.2). Rosso's grid suggests that normal-weight women should be advised to achieve 120% of their prepregnancy reference weight for height but that overweight women (e.g., those weighing up to 140% of reference weight for height) should gain up to 115% of their prepregnancy reference weight. The chart suggests that underweight women gain all their weight deficit up to their prepregnancy reference weight as well as the additional weight needed to achieve 120% of that reference weight during gestation. Additional research will be needed to evaluate information presented by Rosso (123) and others (112) for the appropriate rate of weight gain in women who enter pregnancy underweight or overweight.

A large proportion of tissue accretion during pregnancy is fat. Fat is stored mostly in subcutaneous tissue of the abdomen, upper thighs, and back because of higher levels of maternal protein and steroid hormones. Epidemiologic evidence suggests that adequate maternal weight gain, including some maternal fat storage, is needed to assure that the size of the newborn infant is optimal for survival (113). The effect of limiting energy intake during pregnancy on growth of maternal and fetal tissue is unclear. Results of the Dutch famine during World War II suggest that the fetus is somewhat protected from maternal energy restriction as infants of Dutch mothers were well grown but thin, lacking 300–400 g of subcutaneous fat (124). The report of Abrams and Laros (125) indicates that maternal energy intake and corresponding pregnancy weight gain influence infant birth weight only in women who weigh 135% or less of ideal body weight, as shown in Figure 14.3. This suggests that obese women may deliver infants who are overweight regardless of their energy intake and gestational weight gain.

In summary, women who are within 110–

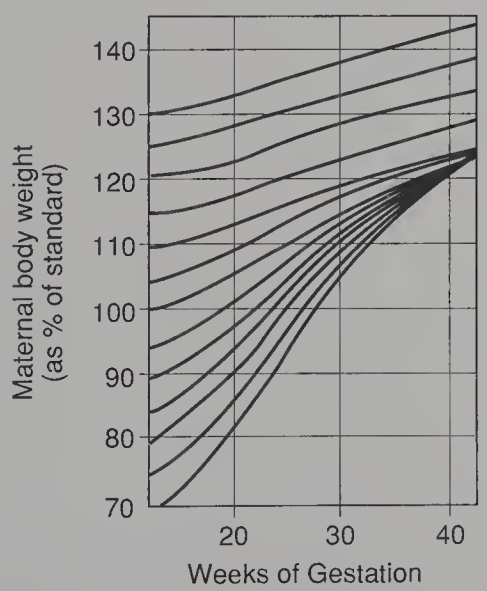


Figure 14.2. Chart to monitor weight gain during pregnancy considering prepregnancy weight and height. With permission from Rosso P: Am J Clin Nutr 1985;41:644.

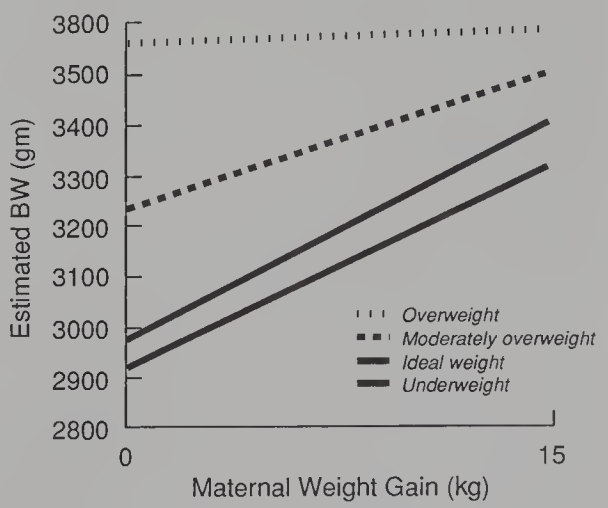


Figure 14.3. Birth weight of live-born infants at term by prepregnancy body mass and weight gain, adjusted for maternal age, race, parity, socioeconomic status, cigarette consumption, and gestational age (n = 2964). With permission from Abrams BF, Laros RK: Am J Obstet Gynecol 1986;154:503.

120% of ideal body weight at conception or have a BMI of 19.8–26 should not limit their energy intake and should be encouraged to gain 11.5–16 kg during pregnancy (112). The risks to the neonate associated with a decrease in infant birth weight far outweigh any advantage of a possible decrease in maternal fat deposition in normal women. Women with an ideal body weight generally require 2000–2400 kcal/day or 36 kcal/kg body weight during pregnancy. Recommendations for energy intake and maternal weight gain in obese pregnant women will be discussed later in this chapter.

Daily Food Guide and Key Nutrients

The quality or nutrient density of the diet needs to be high during pregnancy because energy requirements increase only slightly in comparison to the need for vitamins and minerals. In general, the need for additional protein during pregnancy has been overemphasized. This is reflected in the reduction in protein allowance from an additional 30 g to an additional 10 g of protein per day during pregnancy in the 1989 RDAs. Most American women routinely consume the allowance of 60–65 g of protein per day recommended during pregnancy and lactation. A guide for the selection of a high-nutrient density diet according to the recommended daily food guide for pregnancy and lactation is outlined in Table 14.4.

All vitamins and minerals are needed in increased amounts during pregnancy as indicated in Table 14.1. However, requirements for vitamin B_6, folate, calcium, iron, and zinc increase substantially and deserve special comment. These key nutrients are the same ones most likely to be consumed in inadequate amounts by American women as indicated by the United States Department of Agriculture 1977–1978 Nationwide Food Consumption Survey (126) and the 1986 Continuing Survey of Food Intake of low-income women and their children (127). Food sources and requirements for these key vitamins and minerals are summarized in Table 14.5.

Calcium

Adequate calcium intake during pregnancy is necessary to preserve the maternal skeleton and provide a total of 30 g of calcium (2.5% of maternal skeletal calcium) for mineralization of the fetal skeleton. In addition, recent evidence suggests that an adequate calcium intake may play a role in prevention of pregnancy-induced hypertension (128). This effect is especially important in older primigravida, who are at higher risk for hypertension than younger women.

The 1989 RDAs for calcium in nonpregnant women have been increased to provide 1200 mg of calcium and 10 μg of vitamin D per day through age 24 yr instead of 19 yr (113). This is an attempt to reduce the risk of osteoporosis later in life by assuring that young women reach their genetically programmed peak bone mass. Peak bone mass in women is usually attained by 35 yr of age. It is particularly important that pregnant adolescents receive 1200–1500 mg calcium per day to promote bone deposition.

Prenatal vitamin-mineral supplements provide approximately 100% of the pregnancy RDA for the majority of vitamins and minerals, but most brands contain only 200–300 mg of calcium. If dairy products are not consumed, it is difficult to achieve the pregnancy RDA of 1200 mg of calcium even if a prenatal supplement is taken. Low dietary intakes of calcium (<600 mg/day) are most commonly observed in Blacks, Hispanics, American Indians, and individuals with lactose intolerance (112). Supplements providing 600 mg of calcium per day are recommended if food sources of calcium, such as milk or cheese, are not consumed regularly. One cup of milk and approximately 1 oz of hard cheese each contain approximately 300 mg of calcium. Absorption of calcium from supplements is improved by consuming the supplement with or at the end of a light meal (112).

Iron

Adequate iron intake is needed during pregnancy to prevent iron deficiency anemia in mothers and to allow for accretion of iron stores in newborn infants. The RDA for iron increases from 15 mg to 30 mg/day during pregnancy (113) to provide for the expansion of maternal blood volume, the demands of the fetus and placenta, and blood losses during childbirth. The routine use of an iron supplement during pregnancy is controversial. The U.S. Food and Nutrition Board recommends a daily iron supplement, especially during the last two trimesters, since the typical American diet provides

Table 14.4.
Daily Food Guide For Women[a]

Food Groups	One Serving Equals		Recommended Minimum Servings		
			Nonpregnant		Pregnant/ lactating
			11–24 yr	25+ yr	
Protein Foods Provide protein, iron, zinc, and B-vitamins for growth of muscles, bone, blood, and nerves. Vegetable protein provides fiber to prevent constipation	**Animal Protein:** 1 oz. cooked chicken or turkey 1 oz. cooked lean beef, lamb, or pork 1 oz. or 1/4 cup fish or other seafood 1 egg 2 fish sticks or hot dogs 2 slices luncheon meat	**Vegetable Protein:** 1/2 cup cooked dry beans, lentils, or split peas 3 oz. tofu 1 oz. or 1/4 cup peanuts, pumpkin, or sunflower seeds 1 1/2 oz. or 1/3 cup other nuts 2 tbsp. peanut butter	5	5	7
			A half serving of vegetable protein daily		**One serving of vegetable protein daily**
Milk Products Provide some protein and calcium to build strong bones, teeth, healthy nerves and muscles, and to promote normal blood clotting.	8 oz. milk 8 oz. yogurt 1 cup milk shake 1 1/2 cups cream soup (made with milk) 1 1/2 oz. or 1/3 cup grated cheese (like cheddar, monterey, mozzarella, or swiss)	1 1/2–2 slices pre-sliced American cheese 4 tbsp. parmesan cheese 2 cups cottage cheese 1 cup pudding 1 cup custard or flan 1 1/2 cups ice milk, ice ceam, or frozen yogurt	3	2	3
Breads, Cereals, Grains Provide carbohydrates and B-vitamins for energy and healthy nerves; also provide iron for healthy blood; whole grains provide fiber to prevent constipation.	1 slice bread 1 dinner roll 1/2 bun or bagel 1/2 english muffin or pita 1 small tortilla 3/4 cup dry cereal 1/2 cup granola 1/2 cup cooked cereal	1/2 cup rice 1/2 cup noodles or spaghetti 1/4 cup wheat germ 1 4-inch pancake or waffle 1 small muffin 8 medium crackers 4 graham cracker squares 3 cups popcorn	7	6	7
			Four servings of whole-grain products daily		
Vitamin C-Rich Fruits and Vegetables Provide vitamin C to prevent infection and to promote healing and iron absorption; also provide fiber to prevent constipation	6 oz. orange, grapefruit, or fruit juice enriched with vitamin C 6 oz. tomato juice or vegetable juice cocktail 1 orange, kiwi, mango 1/2 grapefruit, cantaloupe 1/2 cup papaya 2 tangerines	1/2 cup strawberries 1/2 cup cooked or 1 cup raw cabbage 1/2 cup broccoli, Brussels sprouts, or cauliflower 1/2 cup snow peas, sweet peppers, or tomato puree 2 tomatoes	1	1	1

Table 14.4. (*Continued*)

Food Groups	One Serving Equals		Recommended Minimum Servings		
			Nonpregnant		Pregnant/ lactating
			11–24 yr	25+ yr	
Vitamin A-Rich Fruits and Vegetables Provide beta-carotene and vitamin A to prevent infection and to promote wound healing and night vision; also provide fiber to prevent constipation	6 oz. apricot nectar or vegetable juice cocktail 3 raw or 1/4 cup dried apricots 1/4 cantaloupe or mango 1 small or 1/2 cup sliced carrots 2 tomatoes	1/2 cup cooked or 1 cup raw spinach 1/2 cup cooked greens (beet, chard, collards, dandelion, kale, mustard) 1/2 cup pumpkin, sweet potato, winter squash, or yams	1	1	1
Other Fruits and Vegetables Provide carbohydrates for energy and fiber to prevent constipation	6 oz. fruit juice (if not listed above) 1 mediun or 1/2 cup sliced fruit (apple, banana, peach, pear) 1/2 cup berries (other than strawberries) 1/2 cup cherries or grapes 1/2 cup pineapple 1/2 cup watermelon	1/4 cup dried fruit 1/2 cup sliced vegetable (asparagus, beets, green beans, celery, corn, eggplant, mushrooms, onion, peas, potato, summer squash, zucchini) 1/2 artichoke 1 cup lettuce	3	3	3
Unsaturated Fats Provide vitamin E to protect tissue	1/8 med. avocado 1 tsp. margarine 1 tsp. mayonnaise 1 tsp. vegetable oil	2 tsp. salad dressing (mayonnaise-based) 1 tbsp. salad dressing (oil-based)	3	3	3

[a]From Maternal and Child Health Branch. WIC Supplimental Food Branch. California Department of Health Sciences June 1990. NOTE: The Daily Food Guide for Women may not provide all the calories you require. The best way to increase your intake is to include more than the minimum servings recommended.

only 6 mg of iron per 1000 calories. Thus, they reason that the pregnancy RDA of 30 mg iron is difficult to achieve with a daily intake of 2000–2400 calories. There is no RDA recommendation for supplemental iron during lactation, because losses of iron in milk are less than menstrual loss, which is often absent during lactation (113).

The Subcommittee on Dietary Intake and Nutrient Supplements During Pregnancy recommended the routine use of iron supplements during pregnancy in their 1990 Institute of Medicine report (112). Their recommendations include the routine use of 30 mg ferrous iron per day beginning at about week 12 of gestation. Evidence suggests that iron is absorbed more completely from tablets when taken alone, not as part of a multivitamin/multimineral supplement, and when taken between meals with liquids other than milk, tea, or coffee. Fewer side effects have been noted when iron supplements are taken at bedtime. Supplemental vitamin C has not been shown to enhance absorption of iron supplements when given in the ferrous form. Doses of ferrous iron above 30 mg/day may impair the absorption of zinc and should be reserved for the treatment of frank iron deficiency anemia, not for routine prenatal use.

The British investigator Lind argues that

Table 14.5.
Key Nutrients for Pregnancy Often Consumed in Inadequate Amounts by American Women

Nutrient	RDA for Pregnancy[a]	% Increase in RDA	Food Sources
Vitamin B_6	2.2 mg	37	Banana, meat, poultry, fish, legumes, potato
Folacin	400 μg	122	Liver, yeast, orange, spinach, beets, broccoli, peanuts, cantaloupe
Zinc	15 mg	25	Beef, egg, milk, legumes, whole grain cereals, liver, seafood
Calcium	1200 mg	50	Dairy products, fish with bones, dark green leafy vegetables
Iron	30 mg	50	Fortified cereals, liver, beets, raisins, leafy green vegetables, red meat

women who enter pregnancy with sufficient iron stores do not require iron supplementation because absorption of dietary iron increases to meet the additional need for iron (129). The likelihood that most American women enter pregnancy with sufficient iron stores is questionable. Assessment of iron status throughout pregnancy can be useful in identifying women who need iron supplementation.

The normal mean hemoglobin concentration changes considerably during pregnancy as shown in Figure 14.4. Normal hemoglobin levels decline in the 2nd trimester to a mean of 11.6 g/dl and gradually increase during the 3rd trimester reaching a mean value of 12.5 g/dl at 36 weeks' gestation (112). A hemoglobin concentration of less than 11 g/dl during the 1st or 3rd trimesters or below 10.5 g/dl during the 2nd trimester is defined as anemia (112). Anemia accompanied by a serum ferritin concentration of <12 μg/dl strongly suggests the presence of iron deficiency anemia. Treatment

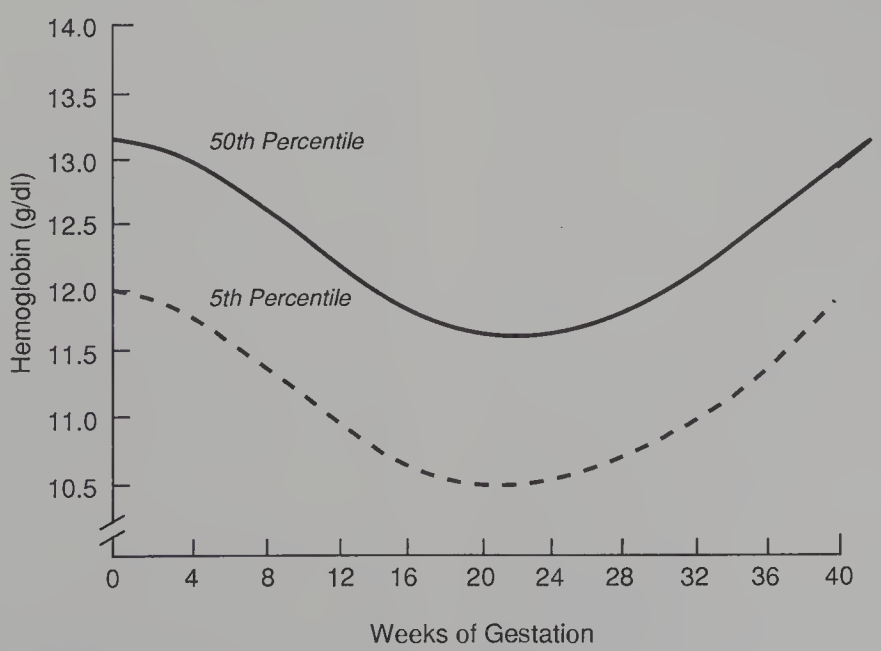


Figure 14.4. Normal hemoglobin values during pregnancy. With permission of National Academy Press, Washington, DC, 1990.

until the hemoglobin concentration becomes normal for the stage of gestation (see Fig. 14.4), and then the dose can be decreased to 30 mg/day).

The principal dietary sources of iron include meat, eggs, vegetables, and cereals, especially fortified cereal products. Food consumption data for women 18–24 yr of age from the National Health and Nutrition Examination Survey (NHANES II) indicated that 31% of daily iron intake came from meat, poultry, and fish and that 25% came from iron fortified cereals (130). Heme iron in animal tissues is highly absorbable in comparison to nonheme iron, which comprises 50% of the iron in animal tissues and all the iron in vegetable products. The absorption of nonheme iron can be enhanced by concomitant ingestion of meat and vitamin C, while the absorption of nonheme iron is reduced by concomitant ingestion of tea, coffee, phytates, and calcium phosphate supplements. Women who do not tolerate iron supplements may enhance their absorption of dietary iron by increasing their intake of red meats, vitamin C, and iron-fortified cereal products.

Folate

Folate is a generic descriptor of compounds with chemical structures and nutritional properties similar to those of folic acid (pteroylglutamic acid) (112). Folates are a key nutrient during periods when rapid tissue growth occurs because they function as coenzymes in the transport of single carbon units. This process is vital to many metabolic processes, including the metabolism of several amino acids and the synthesis of purine and thymidylate-compounds essential to nucleic acid synthesis (112). Low serum folate levels during pregnancy are common although their significance to the course or outcome of pregnancy is unknown. The percentage of folate absorption during pregnancy is unchanged although urinary losses of folate increase compared with those during nonpregnancy (112). Low folate stores may be associated with alterations in folate metabolism due to pregnancy, inadequate dietary folate intake, or prolonged use of oral contraceptives (131). Megaloblastic anemia is one of the first signs of folate deficiency; however, it is rarely observed in pregnant women with low serum folate levels.

Investigators have suggested that reduced folate levels or a change in maternal folate metabolism may be associated with premature birth or neural tube birth defects. Baumslag and colleagues (132) have reported a reduced incidence of premature births in women given supplementary folate. However, a recent study demonstrated that periconceptional use of multivitamins and folate-containing supplements by American women did not decrease the risk of having an infant with a neural tube defect (133). The results of numerous studies to date have been contradictory and inconclusive (112). Clinical trials are currently underway to address the important public health question of whether vitamin supplementation lowers the risk for neural tube defects.

Routine folate supplementation during pregnancy is not currently recommended by the U.S. Food and Nutrition Board (112, 113). Evaluation of the need for folate supplementation during pregnancy should include consideration of current dietary folate intake and folate status, especially if there is a history of long-term use of oral contraceptives. Additional research regarding folate metabolism during pregnancy is needed.

The current RDA for folate during pregnancy is 400 μg, half the previous RDA. This change reflects recognition that diets containing about half the 1980 RDA maintain adequate folate status and liver stores. In addition, folate values in food composition tables are thought to underestimate the true folate content of foods. Good dietary sources of folate include liver, yeast, leafy vegetables, fortified or whole grain breads and cereals, dried peas and beans, and selected fruits, especially oranges and cantaloupe (Table 14.5). Folate is generally unstable and as much as 50% of food folate may be destroyed during food preparation or storage (113).

Zinc

Zinc is essential for cell growth and repair because it is a cofactor or constituent of several important enzymes, including those needed for RNA and DNA synthesis. Plasma concentrations of zinc decrease throughout gestation, which may be due, in part, to hemodilution or uptake of zinc by the fetus or other products of conception. Animal studies indicate that zinc deficiency during pregnancy may lead to developmental disorders in offspring. Evidence from studies of human pregnancy suggest that

lowered maternal serum zinc levels are associated with pregnancy complications and small-for-date babies (134), including a higher incidence of congenital malformations (135).

The 1989 RDA for zinc was reduced from 15 mg to 12 mg to account for the lower body weight of adult women compared to men (113). The RDA for zinc increases by 3 mg during pregnancy, by 7 mg for the first 6 months of lactation, and by 4 mg during the second 6 months of lactation. The typical zinc intake of pregnant women has been estimated to be 9–11 mg/day (131). Among vegetarians, usual zinc intake may be even lower. Zinc absorption increases when zinc stores are low although, in general, pregnancy is not associated with an increase in zinc absorption. Prenatal iron supplements containing more than 30 mg iron have been associated with a reduction in maternal zinc levels (136). Zinc supplementation is recommended when >30 mg of supplemental iron is administered per day (112).

Most of the zinc in the American diet is provided by animal products, in particular meat. Seafood, especially shellfish, poultry, eggs, dairy products, legumes, and whole grains are also good sources of dietary zinc.

Alcohol, Caffeine, and Sugar Substitutes

The adverse effects of excessive alcohol consumption on fetal development have been clearly demonstrated. Infants born to mothers who are chronic alcoholics show a high rate of perinatal mortality and a unique set of characteristics described as the fetal alcohol syndrome (137). Moderate consumption of alcohol during pregnancy is associated with more subtle features of the syndrome, an increased rate of spontaneous abortion, and low birth weight delivery. The lower limit of safety for fetal exposure to alcohol has not been established (138). Therefore, total abstinence from alcohol is recommended during pregnancy. Women who are attempting to become pregnant should also avoid alcoholic beverages because a major part of embryogenesis occurs before 7.5 weeks' gestation, often well in advance of a confirmed diagnosis of pregnancy.

The effect of caffeine ingestion on pregnancy outcome has been the subject of several investigations. In a retrospective study of 12,000 normal pregnant women, Linn et al. (139) found no relationship between coffee consumption and the incidence of low birth weight, short gestation, or congenital malformation. Similarly, Kurppa and associates (140) evaluated prenatal coffee consumption in Finnish women who had given birth to an infant with a significant congenital malformation. They found no difference in consumption in comparison to a control group of women who delivered normal infants. In a more recent prospective study in Connecticut (141), the association of caffeine consumption during pregnancy with late 1st and 2nd trimester spontaneous abortions was studied. In women who consumed >150 mg of caffeine daily, there was a higher incidence of late 1st and 2nd trimester spontaneous abortions compared with women who consumed 0–150 mg of caffeine daily. Overall, there are no convincing human data to suggest that caffeine intake affects pregnancy outcome (131). However, common sense suggests that pregnant women should use caffeine in moderation, for example, no more than 2–3 cups of a caffeine-containing beverage per day.

The sugar substitutes, saccharin, aspartame (trade name Nutrasweet) and acesulfame-K (trade name Sunette) are available in the U.S. Aspartame is the most popular because it is approved for use in a wider variety of foods than saccharin or acesulfame-K. Acesulfame-K is a nonabsorbable derivative of acetoacetic acid that imparts a clean sweet taste and is stable at high temperatures that occur during baking. In the United States, it is approved for use in chewing gum, dry mixes for beverages, instant coffee and tea, gelatins, puddings, nondairy creamers, and tabletop sweeteners. Aspartame is authorized as a sweetener in cold breakfast cereals, chewing gum, dry bases for gelatins, puddings, fillings, dairy products and toppings, soft drinks, and the product Equal, a dry free-flowing sweetener. Equal uses glucose as a carrier for aspartame and one 1-g packet contains approximately 1 g of carbohydrate and 36 mg of aspartame with a sweetness equivalent to 2 tsp of sucrose. One packet of Equal contains 4 kcal versus 16 kcal contained in 1 tsp of sucrose.

Aspartame is a methyl ester of aspartyl phenylalanine, which is metabolized in the small intestine into methanol, and two amino acids, L-aspartic acid and L-phenylalanine. The phenylalanine content of aspartame is the primary reason for concern regarding safety of use during pregnancy. The FDA has set the

allowable or acceptable daily intake of aspartame at 50 mg/kg body weight and projects that the 99th percentile for daily intake will be 34 mg/kg body weight (142). This represents an intake of 9–14 12-oz cans of aspartame-sweetened soda for a 50-kg person, an intake that we have recorded in obese women with polydipsia. Of course, Nutrasweet is present in many other foods that do not record the amount per serving on the label. Thus, it is impossible to calculate reliably the total daily intake of aspartame in pregnant women. The FDA considers aspartame safe for use during pregnancy (143). However, based on experience with maternal phenylketonuria (PKU) and the well-known detrimental effect of phenylalanine on brain development (144), we feel that aspartame should be used sparingly or not at all by pregnant women; for example, no more than 2 cans of soda per day. This is a particular concern for pregnant women with diabetes who are likely to consume larger amounts of aspartame because their diet eliminates foods containing a high concentration of simple sugars. PKU is not a rare genetic trait. Approximately 2% of the population or 1 in 50–60 people are heterozygous for PKU. Unfortunately, unless there is a case of classic PKU in the family, a woman usually does not know she is a PKU heterozygote. No prenatal care program in the United States screens for maternal PKU heterozygosity.

GENERAL PRINCIPLES FOR THE DIETARY MANAGEMENT OF DIABETES

Diabetes has received more intensive use of dietary therapy than any other disease in medical history (110, 111). Extreme approaches have varied from total starvation to emphasis on one type of nutrient, in particular, fat or carbohydrate (110). The objectives for nutritional management of both nonpregnant and pregnant women with IDDM (Type I) and NIDDM (Type II) diabetes differ. The highest priority for IDDM women is a consistent intake of food, distributed to avoid hypoglycemia. In contrast, in obese nonpregnant women with NIDDM, moderate caloric restriction is stressed to achieve weight reduction. Although weight reduction has been demonstrated very clearly to decrease insulin resistance and lower fasting plasma levels of glucose, insulin, and lipids in nonpregnant obese diabetic individuals, weight reduction during pregnancy in NIDDM diabetes is not recommended.

Table 14.6.
1986 Nutritional Recommendations for Individuals with Diabetes Mellitus[a]

Nutrient	Amount
Protein	0.8 g/kg body weight 60 g/day for pregnancy
Carbohydrate	50–60% of total calories
Fiber	25 g/1000 kcal 40–50 g/day
Fat	<30% of total calories[b]
Cholesterol	<300 mg/dl

[a]Adapted from: American Diabetes Association, (1987) Nutritional Recommendations and Principles for Individuals with Diabetes Mellitus, 1986. Diabetes Care 10:126–132; American Diabetes Association Consensus Statement (1989). Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. Diabetes Care 12:573–579; and Recommended Dietary Allowances, 10th edition, 1989.
[b]Saturated fat <10%, polyunsaturated fat <10% (preferably 6–8%), and the rest as monounsaturated fat.

Current American guidelines for dietary management of diabetes are summarized in the 1986 ADA position statement (114)[1] and the 1986 version of the ADA exchange lists (145). The basic goals of diabetes management include restoration of normal blood glucose concentration, optimal lipid levels, and provision of adequate nutrition throughout the life cycle. The 1986 nutritional recommendations for individuals with diabetes mellitus are summarized in Table 14.6. They do not include specific guidelines for the dietary management of carbohydrate intolerance during pregnancy.

Distribution of Nutrients in the Diet

The optimal amount of carbohydrate in the diabetic diet has been a subject of great debate during this century. From 1950–1970, the American Diabetes Association (ADA) conservatively recommended that carbohydrate intake should be low (40% of total calorie intake) and fat intake should be moderate (40% of total calories). Recognition that diets high in both carbohydrate and soluble fiber content enhance insulin sensitivity and that individ-

[1]A copy of the 1986 "Exchanges for Meal Planning" may be purchased from the American Diabetes Association, 1660 Duke St., Alexandria, VA 22314 (Tel. 800-ADA-DISC) or the American Dietetic Association, 208 S. LaSalle St., Suite 1000, Chicago, IL 60604-1003 (Tel. 312-899-0400).

uals with diabetes are at increased risk for cardiovascular disease has resulted in the 1986 ADA dietary guidelines, which encourage an intake low in fat (<30% of total kcal) and high in complex carbohydrate (50–60% of total kcal) and fiber (25 g/1000 kcal) (114, 146). During the past 10 years, diabetes associations around the world have adopted these dietary guidelines.

Recent evidence, however, suggests that high-carbohydrate, low-fiber, low-fat diets may not be optimal for nonpregnant, nonobese adults with NIDDM. Coulston and co-workers (147) have compared plasma lipids and diabetic control in NIDDM-fed diets containing 14–18 g dietary fiber and 40% carbohydrate + 20% fat or 60% carbohydrate + 20% fat for 6 weeks each. They report a persistent 30% increase in plasma triglycerides, lower HDL cholesterol levels, and significant elevations in plasma glucose concentrations, insulin levels, and urinary glucose excretion during consumption of the 60% carbohydrate-20% fat diet (147). These observations raise questions about the effect of a high-carbohydrate, low-fiber, low-fat diet on glycemic control and triglyceride levels. These results also suggest a need to study further the response to variation in carbohydrate intake of individuals with IDDM and NIDDM before making generalizations for all individuals with diabetes.

Individuals with IDDM or NIDDM have a greater risk for developing coronary artery disease, even in the absence of hypertension, smoking, and lipid abnormalities, than the general population (148). A recent ADA consensus statement recommends dietary management aimed at reducing plasma lipid concentrations, in particular, cholesterol levels to reduce the risk of developing coronary heart disease in individuals with diabetes (148). However, it is important to recognize that we currently lack data indicating a decrease in the late complications of diabetes including coronary artery disease when blood sugar levels are tightly controlled and plasma lipid levels are reduced by diet or other means (149).

The relationship of hypertriglyceridemia to the development of macrovascular disease in NIDDM is unclear as is the dietary treatment of hypertriglyceridemia. For example, fish oils have been recommended for treatment of hypertriglyceridemia in individuals without diabetes, but others have reported that ingestion of fish oils may result in deterioration of glycemic control and an increase in LDL apo B levels in NIDDM (150). Further study of the relationship of plasma lipid levels to diet and the development of cardiovascular disease is needed for individuals with diabetes.

Type of Dietary Carbohydrate

Complex, often controversial issues regarding the type of dietary carbohydrate to include in the diabetic diet have received considerable attention. These issues include the relative effects on glycemic control of simple sugars versus complex carbohydrates, use of the "glycemic index," and the potential benefits of an increased intake of dietary fiber.

Simple versus Complex Carbohydrates

In general, it is recommended that most carbohydrates in the diabetic diet come from starches and other complex forms and that ingestion of simple carbohydrates or sugars, such as sucrose, be restricted to those occurring naturally in foods such as fruits. The elimination of added sucrose in the diabetic diet is based on the premise that sucrose will aggravate hyperglycemia. However, several studies in which diabetic subjects consumed sucrose as part of a meal have demonstrated that the plasma glucose response was not different when compared with an isocaloric amount of other forms of carbohydrates such as bread, potato, or rice (151, 152). Caution needs to be used in interpreting these studies because they have addressed only the acute effects of ingesting sucrose in a single meal; other studies have suggested that long-term sucrose ingestion increases postprandial glucose, insulin, and triglyceride levels, and significantly decreases HDL cholesterol concentrations (153). A prudent approach for good nutrition and weight control for individuals with diabetes would appear to involve restriction of sucrose intake to that occurring naturally in foods with occasional ingestion of a sucrose-containing dessert.

Fructose

Fructose consumption has been steadily increasing in the U.S., in part, due to the widespread use of high-fructose corn syrup by the food industry. Some studies have suggested

that dietary fructose may produce a lower postprandial rise in plasma glucose than isocaloric amounts of other common carbohydrates (151). However, chronic fructose ingestion has been associated with hypertriglyceridemia and in vitro studies demonstrate a higher rate of nonenzymatic glycosylation of hemoglobin with fructose than glucose (151). Long-term human studies are needed to assess the effects of chronic ingestion of fructose in the diabetic population.

Glycemic Index

There is some evidence to suggest that plasma glucose response to equivalent amounts of carbohydrate differs depending on the carbohydrate-rich food source. For example, Crapo and associates (154) compared glycemic responses in NIDDM women fed a 50-g carbohydrate load from dextrose, rice, potato, corn, and bread. They noted the highest postprandial serum glucose response with potato and dextrose, the lowest response with rice and corn, and an intermediate response with bread. This initial observation has led to development of the "glycemic index" (155). The glycemic index classified individual foods based on their glycemic response compared with a reference food or standard.

Proponents of the usefulness of a glycemic index suggest that this classification system offers advantages over the exchange system for planning diabetic diets. The premise is that meals containing foods with a low glycemic index will result in lower postprandial glucose responses in patients with diabetes than meals containing foods with a high glycemic index. Critics of the glycemic index note that it provides insight into the differences that exist in the availability of carbohydrate as it is found within a test food but that extrapolation to mixed meals requires further study (153). Several investigators have been unable to demonstrate any significant difference in glucose and insulin responses with ingestion of meals differing as much as twofold in predicted glycemic response using the glycemic index. Thus, at this time, the glycemic index has not been shown to be useful clinically in designing meals for patients with diabetes.

Dietary Fiber and Blood Sugar Control

Diets high in complex carbohydrate and fiber content reduce postprandial blood glucose levels and insulin requirements, lower serum cholesterol levels, and help control food intake (146, 156). This evidence has led to recommendations by the American, Canadian, and British Diabetes Associations (114, 157, 158) to increase the intake of fiber as a means of reducing postprandial blood glucose concentrations. However, several investigators have noted that the beneficial effects of an increased intake of dietary fiber have not always been demonstrated (153). The positive effects of fiber on blood sugar control are primarily apparent when the fiber is consumed with a diet comprising approximately 50% of calories as carbohydrate (146). Patients taking less than 30 units of insulin daily and those with NIDDM are especially sensitive to the beneficial effects of fiber supplementation.

Two studies in pregnant women with diabetes suggest that fiber supplementation during pregnancy may also have beneficial effects on blood glucose control. Patients with gestational diabetes demonstrated a significant improvement in their oral glucose tolerance test when given a supplement of guar gum (159). In addition, we have demonstrated a significant reduction in insulin requirements in pregnant women with IDDM or NIDDM with ingestion of a high-carbohydrate, high-fiber diet compared with a low-fiber, moderately high-fat diet (160) (Fig. 14.5).

The typical American eats approximately 10-30 g of dietary fiber daily (114, 146, 161). The ADA currently recommends 40–50 g of dietary fiber per day (25 g dietary fiber/1000 kcal) for individuals with diabetes (114). Soluble rather than insoluble sources (e.g., wheat bran) of dietary fibers are more effective in improving glycemic control (146). Soluble dietary fiber increases intestinal transit time, delays gastric emptying, and slows glucose absorption. Because the positive effects of soluble fiber are most apparent when consumed in conjunction with at least 50% of total calories as carbohydrate, it is important to consume dietary sources of soluble fiber, which are also high in complex carbohydrate, rather than commercial fiber supplements.

Foods that provide good sources of soluble fiber and complex carbohydrate include fruits, green leafy vegetables, legumes, lentils, oats, and barley. The 1986 ADA exchange lists highlight foods with a high fiber content. Guidelines to increase dietary fiber intake include:

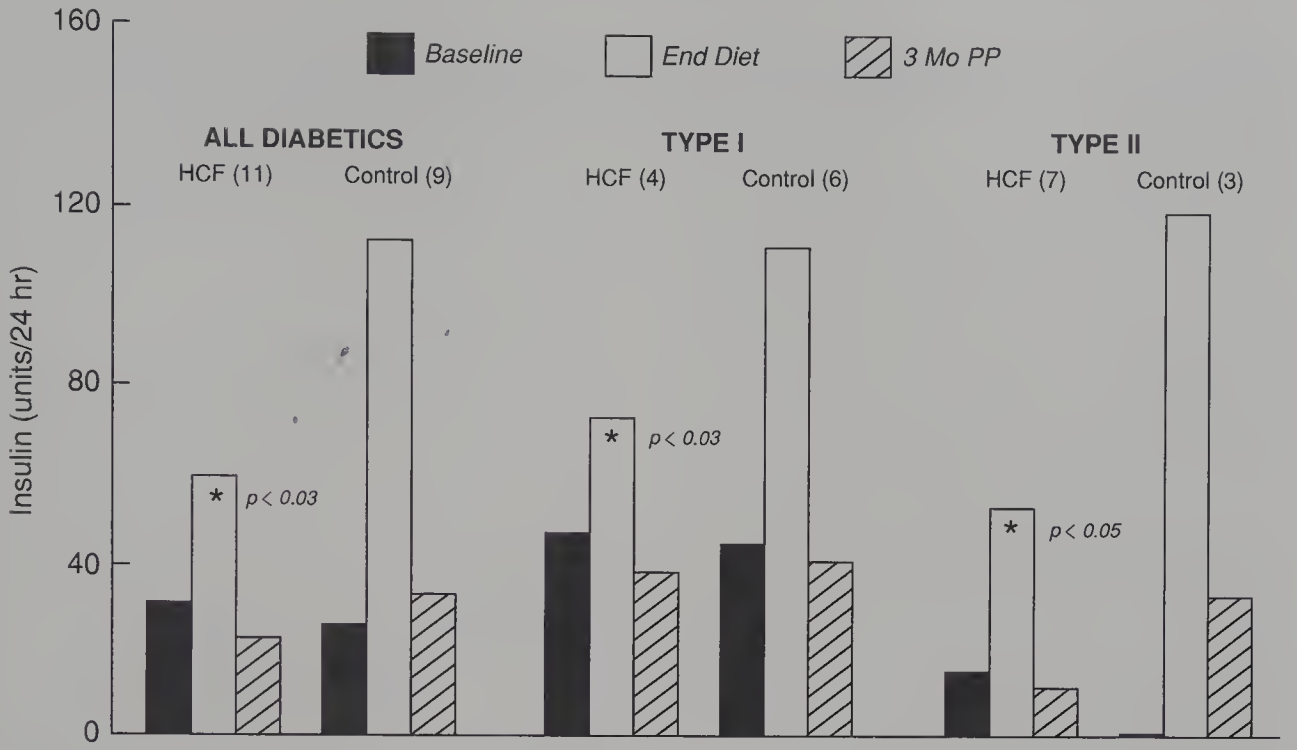


Figure 14.5. Mean daily insulin requirement in pregnant diabetic women who received either a high-carbohydrate, high-fiber diet (HCF) or the control diet at baseline *(solid bars)*, predelivery *(clear bars)*, and 3 months postpartum *(hatched bars)*. Decreases in insulin requirement occurred in both Type I and Type II diabetes. With permission from Ney D, Hollingsworth DR, Cousins L: Decreased insulin requirement and improved control of diabetes in pregnant women given a high-carbohydrate, high-fiber, low-fat diet. Diabetes Care 1982;5:529.

additional servings of vegetables, fruits, legumes, and oats; consumption of raw, unpeeled fruits and vegetables when possible; and use of whole grain breads and cereals in place of refined products. Table 14.7 describes a sample menu for a 2000-kcal high-carbohydrate (50–60% kcal), high-fiber (40–50 g), low-fat (15–20% kcal) diet suitable for women with diabetes during pregnancy. A gradual rather than abrupt increase in dietary fiber intake tends to reduce side effects, such as abdominal cramping, loose stools, and flatulence.

INDIVIDUALIZED NUTRITIONAL MANAGEMENT OF DIABETES DURING PREGNANCY

In the first edition of this book and subsequent publications, we have advised individualized recommendations for nutritional management of IDDM, NIDDM, and GDM patients during gestation because these women demonstrate different hormonal metabolic profiles when studied around the 24-h clock. In addition, the educational and nutritional requirements of women with IDDM and NIDDM differ from those of lean and obese women who develop GDM in the 3rd trimester of pregnancy. A discussion of nutritional management including total energy needs, optimal weight gain, number of meals, and use of an appropriate educational approach for pregnant women with the various types of diabetes is presented in this section.

Gestational Diabetes (GDM, gestational carbohydrate intolerance)

Women who develop gestational diabetes are often but not necessarily overweight. One recent study with a small number of subjects has reported that the majority of women who develop gestational diabetes consume, on the average, an additional 700 calories per day from high-carbohydrate foods, especially sugar-sweetened beverages, cookies, and cakes (162). Excessive caloric consumption from foods high in sucrose can cause an elevation of postprandial blood glucose concentrations during the last half of pregnancy when insulin resistance increases and the metabolic stress of pregnancy is most severe. In GDM, modifications in diet often have a dramatic effect on

Table 14.7.
Sample Menu for a 2000-kcal High-Carbohydrate, High-Fiber, Low-Fat Diet Suitable for Women with Carbohydrate Intolerance During Pregnancy[a]

Breakfast:
1 cup nonfat milk
3/4 cup whole grain cereal
1 slice whole wheat toast
1 banana
1 tsp margarine

Lunch:
1 cup nonfat milk
Chef's salad:
1 cup lettuce
1 oz. turkey
1 oz. skim cheese
1/2 cup garbanzo beans
1 tbsp salad dressing (low fat)
1 whole wheat roll
1 small apple

Dinner:
1 cup nonfat milk
3 oz. chicken breast
1 medium baked potato
1 tsp margarine
1 small corn on the cob
1 cup broccoli
3/4 cup strawberries

Morning Snack:
4 rye crisp crackers

Afternoon Snack:
3 cups popcorn—no fat added
Carrot sticks

Bedtime Snack:
4 graham cracker squares
1 cup nonfat milk

[a]All menus require individualization. Ethnic adaptations for Hispanics, Orientals and Blacks may be needed. This diet includes (%kcal): carbohydrate, 50–60; protein, 12–20; fat, 15–20; dietary fiber is present at the 40–50-g range. Obese women with Type II or GDM may be advised to omit morning and afternoon snacks and to include a small bedtime snack.

normalization of plasma glucose levels to a normal range of 70–120 mg/dl (3.8–6.6 mmol/L) throughout the day. A 1- to 2-week trial period of diet, including intense dietary counseling and monitoring of blood glucose levels at least four times a day, is needed to assess the efficacy of dietary management. Dietary recommendations differ for lean and obese GDM women (Table 14.8). The indications for the use of insulin in GDM are discussed earlier in this section.

In lean GDM patients who have not had excessive weight gain in pregnancy, total caloric intake is not restricted, but free sucrose is eliminated from the diet. Daytime snacks may or may not be advised depending on weight gain and usual dietary patterns. Weight loss or inadequate weight gain should be avoided.

Lean women with GDM, who weigh within 10% of ideal body weight, do not demonstrate a hyperinsulinemic response to food intake. They are metabolically similar to individuals with IDDM and are relatively insulin deficient. Their nutritional recommendations accordingly parallel those of women with IDDM.

Obese GDM women respond well to modest caloric restriction to 1500–1800 kcal/day, elimination of daytime snacks, and, sometimes, the bedtime food supplement. They more often but not always demonstrate accentuated insulin resistance with hyperinsulinemia during pregnancy far greater than when not pregnant or compared with lean GDM, lean NIDDM, and IDDM women. Light activity after meals, such as walking, is useful to help control postprandial blood sugar and insulin elevations and should be encouraged. Nutrition education needs to emphasize the basic principles of dietary management of diabetes and nutrition during pregnancy. An emphasis on behavior modification to help affect long-term changes in eating habits and postpartum weight reduction is important because women with GDM have an increased risk of developing overt diabetes.

Recommendations for energy intake and weight gain in overweight pregnant women with GDM are controversial. Nutritionists, diabetologists, and obstetricians agree that pregnancy is not a time for weight reduction.

Table 14.8.
Nutritional Recommendations for Women with Gestational Diabetes[a]

Lean	Obese
Consistent timing of meals and caloric intake	Stress modification of eating pattern to lower intake of fat and avoidance of sucrose
3 meals plus 3 snacks at midmorning, midafternoon, and bedtime	3 meals with no or very small snack at bedtime
Avoid high-fat and high-sugar meals; adapt meals to usual lifestyle.	Limit breakfast to 20–25% of daily kcal
2000–2400 kcal/day; 36 kcal/kg ideal prepregnancy weight gain; avoid inadequate weight gain, weight loss, or long periods without food; at higher risk for early AM ketonuria; 25–35 lb weight gain.	1500–1800 kcal per day; 25 kcal/kg ideal prepregnancy body weight; 15–20 lb (7–9 kg) weight gain

[a]Body Mass Index (BMI) kg/m^2—lean: 19.8–26, obese: 29–>40.

However, some are not comfortable with even modest caloric restriction during gestation (163, 164). In contrast, a number of other investigators (115, 165–168) who have published a variety of clinical reports feel that a reduction of calories in obese pregnant women has no adverse effect on the mother or baby. Taken together, these latter studies indicate that daily caloric allowances advised for normal women may be excessive for obese GDM and NIDDM women who are not prone to ketosis compared with normals and lean diabetic women. We and others (122) have recommended a lower pregnancy weight gain of 15–20 lb for obese women with a BMI of >29. In the Comprehensive Perinatal Project conducted in the early 1960s, weight gains of less than 10 lb were associated with a doubling of perinatal mortality, suggesting that large fat stores do not protect the fetus from maternal nutritional deprivation (122). This large national study was conducted before the development of the specialties of perinatology and neonatology. Restriction of calories to <25 kcal/kg and of weight gain to less than 15 lb during pregnancy should be avoided. A lower caloric intake, particularly when the diet is not high in complex carbohydrate or well distributed, may be associated with ketonuria in lean and some obese women.

Algert and colleagues (169) have investigated the effect of modest caloric restriction (1700–1800 kcal/day; 25 kcal/kg/day) in 22 obese women with GDM. They observed a lower weight gain in obese subjects than in lean GDM women or normal controls. However, placental weights were higher and their infants were significantly heavier (Fig. 14.6). No ketonuria or untoward effects were observed in any of the subjects or their infants.

The energy needs of obese pregnant women are unclear. Perhaps these individuals have an activity level that is less than expected or their energy utilization is more efficient. Definitive answers will require technical studies comparable to those now underway in nonpregnant women. For obese pregnant diabetic women, we suggest that the most practical approach is to provide caloric prescriptions of 1500–1800 kcal/day, but not less than 25 kcal/kg of the ideal prepregnancy body weight, coupled with careful monitoring of weight gain and subsequent adjustment of food intake.

IDDM (Type I) (170)

For this group of pregnant women, one must consider several important variables. These include the stage of pregnancy when first seen, life-style, cultural food preferences, timing of meals, level of physical activity, and energy needs for gestation.

During the 1st trimester and often before any other sign of pregnancy, such as nausea or vomiting, a well-controlled IDDM patient may note symptoms of hypoglycemia and the presence of unexplained ketonuria. This abrupt metabolic change may reflect a rise in maternal plasma levels of estrogen and pro-

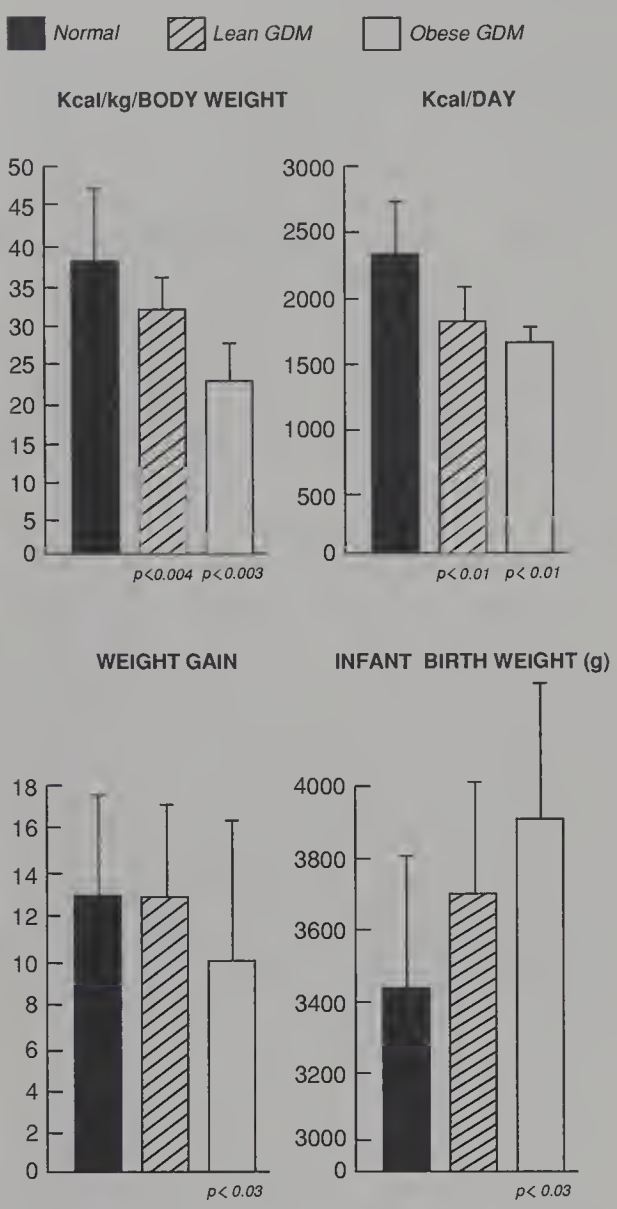


Figure 14.6. Calorie intake calculated as kcal/kg of prepregnancy body weight and total kcal/day, weight gain during pregnancy, and infant birth weight in normal women (n = 10) versus lean (n = 31) and obese (n = 22) patients with gestational diabetes. Values represent means ± SEM. With permission from Algert S, Shragg P, Hollingsworth DR: Moderate calorie restriction in obese women with gestational diabetes. Obstet Gynecol 1985;65:487 and American College of Obstetricians and Gynecologists.

gesterone and an increased tissue sensitivity to insulin.

By 6 weeks' gestation, even mild nausea, with or without vomiting, decreases food intake. Well-controlled IDDM women, as well as those in poor control, may note sudden, wide excursions of plasma glucose levels and mild to severe episodes of hypoglycemia and ketonuria followed by marked hyperglycemia. Symptoms of hypoglycemia are most frequent at night or with daily activities that require added output of energy. Thus, in the 1st trimester, a decreased intake of food and altered food choices have to be taken into account and insulin doses adjusted appropriately downward. Small frequent feedings throughout the day and at bedtime are often the most practical approach. These changes in daily pattern are somewhat counterbalanced by the usual somnolence and fatigue that markedly decrease physical activity early in pregnancy. There is, however, a great deal of individual variation among women who work and have added stresses and strains. The emotional lability so common in the first few weeks of pregnancy may disrupt previously consistent meal patterns. These changes should be mentioned during preconception counseling so that they can be anticipated and diabetic treatment modified by prenatal care begun as early as possible after conception (171). A key feature of dietary management is the initial careful history. We have not found it very rewarding to present patients with a "diet consultation" of didactic lectures and a daunting series of exchange lists. This is especially true in multicultural urban areas. Instead, nutritionists and pregnant women find it far more enjoyable and profitable to exchange information about how each patient and her family actually live and eat. A dietary program should be designed for that family and their life-style. No radical or unacceptable change in dietary habits is advised beyond the guidelines described earlier. Menu selections are adapted for the preferences of different ethnic groups. In San Diego, these menus include those for Anglos, Afro-Americans, Mexican-Americans, Orientals, Southeast Asians, Samoans, and others from the Pacific Basin.

After the above information has been obtained, emphasis is placed on consistent timing of meals. This is perhaps the most important instruction for IDDM women whose glycemic control during pregnancy will be monitored frequently and meticulously. Most IDDM women find a meal pattern of three meals and three snacks each day the most satisfactory. The bedtime snack contains a minimum of 25 g of complex carbohydrate. However, we have had patients who do not get up until noon and others working in restaurants who eat their major meal of the day at 10:00 PM. We enlist

the help of each patient in the management process and then devise an individual dietary plan. No two patients ever have exactly the same dietary plan and, for this reason, we tend to use dietary "guidelines" rather than "protocols" (Table 14.9).

Because no present method of insulin administration completely mimics normal β-cell function, the therapeutic line between control and maternal hypoglycemia in pregnant IDDM women can be quite narrow (as described in detail earlier in this section when insulin was considered as a necessary but dangerous drug). When dietary intake is consistent and blood glucose levels are monitored frequently, much more informed judgment is possible concerning the type, amount, and route of insulin administration. The role of exercise in the therapeutic triad is discussed in the chapter that follows.

In IDDM women who are of normal weight and eat according to appetite, the average daily caloric intake in our clinic is 2282 ± 524 kcal/day. Weight gain during pregnancy is monitored each week and caloric intake is adjusted accordingly to prevent inadequate or excessive weight gain. An occasional IDDM patient is obese; we have noted that these patients tend to gain weight more easily. To prevent excessive weight gain (>25 lb; 11.4 kg), caloric intake may have to be adjusted downward. All patients are followed weekly in an ambulatory clinic where the quality and quantity of food intake is assessed. Pregnancy is a dynamic state, and adjustments have to be made frequently if gastrointestinal symptoms, illnesses, pregnancy complications, or changes in activity occur. Women with IDDM are the most labile and fragile of all pregnant diabetic women. Attempts at "perfect" blood glucose control are unrealistic. In some women, extremely tight control may increase the risk of

Table 14.9.
Nutritional Recommendations for Pregnant Women with Diabetes[a]

	Insulin-Dependent (IDDM, Type I)	Obese Non-Insulin-Dependent (NIDDM, Type II)[c]
General guidelines	Timing and number of meals individually adjusted for life-style and physical activity	Attempt to achieve normal weight before conception
	Regularity of food intake and exercise patern, with ingestion of a carbohydrate-rich snack before exercise	Monitor weight gain carefully each week **Weight reduction not recommended**
Restricted substances	Glucose, fructose, and sucrose Alcohol and non-nutritive sweeteners	Same as for Type I patients
Diet composition	CHO 50–60%[b] PRO 12–20% FAT 30%	Same as for Type I patients
Total calories (kcal)	2000–2400 kcal/day 36 kcal/kg/day for ideal weight	1500–1800 25 kcal/kd/day for ideal weight
Diet distribution (adjust to life-style)	AM 20% kcal Snack 5% Lunch 30% Snack 5% Dinner 35% HS snack 5%	AM 20% Lunch 30% Dinner 40% HS snack 10%
Weight gain	25–35 lb (11.5–16 kg)	15–20 lb (7–9 kg)

[a]These recommendations are rough guidelines. Each woman must have a highly individualized diet prescription based on food preferences, life-style, ethnicity, and activity pattern.
[b]Preferably as complex unrefined carbohydrate (starch associated with fiber).
[c]These patients all require insulin during pregnancy for control of plasma glucose levels.

inapparent hypoglycemia and loss of consciousness. In these patients, six feedings a day, judicious lowering of insulin dose, lower therapeutic goals for glucose values, and frequent telephone communication usually achieve better as well as safer control than that resulting from unsuccessful attempts at "tight control" that result in blood glucose excursions from <30 mg/dl to 200–300 mg/dl in a few hours and unacceptably poor control for the subsequent 1–2 days. Women with no functioning islet cell tissue are at greatest risk for an excessive magnitude of glucose excursions marked by both hyper- and hypoglycemia. Thus, in overall management, and for stability of blood glucose concentrations around the clock, a reasonable and consistent dietary prescription devised in conjunction with the patient is of utmost importance.

Few women actually live according to the idealized management guidelines recommended for IDDM pregnancies. Table 14.10 shows typical examples of five women followed in our clinic. Excellent control was achieved in all five, with smooth prenatal courses and normal babies. Each IDDM patient represents a distinct challenge to achieve "cooperative" treatment; the term "noncompliant" should not be used as a pejorative label for women who are unable (for usually complex emotional, educational, economic, or physical reasons) to follow dietary advice.

NIDDM (Type II)

As described in Section III, pregnant NIDDM women have an entirely different metabolic disorder than women with IDDM, although they share the label diabetes in common. NIDDM women are resistant to ketosis, less labile, and present different types of man-

Table 14.10.
Individualized Approach to Five IDDM Women with Marked Occupational and Life-Style Differences[a,b]

Timing of meals and insulin	Unmarried mother living alone	28-year-old with near blindness, severe nephropathy, and inapparent hypoglycemia	Computer operator who refused to monitor blood glucose levels[c]	Non-English speaking, illiterate in English and Spanish[d]	Nighttime restaurant worker
Breakfast	10:00 AM	8:00 AM	7:00 AM	9:00 AM	4:00 AM
Snack	None	10:00 AM	9:30 AM	None	Sleep
Lunch	1–2:00 PM	12:00 Noon	12–1:00 PM	2:00 PM	2:00 PM
Snack	None	3:00 PM	3:00 PM	5:00 PM	7:00 PM
Dinner	5:00 PM	6:00 PM	7:00 PM	8:00 PM	10:00 PM
Snack	9:00 PM	8:00 PM	11:00 PM	11:00 PM	Intense physical activity
Insulin	10:00 AM NPH regular 5:00 PM NPH regular	8:00 AM NPH regular 12:00 Noon 2 units regular if blood sugar >150 mg/dl 6:00 PM small dose of NPH and regular	7:00 AM NPH regular 7:00 PM NPH regular	9:00 AM NPH regular 2:00 PM regular 8:00 PM NPH regular	10:00 PM NPH regular 4:00 AM regular 2:00 PM NPH regular

[a]These are actual patients followed over the past few years at UCSD Medical Center.
[b]Insulin doses carefully adjusted based on monitoring of blood glucose concentrations at fasting, before meals, bedtime and occasional nocturnal tests.
[c]Insulin dose adjusted weekly based on 24-h fractional urine for quantitative glucose determination.
[d]Color-coded insulin syringes (blue = breakfast; yellow = lunch; green = dinner) were loaded and dispensed at each clinic visit. This woman was so eager to follow all instructions precisely she ate exactly the same foods for each meal at the same times throughout the entire pregnancy.

agement problems. Their insulin therapy is described earlier in this section.

More than half of pregnant women with this form of carbohydrate intolerance are obese at conception. This is the most common form of carbohydrate intolerance; 90% of all diabetic patients have NIDDM. Among some populations (Mexican-Americans, Amerindians, and Pacific Islanders), NIDDM may be present in 50% or more of the population. There are an estimated 1,000,000 women of childbearing age with NIDDM in the United States.

Table 14.9 shows dietary guidelines for obese women with NIDDM. Excessive weight gain is discouraged. Naeye (122) has reported superior obstetric outcome in overweight women with a pregnancy weight gain of 15 lb (7 kg) or approximately half the gain usually recommended. In addition, evidence from developing countries suggests that chronic, mild food restriction in pregnant women does not inhibit fetal growth (121). Taken together, these reports indicate that a lower standard of weight gain may need to be developed for obese pregnant NIDDM women.

We customarily advise omission of morning and afternoon snacks because meals and snacks result in excessive postprandial elevations of plasma glucose and insulin levels. In most women, however, bedtime snacks are prescribed when a long hiatus is present between dinner and breakfast. The appropriate total daily caloric intake for obese diabetic women is a matter of controversy, as discussed earlier.

All obese NIDDM pregnant women are not hyperinsulinemic and markedly insulin resistant. There is no way to document the degree of hyperinsulinemia and insulin resistance (aside from complex clinical investigations) without a glucose loading test to measure insulin and glucose responses, or a short (2-h) or more prolonged (24-h) meal tolerance test (Chapter 7). In most prenatal outpatient settings, it is neither feasible nor practical to obtain this degree of metabolic definition and assessment of functional capacity of the β cell. In our own practice of pregnant and nonpregnant diabetic patients of all ages, however, we have become increasingly dependent on this information and also upon assessment of fasting plasma lipid levels to provide better advice concerning diet, insulin administration, exercise, and postpartum health care, particularly with respect to contraceptive counseling.

Young pregnant NIDDM women are often of normal weight. Some may actually be misclassified because we lack genetic markers for all types of diabetes. Metabolic investigations for insulin reserve and response to meals are not yet part of routine prenatal care. Some women in this group undoubtedly represent "slow-onset" IDDM or they may be so young and of such low parity they have not yet developed the obesity of their mothers and grandmothers. Accordingly, in normal-weight NIDDM patients, we customarily follow the dietary recommendations for IDDM or lean GDM women.

Secondary Diabetes—Cystic Fibrosis

There are many forms of secondary diabetes but most are infrequently or never associated with reproduction (171). The exception is cystic fibrosis (CF), the most common lethal genetic disorder that occurs in about 1 in 2000 Caucasian births. Improved treatment of these patients has resulted in a much longer lifespan. Women with CF now progress through puberty and become pregnant. They may already have secondary diabetes as part of the natural history of CF or develop GDM with the added metabolic stress of pregnancy.

For the few pregnant CF patients who have been referred to us, we have been unable to find dietary recommendations that address the problems of CF requirements, diabetes control, and energy needs of the fetus. The brief discussion that follows is a composite of information gleaned by the author.

Adequate energy intake is the primary concern for pregnant women with CF. Nutritional needs are estimated to increase 30–50% with this disorder because of the additional energy required to breathe against the resistance of mucous secretions and to compensate for the presence of chronic lung infection and malabsorption of nutrients, especially fat. Projected energy needs during pregnancy are 2600–3600 kcal/day (Table 14.11). The work of breathing makes some CF patients anorexic; this increases further the challenge of providing an adequate energy intake.

Optimal pregnancy weight gain for women with CF is 8–10 kg, although this is often quite difficult to achieve. Cohen reported, in 1980, that total weight gain in 41% of pregnant women with CF was less than 4.5 kg (172). Adequate pregnancy weight gain is suggested to be a positive marker for successful preg-

Table 14.11.
Nutritional Considerations for Pregnant Women with Diabetes Secondary to Cystic Fibrosis[a]

Nutritional Factors	Recommendation
Energy	2600–3600 kcal/day; 47–54 kcal/kg of ideal body weight; nutritional supplements may be needed
Weight gain	Strive for at least a minimal 18–22 lb (8–10 kg) weight gain
Nutrients	40% carbohydrate, 20% protein (75–100 g/d), and 40% fat; avoid simple sugars if adequate carbohydrate can be achieved
Meal pattern	Eat to appetite; 3 meals plus 3 snacks; not more than 25% kcal at breakfast
Enzyme replacement[b]	Adjust as necessary at meals and snacks for high-fat foods
Vitamin supplements	Daily prenatal supplement plus: Vitamin A—5,000–10,000 IU Vitamin D—400 IU Vitamin E—200 IU, water-soluble form Vitamin K—5 mg twice a week while on antibiotic therapy (menadiol form)
Salt	At least 600–1200 mg of sodium or 1/2 teaspoon of salt each day; an additional 1–2 tsp of salt during periods of heavy perspiration
Lactose intolerance	Addition of LACT-AID to milk to digest lactose and prevent cramping and diarrhea associated with lactose intolerance

[a]Adapted from Sondel S, Hartman L: Cystic Fibrosis Nutrition Handbook and Cookbook. University of Wisconsin Hospital and Clinics, Madison, WI. p. 12, 1988.
[b]Pancreatic enzymes for treatment of pancreatic insufficiency include: Pancreas (McNeil), Cotazyme-S (Organon) and Creon (Reid-Rowell). A high-fiber diet may interfere with enzyme replacement therapy and should be avoided. Most CF patients are already receiving enzyme supplements. These should be continued.

nancy outcome in these women (173). Enteral or parenteral feeding may be needed in cases where anorexia interferes with adequate energy intake (174). However, aggressive nutritional support has been associated with deterioration of glycemic control. Any increase in doses of insulin must be carefully monitored because CF patients have an increased risk for hypoglycemia. Interestingly, these women with an unusual form of secondary diabetes are not prone to ketosis. Serial assessment of caloric intake and weight gain is important throughout pregnancy.

We recommend a nutrient intake of 40% carbohydrate, 40% fat, and 20% protein to increase the energy density of the diet, and thus facilitate ingestion of a high-energy intake. Pancreatic enzyme replacement therapy should be continued. A high-fiber diet may interfere with enzyme replacement therapy and should be avoided. Beverages and desserts that contain a high concentration of simple sugars should be avoided but may be used occasionally to increase energy intake. In some women, an increase in fat and simple sugars may be the only way to provide adequate fetal nutrition. Maternal hyperglycemia can be carefully monitored and controlled with much lower doses of insulin than those prescribed for IDDM or NIDDM women. Daily supplements of the fat-soluble vitamins A, D, E, and K, twice weekly, are needed as specified in Table 14.11 in addition to a daily prenatal vitamin and mineral supplements. Adequate salt intake is usually not a problem although additional salt may be needed during periods of heavy perspiration. Some individuals with CF also have lactose intolerance and will benefit from the use of Lact-Aid to digest the lactose in milk and dairy products. Breast milk from women with CF is physiologically normal and safe for the infant (175).

Genetic counseling for women with CF is discussed in Section I.

Appendix[a]

Weight		Height, in. (and cm)																						
lb	kg	55.9 (142)	56.7 (144)	57.5 (146)	58.3 (148)	59.1 (150)	59.8 (152)	60.6 (154)	61.4 (156)	62.2 (158)	63.0 (160)	63.8 (162)	64.6 (164)	65.4 (166)	66.1 (168)	66.9 (170)	67.7 (172)	68.5 (174)	69.3 (176)	70.1 (178)	70.9 (180)	71.7 (182)	72.4 (184)	73.2 (186)	74.0 (188)
220	100	49.6	48.2	46.9	45.7	44.4	43.3	42.2	41.1	40.1	39.1	38.1	37.2	36.3	35.4	34.6	33.8	33.0	32.3	31.6	30.9	30.2	29.5	28.9	28.3
218	99	49.1	47.7	46.4	45.2	44.0	42.8	41.7	40.7	39.7	38.7	37.7	36.8	35.9	35.1	34.3	33.5	32.7	32.0	31.2	30.6	29.9	29.2	28.6	28.0
216	98	48.6	47.3	46.0	44.7	43.6	42.4	41.3	40.3	39.3	38.3	37.3	36.4	35.6	34.7	33.9	33.1	32.4	31.6	30.9	30.2	29.6	28.9	28.3	27.7
213	97	48.1	46.8	45.5	44.3	43.1	42.0	40.9	39.9	38.9	37.9	37.0	36.1	35.2	34.4	33.6	32.8	32.0	31.3	30.6	29.9	29.3	28.7	28.0	27.4
211	96	47.6	46.3	45.0	43.8	42.7	41.6	40.5	39.4	38.5	37.5	36.6	35.7	34.8	34.0	33.2	32.4	31.7	31.0	30.3	29.6	29.0	28.4	27.7	27.2
209	95	47.1	45.8	44.6	43.4	42.2	41.1	40.1	39.0	38.1	37.1	36.2	35.3	34.5	33.7	32.9	32.1	31.4	30.7	30.0	29.3	28.7	28.1	27.5	26.9
207	94	46.6	45.3	44.1	42.9	41.8	40.7	39.6	38.6	37.7	36.7	35.8	34.9	34.1	33.3	32.5	31.8	31.0	30.3	29.7	29.0	28.4	27.8	27.2	26.6
205	93	46.1	44.8	43.6	42.5	41.3	40.3	39.2	38.2	37.3	36.3	35.4	34.6	33.7	33.0	32.2	31.4	30.7	30.0	29.4	28.7	28.1	27.5	26.9	26.3
202	92	45.6	44.4	43.2	42.0	40.9	39.8	38.8	37.8	36.9	35.9	35.1	34.2	33.4	32.6	31.8	31.1	30.4	29.7	29.0	28.4	27.8	27.2	26.6	26.0
200	91	45.1	43.9	42.7	41.5	40.4	39.4	38.4	37.4	36.5	35.5	34.7	33.8	33.0	32.2	31.5	30.8	30.1	29.4	28.7	28.1	27.5	26.9	26.3	25.7
198	90	44.6	43.4	42.2	41.1	40.0	39.0	37.9	37.0	36.1	35.2	34.3	33.5	32.7	31.9	31.1	30.4	29.7	29.1	28.4	27.8	27.2	26.6	26.0	25.5
196	89	44.1	42.9	41.8	40.6	39.6	38.5	37.5	36.6	35.7	34.8	33.9	33.1	32.3	31.5	30.8	30.1	29.4	28.7	28.1	27.5	26.9	26.3	25.7	25.2
194	88	43.6	42.4	41.3	40.2	39.1	38.1	37.1	36.2	35.3	34.4	33.5	32.7	31.9	31.2	30.4	29.7	29.1	28.4	27.8	27.2	26.6	26.0	25.4	24.9
191	87	43.1	42.0	40.8	39.7	38.7	37.7	36.7	35.7	34.9	34.0	33.2	32.3	31.6	30.8	30.1	29.4	28.7	28.1	27.5	26.9	26.3	25.7	25.1	24.6
189	86	42.7	41.5	40.3	39.3	38.2	37.2	36.3	35.3	34.4	33.6	32.8	32.0	31.2	30.5	29.8	29.1	28.4	27.8	27.1	26.5	26.0	25.4	24.9	24.3
187	85	42.2	41.0	39.9	38.8	37.8	36.8	35.8	34.9	34.0	33.2	32.4	31.6	30.8	30.1	29.4	28.7	28.1	27.4	26.8	26.2	25.7	25.1	24.6	24.0
185	84	41.7	40.5	39.4	38.3	37.3	36.4	35.4	34.5	33.6	32.8	32.0	31.2	30.5	29.8	29.1	28.4	27.7	27.1	26.5	25.9	25.4	24.8	24.3	23.8
183	83	41.2	40.0	38.9	37.9	36.9	35.9	35.0	34.1	33.2	32.4	31.6	30.9	30.1	29.4	28.7	28.1	27.4	26.8	26.2	25.6	25.1	24.5	24.0	23.5
180	82	40.7	39.5	38.5	37.4	36.4	35.5	34.6	33.7	32.8	32.0	31.2	30.5	29.8	29.1	28.4	27.7	27.1	26.5	25.9	25.3	24.8	24.2	23.7	23.2
178	81	40.2	39.1	38.0	37.0	36.0	35.1	34.2	33.3	32.4	31.6	30.9	30.1	29.4	28.7	28.0	27.4	26.8	26.1	25.6	25.0	24.5	23.9	23.4	22.9
176	80	39.7	38.6	37.5	36.5	35.6	34.6	33.7	32.9	32.0	31.3	30.5	29.7	29.0	28.3	27.7	27.0	26.4	25.8	25.2	24.7	24.2	23.6	23.1	22.6
174	79	39.2	38.1	37.1	36.1	35.1	34.2	33.3	32.5	31.6	30.9	30.1	29.4	28.7	28.0	27.3	26.7	26.1	25.5	24.9	24.4	23.8	23.3	22.8	22.4
172	78	38.7	37.6	36.6	35.6	34.7	33.8	32.9	32.1	31.2	30.5	29.7	29.0	28.3	27.6	27.0	26.4	25.8	25.2	24.6	24.1	23.5	23.0	22.5	22.1
169	77	38.2	37.1	36.1	35.2	34.2	33.3	32.5	31.6	30.8	30.1	29.3	28.6	27.9	27.3	26.6	26.0	25.4	24.9	24.3	23.8	23.2	22.7	22.3	21.8
167	76	37.7	36.7	35.7	34.7	33.8	32.9	32.0	31.2	30.4	29.7	29.0	28.3	27.6	26.9	26.3	25.7	25.1	24.5	24.0	23.5	22.9	22.4	22.0	21.5
165	75	37.2	36.2	35.2	34.2	33.3	32.5	31.6	30.8	30.0	29.3	28.6	27.9	27.2	26.6	26.0	25.4	24.8	24.2	23.7	23.1	22.6	22.2	21.7	21.2
163	74	36.7	35.7	34.7	33.8	32.9	32.0	31.2	30.4	29.6	28.9	28.2	27.5	26.9	26.2	25.6	25.0	24.4	23.9	23.4	22.8	22.3	21.9	21.4	20.9
161	73	36.2	35.2	34.2	33.3	32.4	31.6	30.8	30.0	29.2	28.5	27.8	27.1	26.5	25.9	25.3	24.7	24.1	23.6	23.0	22.5	22.0	21.6	21.1	20.7
158	72	35.7	34.7	33.8	32.9	32.0	31.2	30.4	29.6	28.8	28.1	27.4	26.8	26.1	25.5	24.9	24.3	23.8	23.2	22.7	22.2	21.7	21.3	20.8	20.4
156	71	35.2	34.2	33.3	32.4	31.6	30.7	29.9	29.2	28.4	27.7	27.1	26.4	25.8	25.2	24.6	24.0	23.5	22.9	22.4	21.9	21.4	21.0	20.5	20.1
154	70	34.7	33.8	32.8	32.0	31.1	30.3	29.5	28.8	28.0	27.3	26.7	26.0	25.4	24.8	24.2	23.7	23.1	22.6	22.1	21.6	21.1	20.7	20.2	19.8

152	69	34.2	33.3	32.4	31.5	30.7	29.9	29.1	28.4	27.6	27.0	26.3	25.7	25.0	24.4	23.9	23.3	22.8	22.3	21.8	21.3	20.8	20.4	19.9	19.5
150	68	33.7	32.8	31.9	31.0	30.2	29.4	28.7	27.9	27.2	26.6	25.9	25.3	24.7	24.1	23.5	23.0	22.5	22.0	21.5	21.0	20.5	20.1	19.7	19.2
147	67	33.2	32.3	31.4	30.6	29.8	29.0	28.3	27.5	26.8	26.2	25.5	24.9	24.3	23.7	23.2	22.6	22.1	21.6	21.1	20.7	20.2	19.8	19.4	19.0
145	66	32.7	31.8	31.0	30.1	29.3	28.6	27.8	27.1	26.4	25.8	25.1	24.5	24.0	23.4	22.8	22.3	21.8	21.3	20.8	20.4	19.9	19.5	19.1	18.7
143	65	32.2	31.3	30.5	29.7	28.9	28.1	27.4	26.7	26.0	25.4	24.8	24.2	23.6	23.0	22.5	22.0	21.5	21.0	20.5	20.1	19.6	19.2	18.8	18.4
141	64	31.7	30.9	30.0	29.2	28.4	27.7	27.0	26.3	25.6	25.0	24.4	23.8	23.2	22.7	22.1	21.6	21.1	20.7	20.2	19.8	19.3	18.9	18.5	18.1
139	63	31.2	30.4	29.6	28.8	28.0	27.3	26.6	25.9	25.2	24.6	24.0	23.4	22.9	22.3	21.8	21.3	20.8	20.3	19.9	19.4	19.0	18.6	18.2	17.8
136	62	30.7	29.9	29.1	28.3	27.6	26.8	26.1	25.5	24.8	24.2	23.6	23.1	22.5	22.0	21.5	21.0	20.5	20.0	19.6	19.1	18.7	18.3	17.9	17.5
134	61	30.3	29.4	28.6	27.8	27.1	26.4	25.7	25.1	24.4	23.8	23.2	22.7	22.1	21.6	21.1	20.6	20.1	19.7	19.3	18.8	18.4	18.0	17.6	17.3
132	60	29.8	28.9	28.1	27.4	26.7	26.0	25.3	24.7	24.0	23.4	22.9	22.3	21.8	21.3	20.8	20.3	19.8	19.4	18.9	18.5	18.1	17.7	17.3	17.0
130	59	29.3	28.5	27.7	26.9	26.2	25.5	24.9	24.2	23.6	23.0	22.5	21.9	21.4	20.9	20.4	19.9	19.5	19.0	18.6	18.2	17.8	17.4	17.1	16.7
128	58	28.8	28.0	27.2	26.5	25.8	25.1	24.5	23.8	23.2	22.7	22.1	21.6	21.0	20.5	20.1	19.6	19.2	18.7	18.3	17.9	17.5	17.1	16.8	16.4
125	57	28.3	27.5	26.7	26.0	25.3	24.7	24.0	23.4	22.8	22.3	21.7	21.2	20.7	20.2	19.7	19.3	18.8	18.4	18.0	17.6	17.2	16.8	16.5	16.1
123	56	27.8	27.0	26.3	25.6	24.9	24.2	23.6	23.0	22.4	21.9	21.3	20.8	20.3	19.8	19.4	18.9	18.5	18.1	17.7	17.3	16.9	16.5	16.2	15.8
121	55	27.3	26.5	25.8	25.1	24.4	23.8	23.2	22.6	22.0	21.5	21.0	20.4	20.0	19.5	19.0	18.6	18.2	17.8	17.4	17.0	16.6	16.2	15.9	15.6
119	54	26.8	26.0	25.3	24.7	24.0	23.4	22.8	22.2	21.6	21.1	20.6	20.1	19.6	19.1	18.7	18.3	17.8	17.4	17.0	16.7	16.3	15.9	15.6	15.3
117	53	26.3	25.6	24.9	24.2	23.6	22.9	22.3	21.8	21.2	20.7	20.2	19.7	19.2	18.8	18.3	17.9	17.5	17.1	16.7	16.4	16.0	15.7	15.3	15.0
114	52	25.8	25.1	24.4	23.7	23.1	22.5	21.9	21.4	20.8	20.3	19.8	19.3	18.9	18.4	18.0	17.6	17.2	16.8	16.4	16.0	15.7	15.4	15.0	14.7
112	51	25.3	24.6	23.9	23.3	22.7	22.1	21.5	21.0	20.4	19.9	19.4	19.0	18.5	18.1	17.6	17.2	16.8	16.5	16.1	15.7	15.4	15.1	14.7	14.4
110	50	24.8	24.1	23.5	22.8	22.2	21.6	21.1	20.5	20.0	19.5	19.1	18.6	18.1	17.7	17.3	16.9	16.5	16.1	15.8	15.4	15.1	14.8	14.5	14.1
108	49	24.3	23.6	23.0	22.4	21.8	21.2	20.7	20.1	19.6	19.1	18.7	18.2	17.8	17.4	17.0	16.6	16.2	15.8	15.5	15.1	14.8	14.5	14.2	13.9
106	48	23.8	23.1	22.5	21.9	21.3	20.8	20.2	19.7	19.2	18.8	18.3	17.8	17.4	17.0	16.6	16.2	15.9	15.5	15.1	14.8	14.5	14.2	13.9	13.6
103	47	23.3	22.7	22.0	21.5	20.9	20.3	19.8	19.3	18.8	18.4	17.9	17.5	17.1	16.7	16.3	15.9	15.5	15.2	14.8	14.5	14.2	13.9	13.6	13.3
101	46	22.8	22.2	21.6	21.0	20.4	19.9	19.4	18.9	18.4	18.0	17.5	17.1	16.7	16.3	15.9	15.5	15.2	14.9	14.5	14.2	13.9	13.6	13.3	13.0
99	45	22.3	21.7	21.1	20.5	20.0	19.5	19.0	18.5	18.0	17.6	17.1	16.7	16.3	15.9	15.6	15.2	14.9	14.5	14.2	13.9	13.6	13.3	13.0	12.7
97	44	21.8	21.2	20.6	20.1	19.6	19.0	18.6	18.1	17.6	17.2	16.8	16.4	16.0	15.6	15.2	14.9	14.5	14.2	13.9	13.6	13.3	13.0	12.7	12.4
95	43	21.3	20.7	20.2	19.6	19.1	18.6	18.1	17.7	17.2	16.8	16.4	16.0	15.6	15.2	14.9	14.5	14.2	13.9	13.6	13.3	13.0	12.7	12.4	12.2
92	42	20.8	20.3	19.7	19.2	18.7	18.2	17.7	17.3	16.8	16.4	16.0	15.6	15.2	14.9	14.5	14.2	13.9	13.6	13.3	13.0	12.7	12.4	12.1	11.9
90	41	20.3	19.8	19.2	18.7	18.2	17.7	17.3	16.8	16.4	16.0	15.6	15.2	14.9	14.5	14.2	13.9	13.5	13.2	12.9	12.7	12.4	12.1	11.9	11.6
88	40	19.8	19.3	18.8	18.3	17.8	17.3	16.9	16.4	16.0	15.6	15.2	14.9	14.5	14.2	13.8	13.5	13.2	12.9	12.6	12.3	12.1	11.8	11.6	11.3

[a]Recommended Dietary Allowances for Nonpregnant Women and for Pregnancy and Lactation, Revised 1989. Food and Nutrition Board, National Academy of Sciences-National Research Council.

[b]BMI (metric = $(kg/m^2) \times 100$; BMI (English) = $(lb/in.^2) \times 100$. BMI (metric) × 0.142 = BMI (English): BMI (English) × 7 = BMI (metric).

CHAPTER

15

Exercise in Diabetic Pregnancies

Should diabetic women be enrolled in exercise programs and, if so, which women and for what kinds of exercise? This chapter describes briefly the effects of exercise on normal pregnant women and those with different types of diabetes (176). It follows the general guidelines of The American College of Obstetricians and Gynecologists (177).

PHYSIOLOGIC HEMODYNAMIC CHANGES WITH EXERCISE IN NORMAL PREGNANT WOMEN

Several excellent reviews have provided comprehensive physiologic discussions of both maternal and fetal responses to exercise during pregnancy (178–180). During normal gestation, increases in cardiac output, ventilation, and oxygen consumption are the most important hemodynamic changes. There are, however, marked biological variations among individuals (181). Resting cardiac output in early pregnancy has been reported to range from 5.48–12.0 L/min (182). Because individual variations may in some cases exceed 100%, longitudinal studies that document changes in cardiac output in single individuals have been the most rewarding and have shown that resting cardiac output by midpregnancy increases by 30–50% above nonpregnant values (181, 183, 184).

Other factors that influence observations of cardiovascular status include minute to minute variations in each individual, the conditions under which the observations are made, and differences in methodology utilized by diverse groups of investigators. Most of the increase in cardiac output occurs by the end of the 1st trimester and is maintained until delivery at term.

Figure 15.1 depicts changes in maternal cardiac output, stroke volume, and maternal heart rate from midgestation to 2 months postpartum. These studies by Ueland and colleagues (185) and Metcalfe and Ueland (186) show that maternal cardiac output reaches its highest level by 20–24 weeks of gestation, fluctuates markedly with changes in position, and declines in the last 8 weeks before delivery. As term approaches, venous pooling tends to occur with increased venous distensibility (187), growth of large venous plexuses in the broad ligaments of the uterus, and occlusion of the inferior vena cava by the pregnant uterus in the supine position (188).

Normal hemodynamic changes during gestation include an increase in plasma volume that occurs as early as the 6th week and reaches levels that average 40% above normal. There are, however, extremely wide individual variations (189–191).

Hypervolemia permits filling of the increased vasculature of the pregnant uterus and provides a reserve against hemorrhage at delivery. Red cell mass decreases slightly at the onset of pregnancy but subsequently has a fairly steady rate of gain (181). Hypervolemia of pregnancy results primarily from an increase in plasma volume. Thus, modest hemodilution occurs with a lowering of hemoglobin concentration to 11–12 g/100 ml and hematocrit values of 33–38% in late pregnancy (192).

Hyperventilation occurs normally during gestation and arterial CO_2 tension is approximately 10 mm Hg lower than postpartum. Exercise accelerates the respiratory rate and the work of breathing (193). These changes may be influenced, in part, by a progesterone effect on the respiratory center.

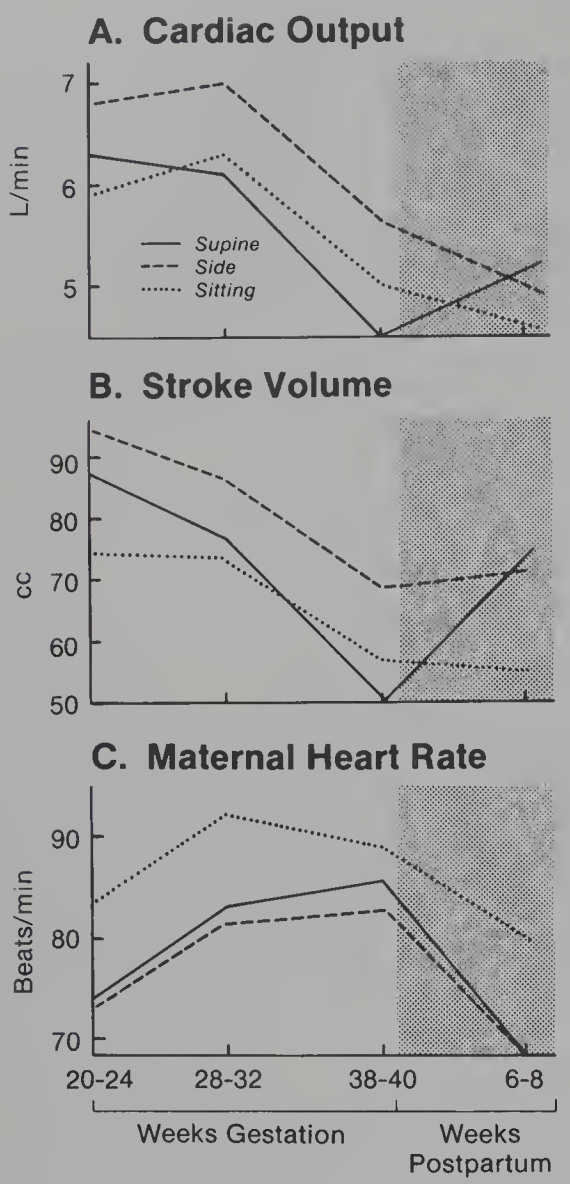


Figure 15.1. The effect of gestational age and maternal posture on cardiac output (*A*), stroke volume (*B*), and maternal heart rate (*C*) in normal pregnancy. With permission from Ueland K, Novy MJ, Peterson EK, Metcalfe J: Maternal cardiovascular dynamics. Am J Obstet Gynecol 1969;856–864.

The clinical correlates of alterations in cardiovascular and hemodynamic factors during pregnancy are an important consideration for recommendations of mild, moderate, or more extreme forms of exercise. Normal physiologic changes result in hyperventilation in the resting state, edema of the lower extremities, and disconcerting changes in balance with a new and awkward shift in the center of gravity. As term approaches, there is a substantial maternal hemodynamic commitment to reproductive tissues, such as the uterus and breasts (179).

EXERCISE IN NORMAL PREGNANT WOMEN

There are very few clinical studies of exercise in normal untrained pregnant women and most reports involve limited observations on small groups of subjects. Figure 15.2 is a schematic representation of Morton's description of the physiologic changes affecting maternal cardiac output at rest and following exercise during normal pregnancy (179). Enlargement of left ventricular volume may reflect hormonal changes. In nonpregnant individuals, exercise results in a diversion of blood flow from the viscera to exercising muscles (194). During pregnancy, there is a redistribution of blood flow to reproductive organs (uterus, breasts, placenta), which is quite marked by term. Physiologic measurements of maternal/fetal changes in blood flow during exercise or other activities throughout human pregnancy have not been possible.

There is little direct evidence on the effect of exercise on human uteroplacental circulation. In an early study by Morris and colleagues (195), radioactive sodium was injected into uterine muscle and the disappearance rate was measured by an external counter to assess blood flow. In late pregnancy, exercise resulted in decreased blood flow to uterine musculature. The effect on the human fetus or placenta of decreased blood flow to the uterine muscle is unknown. The quantitative decrease would likely depend upon type and duration of exercise, previous training, weight bearing, ambient environmental temperature, and many other variables. Morton and colleagues (196) have measured heart rate and stroke volume serially in late gestation in 23 subjects at rest in the sitting position and at the onset and conclusion of a 6-minute period of upright bicycle exercise. They confirmed observations that cardiac output during rest and exercise in late gestation were not different from those in the postpartum period. Heart rates, however, were higher at rest and stroke volume was lower during exercise in late gestation than in the postpartum period. In addition, at the end of exercise, stroke volume fell dramatically in late gestation but not postpartum. Surprisingly, there were no differences between physically fit and nonfit women. In the postpartum period, though, the physically fit women had exercise responses typical of trained persons

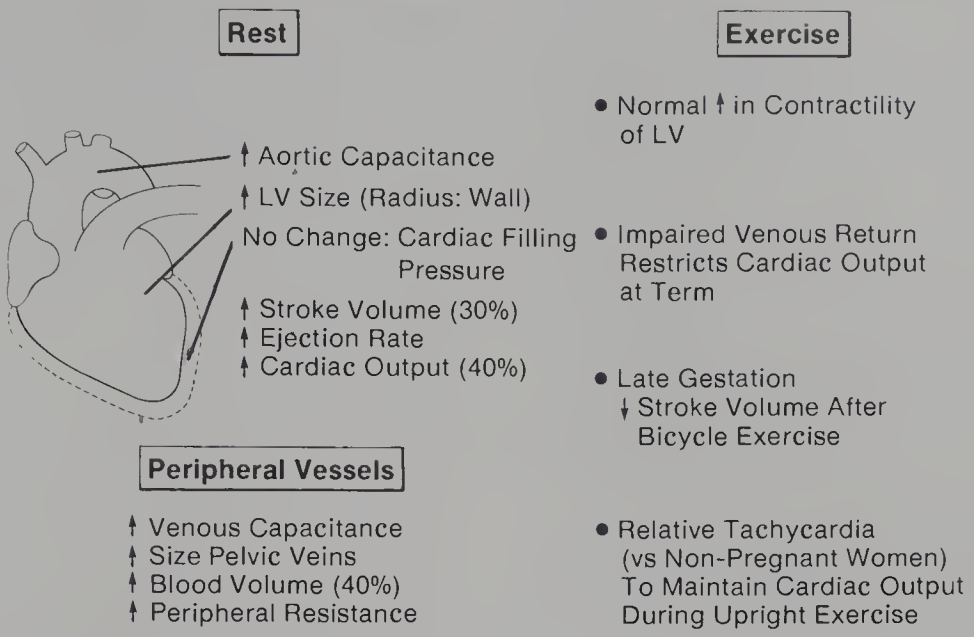


Figure 15.2. Physiologic changes in the heart and peripheral vessels in normal pregnant women at rest and during exercise.

and different from those of the nonfit cohort. They suggested the interesting conclusion that, in late gestation, rest and exercise hemodynamics in subjects in the sitting position appeared to be dominated by factors controlling venous return independent of physical fitness.

In pregnant women, exercise causes a reduction in aerobic capacity, efficiency of oxygen and substrate management, and endurance (197–199). The oxygen cost of exercise (the difference between steady-state oxygen consumption during exercise and resting oxygen consumption) is greater during pregnancy than postpartum. Approximately 50% of this increase is required by the pregnant uterus and its contents (200).

MATERNAL EXERCISE AND RISK TO THE FETUS

The major concern relating to maternal exercise is a possible adverse effect on the fetus. In pregnant animals, severe exercise has been associated with increased fetal mortality, lower birth weights, and delayed fetal bone ossification (201). Several groups of investigators have monitored human fetal responses to exercise (202–207). Maternal exercise invariably resulted in higher maternal concentrations of epinephrine and fetal activity appeared to be associated with increased maternal sympathetic activity independent of maternal exercise (203). In some women, exercise was associated with fewer fetal breathing movements. Inconsistent findings reported in regard to fetal activity and breathing movement by several groups of investigators may have been related to different types of ultrasound scanners, whether the fetus was in an active or sleep cycle, and other unknown factors, such as hypoglycemia, fetal blood levels of catecholamines, and heat transfer to the fetus. No data are available on the possible alterations of human fetal PO_2 concentrations in response to heating and cooling.

It is not known whether maternal exercise is associated with a risk of decreased blood flow in the fetus. Pijpers and co-workers (205) have reported no difference in mean blood flow velocity in the fetal descending aorta as measured by pulsed Doppler ultrasound following moderate short-term bicycle ergometer exercise in 11 mothers in the 3rd trimester. The maternal heart rate increases following exercise (208, 209), but Veille et al. (207) have concluded that moderate prenatal exercise in a highly motivated, trained pregnant population does not increase uterine activity or fetal heart rate in the immediate 30 minutes following the exercise period.

Artal et al. (210) have reported fetal bradycardia in the fetuses of three healthy pregnant women, accompanied by elevated maternal serum levels of catecholamines, fol-

lowing a symptom-limited VO_2 max treadmill test. This is in contrast to the study of Collings and Curet (206) who described fetal tachycardia following 10 minutes of warm-up flexibility activity followed by 30 minutes of continuous aerobic activity at 60.8–75.1% of maximal aerobic capacity. They did not find fetal heart rate changes related to different gestational ages as previously reported by Pernoll and associates (209).

Physical activity and the risk of preterm delivery have been evaluated in a postpartum case-control study by Berkowitz and colleagues (211) in a retrospective analysis of responses to a questionnaire by 175 mothers of singleton preterm infants and 313 mothers of singleton term infants. They found no evidence that employment, housework, child care, and leisure-time physical activity during pregnancy increased the risk of preterm delivery. Moreover, women who participated in sports or physical fitness exercises had a decreased risk of preterm delivery as compared to those who were not similarly active.

HISTORICAL BACKGROUND OF EXERCISE AS A TREATMENT FOR DIABETES

Exercise as a treatment for diabetes has a long historical background. Vranic and colleagues (212) noted that exercise was suggested as an important adjunct in the treatment of diabetes by the Roman physician and philosopher Celsus (30 BC–50 AD). Before the discovery of insulin, Allen and associates (213) reported that exercise could lower blood glucose levels and improve acutely the tolerance to a carbohydrate load in diabetic patients. Hetzel and Long (214) confirmed these physiologic observations and, shortly after insulin became available, other investigators reported that a combination of exercise and insulin therapy produced a greater reduction in blood glucose levels than insulin alone (215–217). Vranic and Berger (218), however, have pointed out that although physical activity in the treatment of diabetes is generally recommended, the evidence to support the benefit of an exercise regimen has been limited. Chronic studies regarding the metabolic and hormonal consequences of different modes of exercise including appropriate controls are scanty.

Zinman and associates (219) have noted that metabolic responses to exercise in normal and diabetic subjects are influenced by many variables such as endocrine status, emotions, anthropometric characteristics, physical fitness, workload, and duration of activity. In nondiabetic patients with extreme obesity, Bjorntorp and co-workers (220) observed no changes in blood glucose values after physical training, but did report a marked decrease in plasma levels of insulin.

Zinman and Vranic (221) have examined the effects of acute exercise and exercise training on various aspects of metabolic control. Figure 15.3 shows the factors in normal individuals that contribute to glucose homeostasis and the hormonal and metabolic responses during exercise. Rapid mobilization and redistribution of metabolic fuels must occur because muscle contraction requires an immediate supply of energy. Muscle glycogen provides an early and limited source of energy. This must quickly be replaced by glucose and free fatty acids and, to a smaller extent, by amino acids and ketone bodies. The increased glucose uptake of exercising muscles is favored by increased blood flow and the availability of insulin.

The need for increased glucose during exercise is met by an increase in hepatic glucose production primarily by glycogenolysis, with gluconeogenesis playing a more prominent role during prolonged exercise (221). Thus, in nondiabetic individuals, glucose utilization is matched by increments of glucose production (222, 223). Maintenance of glucose homeostasis during exercise involves specific hormonal, neural, and cardiovascular responses (221).

Several investigators have studied the various hormonal responses to exercise (219, 224–226). These include a decrease in insulin secretion and a concomitant increase in the circulating concentration of counterregulatory hormones (catecholamines, glucagon, growth hormone, and cortisol). The decrease in insulin secretion facilitates hepatic glucose production and the mobilization of free fatty acids from adipose tissue. Glucagon plays an important role in the stimulation and maintenance of increased hepatic glucose production during exercise to prevent hypoglycemia. Epinephrine helps maintain circulating plasma levels of glucose by stimulating hepatic glucose production, inhibiting glucose uptake by muscle, and stimulating lipolysis to increase free fatty acid production.

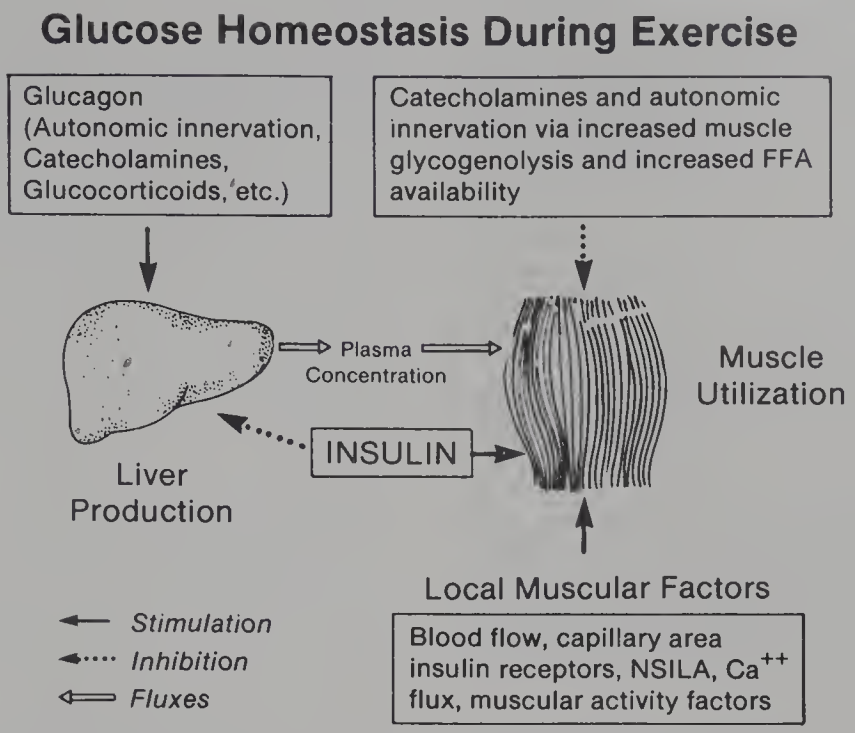


Figure 15.3. Glucose regulation during exercise and the hormonal and metabolic responses in normal humans. See text for description. Adapted with permission from Zinman B, Vranic M: Diabetes and exercise. Med Clin North Am 1985;69:145–157.

Cryer and Gerich (53, 54) have stated that, in general, patients with long-standing IDDM diabetes are more likely to have defective glucose counterregulation. Patients with overt adrenergic neuropathy (e.g., hypoadrenergic postural hypotension) are at special risk for defective counterregulatory responses. A history of hypoglycemia without adrenergic symptoms (sweating, tremor, circumoral numbness, nervousness, headache, hunger pangs) should also be predictive. However, patients who do have these clinical clues can also have defective glucose counterregulation (46).

EXERCISE IN IDDM PREGNANCIES

Exercise has not been a standard therapeutic recommendation for pregnant diabetic women. In fact, diabetes is listed as a relative contraindication for exercise during pregnancy by the American College of Obstetricians and Gynecologists (ACOG) (177). ACOG advises that physicians evaluate each pregnant patient individually with respect to an exercise program.

Many women with IDDM, however, are in physical fitness programs and have integrated regular exercise into their life-styles. Many of these women follow modified exercise programs during gestation. For others, who are usually sedentary and have no experience with their own tolerance and endurance for various types of exercise, pregnancy is not the time to initiate such a program. There are no clear indications for exercise in pregnant IDDM women (Table 15.1). Figure 15.3 depicts glucose regulation during exercise (221) and Figure 15.4 shows the effect of exercise in IDDM women in good control compared with those women in poor control.

If an exercise program is being considered before conception, the guidelines on Table 15.2 should be observed because women with long-standing diabetes complicated by vascular complications, unstable diabetes, and inapparent hypoglycemia are at risk for increasing the instability of their diabetes. Table 15.3 lists guidelines for exercise during pregnancy and Table 15.4 describes clear contraindications for an exercise program for IDDM women that exceeds normal activities of family living. Table 15.5 describes warning signs for pregnant women to stop exercise.

Our own experience with exercise in pregnant IDDM patients is limited. Because simple walking exercise is a recommendation all pregnant women customarily receive, we have prescribed a leisurely 20-minute walk (1 mile)

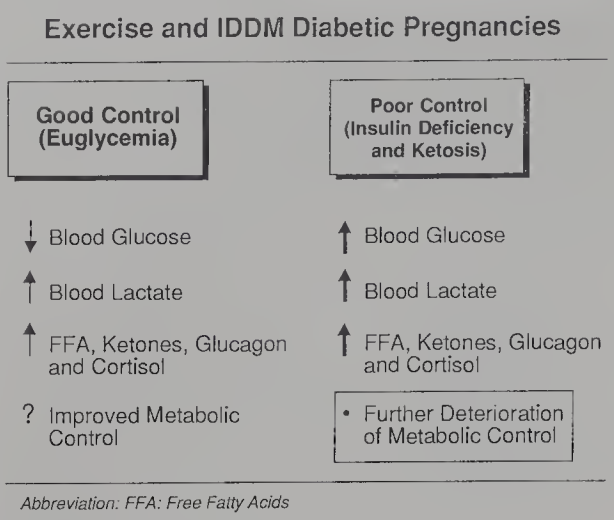


Figure 15.4. *Left:* In IDDM women in good control, exercise results in a fall in blood glucose with a rise in blood lactate, FFA, glucagon, and cortisol. *Right:* In IDDM in poor control, blood glucose rises, there is increased ketogenesis, and metabolic control worsens.

after each meal in 13 pregnant IDDM patients (228). Their pregnancy course and outcome were compared with those of 21 IDDM women who were given no specific exercise instructions. All women in the study wore a walking pedometer to record distance of walking after each meal and per day. The controls recorded a pedometer reading at bedtime.

No patient had been in a physical training program before pregnancy and all were in poor diabetic control at the first prenatal visit (mean HbA1c concentration was 11.8% in the IDDM exercise group and 10.5% in the IDDM controls). All patients were requested to follow a 2000–2300 kcal/day modified high-carbohydrate, high dietary-fiber diet. One subject in the exercise group was shifted from multiple subcutaneous injections of insulin (MSI) to constant subcutaneous insulin infusion (CSII)

Table 15.1.
Indications for Exercise in Pregnant Women With IDDM

None have been clearly established
Continuation of an exercise program initiated before conception; modifications may be necessary with weight gain, postural changes, and later stages of gestation
Possible improvement in psychological and physical sense of well-being
Possible synergistic effect with insulin on control of blood glucose

Table 15.2.
Exercise Guidelines for Women With IDDM in the Reproductive Age Group (15–45 yr)[a]

Complete history, physical examination, and screening for proliferative retinopathy, nephropathy, and cardiovascular disease
Screen for postural hypotension tachycadia and history of hypoglycemia without autonomic symptoms
Establish diabetic control by MSI or CSII, self-glucose monitoring, and dietary modifications
Initiate a gradual program of postprandial exercise on a regular basis in conjunction with self-glucose monitoring
Adjust preexercise insulin dose, food intake, and postexercise carbohydrate supplement
Avoid exercise during peak insulin action
Do not use exercising extremities as insulin injection sites
Alert patients to possibility of exercise-induced hypoglycemia, which may occur several hours after the completion of exercise

[a]Adapted from Zinman B, Vranic M. Diabetes and exercise. Med Clin North Am 1985;69:145–147.

in her 2nd trimester because of wide excursions in plasma glucose levels around the 24-h clock and frequent hypoglycemic reactions.

In our study, we were unable to demonstrate improved diabetic control or an effect on insulin requirements in women who exercised compared with IDDM controls. There was a moderate but not significant increase in preterm labor in the exercise group (20% versus 3.4% in the controls; p = NS).

During our study, we had the opportunity to follow an extremely intelligent and cooperative IDDM patient during two consecutive pregnancies. In the first pregnancy, she was a normal control for a clinical research study of exercise during pregnancy and received no exercise instruction. In the second, she received more intensive treatment with CSII and exercise from 2nd trimester until term delivery and a change in dietary instructions. Table 15.6 shows the marked difference in maternal and infant outcome. Although the patient was in somewhat poorer diabetic control at first prenatal visit in the second pregnancy, she achieved a normal HbA1c concentration with

Table 15.3.
Guidelines for Exercise During Pregnancy[a]

Maternal heart rate should not exceed 140 beats per minute
Strenuous activities should not exceed 15 minutes in duration
No exercise should be performed in the supine position after the 4th month of gestation is completed
Exercises that employ the valsalva maneuver should be avoided
Caloric intake should be adequate to meet not only the extra energy needs of pregnancy, but also those of the exercise performed
Maternal core temperature should not exceed 38° C

[a]With permission from the American College of Obstetricians and Gynecologists (ACOG): Technical Bulletin, Exercise during pregnancy and the postnatal period. ACOG, Washington, DC 1985.

intensive therapy and gained less weight. The most striking observations were the marked decrease in fasting plasma triglyceride (TG) and cholesterol (CHOL) levels and lower infant birth weight and length. Her mean walking distance was 3.5 miles/day. The improved outcome probably reflected both better glycemic control and the exercise regimen. It is not possible to separate clearly the effect of exercise from deliverry of insulin by CSII, which may have been the most important aspect of her improved control. Growth and development of both children has been normal and comparable.

Table 15.4.
Contraindications for Exercise in Pregnant Women With IDDM

Lack of normal counterregulatory responses to hypoglycemia
Myocardial ischemia or arrhythmias
Proliferative retinopathy
Nephropathy with elevated serum creatinine level (>1.0 mg/dl) and evidence of autonomic neuropathy or proteinuria >0.5 g/24 h
Antecedent or pregnancy-induced hypertension
Twins and multiple births
Severe emotional stress

Table 15.5.
Warning Signs and Symptoms for Women to Stop Exercise and Contact Their Physicians[a]

Pain	Faintness
Bleeding	Tachycardia
Dizziness	Back pain
Shortness of breath	Pubic pain
Palpitations	Difficulty walking

[a]With permission from the American College of Obstetricians and Gynecologists (ACOG): Technical Bulletin, Exercise during pregnancy and the postnatal period. ACOG, Washington, DC 1985.

EXERCISE IN PREGNANT NIDDM WOMEN

There are no epidemiologic prospective studies to demonstrate the efficacy of exercise on the outcome of NIDDM pregnancies.

As a group, although there are many exceptions, pregnant women with NIDDM are older and heavier than those with IDDM. In these individuals, exercise would appear to be an ideal therapeutic measure to reduce insulin requirements and achieve better control of plasma glucose and lipid levels.

Artal and colleagues (179) have compared the metabolic responses of normal healthy pregnant women and those with NIDDM following the mild exercise of a 15-minute walk on a motorized treadmill at a speed of 2 mph. They reported a greater decrease in glucose and free fatty acid levels, but a heightened epinephrine and norepinephrine response compared with controls. There are no other published data on short- or long-term effects of exercise in NIDDM during pregnancy. The possible significance of an exercise-induced elevated catecholamine response on the fetus is unknown.

In our clinical investigations, we have followed 14 obese NIDDM women who continued their usual life-style activities as controls and 12 patients who were instructed to walk a 20-minute mile after each meal. There was no significant difference in age, prepregnancy weight, or weight gain during pregnancy. All

Table 15.6.
Maternal and Infant Measurements in Patient L.R. During Two Consecutive Pregnancies[a]

	Pregnancy 1	Pregnancy 2
Insulin	MSI	MSI and CSII
Diet	2000 kcal/day	2000 kcal/day
Exercise	Usual activity	Postprandial walking exercise
Age (yr)	24	27
Prepregnant wt. (kg)	73	66
Wt. gain (kg)	17	13
HbA1c (%)	8.6 → 7.0	9.3 → 5.9
Lipids (35 wk)		
TG (mg/dl)	403	175
Chol. (mg/dl)	326	226
IBW (g)	4139	3570
Length (cm)	55	50
Head circ (cm)	36.7	36.8

[a]Abbreviations: MSI: multiple subcutaneous injections; CSII: continuous subcutaneous insulin infusion; IBW: infant birth weight.

the women were obese and multiparous and were caring for young children at home.

We found that it was extremely difficult to motivate older, physically untrained, obese, pregnant women to take walks each day. Many found fatigue to be a major problem and several developed backache. Two women, who weighed over 300 lb (136 kg), refused to walk at all and spent their entire pregnancies in semireclining positions. In this preliminary study, we found no difference at delivery in the experimental and control groups in HbA1c concentrations (controls, 7.9% versus walkers, 8.0%) or miles walked per day (controls, 3.5 versus walkers, 3.9). There were four premature births in the control group and three in the group that walked. In this small sample of patients, the mean placental weight was lower ($p<0.05$) in the exercise group. In one patient who was an extremely conscientious exerciser, premature labor occurred at 31 weeks, and all exercise was abruptly terminated. No dietary changes were made. Over the following 7 weeks she had worsening of her HbA1c concentration and an abrupt increase in her insulin requirement. This was indirect evidence that exercise had favorably influenced diabetic control and decreased the requirement for insulin but it may have been a contributing factor to her preterm labor.

In contrast to our patients with IDDM, all but two NIDDM subjects presented or were referred for prenatal care in late 2nd trimester. Thus, assessment of the efficacy of walking was difficult because of a shorter treatment time and confounding variables. As diabetic care becomes regionalized in special diabetes centers, a much better approach for women with NIDDM would be to institute exercise and weight control programs before conception.

GESTATIONAL DIABETES AND EXERCISE

There are no reports in the literature of the efficacy of exercise in GDM.

Should exercise be added as specific therapy for GDM? Metabolic studies have shown that there is great variability of insulin levels among thin versus fat women with GDM (229). Both groups of women have delayed insulin release following meal stimulation, but thin subjects have lower insulin values than obese patients following either glucose or meal stimulation (230).

Hydramnios and macrosomia may occur in both thin and fat women with GDM. Exercise is contraindicated if this complication is present because it may precipitate preterm labor. In thin women with GDM who require treatment with insulin, hypoglycemia may occur. On the other hand, extremely obese women (200–300 or more lb; 92–136 kg) with GDM are resistant to ketosis even when food intake is decreased (231) and rarely become hypoglycemic. They are, however, quite ungainly. Many have a variety of skeletal complaints and others lack motivation to perform even the simplest forms of exercise. Preeclampsia is a complication that also excludes exercise as a therapeutic modality. From a realistic point of view, somewhat limited exercise therapy may be more effective in conjunction with modest caloric restriction to 1500–1800 kcal/day.

Our experience with walking exercise in in-

dividuals with GDM is extremely limited. In our medical center, referral of patients from outlying clinics is slow because of the time elapsed between positive screening tests and confirmation of GDM with the 100-g glucose loading test. We have followed 15 women in an exercise study.

In 12 obese (mean age 32 ± SD 7 yr and weight 92 ± SD 17 kg) nonexercising women with GDM, we have observed that normal walking activity averaged 2.6 ± 0.6 miles/day. On a modified high-carbohydrate, high-fiber diet of 1700–1800 kcal/day and treatment with small doses of rapid-acting insulin before each meal, overall diabetic control was good (mean HbA1c at delivery 7.3 ± SD 0.9%). The mean gestational age at delivery was 39 ± SD 1.5 weeks and mean infant birth weight was 3924 ± 636 g. Six of 12 infants were macrosomic.

Three obese women with GDM completed a walking program for 8–10 weeks. They walked an average of 6.3 miles/day, but did not have a lower HbA1c concentration at delivery (7.8%). None of the babies were macrosomic and mean birth weight was lower (3292 ± 212 g).

These data are too few for meaningful comparisons, but this would appear to be a group of pregnant, mildly carbohydrate-intolerant individuals in whom an exercise trial would be warranted. In the selection of cases, however, it will be important to assess factors such as obesity or leanness, HbA1c concentrations, and residual β-cell function to evaluate maternal/fetal outcome variables.

In summary, in this chapter, exercise has been discussed in relation to the special physiologic changes of normal gestation. Throughout this century, pregnant women have been encouraged to take outdoor exercise, but it has always been difficult to specify the exact amount. The American College of Obstetricians and Gynecologists (177) has stated,

> "it is noteworthy that no evidence exists to support the popular notion that regular exercise will improve the outcome of pregnancy. Those studies that have been done reveal no change in the length or quality of labor and no reduction in the number of maternal or fetal complications. There is some evidence that increased occupational activity and heavy endurance exercise will shorten the length of gestation and result in lower infant weights. The significance of these findings can only be speculated upon."

Similarly, since ancient times, exercise has been recommended as an important adjunct in the treatment of diabetes. The evidence to support the benefit of an exercise program in nonpregnant diabetics is limited and no data are presently available to assess the risk/benefit of acute or chronic exercise for pregnant women with IDDM, NIDDM, or GDM. It seems reasonable to recommend that women with IDDM who are in good physical condition and metabolic control continue exercise activities along the lines recommended by The American College of Obstetricians and Gynecologists. They should, of course, be aware of the special precautions suggested to avoid hyper- and hypoglycemia; exercise should not be prescribed for those with antecedent hypertension, preeclampsia, evidence of macro- or microvascular disease, autonomic dysfunction, or lack of normal counterregulatory mechanisms to counteract hypoglycemia.

Pregnant women with NIDDM and GDM would appear to have the most to gain and least to risk from a moderate exercise program. Whether metabolic control is more easily achieved and maintained without risk when exercise is added to treatment with diet and insulin remains to be established. It will be particularly important to assess the risk/benefit ratio in all diabetic pregnancies to the primary patient—the fetus. Pregnancy is not the time to begin strenuous body-building exercise or heavy exercise routines for the first time. Perhaps this is another example of the importance of the role of preconception counseling. Women with both IDDM and NIDDM as well as obese individuals with a strong family history of diabetes who plan to become pregnant might be counseled to enroll in exercise programs before conception. In this way, physical fitness and exercise tolerance would already be established and the effect of exercise adapted to pregnancy could be assessed more accurately. In any case, all pregnant women with established or gestationally provoked diabetes who engage in exercise programs should do so only with the close supervision of their physician.

References for Section IV

1. Zinman B. Medical intelligence. The physiologic replacement of insulin. An elusive goal. N Engl J Med 1989;321:363-368.
2. Polonsky KS, Pugh W, Jaspan JB, et al. C-peptide and insulin secretion relationship between peripheral concentrations of C-peptide and insulin and insulin secretion rates in the dog. J Clin Invest 1984;74:1821-1829.
3. Radziuk J, Morishima T. Assessment of insulin kinetics in vivo. In: Clark WL, Larner J, Pohl SL (eds). Methods in diabetes research. Vol. 2. Clinical methods. New York: John Wiley 1985:91-106.
4. Polonsky KS, Licinio-Paixao J, Given BD, et al. Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. J Clin Invest 1986;77:98-105.
5. Cousins L, Rigg L, Hollingsworth D, Brink G, Aurand J, Yen SSC. The 24-hour excursion and diurnal rhythm of glucose, insulin and C-peptide in normal pregnancy. Am J Obstet Gynecol 1980;136:483-488.
6. Rigg L, Cousins L, Hollingsworth D, Brink G, Yen SSC. Effect of exogenous insulin on excursions and diurnal rhythm of plasma glucose in pregnant diabetics with and without residual β-cell function. Am J Obstet Gynecol 1980;136:537-544.
7. Hollingsworth DR. Alterations of maternal metabolism in normal and diabetic pregnancies. Differences in insulin dependent, non-insulin dependent and gestational diabetes. Am J Obstet Gynecol 1983;146:417-428.
8. Kurtz AB, Nabarro JD. Circulating insulin-binding antibodies. Diabetologia 1980;19:329-334.
9. Anderson O-O. Clinical significance of anti-insulin antibodies. Acta Endocrinol (Copenh) 1976;205:231-240.
10. Walford S, Allison SP, Reeves WG. The effect of insulin antibodies on insulin dose and diabetic control. Diabetologia 1982;22:106-110.
11. Van Haeften TW, Heiling VJ, Gerich JE. Adverse effects of insulin antibodies on postprandial glucose and insulin profiles in diabetic patients without immune insulin resistance: Implications for intensive insulin regimens. Diabetes 1987;36:305-309.
12. Bolli GB, Dimitriadis GD, Pehling GB, et al. Abnormal glucose counterregulation after subcutaneous insulin in insulin-dependent diabetes mellitus. N Engl J Med 1984;310:1706-1711.
13. Bauman WA, Yalow RS. Transplacental passage of insulin complexed to antibody. Proc Natl Acad Sci USA 1981;78:4588-4590.
14. Mylvaganam R, Stowers JM, Steel JM, Wallace J, MacHendry JC, Wright AD. Insulin immunogenicity in pregnancy: Maternal and fetal studies. Diabetologia 1983;24:19-25.
15. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC. Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus. Its role in fetal macrosomia. N Engl J Med 1990;323:309-315.
16. Benedetti MM, Bueti A, Mannino D, et al. Kinetics and metabolic activity of biosyntheic NPH insulin evaluated by the glucose clamp technique. Diabetes Care 1984;7:132-136.
17. Galloway JA, Spradlin CT, Jackson RL, Otto DC, Bechtel LD. Mixtures of intermediate-acting insulin (NPH and Lente) with regular insulin: An update. In: Skyler JS (ed). Insulin update 1982: Proceedings of Symposium, Key Biscayne, FL, December 7-9, 1981. Amsterdam, Excerpta Medica, 1982:111-119.
18. Heine RJ, Bilo HJG, Fonk T, van der Ven EA, van der Meer J. Absorption kinetics and action profiles of mixtures of short- and intermediate-acting insulins. Diabetologia 1984;27:558-562.
19. Mulhauser I, Broermann C, Tsofsalas M, Berger M. Short reports: Miscibility of human and bovine ultralente insulin with soluble insulin. Br Med J 289:1656-1657.
20. Skyler JS (ed). Symposium on human insulin of recombinant DNA origin. Diabetes Care 1982;5:Suppl 2:1-186.
21. Gulan M, Gottesman IS, Zinman B. Biosynthetic human insulin improves postprandial glucose excursions in type I diabetes. Ann Intern Med 1987;107:506-509.
22. Heine RJ, van der Heyden EAP, van der Veen EA. Responses to human and porcine insulin in healthy subjects. Lancet 1989;2:946-949.
23. Tunbridge FKE, Newens A, Home PD, et al. Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. Diabetes Care 1989;12:115-119.
24. Bressler R, Galloway JA. Insulin treatment of diabetes mellitus. Med Clin North Am 1971; 55:861-876.
25. Galloway JA, Spradlin CT, Nelson RL, Went-

worth SM, Davidson JA, Swarner JL. Insulin concentration and blood glucose responses after injections of regular insulin, and various insulin mixtures. Diabetes Care 1981;4:366-376.
26. Rizza RA, Gerich JE, Haymond MW, et al. Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion and intensified conventional insulin therapy. N Engl J Med 1980;303:1313-1318.
27. Schiffrin A, Belmonte M. Combined continuous subcutaneous insulin infusion and multiple subcutaneous injections in Type I diabetic patients. Diabetes Care 1981;4:595-600.
28. Galloway JA, Spradlin CT, Howey DC, Dupre J. Intrasubject difference in pharmacokinetic and pharmacodynamic responses: The immutable problem of present day treatment? In: Serrano-Rios M, Lefebvre PJ (eds). Diabetes 1985: Proceedings of the 12th Congress of the International Diabetes Federation, Madrid, 23-28 September 1985. International Congress Series no. 700. Amsterdam: Excerpta Medica, 1986:877-886.
29. Bantle JP, Weber MS, Rao SMS, Chattopadhyay MK, Robertson RP. Rotation of the anatomic regions used for insulin injections and day-to-day variability of plasma glucose in Type I diabetic subjects. JAMA 1990;263:1802-1806.
30. Koivisto VA, Felig P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. N Engl J Med 1980;92:59-61.
31. Zinman B, Vranic M, Albisser AM, Leibel BS, Marliss ED. The role of insulin in the metabolic response to exercise in diabetic man. Diabetes 1979;28:Suppl:76-81.
32. Jovanovic L, Peterson CL, Saxena BB, Dawood MY, Saudek CD. Feasibility of maintaining normal glucose profiles in insulin dependent diabetic women. Am J Med 1980;68:105-112.
33. Rudolf MCJ, Coustan DR, Sherwin RS, Bates SE, Felig P, Genel M, Tamborlane W. Efficacy of the insulin pump in the home treament of pregnant diabetics. Diabetes 1981;30:891-895.
34. Potter JM, Reckless JPD, Cullen DR. The effect of continuous subcutaneous insulin infusion and conventional insulin regimes on 24-hour variations of blood glucose and intermediary metabolism in the third trimester of diabetic pregnancy. Diabetologia 1981;21:534-539.
35. Coustan DR, Reece EA, Sherwin RS, et al. A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. JAMA 1986;255:631-636.
36. Pickup JC, Keen H, Viberti GC, Bilous RW. Patient reactions to long-term outpatient treatment with subcutaneous insulin infusion. Br Med J 1981;282:766-768.
37. Pickup JC. Continuous subcutanous insulin infusion. Br Med J 1982;285:49-50.
38. Chantelau E, Spraul M, Muhlhauser I, Gause R, Berger M. Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for Type 1 (insulin-dependent) diabetes mellitus: A one centre experience. Diabetologia 1989;32:421-426.
39. Casparie AF, Elving LD. Severe hypoglycemia in diabetic patients: Frequency, causes, prevention. Diabetes Care 1985;141-145.
40. Arias P, Kerner W, Zier H, Navascues I, Pfeiffer EF. Incidence of hypoglycemic episodes in diabetic patients under continuous subcutaneous insulin infusion and intensified conventional insulin treatment: Assessment by means of semiambulatory 24-hour continuous blood glucose monitoring. Diabetes Care 1985;8:134-140.
41. Mecklenburg RS, Benson EA, Benson JW, et al. Long-term metabolic control with insulin pump therapy. N Engl J Med 1985;313:465-468.
42. Ronn B, Vang L, Deckert T. Seven years of routine insulin pump treatment. In: 7th Workshop of the AIDSPIT-Study Group, booklet of abstracts. January 31-February 2, 1988, Igls (Austria).
43. Knight G, Jennings AM, Ward DJ. Outcome of a 5-year programme of glycemic control intensification using CSII. Diabetes 1988 37 (Suppl 1): 25A (Abstract).
44. Teutsch SM, Herman WH, Dwyer DM, Lane JM. Mortality among diabetic paients using continuous subcutaneous insulin-infusion pumps. N Engl J Med 1984;310:361-368.
45. Teutsch SM, Herman WH, Lane JM. Letter. N Engl J Med 1984;311:1053.
46. White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983;308:485-491.
47. Bolli GB, DeFeo P, DeCosmo S, et al. A reliable and reproducible test for adequate glucose counterregulation in Type I diabetes mellitus. Diabetes 1984;33:732-737.
48. Orzeck E. Sleep sentry. Diabetes Supplies, 8181 N. Stadium Drive, Suite 202, Houston, Texas, 77054 (1990).
49. Johansen K, Ellegaard S, Wex S. Detection of nocturnal hypoglycemia in insulin-treated diabetics by a skin temperature-skin conductance meter. Acta Med Scand 1986;220:213-217.
50. Saudek CD, Selam JL, Pitt HA, et al. A preliminary trial of the Programmable Implantable Medication System for insulin delivery. N Engl J Med 1989;321:574-579.
51. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 1988;37:901-907.
52. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care 1987;10:1-19.
53. Gerich JE. Lilly Lecture 1988. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 1988;37:1608-1617.

54. Cryer PE, Binder C, Bolli GB, et al. Conference Summary. Hypoglycemia in IDDM. Diabetes 1989;38:1193-1199.
55. Sadler TW, Hunter ES III. Hypoglycemia: How little is too much for the embryo? Am J Obstet Gynecol 1987;157:190-193.
56. Chatot CL, Klein NW, Piatek J, Pierro LJ. Successful culture of rat embryos in human serum: use in the detection of teratogens. Science 1980;207:1471-1473.
57. Gupta M, Beck F. Growth of 9.5 day rat embryos in human serum. J Embryol Exp Morphol 1983;76:1-8.
58. Ellington SKL. In-vivo and in-vitro studies on the effects of maternal fasting during embryonic organogenesis in the rat. J Reprod Fertil 1980;60:383-388.
59. Somogyi M. Insulin as a cause of extreme hyperglycemia and instability. Wkly Bull St Louis Med Soc 1938;32:498-500.
60. Somogyi M. A new reagent for the determination of sugars. J Biol Chem 1945;160:61-68.
61. Somogyi M. Determination of blood sugar. J Biol Chem 1945;160:69-73.
62. Somogyi M. Exacerbation of diabetes by excess insulin action. Am J Med 1959;26:169-191.
63. Rosenbloom AL, Giordano BP. Chronic overtreatment with insulin in children and adolescents. Am J Dis Child 1977;131:881-885.
64. Perriello G, De Feo P, Torlone E, et al. The effect of nocturnal hypoglycemia on glycemic control in diabetes mellitus. N Engl J Med 1988;319:1233-1239.
65. Kollind M, Adamson U, Lins P-E. Studies of insulin resistance following hypoglycemia in insulin-dependent diabetes mellitus. Acta Med Scand 1988;223:153-157.
66. Gale EA, Kurtz AB, Tattersall RB. In search of the Somogyi effect. Lancet 1980;2:279-282.
67. Dorman TL, Peckar CO, Mayon-White VA, et al. Unsuspected hypoglycaemia, hemoglobin A1 and diabetes control. Quart J Med 1981; 50:31-38.
68. Vonesch HJ, Gerold S, Dubach UC, Berger W. Nachtliche hypoglykamien bei typ-I-diabetikern, ein unterschatztes risiko? Schweiz Med Wochenschr 1984;114:1674-1678.
69. Raskin P. The Somogyi phenomenon: Sacred cow or bull? Arch Intern Med 1984;144:781-787.
70. Pramming S, Thorsteinsson B, Bendtson I, Ronn B, Binder C. Nocturnal hypoglycaemia in patients receiving conventional treatment with insulin. Br Med J 1985;291:376-379.
71. Tordjman KM, Havlin CE, Levandoski LA, White NH, Santiago JV, Cryer PE. Failure of nocturnal hypoglycemia to cause fasting hyperglycemia in patients with insulin-dependent diabetes mellitus. N Engl J Med 1987; 317:1552-1559.
72. Havlin CE, Cryer PE. Nocturnal hypoglycemia does not commonly result in major morning hyperglycemia in patients with diabetes mellitus. Diabetes Care 1987;10:141-147.
73. Gill GV, Walford S, Alberti KGMM. Brittle diabetes—present concepts. Diabetologia 1985; 28:579-589.
74. Woodyatt RT. Diabetes mellitus. In: Cecil R (ed). A textbook of medicine, 4th edition. Philadelphia: WB Saunders, 1938:620.
75. Rosenbloom A. The management of brittle diabetes in children. South Med J 1971;64:729-733.
76. Tattersall R. Brittle diabetes. Clin Endocrinol Metab 1977;6:403-419.
77. Perriello G, De Feo P, Torlone E, et al. Nocturnal spikes of growth hormone secretion cause the dawn phenomenon in Type I (insulin-dependent) diabetes mellitus by decreasing hepatic (and extra hepatic) sensitivity to insulin in the absence of insulin waning. Diabetologia 1990;33:52-59.
78. Hollingsworth DR, Ney D, Fujimoto V, Milewski M, Murphy H. Further observations in lean and obese women with gestational diabetes during a 400-kilocalorie meal tolerance test. In: Sutherland HW, Stowers JM, Pearson DWN (eds). Carbohydrate metabolism in pregnancy and the newborn IV. London: Springer-Verlag 1989:245-256.
79. Heik M, Schadlich M, Warnle H. Das elektroenzephalogramm des diabetischen kindes. Zschr Inn Med 1962;17:616-624.
80. Eysold R. Cerebrale storungen bei diabetes mellitus und elektrencephalographische untersuchungen bei diabetischen kindern. Mschr Kinderheilk 1965;114:94-101.
81. Schlack H, Palm D, Jochmus I. Der einflu β rezidivierender hypoglykamien auf das EEG des diabetischen kindes. Mschr Kinderheilk 1969;117:251-253.
82. Eeg-Olofsson O, Petersen I. Childhood diabetic neuropathy. A clinical and neurophysiological study. Acta Paediatr Scand 1966;55:163-171.
83. Abramowicz I, Margolis A, Wawrzynkiewicz T. Zmiany elektroencefalograficzne u dzicci chorych na cukrzyce. Pediatr Pol 1969;44:693-700.
84. Laron Z, Karp M, Freinkel JJ. Electroencephalographic examination, A study of rehabilitation of juvenile and adolescent diabetics in the central region of Israel. Petah Tikva: Kupat Holim Press, 1972:35-37.
85. Gilhaus KH, Daweke H, Lulsdorf HG, Sachsse R, Sachsse B. EEG-veranderungen bei diabetischen kindern. Dtsch Med Wschr 1973;98: 1449-1454.
86. Fallstrom K. On the personality structure in diabetic school children. Acta Paediatr Scand 1974;251 (Suppl):36, 1-71.
87. Lerman P, Karp M, Kaushanski A, Laron Z. Electroencephalographic findings in diabetic children and adolescents. Medical aspects of balance of diabetes in juveniles. Basel:Karger, 1977:191-195.
88. Haumont D, Dorchy H, Pelc S. EEG abnormalities in diabetic children. Clin Pediatrics 1979;18:750-753.
89. Soltesz G, Ascadi G. Association between diabetes, severe hypoglycemia, and electroen-

cephalographic abnormalities. Arch Dis Child 1989;64:992-996.
90. Eeg-Olofsson O. Hypoglycemia and neurological disturbances in children with diabetes mellitus. Acta Paediatr Scand 1977;270 (Suppl):91-95.
91. Rovet JF, Ehrlich RM, Hoppe M. Intellectual deficits associated with early onset of insulin-dependent diabetes mellitus in children. Diabetes Care 1987;10:510-515.
92. Rovet JF, Ehrlich RM, Hoppe M. Specific intellectual deficits in children with early onset diabetes mellitus. Child Dev 1988;59:226-234.
93. Ryan C, Vega A, Drash A. Cognitive deficits in adolescents who developed diabetes early in life. Pediatrics 1985;75:921-927.
94. Holmes C, Richman L. Cognitive profiles of children with insulin-dependent diabetes. J Dev Behav Pediatr 1985;6:323-326.
95. Ack M, Miller M, Weil W. Intelligence of children with diabetes mellitus. Pediatrics 1961; 28:764-777.
96. Ryan CM. Neurobehavioral complications of type I diabetes: examination of possible risk factors. Diabetes Care 1988;11:86-93.
97. Golden MP, Ingersoll GM, Brack CJ, Russell BA, Wright JC, Huberty TJ. Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. Diabetes Care 1989;12:89-93.
98. Ryan CM, Atchison J, Puczynski S, Puczynski M, Arslanian S, Becker D. Mild hypoglycemia associated with deterioration of mental efficiency in children with insulin-dependent diabetes mellitus. J Pediatr 1990;117:32-38.
99. DeFeo P, Gallai V, Mazzotta G, et al. Modest decrements in plasma glucose concentration cause early impairment in cognitive function and later activation of glucose counterregulation in the absence of hypoglycemic symptoms in normal man. J Clin Invest 1988;82:436-444.
100. Blackman JD, Towle VL, Lewis GF, Spire J-P, Polonsky KS. Hypoglycemic thresholds for cognitive dysfunction in humans. Diabetes 1990; 39:825-835.
101. Pramming S, Thornsteinsson B, Theilgaard A, Pinner EM, Binder C. Cognitive function during hypoglycemia in type I diabetes mellitus. Br Med J 1986;292:647-650.
102. Songer TJ, La Porte RE, Dorman JS, et al. Motor vehicle accidents and IDDM. Diabetes Care 1988;11:701-707.
103. Hepburn DA, Steel JM, Frier BM. Hypoglycemic convulsions cause serious musculoskeletal injuries in patients with IDDM. Diabetes Care 1989;12:32-34.
104. Wredling R, Levander S, Adamson U, Lins PE. Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. Diabetologia 1990;33:152-157.
105. Stangenberg M, Persson B, Stange L, Carlstrom K. Insulin-induced hypoglycemia in pregnant diabetics. Maternal and fetal cardiovascular reactions. Acta Obstet Gynecol Scand 1983;62:249-252.
106. Roversi GD, Gargiuolo M, Nicolini U, et al. Maximal tolerated insulin therapy in gestational diabetes. Diabetes Care 1980;3:489-494.
107. Coustan DR, Lewis SB. Insulin therapy for gestational diabetes. Obstet Gynecol 1978;51:306-310.
108. Felice ME, Shragg P, James M, Hollingsworth DR. Clinical observations in Hispanic, White and Black pregnant teenagers. J Adol Health Care 1986;7:305-310.
109. Goldberg JD, Franklin B, Lasser D, et al. Gestational diabetes. Impact of home glucose monitoring on neonatal birth weight. Am J Obstet Gynecol 1986;154:546-550.
110. Ney D, Hollingsworth DR. Nutritional management of pregnancy complicated by diabetes: Historical Perspective. Diabetes Care 1981; 4:647-655.
111. Joslin EP. The treatment of diabetes mellitus with observations upon the disease based upon one thousand cases. Philadelphia: Lea & Febiger, 1916.
112. Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Nutrition During Pregnancy. Washington, DC: National Academy Press, 1990.
113. Food and Nutrition Board, National Academy of Sciences—National Research Council. Recommended Dietary Allowances, 10th Ed. National Academy Press, Washington, DC, 1989.
114. American Diabetes Association. Nutritional recommendations and principles for individuals with diabetes mellitus. Diabetes Care 1986;10:126-132.
115. Campbell DM, Gillmer MDG (eds). Proceedings of the Tenth Study Group of the Royal College of Obstetricians and Gynaecologists, September, 1982. The Royal College of Obstetricians and Gynaecologists, London, 1983.
116. WHO (World Health Organization). Energy and Protein Requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Technical Report Series 724. World Health Organization, Geneva, 206 pp. 1985.
117. Durnin, JVGA. Energy requirements of pregnancy. An integration of the longitudinal data from the 5-country study. In: Nestle Foundation Annual Report. Switzerland: Nestle Foundation, Lausanne 1986:147-154.
118. Van Raaij JMA, Schonk CM, Vermaat-Miedema SH, Peck MEM, Hautvast JGAJ. Body fat mass and basal metabolic rate in Dutch women before, during and after pregnancy: A reappraisal of energy cost of pregnancy. Am J Clin Nutr 1989;49:765-772.
119. Forsum E, Sadurkis A, Wagner J. Resting metabolic rate and body composition of healthy Swedish women during pregnancy. Am J Clin Nutr 1988;47:942-947.
120. Prentice AM, Goldberg GR, Davies HL, Murgatroyd PR, Scott W. Energy adaptations in human pregnancy assessed by whole-body calorimetry. British J Nutr 1989;62:5-22.

121. King JC. Nutrition during pregnancy. In: Kretchmer N (ed). Frontiers of clinical nutrition. Rockville, MD: Aspen Publication, 1986: 3-13.
122. Naeye RL. Weight gain and the outcome of pregnancy. Am J Obstet Gynecol 1979;135:3-9.
123. Rosso P. A new chart to monitor weight gain during pregnancy. Am J Clin Nutr 1985;41: 644-652.
124. Stein Z, Susser M, Saenger G, Marolla F. Famine and human development: The Dutch hunger winter of 1944-45. New York: Oxford University Press, 1975.
125. Abrams BF, Laros RK. Prepregnancy weight, weight gain and birth weight. Am J Obstet Gynecol 1986;154:503-509.
126. Cleveland LE, Pfeffer AB. Planning diets to meet the National Research Council's guidelines for reducing cancer risk. J Am Diet Assoc 1987;87:162-168.
127. Nutrition Monitoring Division. Human Nutrition Information Service. Nationwide Food Consumption Survey: CSF II - 1986. Nutrition Today 1986;24:35-38.
128. Belizan JM, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. Am J Obstet Gynecol 1988;158:898-902.
129. Lind T. Iron supplementation during pregnancy. In: Campbell DM, Gillmer MDG (eds). Proceedings of the Tenth Study Group of the Royal College of Obstetricians and Gynaecologists, September, 1982. The Royal College of Obstetricians & Gynaecologists, London, 1983, pp 181-191.
130. Murphy SP, Calloway DH. Nutrient intakes of women in NHANES II emphasizing trace minerals, fiber and phytate. J Am Diet Assoc 1986;86:1366-1372.
131. Worthington-Roberts BS. Maternal nutrition and the outcome of pregnancy. In: Worthington-Roberts BJ, Williams SR (eds). Nutrition in pregnancy and lactation, 4th ed. St. Louis, Times Mirror/Mosby, 1989:51-120.
132. Baumslag N, Edelstein T, Metz J. Reduction of incidence of prematurity by folic acid supplementation during pregnancy. Br Med J 1970;1:16-17.
133. Mills JL, Rhoads GG, Simpson JL, et al. The absence of a relation between the periconceptual use of vitamins and neural-tube defects. N Engl J Med 1989;321:430-435.
134. Lazebnik N, Kuhnert BR, Kuhnert PM, Thompson KL. Zinc status, pregnancy complications and labor abnormalities. Am J Obstet Gynecol 1988;158:161-166.
135. Soltan MH, Jenkins MH. Maternal and fetal plasma zinc concentration and fetal abnormality. Br J Obstet Gynaecol 1982;89:56-58.
136. Hambridge KM, Krebs NF, Sibley L, English J. Acute effects of iron therapy on zinc status during pregnancy. Obstet Gynecol 1987;70:593-596.
137. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973;2:999-1001.
138. Council on Scientific Affairs. Fetal effects of maternal alcohol use. JAMA 1983;249:2517-2521.
139. Linn S, Schoenbaum SC, Monson RR, Rosmar B, Stubblefield PG, Ryan KJ. No association between coffee consumption and adverse outcomes of pregnancy. N Engl J Med 1982;306: 141-145.
140. Kurppa K, Holmberg PC, Kuosma E, Saxen L. Coffee consumption during pregnancy. N Engl J Med 1982;306:1548-1550.
141. Scrisuphan W, Bracken WB. Caffeine consumption during pregnancy and association with late spontaneous abortion. Am J Obstet Gynecol 1986;154:14-20.
142. Stegink LD, Filer LJ, Baker GL, et al. Repeated ingestion of aspartame-sweetened beverage: effect on plasma amino acid concentration in individuals heterozygous for phenylketonuria. Metabolism 1989;38:78-84.
143. Filer LJ, Stegink LO. Aspartame metabolism in normal adults, phenylketonuric heterozygotes and diabetic subjects. Diabetes Care 1989;12:67-74.
144. Levy HL, Waisbren SE. Effects of untreated maternal phenylketonuria and hyper-phenylalaninemia on the fetus. N Engl J Med 1983;309:1269-1274.
145. Committees of the American Diabetes Association and the American Dietetic Association. Exchange Lists for Meal Planning. Chicago: American Dietetic Association and American Diabetes Association, in cooperation with the National Institute of Arthritis, Metabolism, and Digestive Disease and the National Heart, Blood, and Lung Institute. U.S. Department of Health, Education, and Welfare, 1986.
146. Vinik AI, Jenkins DJA. Dietary fiber in management of diabetes. Diabetes Care 1988;11: 160-173.
147. Coulston AM, Hollenbeck CB, Swislocki ALM, Reaven GM. Persistence of hypertriglyceridemic effect of low-fat high-carbohydrate diets in NIDDM patients. Diabetes Care 1989;12:94-101.
148. American Diabetes Association Consensus Statement. Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. Diabetes Care 1989;12:573-579.
149. Wood FC, Bierman EL. Is diet the cornerstone in management of diabetes? N Engl J Med 1986;315:1224-1226.
150. Schectman G, Kaul S, Kissebah AH. Effect of fish oil concentrate on lipoprotein composition in NIDDM. Diabetes 1988;37: 1567-1573.
151. Bantle JP. Clinical aspects of sucrose and fructose metabolism. Diabetes Care 1989;12:56-61.
152. Cologiuri S, Miller JJ, Edwards RA. Metabolic efects of adding sucrose and aspartame to the diet of subjects with noninsulin-dependent diabetes mellitus. Am J Clin Nutr 1989;50:474-478.

153. Hollenbeck CB, Coulston AM, Reaven GM, Slama G, Mann JI. The diabetic dietary prescription: an ongoing controversy. Diab Nutr Metab 1988;3:239-254.
154. Crapo PA, Insel J, Sperling M, Kolterman OG. Comparison of serum glucose, insulin and glucagon responses to different types of complex carbohydrate in noninsulin-dependent diabetic patients. Am J Clin Nutr 1981;34:184-190.
155. Jenkins DJA, Wolever TMS, Taylor RH, et al. Glycemic index of foods: A physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362-366.
156. Anderson JW, Gustafson NJ, Bryant CA, Tietyen-Clark J. Dietary fiber and diabetes: a comprehensive review and practical application. J Am Diet Assoc 1987;87:1189-1197.
157. Canadian Diabetes Association. Guidelines for the nutritional management of diabetes mellitus. J Can Dietet Assoc 1981;42:110-118.
158. Nutrition Sub-Committee of the British Diabetic Association Medical Advisory Committee. Dietary Recommendations for the 1980s—a policy statement by the British Diabetic Association. Hum Nutr Appl Nutr 1982;36:378-386.
159. Gabbe SG, Cohen AW, Herman GO, Schwarz S. Effect of dietary fiber on the oral glucose tolerance test in pregnancy. Am J Obstet Gynecol 1982;143:514-517.
160. Ney D, Hollingsworth DR, Cousins L. Decreased insulin requirement and improved control of diabetes in pregnant women given a high-carbohydrate, high-fiber, low-fat diet. Diabetes Care 1982;5:529-533.
161. Anderson JW, Bridges SR, Tietyen J, Gustafson NJ. Dietary fiber content of a simulated American diet and selected research diets. Am J Clin Nutr 1989;49:352-357.
162. Singh RH. Studies of factors that precipitate gestational diabetes in humans. Department of Foods and Nutrition [Dissertation]. Athens, Georgia: University of Georgia, 1989, pp 75-92.
163. Mintz DH, Skyler JS, Chez RA. Diabetes mellitus and pregnancy. Diabetes Care 1978;1:49-63.
164. Pitkin RM. Nutritional influences during pregnancy. Med Clin North Am 1977;61:3-15.
165. Pedersen J. Final general discussion. In: Pregnancy Metabolism, Diabetes and the Fetus. CIBA Foundation Symposium 63 (new series). Excerpta Medica, Amsterdam, 1979, p 310.
166. Coetzee EJ, Jackson WPU, Berman PA. Ketonuria in pregnancy with special reference to calorie-restricted food intake in obese diabetics. Diabetes 1980;29:177-181.
167. Mac Gillivray I. Weight and weight gain in pregnant women. In: Sutherland HW, Stowers JM (eds). Carbohydrate metabolism in pregnancy and the newborn. Berlin: Springer Verlag, 1979:500-508.
168. Boberg C, Gillmer MDG, Brunner EJ, Gunn PJ, Oakley NW, Beard RW. Obesity in pregnancy: The effect of dietary advice. Diabetes Care 1980;3:476-481.
169. Algert S, Shragg P, Hollingsworth DR. Moderate caloric restriction in obese women with gestational diabetes. Obstet Gynecol 1985;65: 487-491.
170. Hollingsworth DR, Ney DM. Dietary management of diabetes during pregnancy. In: Reece EA, Coustan DR (eds). Diabetes mellitus in pregnancy. principles and practice. New York: Churchill Livingstone, 1988:294-296.
171. Hollingsworth DR. Diabetes. In: Hollingsworth DR, Resnik R (eds). Medical counseling before pregnancy. New York: Churchill Livingstone, 1988:281-283.
172. Cohen LF, Di Sant'Agnese PA, Friedlander J. Cystic fibrosis and pregnancy. Lancet 1980;2: 842-844.
173. MacMullen NJ, Brucker MC. Pregnancy made possible for women with cystic fibrosis. Maternal and Child Nursing 1989;14:196-198.
174. Vlenzuela GJ, Comunale FL, Davidson BH, Dooley RR, Foster TC-S. Clinical management of patients with cystic fibrosis and pulmonary insufficiency. Am J Obstet Gynecol 1988;159: 1181-1183.
175. Shiffman ML, Seale TW, Flux M, Rennert OR, Swender PT. Breast-milk composition in women with cystic fibrosis: report of two cases and a review of the literature. Am J Clin Nutr 1988;49:612-617.
176. Hollingsworth DR. Exercise in normal and diabetic pregnancies. In: Reece EA, Coustan DR (eds). Diabetes mellitus in pregnancy. principles and practice. New York: Churchill Livingstone 1988:313-346.
177. American College of Obstetricians and Gynecologists (ACOG) Technical Bulletin. Exercise during pregnancy and the postnatal period. Washington, D.C. May, 1985.
178. Lotgering FK, Gilbert RD, Longo LD. Maternal and fetal responses to exercise during pregnancy. Physiol Rev 1985;65:1-36.
180. Morton MJ, Paul MS, Metcalfe J. Exercise during pregnancy. Med Clin North Am 1985;69:97-108.
179. Artal R, Wiswell RA (eds). Exercise in pregnancy. Baltimore: Williams & Wilkins, 1986.
181. Lees MM, Taylor SH, Scott DB, et al. A study of cardiac output at rest throughout pregnancy. J Obstet Gynaecol Br Commonw 1967;74:319-328.
182. Werko L. Toxaemias of pregnancy. CIBA Foundation Symposium, Churchill, London, 1950: 155.
183. Atkins AF, Watt JM, Milan P, et al. A longitudinal study of cardiovascular dynamic changes throughout pregnancy. Eur J Obstet Biol Repro Biol 1981;12:215-224.
184. Lotgering FK, Gilbert RD, Longo LD. The interactions of exercise and pregnancy: A review. Am J Obstet Gynecol 1984;149:560-568.
185. Ueland K, Novy MJ, Peterson EN, et al. Maternal cardiovascular dynamics: IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 1969;104:856-864.

186. Metcalfe J, Ueland K. Maternal cardiovascular adjustments to pregnancy. Prog Cardiovasc Dis 1974;16:363-374.
187. McCausland AM, Hyman C, Winsor T, et al. Venous distensibility during pregnancy. Am J Obstet Gynecol 1961;81:472-479.
188. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. Br Med J 1964;1:532-533.
189. Pritchard JA. Hematologic aspects of pregnancy. Clin Obstet Gynecol 1960;3:378-385.
190. Hytten FE, Paintin DB. Increase in plasma volume during normal pregnancy. J Obstet Gynaecol Br Commomw 1963;70:402-407.
191. Chesley LC. Plasma and red cell volumes during pregnancy. Am J Obstet Gynecol 1972;112:440-450.
192. Hytten FE, Thomson AM. Maternal physiological adjustments. In: Assali NS (ed). Biology of gestation. Orlando, FL:Academic Press, 1968; 449-479.
193. Edwards MJ, Metcalfe J, Dunham MJ, Paul MS. Accelerated respiratory response to moderate exercise in late pregnancy. Respir Physiol 1981;45:229-241.
194. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 1974;54:75-159.
195. Morris N, Osborn SB, Wright HP. Effective uterine bloodflow during exercise in normal and preeclamptic pregnancies. Lancet 1956; 2:481-484.
196. Morton MJ, Paul MS, Campos GR, et al. Exercise dynamics in late gestation: Effects of physical training. Am J Obstet Gynecol 1985;159:91-97.
197. Novy MJ, Petersen EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age in the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 1969;104:859.
198. Ginsburg J, Duncan SLB. Peripheral blood flow in normal pregnancy. Cardiovasc 1967;1:356-361.
199. Rauramo I, Andersson B, Laatikainen T, Pettersen J. Stress hormones and placental steroids in physical exercise during pregnancy. Br J Obstet Gynaecol 1982;89:921-925.
200. Metcalfe J, Romney SL, Ramsey LH, et al. Estimation of uterine blood flow in normal human pregnancy at term. J Clin Invest 1955;34:1632-1638.
201. Terada M. Effect of physical activity before pregnancy on fetuses of mice exercised forcibly during pregnancy. Teratology 1974;10:141-144.
202. Naeye RL, Peters EL. Working during pregnancy: Effects on the fetus. Pediatrics 1982; 69:724-727.
203. Platt LD, Artal R, Semel J, et al. Exercise in pregnancy. II. Fetal responses. Am J Obstet Gynecol 1983;147:487-491.
204. Collings CA, Curet LB, Mullin JP. Maternal and fetal responses to a maternal aerobic exercise program. Am J Obstet Gynecol 1983; 145:702-707.
205. Pijpers L, Wladimiroff JW, McGhie J. Effect of short-term maternal exercise on maternal and fetal cardiovascular dynamics. Br J Obstet Gynaecol 1984;91:1081-1086.
206. Collings C, Curet LB. Fetal heart rate response to maternal exercise. Am J Obstet Gynecol 1985;151:498-501.
207. Veille J-C, Hohimer AR, Burry K, Speroff L. The effect of exercise on uterine activity in the last eight weeks of pregnancy. Am J Obstet Gynecol 1985;151:727-730.
208. Pommerance JJ, Gluck L, Lynch VA. Maternal exercise as a screening test for uteroplacental insufficiency. Obstet Gynecol 1974;44:383-387.
209. Pernoll ML, Metcalfe J, Paul M. Fetal cardiac response to maternal exercise. In: Longo LD, Reneau DD (eds). Fetal and newborn cardiovascular physiology. Vol 2, New York:Garland STPM Press. 1978:389-398.
210. Artal R, Paul RH, Romen Y, Wiswell R. Fetal bradycardia induced by maternal exercise. Lancet 1984;2:258-260.
211. Berkowitz GS, Kelsey JL, Holford TR, et al. Physical activity and the risk of spontaneous preterm delivery. J Repro Med 1983;28:581-588.
212. Vranic M, Horvath S, Wahren J. Exercise and diabetes: an overview. Summary of the Conference on Diabetes and Exercise sponsored by the Kroc Foundation and held in Santa Ynez, California, March 13-17, 1978. Diabetes 1978 28(Suppl 1): 1-113.
213. Allen FM, Stillman E, Fritz R. Total dietary regulation in the treatment of diabetes. In: Exercise, New York: Rockefeller Institute of Medical Research. Monograph. 1919:486-499.
214. Hetzel KL, Long CNH. Metabolism of the diabetic individual during and after muscular exercise. Proc Royal Soc Lond Biol Soc 1926; 99:279-306.
215. Lawrence RD. The effects of exercise on insulin action in diabetes. Br Med J 1926;1:648-652.
216. Joslin EP, Root HF, White P, Marble A. The treatment of diabetes mellitus, 5th ed. Philadelphia: Lea & Febiger, 1936:299-301.
217. Marble A, Smith RM. Exercise in diabetes mellitus. Arch Int Med 1936;58:577-588.
218. Vranic M, Berger M. Review and abstracts. Exercise and diabetes mellitus. Diabetes 1978; 28:147-167.
219. Zinman B, Vranic M, Albisser AM, Leibel BS, Marliss EB. The role of insulin in the metabolic response to exercise in diabetic man. Diabetes 1979;28 (Suppl) 1:76-81.
220. Bjorntorp P, deJourge K, Sjostrom L, Sullivan L. The effect of physical training on insulin production in obesity. Metabolism 1970;19: 631-638.
221. Zinman B, Vranic M. Diabetes and exercise. Med Clin North Am 1985;69:145-157.
222. Vranic M, Kawamori R, Pek S, et al. The essentiality of insulin and the role of glucagon in regulating glucose turnover during strenuous exercise. J Clin Invest 1976;57:245-255.
223. Zinman B, Murray FT, Vranic M. Glucoregulation during moderate exercise in insulin

treated diabetes. J Clin Endocrinol Metab 1977;45:641-652.
224. Issekutz B Jr. Role of beta-adrenergic receptors in mobilization of energy sources in exercising dogs. J Appl Physiol 1978;44:869-876.
225. Christensen NJ, Galbo H, Hanset JF, et al. Catecholamines and exercise. Diabetes 1979; 28 (Suppl 1): 58-62.
226. Issekutz B Jr, Vranic M. Role of glucagon in regulation of glucose production in exercising dogs. Am J Physiol 1980;238:E13-E20.
227. Edwards MJ, Metcalfe J, Dunham MJ, Paul MS. Accelerated respiratory response to moderate exercise in late pregnancy. Respir Physiol 1981;45:229-241.
228. Hollingsworth DR, Moore TR. Postprandial walking exercise in pregnant insulin-dependent (Type I) diabetic women. Reduction of plasma lipid levels but absence of a significant effect on glycemic control. Am J Obstet Gynecol 1987;157:1359-1363.
229. Hollingsworth DR, Ney D, Stubblefield N, Fell T. Heterogeneity of lean and obese women with gestational diabetes. Metabolic assessment with isocaloric meal tolerance tests. Diabetes 1985; 34 (Suppl 2): 81-87.
230. Cheney C, Shragg P, Hollingsworth DR. Demonstration of heterogeneity in gestational diabetes by a 400 kcalorie breakfast meal tolerance test. Obstet Gynecol 1985;65:17-23.
231. Algert S, Shragg P, Hollingsworth DR. Moderate caloric restriction in obese women with gestational diabetes. Obstet Gynecol 1985;65: 487-491.

SECTION

V

Maternal Surveillance

Dorothy R. Hollingsworth

CHAPTER

16

Assessment of Diabetic Control During Pregnancy

If preconception counseling has been provided over 3–6 months and early diabetic care has been implemented successfully in a prenatal clinic, how do we evaluate success (or failure) of diabetic control? Certain reasonable objectives should be kept in mind because a term pregnancy (38–42 weeks) is a long time. Simple, yet not impossible goals to encourage diabetic pregnant women and their families are outlined on Table 16.1.

All women will need some help to achieve a good metabolic balance—some more than others. Diabetic control should not consume all one's energy; but it does require attention and supervision when not pregnant and weekly surveillance during gestation.

HOME BLOOD GLUCOSE MONITORING

Self-monitoring of blood glucose levels by patients has become a popular and valuable technique because it involves the patient in her own care and permits an immediate confirmation of hypo- or hyperglycemia. What is the normal pattern of glucose excursion in pregnant women who do not have diabetes? Figure 16.1 illustrates our observations of 24-h, around the clock hourly plasma glucose profiles in 10 normal-weight pregnant women (1, 2). The plasma glucose values measured in these clinical studies are 10–15% **lower** than measurements for capillary whole blood reported by Weiner and colleagues using an Accuchek-II meter during a 3-h glucose tolerance test study to detect gestational diabetes (3).

Our therapeutic goal in pregnant diabetic women has been to try to replicate the glucose excursions of normal pregnant women. We do not aim for "tighter than normal" control because glucose is the most vital substrate for normal embryonic and fetal growth and development. This range of maternal diurnal glucose concentrations also reduces the likelihood of iatrogenic episodes of hypoglycemia.

Several types of meters are available at diabetes supply centers. Most clinics settle on a model that suits their needs; patients often have a personal preference based on ease of use, reliability, and cost. Test strips are expensive but costs can be halved by carefully cutting the strips in half. To prevent deterioration of the glucose detection component, they should be kept in a dry place with the vial of the cap screwed on tightly. Prices of equipment and supplies and insulin preparations vary considerably. It is worthwhile to compare costs.

In prenatal clinics, we prefer to use glucose meters rather than visually read strips, because they permit more precise readings for the "normal-like" patterns of glucose control we strive to maintain during pregnancy. Mathematically oriented patients and doctors are comforted by "meters with a memory." In real life, it is hard for most patients and their doctors to translate a string of numbers or a mean value of those figures into day to day or week by week adjustment of insulin doses, especially if this is attempted without regard for dietary intake, exercise, psychological and economic variables.

Meter Seduction

Some extremely compulsive women become so bonded to their meters they want to see a number flash on the screen every few hours (4). The reflectance meter becomes a toy. Physicians, too, are not immune to meter seduc-

Table 16.1.
Reasonable, Achievable Goals That Should Be Possible for Most Diabetic Women

Assess and try to ameliorate or learn to live with the stress factors in your life
Strive for economic security with a full- or part-time job with health benefits
Learn about your type of diabetes, current treatment, and the details of prenatal care
Reduce the magnitude of daily excursions of blood glucose by avoiding hyper- and hypoglycemia; a good range is 70–130 mg/dl (3.9–7.2 mmol/L)
Adjust a nutritious diet to life-style, food preferences, and a consistent pattern
Engage in an active, not sedentary, activity pattern

tion. In outpatient clinics or private offices, how tempting it is to pore over the numbers—to average all the breakfast, lunch, dinner, and bedtime values—separately and together and suddenly select a new insulin dose based on "data."

The major problem with meter seduction is that outliers—values both high and low—do not come with an explanation from the machine. It is probably best for physicians and nurse-clinicians to **avoid looking at the numbers** until they have chatted with the patient about how things have gone since the last visit. How many and what type of insulin reactions occurred? Were any low readings a surprise and not accompanied by symptoms. Did any morning high values follow a terrible nightmare or night sweat? Have the patient's husband or others noted any periods of confusion or cognitive changes? After physician eye contact, interest, and a sympathetic ear, the numbers can then be interpreted together with the patient in light of the interim history.

There is no substitute for a visual interpretation of glucose values. After many years, we have developed a simple scheme that can be viewed quickly and meaningfully yet understood easily by both patients and inexperienced physicians in training. Figure 16.2 shows, in the background, the glucose excursions ±2 SD of perfectly normal pregnant women shown in Figure 16.1. We imprinted this curve that shows excursions of glucose levels following meals and the nocturnal blood glucose pattern of sleeping pregnant women to the daily home blood glucose monitoring record maintained by each patient. Patients plot their values each day; explain outliers in the comments at the bottom of the form and bring seven records to clinic each week. This patient-managed record

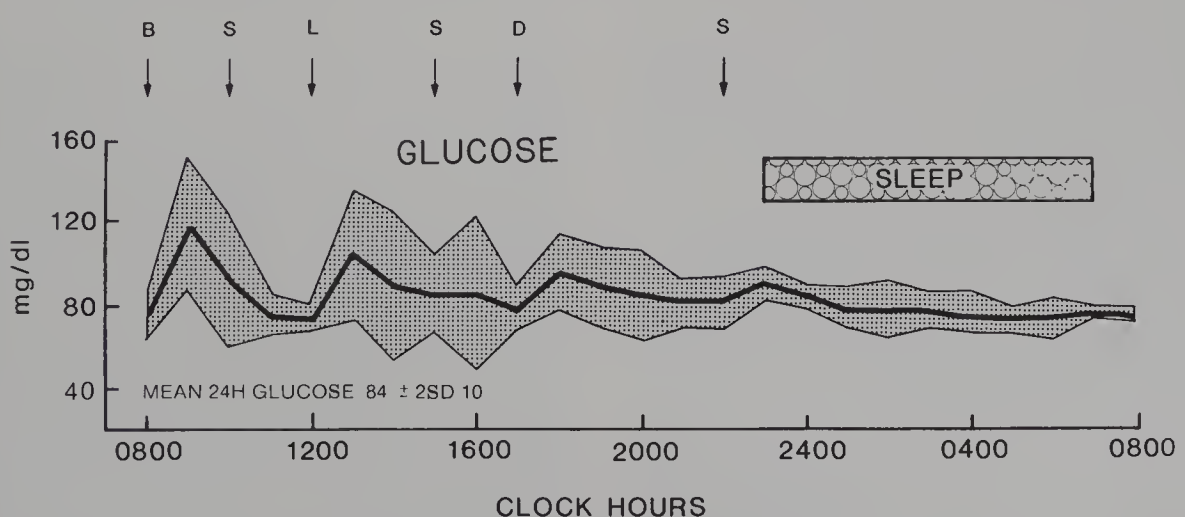


Figure 16.1. Profile of hourly blood glucose levels around the 24-h clock in 10 normal-weight, nondiabetic women at 35 weeks' gestation in response to a 2000-kcal isocaloric diet given as three meals and three snacks at the times indicated by the *arrows*. *B*, breakfast; *S*, snack; *L*, lunch; *D*, dinner. Note how small the meal-evoked excursions are. The **mean fasting blood glucose level** in normal-weight pregnant women is 75 ± SD 7 mg/dl (4.2 mmol/L) and the **mean 24-h plasma glucose value** is 84 ± 2 SD **of 10** mg/dl (4.7 mmol/L). Values are 5 mg/dl (0.3 mmol/L) higher in obese normal women (1).

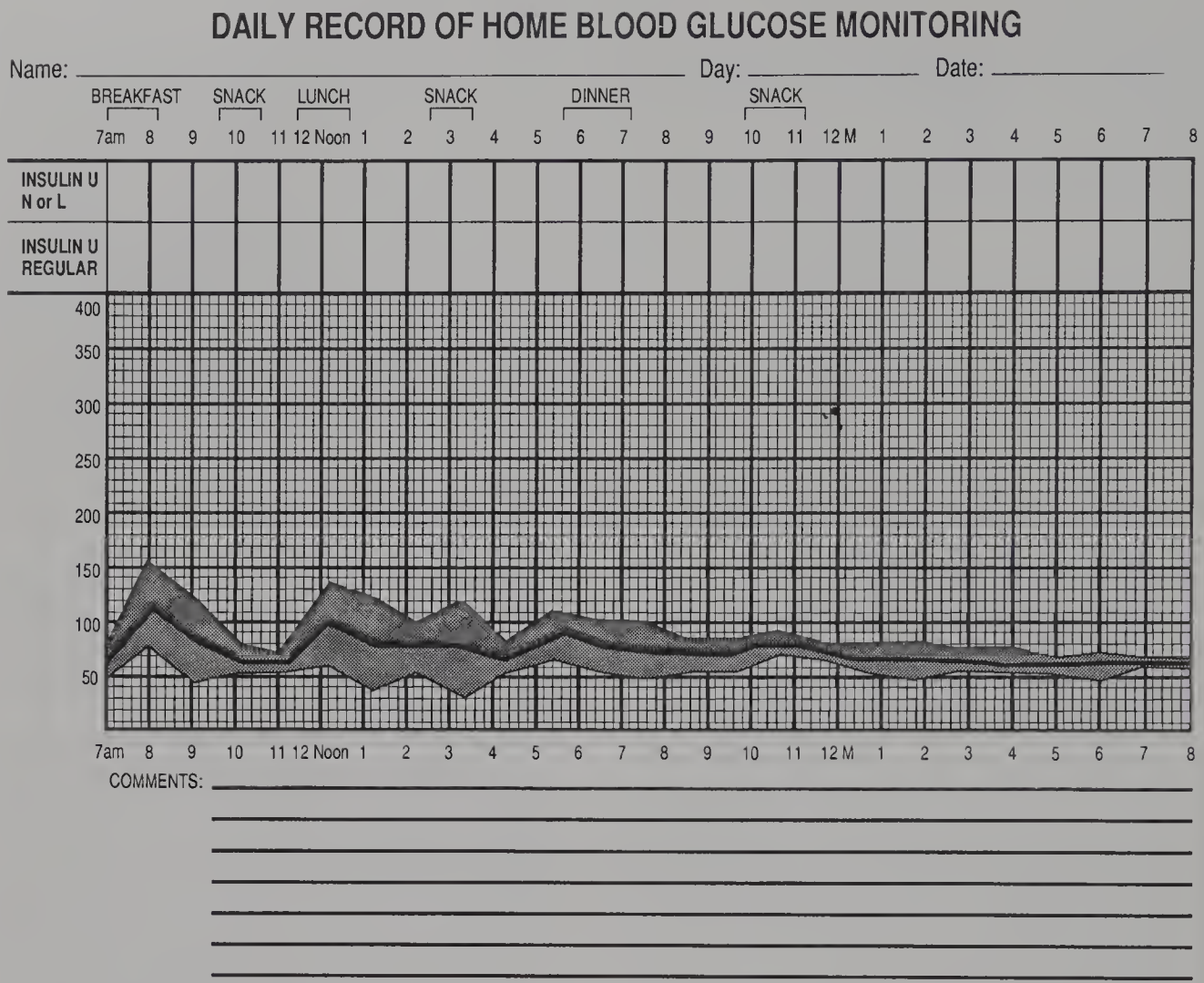


Figure 16.2. Daily record for home blood glucose monitoring maintained by each pregnant diabetic woman. The **shaded background area** represents plasma glucose values in normal pregnant women ±2 SD around the 24-h clock.

keeping helps avoid meter seduction. The technique for home monitoring we use in an ambulatory clinic for control of hyperglycemia is outlined on Table 16.2.

ALTERNATIVE METHOD FOR MONITORING DIABETIC CONTROL DURING PREGNANCY BY MEASUREMENTS OF 24-H GLUCOSE LOSS IN FRACTIONAL URINE COLLECTIONS

Is there ever a reason to measure quantitative urinary glucose loss in fractional urines? Most obstetricians and medical diabetologists would say no; we do not ever need that archaic method to assess diabetic control. By and large, this is true, and prenatal diabetic clinics already resemble a sea of urine with so many 24-h containers for serial creatinine clearances and little urine receptacles for weekly dip-stick tests for proteinuria and acetone, or baseline and subsequent cultures for bacteriuria.

With the development of simple, accurate glucose meters, almost all diabetologists would agree that quantitative measurement of urine glucose loss in four fractional samples for 24-h is a method we rarely, if ever, need. In some settings and circumstances, however, there are exceptions when this old-fashioned approach is invaluable in both pregnant and nonpregnant patients. A description is retained in this edition for easy reference to the method.

In many clinic settings and for pregnant women of limited means, access to newer methods to monitor blood glucose may not be available. Some patients (computer operators, seamstresses, musicians, and others) are either unable or unwilling to check their blood

Table 16.2.
Home-Monitoring Techniques for Control of Blood Glucose Levels During Pregnancy

Period of stabilization and insulin dosage adjustments
Before and 2 h after meals and bedtime
Fasting, prelunch, predinner
Two hours after meals, bedtime
Nocturnal tests as indicated for possible symptomatic or asymptomatic hypoglycemia
In exceptional cases or in clinical settings where all patients cannot afford a glucose meter and expensive supplies, excellent control can be established by collecting 24-h fractional urines and measuring glucose quantitatively
Long-range control
Fasting, prelunch, predinner, bedtime, **daily** during gestation, 3 days a week before and after pregnancy
Combine four blood glucose measurements with urine pregnancy acetone tests (Ketodiastix) daily with illness, fever, or unexplained high glucose values
Suspected hypoglycemia
At time of symptoms and nocturnal testing when morning fasting glucose levels are inexplicably high (rebound effect following unrecognized nocturnal hypoglycemia)

glucose levels with strips or meters. Still others are blind, illiterate, mentally ill, retarded, or live in poverty. Some of our patients have been homeless. With poor diabetic control and unfortunate or exceptional circumstances, it is always easier to void and collect urine 1 day a week than to stick your own finger many times a day and keep up with monitoring records. As mentioned in the previous section, we still like to use this technique along with hourly blood glucose monitoring in our 24-h hospital assessment of poor control in our most difficult pregnant women. Moreover, the four fractional urine collections can be pooled easily to determine total urinary protein loss in 24-h, as well as urinary creatinine levels and a creatinine clearance value. In these women and others who are difficult to control or who report erratic blood glucose values by self-monitoring, excellent diabetic control can be achieved by assessment of quantitative urinary glucose loss in fractional periods of the 24-h day (Fig. 16.3).

The information provided by this test is extremely useful for adjustment of type and timing of insulin doses. The disadvantage of the method is the necessity for accurate collections of urine over specified time periods and the variable costs of different laboratories for performing quantitative determinations for urinary glucose. In our experience, pregnant women are highly motivated to achieve good control and have not found a 24-h collection of urine only 1 day each week to be burdensome. Urine collections are easier and cheaper than repeated finger sticks and yield more valuable information in patients in poor control than three or four blood glucose values in 24 h. In addition, we have found this test to be a useful adjunct to home monitoring because it measures total urinary loss of glucose, an excellent index of diabetic control and loss of dietary calories during the 24-h day. Again, the patient is involved in her own care and a participant in tests that help with decisions concerning the type and distribution of insulin doses.

Method for Determination of 24-h Fractional Urinary Glucose Loss

On the day before each weekly clinic visit, the patient discards the first AM urine on awakening. Subsequent urine collections are made in a large receptacle or plastic pitcher (to avoid collection losses) and poured carefully using a funnel, into a labeled plastic bottle that contains sodium benzoate as a preservative for each collection period.

Each fractional time period is divided as follows and the four individual containers kept in a cool place: number 1: 8 AM to 12 noon; number 2: 12 noon to 4 PM; number 3: 4 PM to 8 PM; number 4: 8 PM to 8 AM. The patient is instructed to void as needed and at the end of each time period.

The laboratory reports the total volume and quantitative measurement of glucose in each of the four urine collections. Total grams of glucose per collection period are calculated as in the following example: specimen 1, volume, 320 ml; glucose, 950 mg/dl; calculation, $3.2 \times 0.950 = 3.04$ g glucose in specimen 1. The total

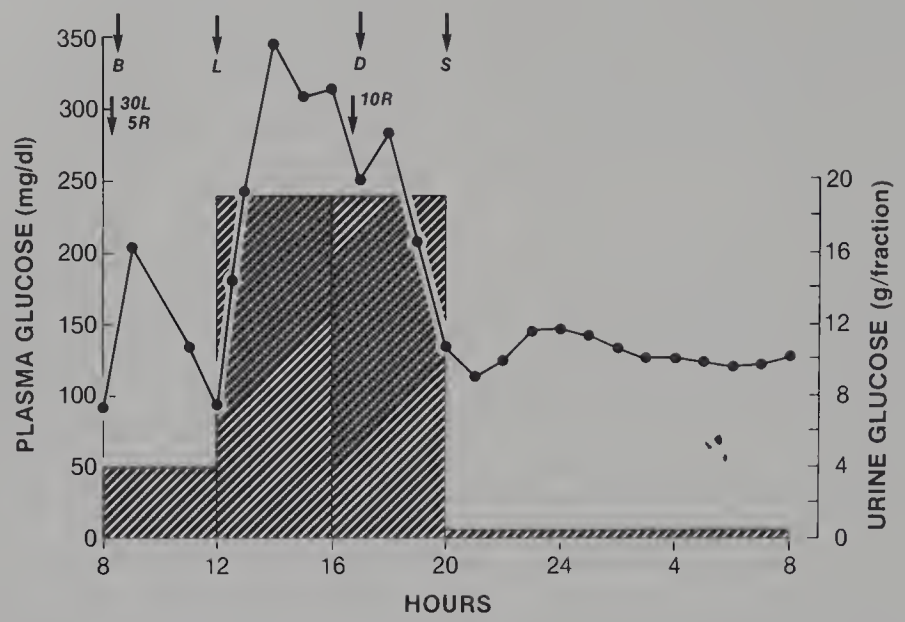


Figure 16.3. Excursions of plasma glucose levels (*solid lines*) during the 24-h metabolic clock in a baseline study of a poorly regulated IDDM at 18 weeks of gestation. Urinary glucose loss (*hatched areas*) during fractional urine collections (8:00 AM–12:00 noon; 12:00 noon–4:00 PM; 4:00 PM–8:00 PM; and 8:00 PM through and **including** the first voided urine the following morning) mirrors mean plasma glucose values during the same time periods (5).

urinary glucose loss in 24 h is equal to the sum of the glucose values in the four specimens. From the same 24-h collection, total protein loss can also be determined as well as a creatinine clearance, which is usual in each trimester in IDDM patient or, more frequently, in women with problems such as renal disorders or preeclampsia. Figure 16.3 illustrates the pattern of urinary glucose loss around the 24-h clock in a 17-year-old woman with IDDM in poor control on admission to the prenatal diabetes program. Urinary loss of glucose in fractional urine collections correlated nicely with hourly plasma glucose values during the same time periods. A further advantage of this method is information gained concerning the renal threshold for glucose. It is not a reliable method to evaluate diabetic control in patients with severe diabetic nephropathy who have proteinuria exceeding 3 g in 24 h; elevated levels of serum creatinine and blood urea nitrogen because urinary glucose levels, in this circumstance, do not reflect accurately the blood glucose levels.

HbA1c CONCENTRATION

Measurements of glycosylated hemoglobin (HbA1c) have proved to be a useful index of long-term (4–6 week) control of hyperglycemia during diabetic pregnancy (6). HbA1c is a normal minor hemoglobin that has glucose linked to the N-terminal end of the β chain. Glycosylation of hemoglobin occurs nonenzymatically throughout the life-span of the red blood cell as a postsynthetic modification of hemoglobin A. HbA1c levels depend on the mean circulatory glucose levels to which the erythrocyte is exposed during its 120-day life-span. Thus, levels of HbA1c provide information concerning glucose control when erythrocyte survival time is normal.

Pollak and colleagues (7) have measured HbA1c in 178 women during pregnancy and immediately postpartum by a thiobarbituric acid and spectrophotometric method. In women with normal glucose tolerance, HbA1c levels were unchanged in the 2nd and 3rd trimesters of pregnancy or the immediate postpartum period. They found a significantly higher concentration of HbA1c in women with an abnormal glucose tolerance test during pregnancy. The highest values were noted in pregnant women with insulin-dependent diabetes and there was a positive correlation between maternal HbA1c concentration and infant birth weight.

Ylinen and co-workers (8) have measured HbA1c values in 112 insulin-dependent diabetic pregnancies. They noted that high values at 2nd trimester were associated with severe fetal malformations in three patients and per-

inatal death in six others. Higher levels were also found in mothers of infants with neonatal hypoglycemia and hyperbilirubinemia.

Steel and colleagues (9) have found it useful to measure HbA1c on the 1st or 2nd day after delivery in mothers who have delivered infants at >95th percentile weight for gestational age. Nine of 50 women with large infants but only one of 50 controls had HbA1c concentrations above the normal range. Since all the women had normal glucose tolerance 6 weeks after delivery, the postpartum HbA1c value was useful in the retrospective documentation gestational diabetes.

Madsen and associates (10) investigated the relationship of 3rd trimester HbA1c concentrations to average blood glucose values and to birth weight of infants of diabetic mothers in 42 consecutive insulin-dependent pregnancies. In this report, fasting and postprandial glucose values were averaged and a positive correlation was found for HbA1c and average blood glucose levels, but not for relative birth weight ratio of the infants. However, when individual pregnancies were examined, HbA1c determinations were often a poor predictor of average blood glucose levels. In our own studies around the 24-h metabolic clock, we have observed that HbA1c values correlated with mean 24-h glucose values, but did not reflect the mean amplitude of glycemic excursions.

Acute improvement of glycosylated hemoglobin (A + B + C) has been reported after short periods of treatment on the artificial pancreas (Biostator). This has been attributed to an unstable component of HbA1c, which may represent Schiff base that is formed as the initial step in the formation of glycosylated hemoglobin. The presence of unstable HbA1c may result in large errors in routine outpatient studies. The unstable component can be eliminated by incubation of red cells in a low glucose medium at 37°C for several hours or by dialysis. In the presence of severe hyperglycemia, HbA1c concentrations can increase within a few hours. Reversal of high values can occur in 6 h with the artificial pancreas, but the same response requires several days if routine insulin therapy is used.

HbA1c concentrations are lower in hemoglobinopathies and hemolytic anemias and are elevated in iron deficiency anemia. Correction factors are necessary in these situations. There is no universal HbA1c method and temperature control is an important variable. Despite these kinetic and methodologic problems, a normal level of HbA1c concentration in a clinic setting usually indicates good overall control of blood glucose in the previous 4–6 weeks and is a useful test.

Measurement of HbA1c concentrations is not a good procedure for detection of gestational diabetes and should not be used for this purpose in lieu of any of the several diagnostic approaches to this problem. Measurement of HbA1c concentrations in women already diagnosed with GDM is useful because, if done early (<20 weeks' gestation) or when high values are present, it is more likely that the patient has NIDDM rather than GDM. In any event, postpartum reassessment is important and should be routine standard of care for all these individuals (Section III).

PLASMA FRUCTOSAMINE

Measurements of fructosamine, a glycosylated serum protein, have been used in some clinics as an index of short-term control of diabetes, often in conjunction with tests of glycosylated hemoglobin concentration, which measures medium- to longer-term control (11). In some obstetric clinics, fructosamine determinations have been used to assist in the diagnosis of gestational diabetes (12, 13). Doery and co-workers (11) found no significant difference in fructosamine levels in women with GDM compared with normals. They also found the test of no value in the management of diabetes during pregnancy. Several other studies have reported that neither HbA1c nor fructosamine determinations are suitable for the diagnosis of mild abnormalities in glucose tolerance (14–17).

LONGITUDINAL ASSESSMENT OF IMPORTANT CLINICAL VARIABLES DURING DIABETIC PREGNANCY

In 1991, there is great variation in type of obstetric care. Some, but not many, obstetricians are in solo practice. Others form partnerships or groups or join health maintenance organizations (HMOs), community clinics, or teaching hospitals. All obstetricians are busy and rely increasingly on nurse-clinicians to provide a high standard of care and avoid preventable problems. No physician chooses ob-

stetrics as a specialty to subsequently become primarily a diabetologist, but many, if not most, obstetricians and clinics who have many diabetic patients find it useful to set up a separate diabetic prenatal clinic using an ambulatory care team approach and the help of nurse-clinicians.

How can you keep all the details of diabetes management straight and treatment on track in some simple format, yet have all the information available for each patient on a single page in the chart that can be viewed quickly to summarize the patient's progress and problems? In the first edition of this book, we included a longitudinal record that we have now had an opportunity to evaluate for a decade. In our busy clinic with medical students, house officers from many different medical schools, attendings, nurses, nutritionists, and social workers, this single page record has become a real asset for patient care and we regard it as a useful "crutch." Figure 16.4 is a revised version of our longitudinal clinic record for diabetic women that can easily be replicated to meet the needs of individual obstetricians, medical diabetologists, or clinics. A similar format is also convenient for pregnant women with other chronic disorders, e.g., Graves' disease.

OUTCOME MEASUREMENTS TO ASSESS EFFICACY OF DIABETIC CONTROL

There are three different types of measurement of progress in achieving overall metabolic stability for diabetic women in an outpatient clinic: (*a*) a 2-h postbreakfast capillary blood glucose value (meter) performed at each clinic visit. This tells us only the level of blood glucose at that second—1 of 86,000 sec-

Name _____
Birthdate: _____
Hospital #: _____

LONGITUDINAL MEDICAL RECORD FOR PREGNANT DIABETIC PATIENTS

Date																					
Week of Gestation Sonogram ✓ Retinal Exam ✓																					
Weight																					
BP																					
Blood	BUN/Creat.																				
	Glu. Fast.																				
	2 hr																				
	Other																				
	HbA_{1c}																				
	Chol.																				
	Triglycerides																				
Urine	Glucose g/24 h 40																				
	30																				
	20																				
	10																				
	Protein 0-4+																				
	Cr. CL. ml/min																				
Rx	Diet kcal/day																				
	Insulin AM																				
	Insulin PM																				
	Other Medications																				
Pregnancy Problems and Complications																					

Figure 16.4. Simple longitudinal chart for recording data each week of diabetic pregnancy in an ambulatory care setting. HbA1c determinations are obtained monthly. Creatinine clearance determinations are not routine; baseline values are usually obtained in IDDM women and repeated each trimester if serum creatinine values are elevated or if the pregnancy is complicated by chronic hypertension or preeclampsia. It is informative to measure fasting CHOl and TG at first visit and late 3rd trimester to detect women with hyperlipidemia. Thyroid function tests: T_4, sensitive TSH, and microsomal antibody titers should be requested for all women with IDDM.

onds on that particular day; (*b*) a review and interpretation of weekly profiles of home blood glucose monitoring described previously to give a better overall day-to-day assessment of insulin doses, dietary habits, and physical activity; and (*c*) a HbA1c concentration at monthly intervals to evaluate long-term control over the previous month or 6 weeks. This test does not measure the possibility of a relatively normal HbA1c concentration in the presence of poor diabetic control manifested by severe episodes of hypoglycemia with many values below 60 mg/dl (3.3 mmol/L) balanced by high values of greater than 200 mg/dl (11.1 mmol/L).

All three outcome measurements are extremely helpful and they provide us with different kinds of important information. Taken together, they give us a very good view of how successful (or unsuccessful) our treatment is in each pregnancy. No single measurement provides sufficient information.

In conclusion, this section is a description of longitudinal surveillance and methods of assessment of the total impact of combined measures, e.g., insulin, diet, and physical activity used to achieve and maintain hyperglycemic control in diabetic pregnancies. Graphic methods are used to illustrate patient monitoring records and easy visualization of a patient's clinical data on a single page placed in the front of the chart.

Always, there are the really difficult patients and their pregnancies are a challenging trial for everyone. It is always best to keep things simple and, if totally frustrated, even an old-fashioned method like a weekly 24-h urine collection may achieve excellent results.

References for Section V

1. Hollingsworth DR, Moore T. Diabetes and pregnancy. In: Creasy RK, Resnik R (eds). Maternal-fetal medicine: Principles and practice. Philadelphia: WB Saunders, 1989:934.
2. Hollingsworth DR. Further observations in lean and obese women with gestational diabetes during a 400-kilocalorie meal tolerance test. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in pregnancy and the newborn. IV. London: Springer-Verlag, 1989:245–256.
3. Weiner CP, Faustich MW, Burns J, Fraser M, Whitaker L, Klugman M. Diagnosis of gestational diabetes by capillary blood samples and a portable reflectance meter: Derivation of threshold values and prospective validation. Am J Obstet Gynecol 1987;156:1085–1089.
4. Beer SF, Lawson C, Watkins PJ. Neurosis induced by home monitoring of blood glucose concentrations. Br Med J 1989;298:362–363.
5. Hollingsworth DR, Cousins L. Diabetes in pregnancy: a new perspective. In: Milunsky A, Friedman EA, Gluck L (eds). Advances in perinatal medicine. Vol 20, New York: Plenum Publishing, 1982:245–320.
6. Kjaergaard J-J, Hansen P, Madsen H, Ditzel J. Hemoglobin A1c as an indicator of long term blood glucose levels in diabetics with special reference to diabetic pregnancy. Acta Endocrinol (Suppl 94) 1980;238:25–29.
7. Pollak A, Widness JA, Schwartz RL. Minor hemoglobins: an alternative approach for evaluating glucose control in pregnancy. Biol Neonate 1979;36:185–192.
8. Ylinen K, Raivo K, Teramo K. Hemoglobin A1c predicts the perinatal outcome in insulin-dependent pregnancies. Br J Obstet Gynaecol 1981; 88:961–967.
9. Steel JM, Thomson P, Johnstone F, Smith AF. Glycosylated hemoglobin concentrations in mothers of large babies. Br Med J 1981; 282:1357–1358.
10. Madsen H, Ditzel J, Hansen P, Hahnemann N, Anderson O, Kjaergaard J-J. Hemoblobin A1c determinations in diabetic pregnancy. Diabetes Care 1981;4:541–546.
11. Doery JCG, Healy D, Bishop S, Tippett C. Fructosamine in gestational diabetes. Am J Obstet Gynecol 1990;162:1635–1636.
12. Roberts AB, Baker JR, Court DJ, James AG, Henley P, Ronayne ID. Fructosamine in diabetic pregnancy. Lancet 1983;2:998–999.
13. Roberts AB, Baker JR. Serum fructosamine: a screening test for diabetes in pregnancy. Am J Obstet Gynecol 1986;154:1027–1030.
14. Cousins L, Dattel BJ, Hollingsworth DR, Zettner A. Glycosylated hemoglobin as a screening test for carbohydrate intolerance in pregnancy. Am J Obstet Gynecol 1984;150:455–460.
15. Cousins L, Dattel B, Hollingsworth D, Hulbert D, Zettner A. Screening for carbohydrate intolerance in pregnancy. A comparison of two tests and reassessment of a common approach. Am J Obstet Gynecol 1985;153:381–385.
16. Guillausseau PJ, Charles M-A, Paolaggi F. Comparison of HbA1 and fructosamine in diagnosis of glucose-tolerance abnormalities. Diabetes Care 1990;13:898–900.
17. Cefalu WT, Prather KL, Chester DL, Wheeler CJ, Biswas M, Pernoll ML. Total serum glycosylated proteins in detection and monitoring of gestational diabetes. Diabetes Care 1990; 13:872–875.

SECTION

VI

Medical and Obstetric Complications of Diabetic Pregnancies: IDDM, NIDDM, and GDM

Dorothy R. Hollingsworth

CHAPTER

17

Medical Complications

Diabetic pregnancies can be associated with every known obstetric complication. Because even trivial problems upset diabetic control and pose greater hazards for the mother and fetus, every effort is made to ensure early recognition and treatment of untoward events.

Prevention of most medical problems in diabetic pregnancies is possible with preconception counseling that includes diabetes reeducation and attention to chronic medical problems, as discussed in detail in Section I.

Table 17.1 is a list of the 12 most frequently encountered medical problems in pregnant diabetic women.

EMOTIONAL STRESS

In pregnant women with diabetes, the three most common problems that adversely affect metabolic control are emotional stress, infection, and iatrogenic hypoglycemia. Emotional upsets, anxiety about pregnancy outcome, and financial difficulties are such disturbing factors in many pregnancies that good diabetic control cannot be established until some solution is found. In some patients, these problems can be resolved by the efforts of the physicians, family, and social workers. In others, however, ongoing psychologic counseling is necessary.

The most difficult emotional problems for the diabetic patient and her family arise when spontaneous abortions or stillbirths occur or an infant is born with a congenital anomaly that is incompatible with life. Early fetal loss happens most often in women with elevated HbA1c concentrations. Psychologic and medical support should be continued by the obstetric staff rather than abandoning the patient to deal with grief and possible guilt without help. Often, these patients are motivated to improve their own care and complete successful pregnancies a short time later.

Stillborn infants of diabetic mothers are rare in modern obstetric clinics. However, they still occur in women with no prenatal care or unrecognized and untreated GDM who present late in gestation with no fetal movement. The diagnosis of diabetes can sometimes be confirmed by elevated levels of HbA1c. A great deal of support has to be provided for these women along with careful medical explanations, advice for preventive health measures, and instruction for early prenatal care in subsequent pregnancies.

INFECTION

A sudden change in plasma glucose levels or an increase in urinary loss of glucose in a 24-h quantitative fractional urine from a well-regulated patient is often the first sign of a seemingly minor infection. The most common problems are viral illnesses and urinary tract infections. Worsening of control also occurs during acute cholecystitis, otitis media, sinusitis, gastroenteritis, toothaches, and ingrown toenails. Poor control lasts longer than might be expected despite an increase in dosage of insulin and appropriate medical therapy.

HYPOGLYCEMIA

The risks of hypoglycemia have been discussed in Section IV, Chapter 12. The common causes of hypoglycemia are outlined in Table 17.2. Blood glucose levels of <50 mg/dl (2.8 mmol/L) are in the hypoglycemic range and usually are accompanied by autonomic symptoms or mental confusion in most patients with diabetes. The range of symptoms is quite variable and each patient tends to have a char-

Table 17.1.
Medical Problems in Pregnant Diabetic Women

1. Emotional stress
2. Hypoglycemia
3. Infections
4. Starvation ketosis
5. Diabetic ketoacidosis
6. Hyperosmolar hyperglycemia nonketotic syndrome (HHNS)
7. Retinopathy
8. Nephropathy
9. Cardiovascular problems
10. Neuropathy
11. Edema
12. Noncooperative patients and physician failure

acteristic pattern. The earliest symptom may be a sensation of circumoral numbness followed by tremulousness, tremor, increased sweating, tachycardia, and a feeling of intense hunger or headache. In some individuals, the only premonitory sensation is a feeling of "tiredness." In others, outbursts of temper or weeping may indicate a low blood sugar.

In some women who have had IDDM for a long time (usually >10 years), severe hypoglycemia (plasma glucose, <40 mg/dl, 2.2 mmol/L) may occur without warning. Inapparent hypoglycemia in pregnant women who are tightly controlled on a constant subcutaneous infusion or by multiple subcutaneous injections of insulin is a special risk during both day and night. Frightening nightmares may be the only indication of this problem. Hypoglycemic coma can occur, which is life threatening.

The most common cause of hypoglycemia is overinsulinization by a zealous patient or her physician in the attempt to achieve "perfect control." Wilson (1) has reviewed the biochemical effects and clinical repercussions of excessive insulin therapy. Low blood glucose levels often occur (particularly in IDDM patients) during excessive or unplanned exercise, as described in detail in Section IV.

Table 17.2.
Causes of Hypoglycemia in Diabetic Patients

Overinsulinization
Abnormal counterregulatory responses
Anti-insulin antibodies
Antibodies to the insulin receptor
Impaired subcutaneous absorption of insulin

Table 17.3.
Recommendations for Pregnant Women with Insulin-dependent Diabetes (IDDM; Type I) and Metabolic Instability to Prevent Severe and Often Asymptomatic Hypoglycemia

1. Meals at fixed times with consistent caloric intake
2. Snacks at 10 AM, 3 PM, bedtime; carry snack in purse or car at all times; additional snacks before, during, and after exercise
3. Monitoring of blood glucose with glucometer or test strips before each meal, at bedtime, and during minor or unexplained symptoms
4. Glucagon kit and instruction of family in glucagon administration
5. In women who lack counterregulatory responses to hypoglycemia, use a baseline-fixed insulin dose regimen that permits less stringent control; work out individual adjustment schedule of only ± 2–4 U of regular insulin based on meter or test strip readings before each meal and at bedtime; goals for "CONTROL" should be set at a higher level

During pregnancy, frequent and severe episodes of hypoglycemia are a serious risk for both mother and fetus. It may be possible to identify individuals who lack normal counterregulatory mechanisms before conception. There is a serious danger during pregnancy that lack of cooperation or overcompulsiveness during intensive treatment regimens will increase the danger of severe hypoglycemia.

Because there are no practical and inexpensive tests to detect the causes of hypoglycemia in women at increased risk during gestation other than overinsulinization, the measures outlined in Table 17.3 are recommended as practical suggestions for the prevention of dangerously low levels of blood glucose. Table 17.4 outlines the treatment of mild and severe episodes of hypoglycemia.

STARVATION KETOSIS

Ketonuria in pregnant IDDM women usually indicates a prolonged period without food (long overnight fast, e.g., 12–14 h). The meta-

Table 17.4.
Treatment of Hypoglycemia in Pregnant Diabetic Women

Mild but Symptomatic

1. Confirm low blood glucose by test strip (between 40 and 80 mg/dl; 2.2–4.4 mmol/L) or glucose meter
2. Snack: 1 cup low fat milk and two crackers (25 g of carbohydrate)
3. Persistent symptoms: Recheck blood glucose in 15 min and repeat snack if symptoms persist and blood sugar remains low (40–80 mg/dl; 2.2–4.4 mmol/L on visually read strips or <60 mg/dl; 3.3 mmol/L by meter)
4. Rarely, a third blood glucose test and snack will be necessary

Severe: Treatment Requires Assistance from Another Person or Patient is in Coma

1. Subcutaneous injection of 0.15 mg of glucagon; recheck blood glucose; if <50 mg/dl (2.8 mmol/L), repeat glucagon injection; start oral feeding if patient is conscious or glucose IV if she is not responsive
2. Judicious use of glucagon may also prevent starvation ketosis or hypoglycemia in patients with severe morning sickness[b]

[a]Adapted and modified from Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD. Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. Am J Med 1980;68:105–112; and Jovanovic L, Braun CB, Druzin ML, Peterson CM. Protocols for Managing Diabetes in Pregnancy. A Guide for Physicians and Allied Health Care Professionals. Bio-Dynamics, A Boehringer Mannheim Corp. Indianapolis, IN.

[b]All patients with IDDM and their families should be instructed in the use of glucagon and have a glucagon kit.

bolic effects of fasting or decreased food intake are accentuated during gestation. Starvation ketosis generally results in only a weakly positive serum nitroprusside test (application of undiluted plasma to Acetest tablet). A purple color develops in the presence of acetoacetate and causes only minor systemic acidosis.

Starvation ketosis is differentiated from metabolic diabetic ketoacidosis (DKA) by low levels of serum acetoacetate and β-hydroxybutyrate and normal serum osmolality and electrolytes. It is rare to measure a serum bicarbonate level of less than 16–18 mEq/L or a blood pH less than 7.35. The most frequent causes of anion-gap metabolic acidosis are discussed later in this chapter. Glycosuria may or may not be present depending upon plasma glucose levels and the renal threshold for glucose. This complication responds well to adjustment in dietary intake (an increment in complex carbohydrate), a lower dose of insulin at night, and a 25-g carbohydrate snack at bedtime.

Ketonuria probably occurs sporadically in most normal pregnancies (4). A report 20 years ago by Churchill and colleagues (5, 6) suggested that children of diabetic and nondiabetic mothers who had acetonuria during pregnancy had lower mental and motor scores at 8 months and lower IQ values at 4 years of age than children not so exposed. A later report by Stehbens and associates (7) from a prospective study of infants of diabetic mothers at 1, 3, and 5 years of age described atypical intrauterine growth, an increase in neonatal problems, and congenital malformations. Not surprisingly, they found an increased incidence of intellectual delay at 3 and 5 years of age, which they ascribed to the presence of acetone in the urine during pregnancy.

Naeye and Chez (8), who extracted data from the same population reported by Churchill, found that maternal acetonuria, low weight gain, and weight loss during pregnancy had little or no effect on neonatal, infant, and childhood psychomotor functions including IQ (9). They attributed their different results from those of Churchill to their methodology, which controlled for a number of non-nutritional factors that influence psychomotor development and IQ.

Coetzee and co-workers (10) in South Africa care for a large population of pregnant women, most of whom have non-insulin-dependent diabetes (NIDDM); more than half are obese. Diabetes is controlled by reducing diets of 1000–1600 kcal/day (4200–6700 kj). In their study, ketonuria was frequent (19% with 1000 kcal, 14% with a 1400–1800 kcal, and 7% of normal pregnant women who ate 1600 kcal/day). The Ketostix test was never found to be positive in blood even when it was in urine samples. Serum acetoacetate levels in all subjects were always below 1 mmol/L. The highest serum β-hydroxybutyrate (β-OHB) level measured was 0.94 mmol/L with total ketoacids of 1.2 mmol/L. These levels are considered to be nontoxic since a change of 5 mmol/L is required to alter acid-base balance.

In pregnant IDDM women who are in poor control, we do not know whether augmented

ketogenesis is harmful to the fetus and do not monitor plasma β-OHB values in most prenatal clinics. Because the data from the Comprehensive Perinatal Project described previously were collected in 1966 (9), before the development of perinatal and neonatal subspecialties, this question should be re-examined by a prospective study of infants of IDDM and NIDDM mothers.

It is not usual in the United States to restrict dietary intake of pregnant obese NIDDM to the low levels employed by Coetzee. In our clinic, we rarely document ketonuria in obese NIDDM women on diets of 1700–1800 kcal (11). In IDDM women, however, and in lean NIDDM and lean GDM women, ketonuria in 1st trimester or later is frequent. Now that the issue of fuel-mediated teratology has been raised (12), the possibility of maternal augmented ketogenesis and its effect on infants of IDDM women in poor control, lean NIDDM and GDM women, and all women with hyperemesis gravidarum should be re-evaluated and compared with the experience in infants of nondiabetic women who do or do not have ketonuria during gestation.

DIABETIC KETOACIDOSIS

Pregnant women with IDDM are at increased risk for mild or more severe forms of diabetic ketoacidosis (DKA). Infection with a concomitant deficiency of insulin is the most common precipitating factor (Table 17.5). Early in the illness, there is an elevation of plasma glucose values and an increase in plasma ketones (acetoacetic acid and β-hydroxybutyric acid). If hyperglycemia is uncorrected, marked diuresis, dehydration, and hyperosmolality follow. In pregnant women with mild illnesses, the early stages of ketoacidosis respond quickly to appropriate treatment of the initiating cause, additional doses of rapid-acting insulin, and adjustment of food and fluid intake.

Table 17.5.
Precipitating Factors for Diabetic Ketoacidosis in IDDM Pregnant Women

Infection
Acute illness
Omission of insulin therapy
Newly diagnosed IDDM
Insulin pump malfunction or failure
Drugs
Steroids
Adrenergic agonists

In pregnant diabetic women who become severely ill, or in whom treatment has been delayed, more profound metabolic alterations occur. The combined efforts of a perinatologist and diabetologist should be utilized for treatment of the maternal-fetal pair.

The pathogenesis of DKA is illustrated in Figure 17.1 (13). Comprehensive discussions of the pathophysiology, clinical aspects, and treatment of DKA provide invaluable background information for this potentially life-threatening complication (14–17). The primary problem is a deficiency in insulin that initiates a chain of events leading to increased hepatic glucose production and hyperglycemia. The subsequent osmotic diuresis results in loss of water and electrolytes, hyperosmolality, and volume depletion. The release of stress hormones (catecholamines, glucagon, growth hormone, and cortisol) impairs insulin action and contributes to insulin deficiency. This combination of events leads to a decreased tissue uptake of ketones, increased production of hepatic ketones, and ketonemia.

Impaired insulin action characterized by insulin resistance contributes significantly to DKA. The metabolic acidosis resulting from hyperketonemia is an anion-gap acidosis that must be differentiated from hyperchloremic acidosis (13). A gap of greater than 14–16 mEq/L is an indication of anion-gap. In DKA, the anion-gap ranges from 25–35 mEq/L. This corresponds to the quantity of ketone present in plasma, usually 15–20 mEq/L. Table 17.6 lists the usual causes of anion-gap metabolic acidosis. In pregnant IDDM patients, hyperventilation is a normal occurrence. Arterial CO_2 tension is approximately 10 mm Hg lower than postpartum.

Some patients may present with a pure hyperchloremic acidosis with a normal anion-gap. In these women, there may be a slower rate of recovery (16). Table 17.7 illustrates serum electrolyte values and the anion-gap in hyperchloremic and anion-gap acidosis.

Lactic acidosis can be differentiated from DKA by a serum lactate level of >5 mmol/L. An extremely large anion-gap (>40 mEq/L) may be an early sign of lactic acidosis or a combination of lactic ketoacidosis. In the latter

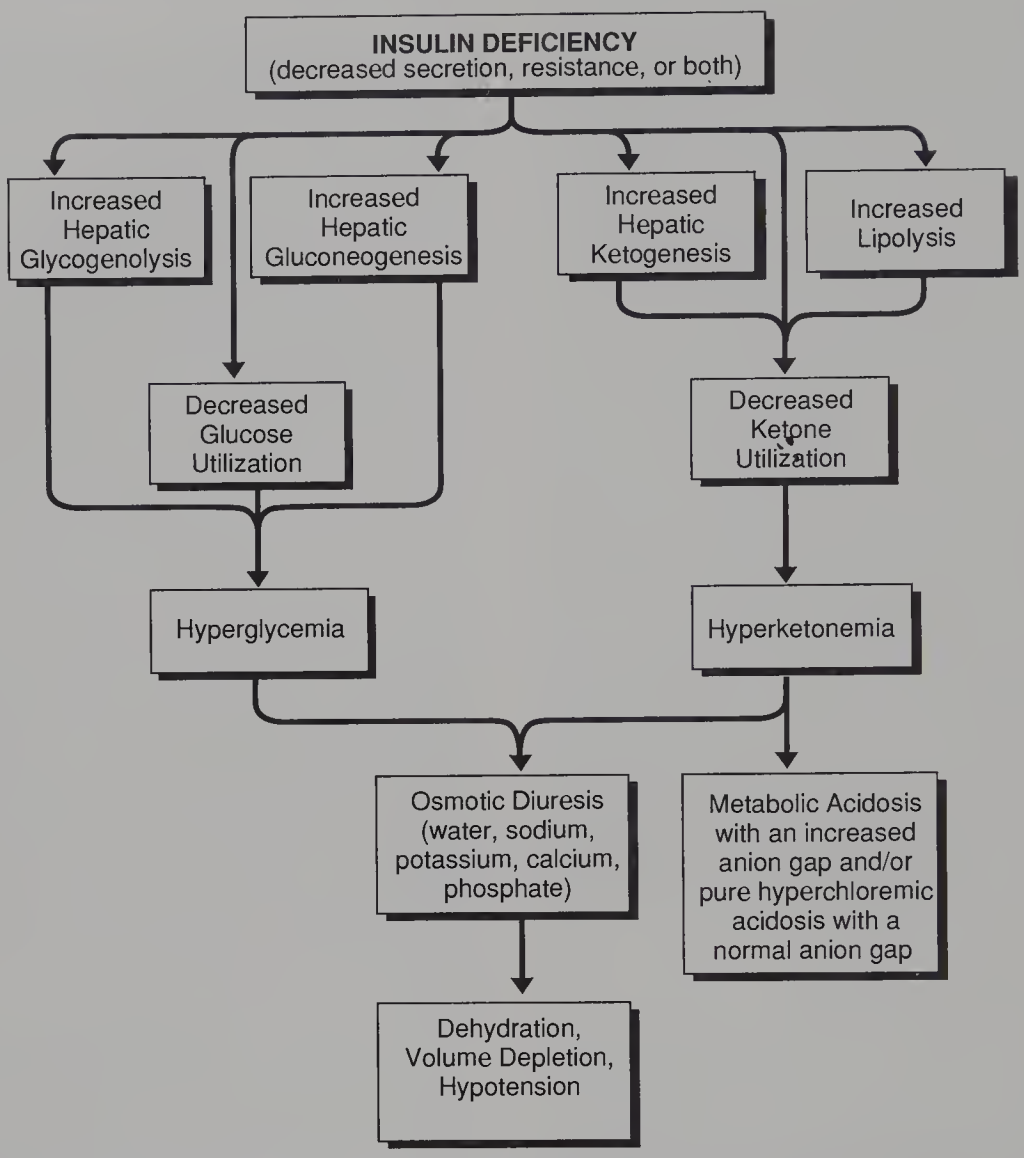


Figure 17.1. Physiologic consequences of insulin deficiency in IDDM women. Adapted with permission from Barrett EJ, De Fronzo RA. Diabetic ketoacidosis: Diagnosis and treatment. Hosp Pract 1984; April:90–94.

Table 17.6.
Causes of Anion-Gap Metabolic Acidosis in Pregnant IDDM Women

Ketoacidosis
Diabetes
Starvation
Lactic Acidosis
Tissue ischemia and/or hypoxemia
Chronic Renal Failure[a]
GFR <20 ml/min
Drugs
Salicylates

[a]Abbreviation: GFR, Glomerular filtration rate. Adapted with permission from Barrett EJ, DeFronzo RA. Diabetic ketoacidosis. Diagnosis and treatment. Hosp Pract 1984; April: 90–104.

case, which is not rare, there is usually a response to treatment of DKA.

Salicylate ingestion with toxicity is the most common cause of anion-gap acidosis in nonpregnant women but can occur inadvertently during gestation. In these patients, hyperventilation is out of proportion to the degree of acidosis; combined metabolic acidosis and respiratory alkalosis often result in a **normal blood pH** (13).

In pregnant diabetic women, **diabetic ketoalkalosis** may occur. These patients have the usual clinical and biochemical features of DKA except that the arterial pH is **higher** than normal. Several factors may precipitate this problem during pregnancy: severe vom-

Table 17.7.
Serum Electrolytes and the Anion Gap in Acidosis[a]

	Sodium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Anion Gap[b] (mEq/L)
Normal	140	105	25	10
Hyperchloremic acidosis	140	115	15	10
Anion-gap acidosis	140	105	15	20

[a]Adapted with permission from Barrett EJ, DeFronzo RA. Diabetic ketoacidosis: Diagnosis and treatment. Hosp Pract 1984; April:90–104.
[b]The normal anion gap is 12 ± 12 mEq/L and is calculated as follows: Anion gap = Na − (Cl + HCO_3)

iting, excessive hyperventilation, and diuretic therapy (18, 19).

Pregnant women with DKA present with the usual findings, including hyperventilation, normal or obtunded mental status (depending on severity of the acidosis), dehydration, hypotension, and a fruity odor to the breath. Abdominal pain and vomiting may be prominent symptoms. The diagnosis of DKA is confirmed by hyperglycemia (>300 mg/dl; 16.7 mmol/L) and ketonemia. The quantification of ketonemia by a positive nitroprusside reaction (Acetest tablet) is unsatisfactory because visual observations are subjective and nitroprusside does not react with β-hydroxybutyrate, the predominant circulating ketone. A specific enzymatic assay for serum levels of β-hydroxybutyrate is useful to confirm DKA when the nitroprusside test is negative or weakly positive.

DKA is life threatening to mother and fetus and is regarded as a bad prognostic sign of pregnancy. Prompt treatment is essential and fetal well-being is in jeopardy until maternal metabolic homeostasis is re-established. High levels of plasma glucose and ketones are readily transported to the fetus, which may be unable to secrete sufficient quantities of insulin to prevent DKA in utero. When DKA occurs after 28 weeks' gestation, the fetal heart rate should be monitored carefully. If fetal distress is documented, the risk of early delivery has to be weighed against the danger of fetal immaturity. Conservative measures (hydration, maintenance of blood pressure) and correction of ketoacidosis are generally preferable to premature delivery.

Treatment of Diabetic Ketoacidosis

In pregnant diabetic women followed by clinic visits each week and by frequent telephone communication, severe DKA is a rare event. Mild to moderate ketoacidosis does occur in some circumstances and pregnant women with DKA are occasionally transported to medical centers for their first prenatal visit as an emergency. If the patient is unconscious, she should be admitted promptly to the medical intensive care unit. Less severe cases are more often admitted to a high-risk pregnancy ward.

The use of a standard treatment protocol is a helpful **guideline** but this must be accompanied by meticulous attention to detail and maintenance of an accurate hour by hour flow sheet.

There are six essential components for treatment of DKA. These are outlined in Table 17.8. Excellent recent discussions and an overview of the clinical aspects and pathophysiology of DKA have been published by Walker and associates (17) and Kitabachi (20). Diagrammatic representations of the effects of normal and abnormal serum potassium concentrations are shown in Figure 17.2.

Complications of Treatment of DKA

Most deaths that occur in DKA are due to complications of treatment and are largely preventable (21–24). Of course, in pregnancy, the clinical problem is more complex because we must consider the mother and fetus as a pair. It is imperative to treat (but not overtreat) the mother promptly and effectively.

Table 17.9 shows complications that may occur during treatment of DKA and suggests methods for their prevention. Cerebral edema is described more often in children but can occur in adults.

HYPERGLYCEMIC, HYPEROSMOLAR NONKETOTIC SYNDROME (HHNS)

In uncontrolled diabetic patients, a hyperglycemic hyperosmolar nonketotic syndrome

Table 17.8.
Treatment Protocol for Diabetic Ketoacidosis in Pregnant IDDM Women[a]

	Initial Phase	Recovery Phase
Fluids	0.9% NaCl at 1000 ml/h Replace sodium deficit in 4–6 h (average = 500 mEq)	When blood pressure is stable, urine output brisk, and serum glucose falling, 0.45% NaCl at 250–500 ml/h When serum glucose <250 mg/dl, add 5% glucose to IV fluids Replace H_2O deficit over 12–24 h (average, 5–10 L)
Insulin	10–20 U regular insulin intravenous (IV) bolus +5–10 U/h IV (infusion), or IM, or subcutaneously[b] the IV route should be used in any hypotensive patient[b] Increase hourly dose if serum glucose does not fall despite adequate fluid therapy	As acidosis is reversed, 5–10 U every 2–4 h When patient is eating, begin subcutaneous insulin
Potassium	Serum K^+ high; begin KCl at 20 mEq/h after urine output established Serum K^+ normal or low; begin KCl at 20 mEq/h immediately; reduce rate by 50% if patient is oliguric Monitor ECG; measure serum K^+ every 1–2 h	Adjust dose of KCl by serum K^+ measurements Continue oral KCl replacement for 1 week for correction of total deficit
Bicarbonate	pH <7.0; give as needed to raise pH to 7.0 pH ≥ 7.0; no bicarbonate	No bicarbonate No bicarbonate
Phosphorus	If patient is not oliguric, may give potassium phosphate 10 mEq/h (decrease dose of KCl accordingly) Measure serum phosphorus and calcium frequently	No phosphorus
General measures	Comatose patient: nasogastric tube, bladder catheter Identify and treat any precipitating illness Cardiac monitoring for changes in serum K (Fig. 17.2) Consider low-dose heparin Monitor blood glucose hourly at the bedside	Remove bladder catheter as soon as possible Continue to observe for signs of a precipitating or complicating illness Monitor glucose: fasting, before meals, 2 h after meals, and HS until control is re-established.

[a]These are general guidelines. Since there may be wide variation of individual patient needs, there is no substitute for careful monitoring of each patient, particularly in the early phase of therapy of DKA. **Start a DKA flow sheet and maintain hour by hour.**
[b]In pregnant women, constant IV insulin infusion with an intravenous controlled infusion pump is preferable.

(HHNS) (14, 25–27) may occur with or without stupor or an altered mental state. A change in mental status correlates more often with hyperglycemia and the rapid development of hyperosmolality than with acidosis.

Precipitating factors for HHNS during pregnancy are uncontrolled diabetes, new or previously unrecognized diabetes, infection, reduction or omission of insulin dose, medications, such as corticosteroids, thiazide di-

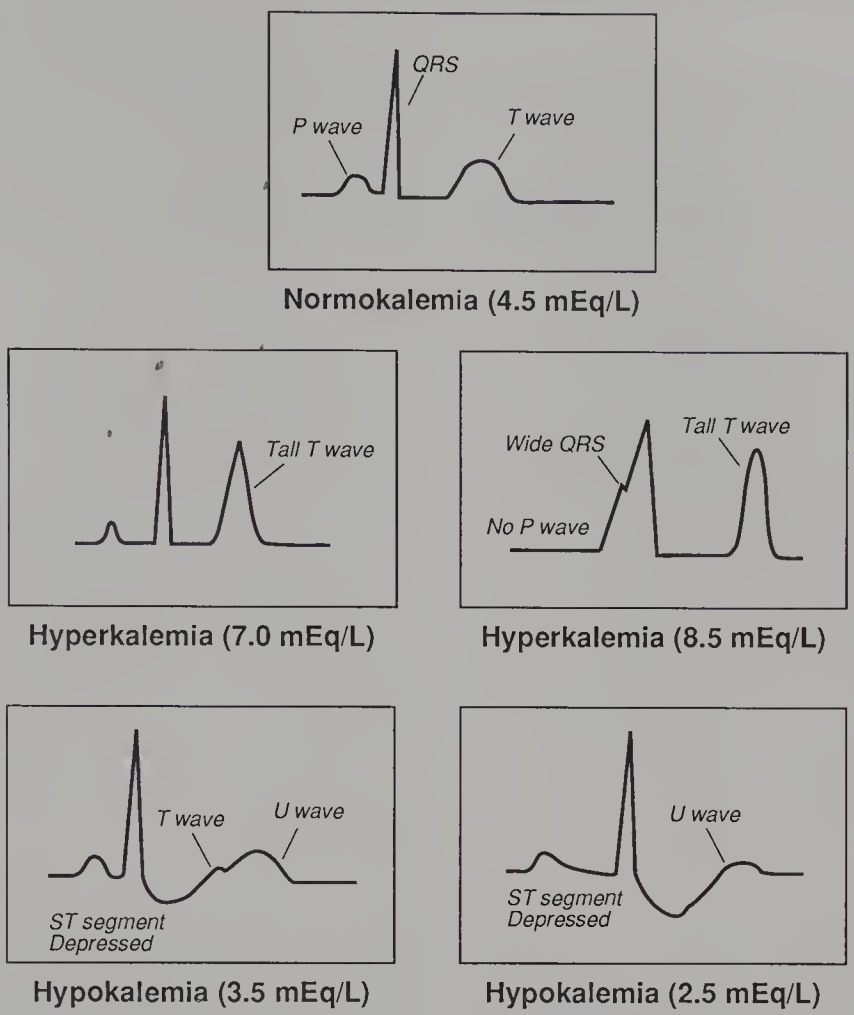


Figure 17.2. Profiles of serum potassium levels are reflected in characteristic ECG tracings: normokalemia (*top panel*); tall T waves in hyperkalemia, with loss of the P wave and widening of the QRS complex; ST-segment depression in hypokalemia. Adapted with permission from Barrett EJ, De Fronzo RA. Diabetic ketoacidosis: Diagnosis and treatment. Hosp Pract 1984; April:90–94.

uretics or β-sympathomimetic drugs that are administered for tocolysis in treatment of preterm labor. Several investigators have observed that HHNS is not a distinct clinical entity; it represents one end of a wide spectrum of severe diabetic metabolic decompensation (27, 28); Fig. 17.3).

Patients with HHNS present following a rapid or prolonged period of osmotic diuresis with depletion of both intracellular and extracellular fluid volumes. Hyperglycemia ranges from 600–2400 mg/dl (33–133 mmol/L) in the absence of overt ketoacidosis. Dehydration, hypovolemia, and, ultimately, disorientation and coma can lead to death.

Table 17.10 describes the calculation of serum osmolity. The normal value is 280 ± 10 mOsm/L. Values that exceed 300 mOsm/L are abnormal; **those above 320 mOsm/L indicate clinically significant hyperosmolarity.**

The treatment of patients with the HHNS syndrome is presented in Table 17.11 (25). The first priority is expansion and maintenance of intravascular volume, perfusion of vital organs, and an adequate urine output. These measures assume even greater importance during pregnancy when placental perfusion is critical for fetal well-being. If hypotension is present, a volume expander, such as albumin or plasmanate, should be given until blood pressure and tissue perfusion are restored. Matz recommends hypotonic (one-half normal) multielectrolyte solutions initially (25). This avoids the administration of excessive chloride with resultant, almost inevitable, hyperchloremia. As described earlier in the treatment of DKA, clinical judgment is critical and details of therapy must be individualized for each patient. Consultation should be requested from an experienced diabetologist and it may be necessary to implement invasive monitoring of cardiac filling pressures by means of a Swan-Ganz catheter or central venous pressure line.

Table 17.9.
Complications of Treatment of Diabetic Ketoacidosis[a]

Complication	Prevention
Cerebral edema with sudden deterioration in consciousness level and respiratory arrest	Avoid a rapid fall in plasma osmolality Initial use of isotonic rather than half-normal saline Brain herniation and death occur only when fluid replacement exceeds 4 L/m^2/d (23)
Adult respiratory distress syndrome with dyspnea, hypoxemia, decreased lung compliance, and evidence of pulmonary edema on chest x-ray (22) No clinical signs of left ventricular failure and pulmonary wedge pressure is normal	Rare, complication with high mortality Avoid use of crystalloid fluids Avoid or treat risk factors of sepsis, hypovolemia, or aspiration
Thromboembolism secondary to activated intravascular coagulation pathway and endothelial damage (28), hypovolemia, hyperosmolality, disseminated intravascular coagulation (DIC), and immobility secondary to decreased level of consciousness	Consider use of prophylactic heparin 5000 U every 8 h; there are persuasive theoretical reasons to initiate this treatment in pregnant women
Hypoglycemia	Avoid excessive insulin administration
Hypo- or hyperkalemia	ECG monitoring Serial measurements of serum K Careful adjustment of doses of KCl

[a]Adapted from Walker M, Marshall SM, Alberti KGMM. Clinical aspects of diabetic keotacidocis. Diabet Metab Rev 1989;5:651–663.

In contrast to most circumstances that evoke HHNS, pregnancy presents a special challenge and a responsibility to try to prevent fetal demise. Fetal surveillance should include fetal heart rate monitoring and serial evaluations of the biophysical profile (BPP) described in greater detail in Section VII, Chapter 20.

RETINOPATHY

This important topic and a comprehensive summary of the most recent reports of retinopathy during pregnancy have been discussed extensively in Section I. The 1988 guidelines for women with diabetes who anticipate becoming or are already pregnant are provided in Table 1.2. Section I and this section are intended to be complementary reviews to reinforce the concept of preconception counseling, point out differences in retinopathy risks in the reproductive age group in IDDM and NIDDM women, and describe the course and treatment of retinopathy during gestation.

Diabetic Retinopathy

The cause of diabetic retinopathy is not known. Recent reports indicate that this complication is more common early in the disease than previously suspected. Numerous interrelated factors have been proposed as possible contributors to the neovascular changes that are characteristic of diabetic retinopathy. These include genetic differences among patients, poor control of diabetes with increased transport of glucose across cell membranes, accumulation of sorbitol in retinal endothelial cells, and unidentified hormones that might stimulate angiogenesis.

IDDM

In the past, there has been great concern that pregnancy would accelerate vascular changes in the eye and hasten blindness. Women with IDDM of 10–15 years' duration are estimated to have a 50% chance of developing retinopathy. The prognosis for blindness is much worse if neovascularization is present. Before modern laser treatment and vitrectomy were available, IDDM patients who developed this complication before age 20 yr had a 30–40% chance of blindness after 5 yr.

During the last few years, major advances have occurred in both the diagnostic techniques and treatment of diabetic retinopathy.

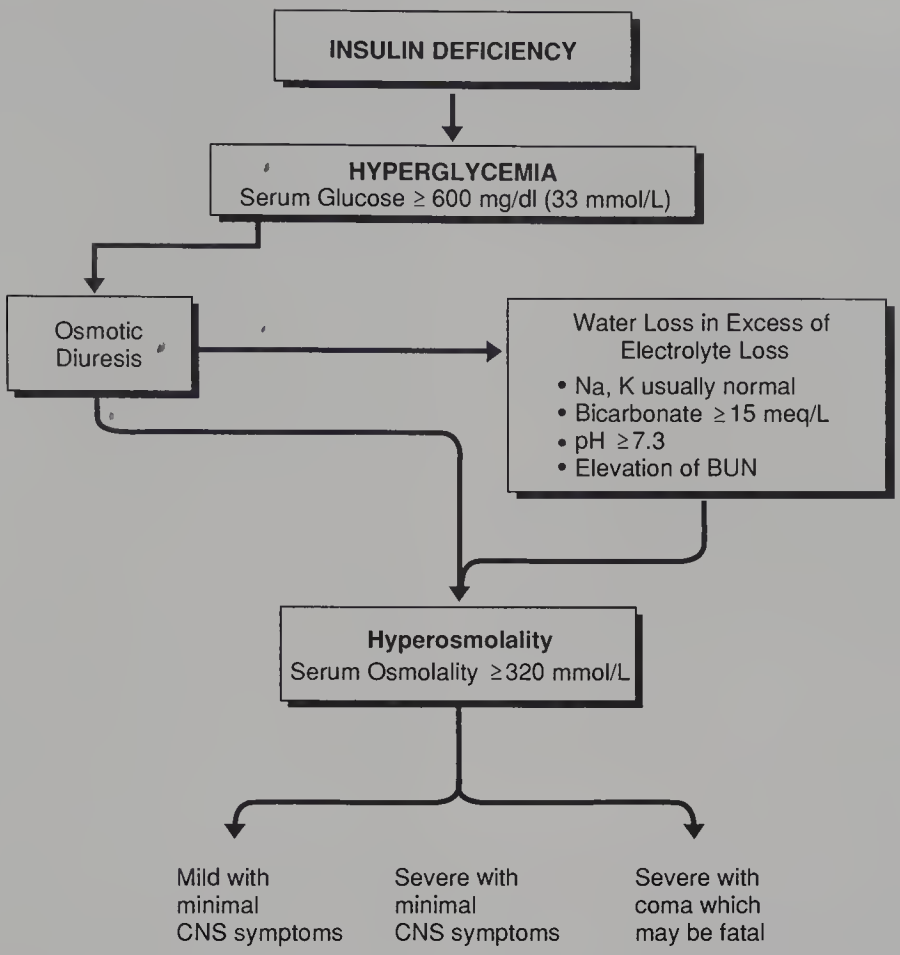


Figure 17.3. Pathophysiology of the hyperosmolar, hyperglycemic nonketotic syndrome (HHNS). See text for description.

In pregnant diabetic women with retinopathy, the outlook is also more encouraging (Section I).

Several reports in nonpregnant and pregnant diabetic women have described worsening of retinal abnormalities associated with tightening of glucose control (29–38). These reviews from centers all over the world are disquieting. In a study from Finland by Helve and co-workers (35), even a moderate improvement in metabolic control induced by continuous subcutaneous insulin infusion (CSII) was associated with a risk of progression of retinopathy during the 1st months of therapy. The net impairment in retinopathy grading and individual lesions was significant during CSII compared with conventional subcutaneous multiple injection therapy.

Some studies have shown that accelerated progression of mild to moderate retinopathy is not sustained and does not initiate vasoproliferative deterioration (39). A more complete analysis of the separate effects of pregnancy and rapid improvement in glucose control on retinopathy may be possible after completion of the NIH study of Diabetes in Early Pregnancy (DIEP).

When diabetic control is tightened rapidly during gestation, sudden and rapid retinal changes have been documented as shown in Figure 17.4. This patient, who was cared for by Dr. Lois Jovanovic-Peterson (40), was a 33-yr-old homeless IDDM woman in her first pregnancy who was hospitalized at Cornell University early in 1st trimester for immediate normalization of blood glucose values. Her HbA1c concentration was 11.0%. Control of hyperglycemia was accomplished in 3 days. Six weeks later, the patient experienced a severe vitreous hemorrhage. She remained in the hospital and was kept at bed rest in an upright position for the remainder of the pregnancy. A cesarean section was performed at 39 weeks' gestation with the delivery of a 3863-g male

Table 17.10.
Calculation of Serum Osmolality[a]

The normal serum osmolality is 280 ± 10 mOsm/L.

A rough approximation of the serum osmolality can be derived from the following calculation:

$$\text{Serum osmolality (mOsm/L)} = 2Na^{+}(\text{mEq/L}) + K^{+}(\text{mEq/L}) + \frac{\text{Plasma glucose (mg/dl)}}{18} + \frac{\text{BUN (mg/dl)}}{2.8}$$

Since urea is freely diffusible across cell membranes, it contributes little or nothing to the effective serum osmolality, which is the critical determinant in hyperosmolar states. Matz uses the term "effective serum osmolality" (Eosm), which he calculates as follows:

$$\text{Eosm (mOSm/L)} = 2[Na^{+} + K^{+}\ (\text{mEq/L})] + \frac{\text{Plasma glucose (mg/dl)}}{18}$$

When Eosm exceeds 320 mOsm/L, significant hyperosmolality is present.

[a]With permission from Matz R. Hyperosmolar non-acidotic diabetic coma. Pract Diabetol 1984; May/June:10–12.

infant. Following delivery, there was improvement in the right eye with some resorption of the hemorrhage (follow-up photographs are not available).

The worsening of retinopathy in addition to added risks of severe hypoglycemia during embryogenesis and later have resulted in a more cautious and **gradual** (weeks versus days) accomplishment of control in early IDDM pregnancies. Phelps and colleagues (38) provide further support for this approach with their observation that intensive therapy for diabetes mellitus resulted in improved diabetic control by the time of delivery but retinal abnormalities worsened as gestation proceeded in 55% of the pregnancies. Moreover, they observed a highly significant correlation between worsening retinopathy, the degree of hyperglycemia at entry into pregnancy, and the magnitude of improvement in glycemic control. They and others (41) emphasize, nonetheless, that the above studies should not lessen our enthusiasm for the achievement of normoglycemia during pregnancy that has clearly been associated with better pregnancy outcome as well as improvement in retinopathy postpartum. Again, a preventive approach to microvascular complications should be emphasized to establish good diabetic control with retinal examinations and treatment before conception. The adverse factors that increase the risk of progression of retinopathy during gestation are listed on Table 17.12. Figures 17.5–17.7 illustrate changes in background and preproliferative retinopathy, severe proliferative changes on the optic nerve and more peripheral neovascularization.

Baseline and longitudinal ophthalmoscopic observations by obstetricians are important in prenatal clinics for diabetic women. An ophthalmologist with expertise in diabetic retinopathy should also do baseline examinations on every diabetic pregnant woman with follow-up evaluations each trimester and postpartum.

Two other complications deserve mention: acute optic disc edema (pseudopapilledema) and macular edema (42) (Fig. 17.8). In our experience, these complications have occurred in association with preeclampsia in diabetic women and have been reversible postpartum.

Color fundus photography is extremely helpful to document changes and photographs can be read and graded by standard criteria. Although fluorescein angiography is a helpful tool in nonpregnant patients, its use is not recommended during gestation because of uncertainty of the effect and possible toxicity in the fetus. There is not universal agreement concerning the advisability of laser treatment during gestation. The decision to employ laser photocoagulation will vary among ophthalmologists and it may be useful to seek more than one opinion from individuals experienced in retinal changes during diabetic pregnancies. Figures 17.9 and 17.10 show photographs of the patient in Figure 17.6 after completion of full scatter laser coagulation and 6 months later.

NIDDM Women

Retinopathy in NIDDM is described in Section I. There are no prospective pregnancy studies to assess the prevalence of this complication. In 12 yr, we have observed severe retinopathy in a 40-yr-old American Indian NIDDM woman with a HbA1c value of 12.5%, fasting blood glucose level of 220 mg/dl (12.2 mmol/L), and mean 24-h glucose value of 178

Table 17.11.
Therapy for the Hyperosmolar Diabetic Patient[a]

Rx	Hours of Therapy				Comments[b]
	1	2	3	4	Obtain blood glucose, P, Ca^{2+}, Mg^{2+}, electrolytes, BUN, CBC, urinalysis, chest x-ray, ECG, appropriate cultures; arterial pH, PO_2, PCO_2 Aspirate stomach; if guaiac positive, leave tube in Give thiamine and B-complex Antibiotics if infected Check for hypothermia, hypotension
Fluids: 1/2 normal multielectrolytes	1500 ml/h	1000 ml/h	1000 ml/h	500–750 ml/h	May require CVP or PCWP to guide Rx. Change to isotonic solution when Eosm < 320 Add glucose (5% D/W) when serum glucose is 250–300 mg/dl.
Insulin (rapid-acting)	15 unit IV bolus	← 0.1 U/kg/hr (IV/IM/SC) →			Decrease dose to 2–3 U/h when plasma glucose is 250–300 mg/dl If plasma glucose fails to decrease over 2–4 h and urine output adequate, double dose hourly until response
Potassium	← 20 mEq/hr as K acetate and K phosphate (if serum K^+ is 4–5 mEq/L) →				If serum K^+ >5.0 mEq/L, give no K^+ If serum K^+ 3–4 mEq/L, give 40 mEq/h If serum K^+ <3.0 mEq/L, give 60 mEq and re-check Hourly ECG strip for T-waves

(*Continued*)

Table 17.11. (*Continued*)

Rx	Hours of Therapy	Comments[b]
Phosphate ←	10 mM/h →	Repeat arterial pH hourly if <7.25 Repeat serum K^+ hourly as needed Repeat Na^+, CO_2, BUN q 2–4 h
Magnesium	500 ml of 2% $MgSO_4$ over 4 h if Mg^{2+} is low or for tentany	
Calcium	If Ca^{2+} is low, for tetany, give 10 mEq as IV bolus as needed	Use Chemstrip bG or comparable bedside test of plasma glucose hourly once blood glucose <800 mg/dl. Repeat T° hourly if hypothermic (<95°F) Follow intake and output hourly

[a]With permission from Matz R. Hyperosmolar non-acidotic diabetic coma. Pract Diabetol 1984; May/June:10–12.
[b]CVP-Central venous pressure; Eosm = effective serum osmolality; PCWP = pulmonary capillary wedge pressure.

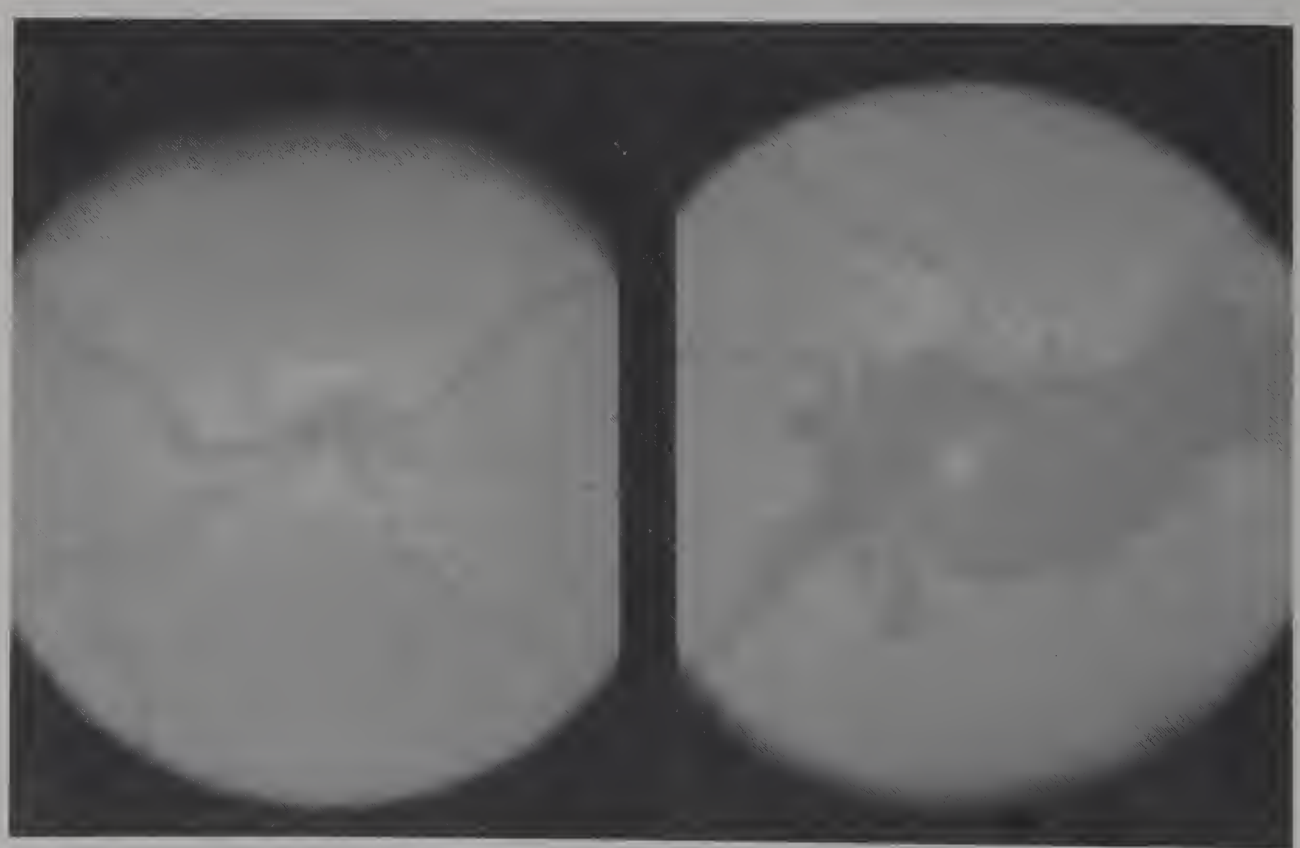


Figure 17.4. Worsening of ophthalmic findings following rapid control of hyperglycemia. *Left:* Photograph of retina on admission October 4, 1982. Diabetic retinopathy with a splinter retinal hemorrhage. The veins are dilated indicating venous stasis. When the slide of the photograph was projected and enlarged, evidence of neovascularization of the disc was apparent. *Right:* Six weeks later, November 15, 1982. Vitreous hemorrhage from neovascularization of the disc. Photographs provided by Dr. Lois Jovanovic-Peterson, MD, Sansum Medical Foundation, Santa Barbara, California, and read by J. Terrence Daly, MD, Vitreoretinal Surgeon and Consultant, La Jolla, California.

Table 17.12.
Factors Related to the Presence and Progression of Retinopathy

No preconception counseling, eye care, or retinal evaluation
Duration of diabetes (>10 yr) after onset of puberty
Degree of retinopathy at conception
Marked elevation of glycosylated hemoglobin (HbA1c > 10%) at first prenatal visit
Rapid intensification of glucose control in patients with most severe and prolonged hyperglycemia (HbA1c > 10%)
Hypertension
Proteinuria

mg/dl (9.8 mmol/L), measured at first hospitalization at 27 weeks' gestation. She experienced severe worsening of her extensive baseline background and preproliferative retinopathy within 1 week after starting an intensive insulin regimen to achieve normalization of blood glucose values. Prospective studies will be necessary to assess the prevalence of this complication in geographic areas where NIDDM pregnancies are common.

In sum, behavior of diabetic eye complications in IDDM women during pregnancy is highly variable. It has not been possible to predict reliably the women in whom retinopathy will worsen. Caution should be exercised in the

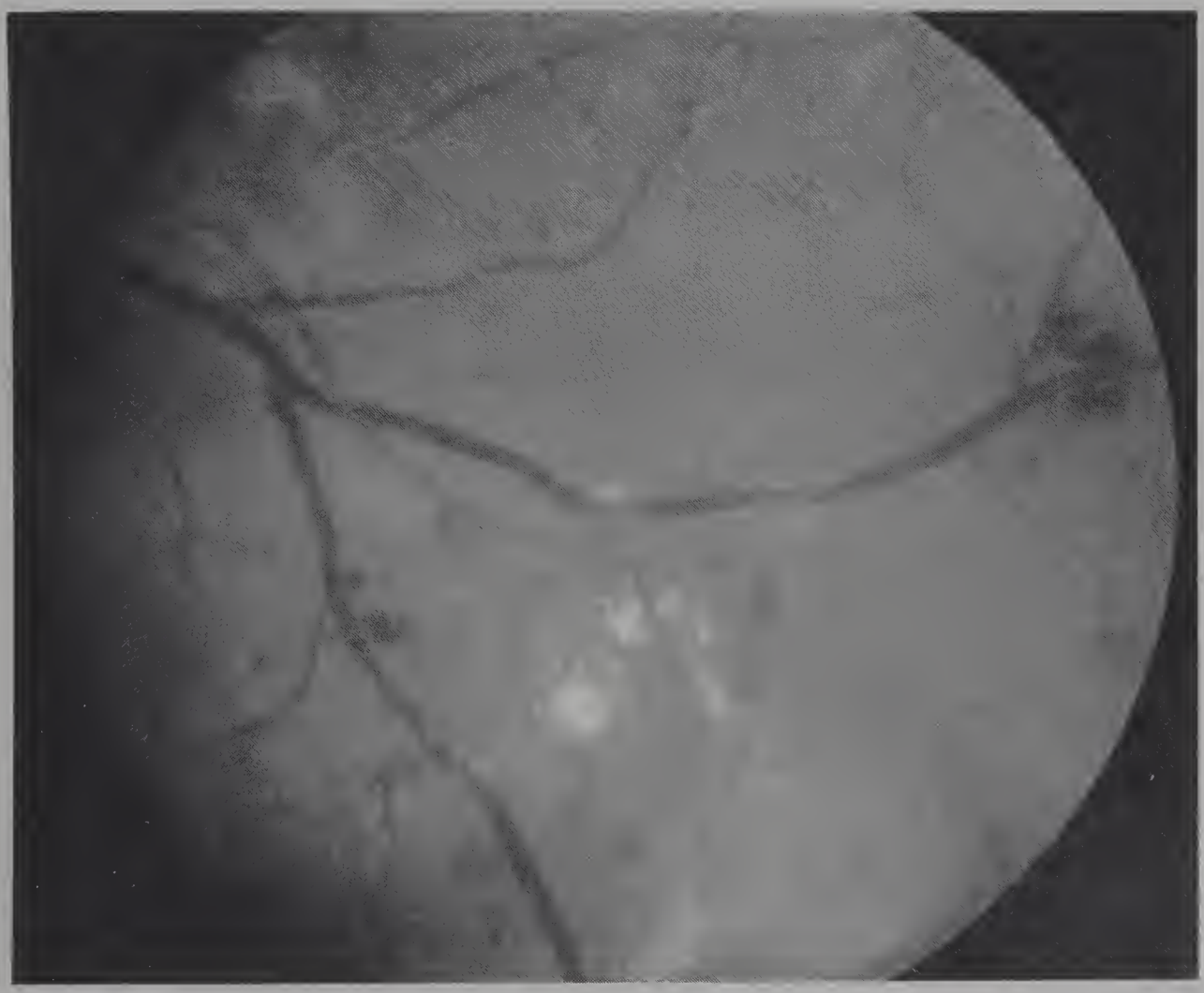


Figure 17.5. Background and preproliferative diabetic retinopathy. Note the clustered, white "cotton-wool" spots just above the vein near the center of the photograph. There are also multiple blot hemorrhages, dilated veins of somewhat irregular caliber, and some fine, tortuous vessels that do not quite look as though they should normally be present. These latter vessels probably represent "intraretinal microvascular abnormalities," the earliest neovascular sprouts within the retina. With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

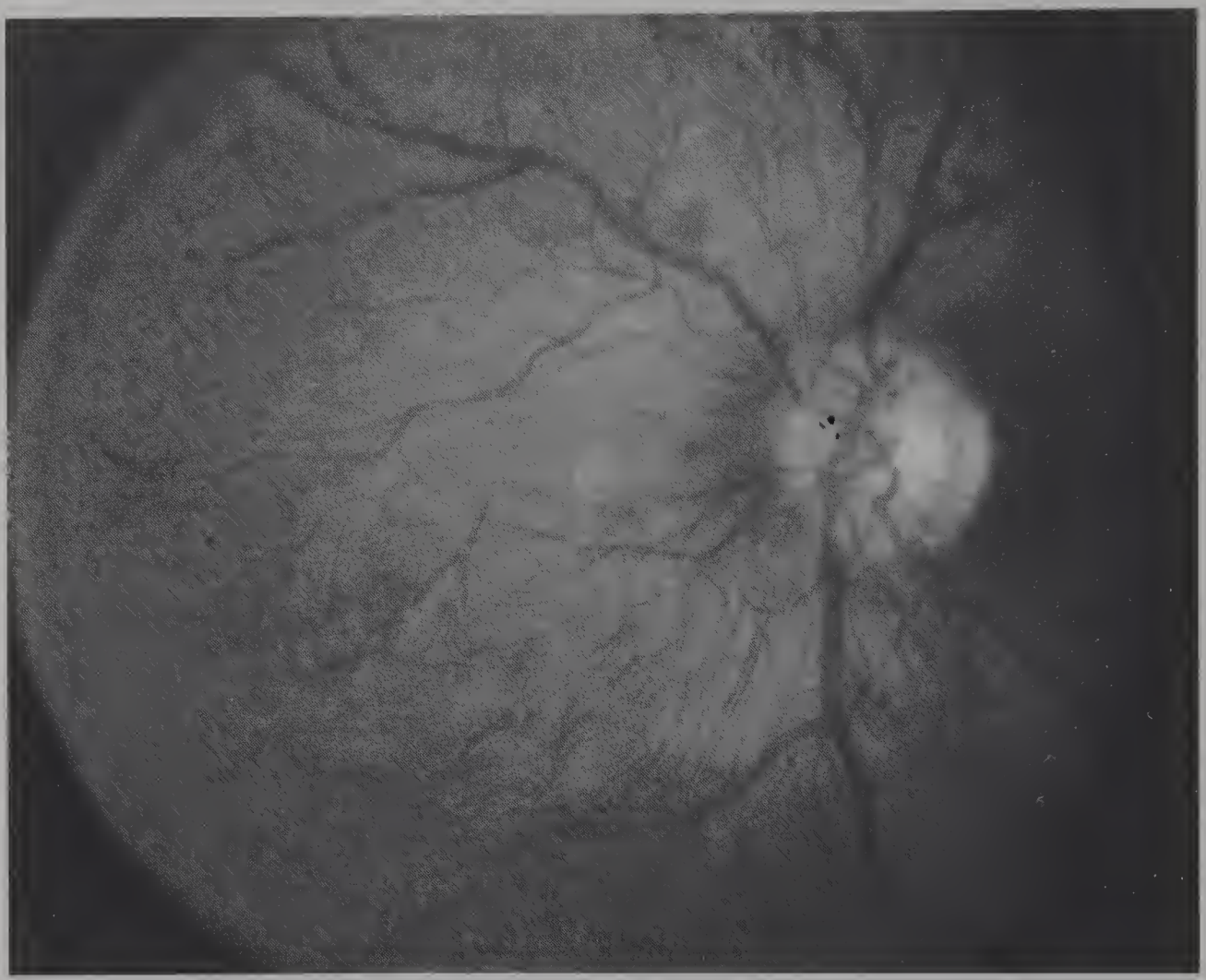


Figure 17.6. The optic nerve head of a 30-yr-old diabetic woman with severe proliferaive diabetic retinopathy. Note the extensive networks of flat (i.e., nonelevated) new vessels surrounding the optic disc. Optic nerve head neovascularization of this extent constitutes one of the high-risk characteristics defined by the national Diabetic Retinopathy Study. (The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: Clinical application of Diabetic Retinopathy Study (DRS) findings. DRS report no. 8. Ophthalmology 1982;88:583–600.) With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

institution of excessively rapid achievement (days versus weeks) of diabetic control. There is no evidence that an abortion at any stage of pregnancy will affect the ultimate outcome of diabetic retinopathy or that the presence of retinopathy is a contraindication for becoming pregnant. There are no reports of the prevalence or course of ophthalmologic complications during gestation in NIDDM women. These observations would be of importance because of the high prevalence of hypertension in these women.

DIABETIC NEPHROPATHY

In Section I, diabetic nephropathy is discussed with respect to preconception counseling. In this chapter, emphasis is placed upon management of diabetic nephropathy during gestation and the different characteristics of this problem in NIDDM and IDDM patients.

NIDDM Women

Renal function in NIDDM women is influenced by metabolic control although to a lesser extent than is seen in IDDM women (43). Microalbuminuria is common (even at first diagnosis) and is improved by normoglycemia. Renal pathophysiology differs in NIDDM compared with IDDM women; this topic has been reviewed in detail by Morgensen and colleagues (44). Because NIDDM occurs in older women, renal complications have not been de-

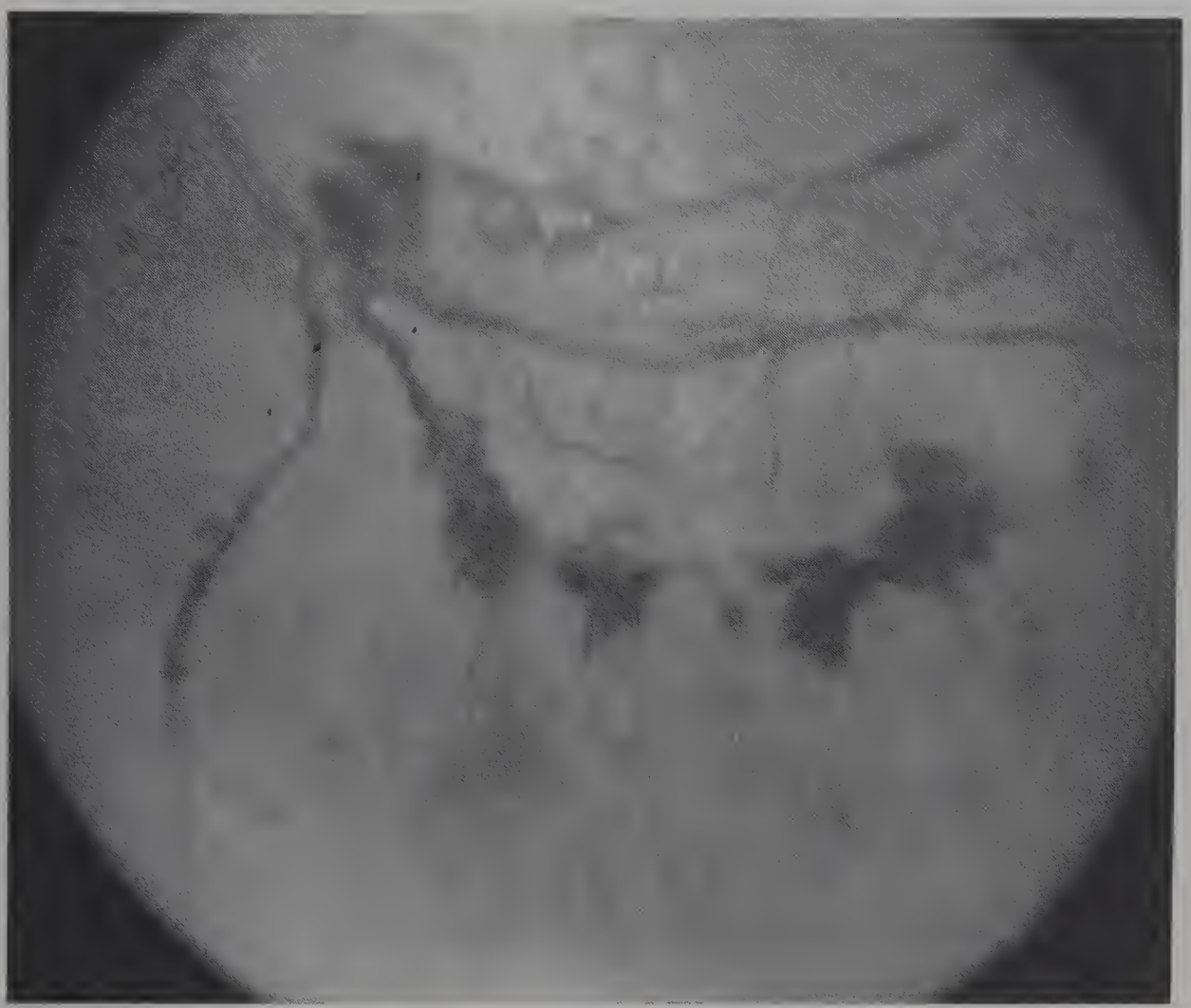


Figure 17.7. Neovascularization elsewhere, i.e., not on the optic nerve head, in the same patient as shown in Figure 17.6. The tuft of new vessels along the inferior temporal vascular arcade is surrounded by early hemorrhage into the vitreous cavity. Neovascularization elsewhere, greater than one-half of an optic disc area, together with vitreous or preretinal hemorrhage, constitutes another of the high-risk characteristics of the national Diabetic Retinopathy Study, and requires extensive photocoagulation treatment. (The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: Clinical application of Diabetic Retinopathy Study (DRS) findings. DRS report no. 8. Ophthalmology 1982;88:583–600.) With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

scribed as a problem during gestation. However, there can be renal deterioration when hypertension or preeclampsia supervene. Ordinarily, microalbuminuria or albuminuria are stable throughout uncomplicated pregnancy; no pregnancy data are available in young NIDDM women (Maturity Onset Diabetes of the Young, MODY) (45).

IDDM Women

Microvascular lesions in the kidneys of patients with IDDM represent a serious and potentially life-threatening complication. After 10 yr of diabetes, diffuse glomerulosclerosis is present in many patients and proteinuria (initially without a decrease in the glomerular filtration rate) is not uncommon after that time. Decompensated renal disease occurs after about 17–20 yr when serum creatinine levels rise and the glomerular filtration rate decreases. Progression of renal disease can be slowed by control of hypertension and abstinence from smoking.

The pathogenesis of small vessel disease in diabetes has not been established and the relative roles of genetics and control (or lack of) of hyperglycemia are not clear. During pregnancy or preferably before conception, it is important to assess maternal renal function.

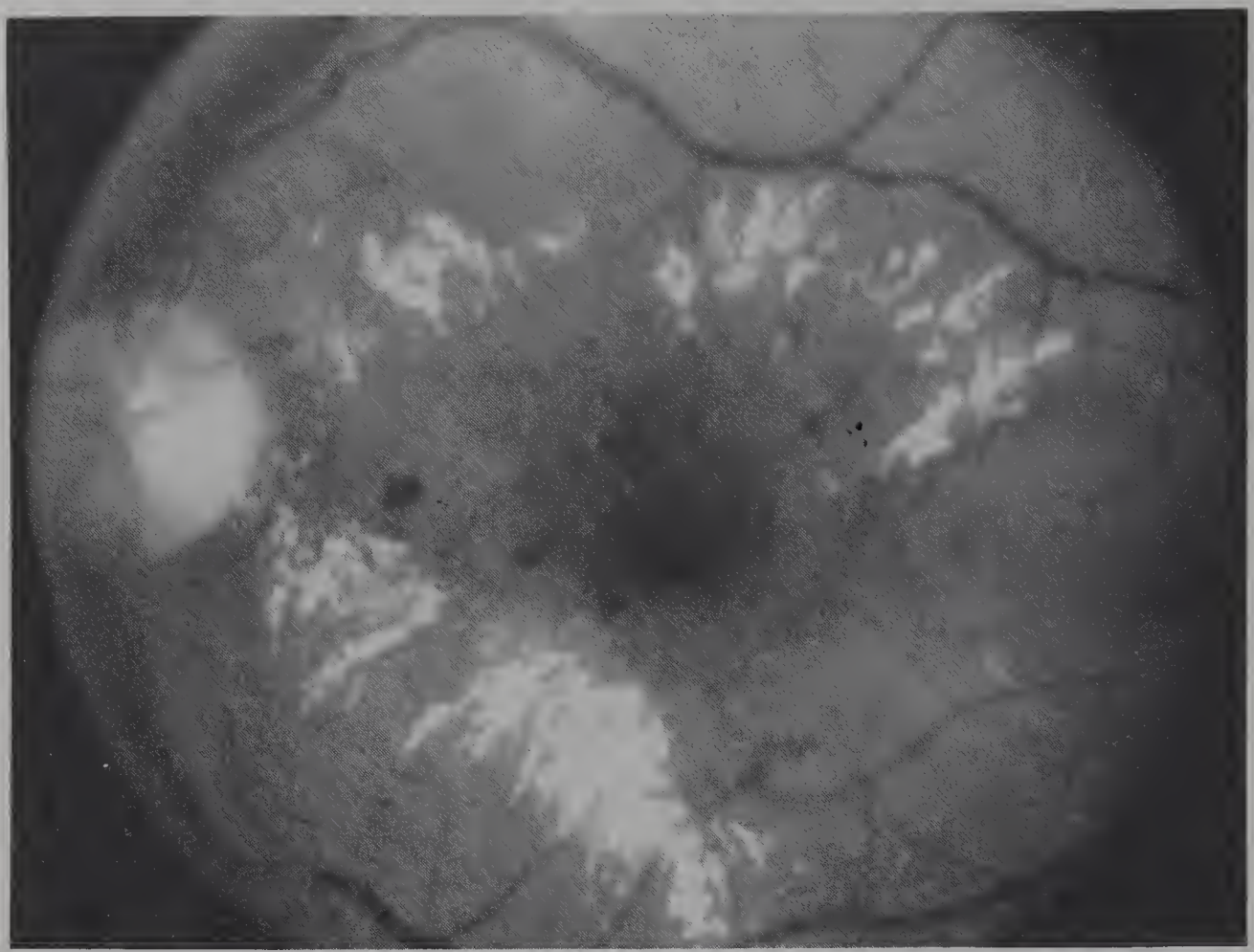


Figure 17.8. Diabetic macular edema. Note the partial ring of "hard" exudates surrounding the center of the macula. Blot hemorrhages can be seen within the ring. Collections of intraretinal fluid are poorly seen near the center of the macula, almost directly in the center of the photograph. Because they are not surrounded by a wall, they are not true cysts, which gives this particular condition the name "cystoid" macular edema. The macular portion of the retina is thickened, hence the term "edema" is appropriate, but this cannot be appreciated from the photograph, which is not stereoscopic. With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

Older studies of renal microangiopathy and pregnancy (46) reported before the advent of drugs for hypertension, hemodialysis, renal transplantation, or perinatal intensive care for mothers and infants showed a progressive rise in perinatal infant mortality with progressive severity of maternal renal disease (46). Fetal growth was impaired and smaller placentas with extensive vascular changes were described (47).

In the long-term follow-up of patients with IDDM Knowles and colleagues (48) reported in 1965 on the pregnancy outcome of 42 women with severe diabetic nephropathy. Infant survival rate was 55%, and 16% of women developed preeclampsia. There were no maternal deaths and no evidence that renal disease worsened during pregnancy. Sims also found no evidence that pregnancy in diabetic women affected renal status adversely (49). Early and Gottschalk (50) have stated that the course of diabetic nephropathy during pregnancy is similar to that of other renal diseases with little or no evidence that renal disease is worsened. Lindheimer and Katz (51) have found renal complications in pregnant diabetic women to be quite rare.

When fetal survival rates are considered, recent experience is also encouraging. Hare and White in 1977 reported a 94% fetal survival rate in IDDM without nephropathy and 72% in infants of mothers with nephropathy (52). Kitzmiller and colleagues described an 89% neonatal survival rate without substantial ma-

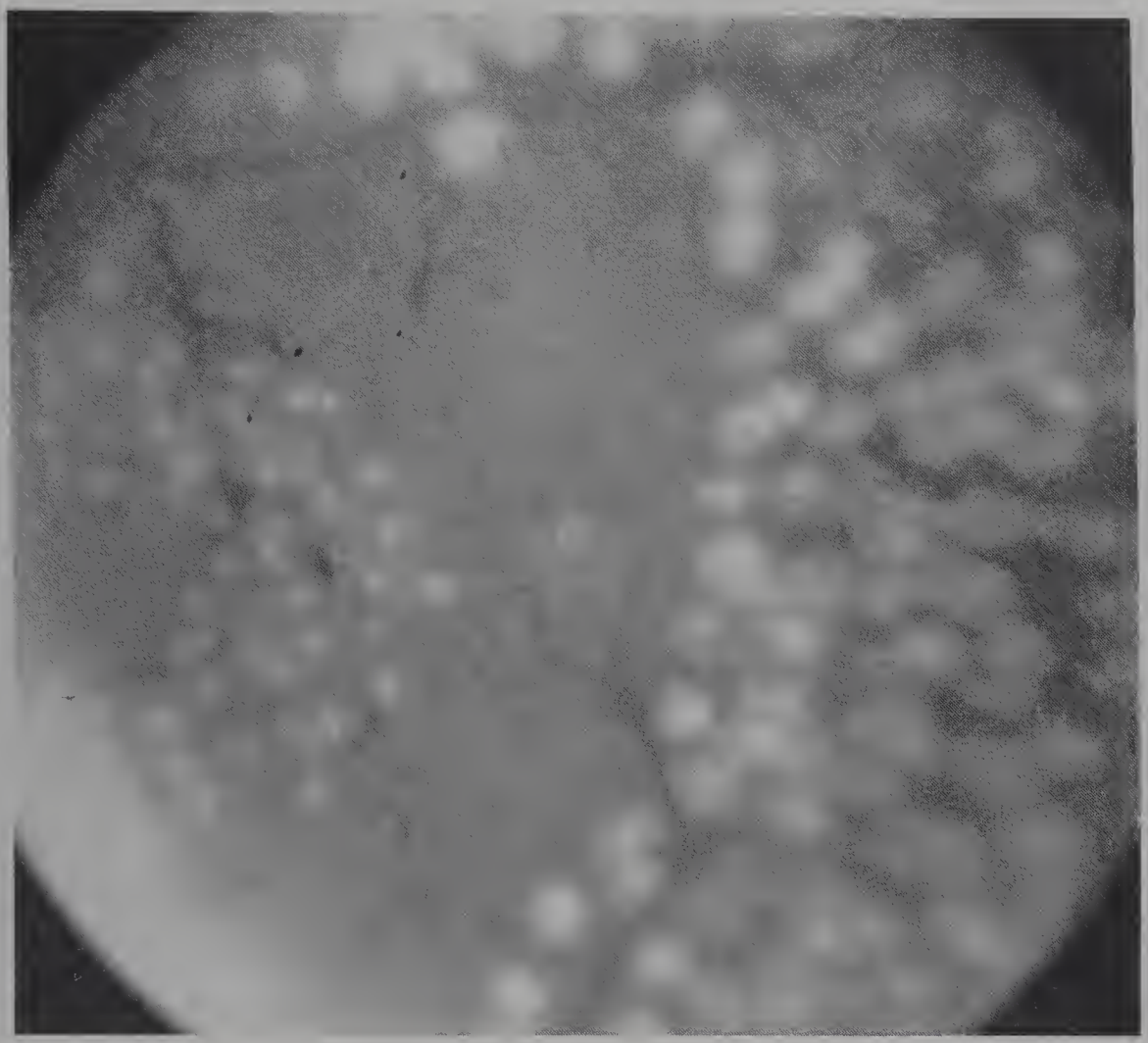


Figure 17.9. A portion of the acute photocoagulation pattern in the patient described in Figure 17.6. This photograph was taken just after completion of the laser treatment. Note the clusters of large, white photocoagulation burns at the right side and the top of the photograph. These were placed in the "full scatter" pattern, in which argon laser burns are placed throughout the posterior and mid-peripheral retina, sparing the macula, with a nominal burn diameter of 500 μm and a spacing of one-half burn diameter between burns. Because of the swelling that occurs immediately after treatment, the burns now appear even closer together. At the *left side* of the photograph is a cluster of smaller (100-μm nominal diameter) laser burns, constituting a "grid" pattern within the macula. This is used to treat macular edema, which was also present in this patient. With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

ternal complications in 26 women with nephropathy (53).

Reece and co-workers have reported a retrospective chart review study of 31 pregnancies at Yale from 1975–1984 complicated by nephropathy (54). They assessed pregnancy performance and fetomaternal outcome and observed that although 71% of mothers experienced an increase in blood pressure and proteinuria as pregnancy progressed, these changes were reversible postpartum and there was **no apparent adverse effect of pregnancy** on the natural course of the underlying renal disease. There were only two stillbirths (6%); 70% of the 29 live-born infants born at 36 ± SD 2.7 weeks were appropriate in size for gestational age while 16% were small and 13% were large. The complications in the fetus were considerable. Although cesarean section rate was comparable to that reported in other institutions (49%), preterm deliveries occurred in one-third of women. The neonatal complications of respiratory distress, hypoglycemia, and hyperbilirubiemia were high and almost 10% of infants had congenital malformations. Nevertheless, the uncorrected perinatal sur-

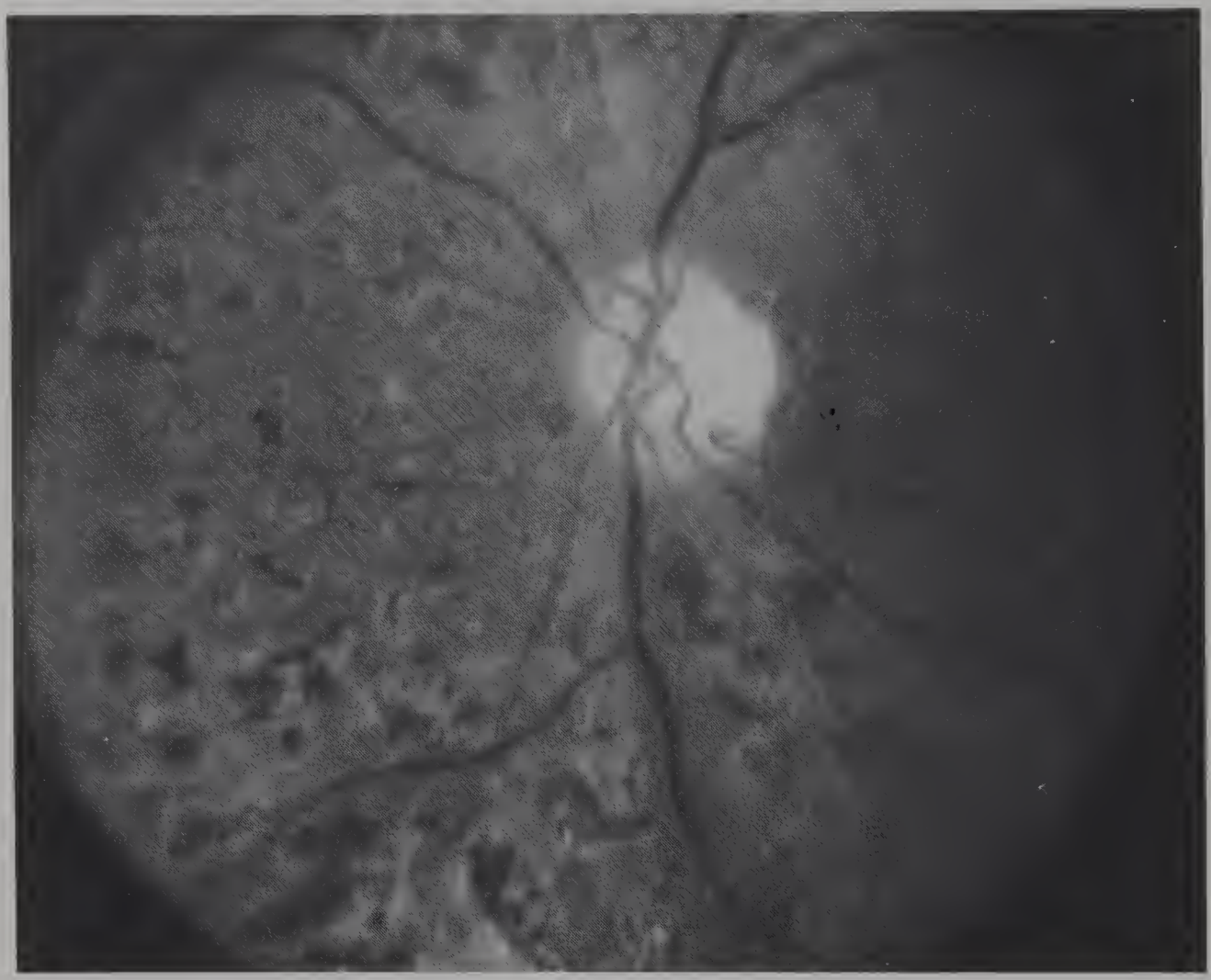


Figure 17.10. A photograph of the posterior retina and optic nerve head of the patient in Figure 17.9, 6 months later. Note the irregular, pigmented appearance of the laser-burn scars. The neovascularization has disappeared completely, and the caliber of the major retinal arteries and veins has notably decreased. A fibrous band, all that remains of the extensive neovascular network, extends in an arcuate pattern from the 1-o'clock to the 5-o'clock border of the photograph, touching the optic nerve head at its 3-o'clock margin. The visual acuity in this patient's eye remained at 20/40, its level before laser treatment. With permission from Elman KD, Welch RA, Frank RN, et al. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119–127.

vival rate was excellent (94%) and even higher when corrected for major congenital anomalies) (97%). At 0.5–9 yr postpartum, most women (74% of 27 women contacted) enjoyed active productive lives and remained capable of caring for their children. Two women had received renal transplants and four were on dialysis therapy. With one exception, all infants were reported to have normal developmental examinations.

Management guidelines for diabetic nephropathy before and after pregnancy are shown on Table 17.13. Fetal surveillance is begun at 25–26 weeks' gestation and continued until delivery. The most serious potential maternal complications include preterm labor with or without rupture of membranes, preeclampsia—often superimposed on chronic hypertension, infection with poor control of hyperglycemia, and severe hypoglycemia secondary to overinsulinization. Even with severely compromised renal function (proteinuria >5 g/day, creatinine clearance <40 ml/min and serum creatinine >2.0 mg/dl), it is rarely necessary to institute renal hemodialysis during pregnancy. Microalbuminuria is predictive of future diabetic nephropathy and should be measured in a 24-h urine collection in all diabetic pregnant women who have negative tests for albumin by conventional dip-stick testing. McCance and co-workers have observed a modest in-

Table 17.13.
Recommendations for Diagnosis and Treatment of Nephropathy in Women of Childbearing Age (14–45 yr) with IDDM

Preconception		Pregnancy[a]
I. Annual evaluation of renal status		
URINE DIPSTICK		
Positive	Negative	
1. Measure quantitative 24-h urinary protein loss, serum BUN, creatinine, and creatinine clearance	1. Measure urinary albumin excretion for microalbuminuria (30–300 mg/24 h)	1. Schedule renal function assessment: serum BUN, creatinine, creatinine clearance, uric acid and measurement of 24-h urinary protein loss and creatinine
2. Renal consultation if creatinine level is >3.0 mg/100 ml to consider intermittent hemodialysis, continuous ambulatory peritoneal dialysis, or renal transplantation	2. Maintain near-normoglycemic diabetic control	2. Urine culture
	3. High-complex carbohydrate diet (50–55%)	3. Close attention for signs of pregnancy-induced hypertension
		4. Control of hyperglycemia by multiple-dose insulin regimen; women with IDDM and severe nephropathy may require less insulin and are at greater risk for hypoglycemia without warning
		5. Reassessment of renal function each month or more often if preeclampsia occurs
II. Establish and maintain good diabetic control		
II. High-complex CHO diet with moderate protein restriction		
IV. Treatment of hypertension		

[a]With these therapeutic measures, patients with diabetes who are treated early do almost as well as nondiabetic patients with end-stage renal disease. Pregnancy, however, should be undertaken only with full realization of the risks involved for the fetus.

crease in urinary albumin in normal pregnancy from 28 weeks onward (55). In pregnant diabetic women without microalbuminuria at conception, they reported an exaggeration of the normal pattern with levels returning to normal after delivery.

Biesenbach and Zazgornik confirmed the findings in the McCance study and also showed that diabetic women with pre-existing microalbuminuria had a significant increase in proteinuria during gestation (56). In addition, they observed a transient nephrotic syndrome with peripheral edema during 3rd trimester in 3 women with pre-existing albuminuria.

All women with severe diabetic nephropathy should be managed at a tertiary care hospital and followed jointly by a nephrologist with expertise in nephropathy and hypertension during pregnancy. Diabetic renal disease is not a contraindication for becoming pregnant or a reason for abortion (unless desired and requested by the patient) for a pregnancy already underway. Women with diabetic and/or hypertensive renal disease must be fully informed about the details of their medical care during pregnancy and potential fetal risks. With comprehensive care and modern perinatal technology, the maternal and fetal outcomes in these pregnancies in special tertiary diabetes centers are now comparable to

those of other women with IDDM. This optimistic outcome is not reported in other types of health care centers or in clinics unable to provide a coordinated ambulatory care team approach, weekly clinic visits, and close telephone supervision of these complicated patients.

CARDIOVASCULAR PROBLEMS

In diabetic women with IDDM, there may be impaired adaptation of the cardiovascular system to pregnancy. Although coronary heart disease with angina or myocardial infarction are rare complications, two other problems are not unusual: autonomic neuropathy and cardiomyopathy.

Airaksinen and colleagues have studied cardiac function in pregnant normal and IDDM women (57). In a longitudinal study of 17 IDDM women during each trimester and postpartum, they assessed left ventricular function by serial echocardiography and by recording systolic time intervals. Diabetic women had less than the normal increase in left ventricular size and stroke volume. In addition, heart rate increases were lower, which resulted in a smaller increment in cardiac output. Minor collections of pericardial fluid occurred in 76% of diabetic women (45% in controls) and two women had classical pericardial effusions. They concluded that the normal hemodynamic adjustments to pregnancy seem to be impaired in women with IDDM and that preclinical diabetic cardiomyopathy and autonomic neuropathy that antedate gestation may be involved in the observed alterations. Because these changes are likely to be asymptomatic, they may not be appreciated unless other complications of pregnancy occur or there has been a careful cardiac assessment before gestation.

Reduced maternal cardiac output and decreased uteroplacental blood flow, particularly in the 3rd trimester, may be of clinical importance in situations in which other concomitant factors, such as anemia or preeclampsia, decrease fetal oxygen supply (58). Preterm labor treated with tocolytic agents or fluid overload for any reason are dangerous situations that place IDDM women at higher risk for pulmonary edema, hypovolemia, and diabetic ketoacidosis. Because unsuspected diabetic cardiomyopathy may lead to serious consequences as pregnancy progresses and complications occur, we recommend a maternal cardiac evaluation and echocardiography in all pregnant women with IDDM of more than 10 years' duration before conception or shortly after the first prenatal visit.

Exercise can also induce left ventricular dysfunction in IDDM women. Prepregnant women with microvascular and autonomic complications should be evaluated carefully and given advice about physical activity during gestation. Diversion of cardiac output by exercise causes a further temporary decrease in fetal blood flow in pregnant IDDM diabetic women that can be of clinical significance (59).

Little information is currently available on pregnancy in diabetic patients with significant coronary artery disease but without myocardial infarction. Reece and colleagues have reported a successful outcome in a 32-yr-old IDDM in her first pregnancy; 2 yr previously, she had had coronary artery disease that required an emergency coronary artery bypass graft to the left descending coronary artery (60). She also had additional complications of retinopathy and nephropathy. In their review of the literature (12 case reports), there were eight maternal deaths (67%) and five fetal losses (42%) in women with myocardial infarctions before, during, or up to 4 weeks postpartum. There are only two reports of women who have had coronary artery bypass procedures before pregnancy (52).

There have been no studies reported of cardiac function with or without exercise in pregnant NIDDM women. This information would be informative because these women are older and more likely to be obese and hypertensive but have fewer macro- and microvascular complications during the reproductive years.

Some pregnant diabetic women may have congenital or valvular heart disease and an occasional IDDM patient presents with Graves' disease and hyperthyroidism or Hashimoto's chronic thyroiditis. Women with these problems may develop arrhythmias or congestive heart failure during pregnancy or at labor and delivery. Their cardiac status should be assessed by careful history, physical examination, and appropriate laboratory studies.

NEUROPATHY

Diabetic autonomic neuropathy (62–66) is a serious complication of IDDM and NIDDM.

Subclinical abnormalities may be found early in the course of diabetes. Although this problem was once considered to result only from poor diabetic control, neurologic involvement is now generally thought to be a result of insulin deficiency and its metabolic consequences (65–66). The extent to which glucose-related metabolic factors, such as polyol pathway activation or nonenzymatic glycation, act directly on peripheral neurons and Schwann cells or through secondary microvascular alterations in various diabetic neuropathic syndromes remains controversial (67, 68). Many symptoms of autonomic neuropathy are similar to those of pregnancy and there is a low index of suspicion for this complication in most prenatal clinics. Cardiovascular neuropathy is characterized by postural hypotension (a fall in systolic blood pressure of >30 mm Hg on standing with a failure of compensatory tachycardia), lower cardiac output during exercise, and diminished catecholamine responsiveness. On 24-h ECG monitoring, diabetic individuals have faster heart rates through the day than normal subjects. Pregnant women with long-standing IDDM should be warned not to change position quickly and to avoid strenuous exercise programs if they have signs or symptoms of neuropathy. Postural hypotension is ameliorated by the use of body stockings. Women with cardiac denervation syndrome (a fixed heart rate of 80–90 beats per minute) should be evaluated for painless myocardial ischemia before conception or beginning an exercise program (65).

Gastrointestinal neuropathy (atony, gastroparesis diabeticorum), gallbladder dysfunction, and diabetic explosive diarrhea or constipation may require pharmacologic or dietary interventions (69). These symptoms can be especially distressing and may worsen as the uterus enlarges. Diabetic women often experience anorexia, nausea, vomiting, fullness, and early satiety. Although metaclopramide may be helpful in nonpregnant women, there are no adequate or well-controlled studies in pregnant or lactating women. Because of delayed gastric emptying, there is irregular absorption of nutrients that leads to more difficult control of hyperglycemia. A high-fiber diet is **contraindicated** because of the risk of developing fiber besoars. The most practical therapy is often the use of multiple (six to eight) very small meals spread over 12–16 h.

Neurogenic bladder dysfunction causes a loss of bladder sensation, overflow incontinence, and significant bacteriuria. Diabetic women with cardiovascular autonomic neuropathy appear to be at increased risk of developing bacteriuria. This should be kept in mind when pregnant IDDM women have repeated asymptomatic bladder infections.

EDEMA

Severe, generalized edema, often occurring early in pregnancy and persisting until term, is not unusual in women with IDDM and compromised renal function. It is usually treated with bed rest. The presence of congestive heart failure should be excluded. Women with NIDDM or GDM more often have dependent edema when preeclampsia is also present.

NONCOOPERATIVE PATIENTS AND PHYSICIAN FAILURE

It is difficult for many adolescent and young adult women with IDDM to accept and live with a chronic metabolic problem that requires daily treatment with injections and a constant adjustment or adaptation of life-style. Some solve the problem by an obsessive compulsiveness; others consciously or subconsciously deny that they have a disorder that requires attention. Obese women with NIDDM may find it difficult to adjust to therapeutic advice during pregnancy because they are usually asymptomatic and have often been quite casual about medical advice until this time. On the other hand, pregnancy in diabetic women provides a great deal of motivation and an opportunity for patient education and preventive health measures.

When pregnancy occurs, each diabetic woman arrives in prenatal care with her past diabetic educational experience and her own approach to life. If a prenatal program is too rigid or demanding, she may be unable to cope emotionally with a totally new plan for diabetic control. She and her family may be excessively worried about the pregnancy and possible outcome of the infant. These fears are heightened if her glycemic control is suboptimal and she becomes labeled "noncompliant" by the individuals responsible for her care.

Fortunately, pregnancy for most diabetic women is a highly motivating experience. In

most instances, these are wanted pregnancies and almost all women are eager to learn about the new advances in diabetic care. Thus, it is both possible and highly rewarding to try to adjust prenatal care to the individual needs of each family. A sympathetic patient-physician relationship and bilateral trust are carefully nurtured during initial hospitalization and the first prenatal visits. It is helpful to have the patient's husband, the father of the baby, close family member, or significant other person participate in the obstetric plans and attend clinic visits when possible.

On the initial visit, the previous medical history is carefully compiled and a complete physical examination performed with particular attention to funduscopic, neurologic, and cardiovascular examination. Goiter and Hashimoto's thyroiditis are common in women with IDDM and the possibility of hypo- or hyperthyroidism should not be overlooked. Renal status is evaluated by history of previous problems, careful urinalysis, and serum blood urea nitrogen (BUN) and creatinine determinations. With this information, it is possible for the physicians, (preferably the obstetrician and diabetologist) to have a relaxed, comfortable, and informative bilateral discussion with the patient and her family.

For women in poor control, hospitalization can be arranged and medical education and treatment initiated under optimal conditions. Arrangements also have to be made for each patient to have the phone number of her physician or a patient care coordinator 24 h a day. Most women do not abuse this line of communication and feel much more secure in case a problem arises. From the standpoint of the physician, minor illnesses and other difficulties are quickly brought to attention. This permits early diagnostic and therapeutic procedures and prevents unnecessary hospitalization. The utilization of a team approach is a practical and much less expensive method for ambulatory care of pregnant women with diabetes.

Although the approach outlined is obviously time-consuming initially, it is well worth the effort in the prevention of problems and the enhanced quality of care possible throughout the subsequent course of the pregnancy.

Patients who appear noncooperative are usually women with emotional problems who are unable or sometimes unwilling to fit into regimens that are structured with too much rigidity. The label noncompliant is unfortunate because it may unfairly prejudice medical care. In these difficult situations, it is best to work out an approach that the patient will follow and enlist the help of significant or sympathetic others.

It is frustrating to physicians when patients fail to follow instructions or are unable to make the considerable behavioral modifications advised during pregnancy. In some instances, the personality of the patient and the physician are incompatible. In these circumstances, the easiest course is for another physician in the group to assume primary responsibility for the patient. For some women, it may be easier to express problems and fears to the nurse clinician, dietitian, or social worker who can then act as an intermediary in helping with therapeutic advice and plans for delivery. In any case, isolation of the patient or judgmental labels by the staff should be avoided. For a variety of reasons, all physicians can and do fail with some patients.

In conclusion, the management of complications of diabetic pregnancies is a challenging experience for both obstetricians and internists. Women with diabetes are an ideal model for instruction in obstetric prenatal care because these patients may present with or develop every known complication of reproductive medicine. When the usual problems of pregnancy are superimposed upon a heterogeneous metabolic disorder, they require patience, expertise in perinatal medicine and psychiatry, and familiarity with the pathogenesis, course, and treatment of carbohydrate intolerance.

CHAPTER

18

Obstetric Complications—Maternal

Thomas R. Moore

CHRONIC HYPERTENSION

Chronic hypertension (69) is defined as high blood pressure (>140/90 mm Hg) present and observable before pregnancy or the 20th week of gestation. Hypertension that is diagnosed for the first time during pregnancy and that persists beyond the 42nd day postpartum is also classified as chronic hypertension.

There has been a great deal of confusion and some disagreement about the diagnosis and treatment of hypertensive disorders of pregnancy. This section and the one that follows on preeclampsia and eclampsia include several points of view represented in the current literature and rely heavily on the 1990 National High Blood Pressure Education Program (NHBPEP) working group consensus report sponsored by the National Institutes of Health (69).

The consensus group recommends the scheme for hypertensive disorders of pregnancy proposed by the American College of Obstetricians and Gynecologists in 1972, which has been in use for two decades (70). Hypertension associated with gestation is defined in only four categories (Table 18.1) (69). Classifications of hypertensive disorders of pregnancy are also available from the American College of Obstetricians and Gynecologists (71) and the World Health Organization (WHO) (72). The reason for the consensus group choice was that, although imperfect, the 1972 classification has been in use a long time and has the advantage of simplicity and clarity. Because preeclamptic syndromes and essential hypertension comprise over three quarters of the hypertensive disorders in pregnancy, the consensus document focuses on the presentation, pathophysiology, and management of these diseases. It will undoubtedly serve as the standard of care for the next few years. Hypertension complicates approximately 10% of all pregnancies and is a significant cause of fetal and maternal morbidity (73). Preeclampsia and eclampsia are the most serious forms of hypertension during pregnancy.

The interaction between diabetes and preeclampsia has been unclear (74). Although the Mayo Clinic Group (75) reported a twofold increase in this problem among diabetic pregnancies, others have found no significant differences between nondiabetic and diabetic women even when they required insulin therapy (76, 77). Importantly, preeclampsia did not occur at a significantly higher rate in pregnancies in classes D-R in the White classification (women with IDDM with microvasular abnormalities).

In the 1987 report of risk factors for the occurrence of preeclampsia by Guzick and colleagues at Parkland Hospital in Dallas, Texas, a computerized data base was used to assess 28,838 women who delivered between 1978 and 1980 (74). Of the total, 5190 (18%) developed preeclampsia. When the data were ana-

Table 18.1.
Classification of the Hypertensive Disorders of Pregnancy[a]

Chronic hypertension
Preeclampsia-eclampsia
Preeclampsia superimposed upon chronic hypertension
Transient hypertension

[a]With permission from National High Blood Pressure Education program (NHBPEP) working group report on high blood pressure in pregnancy. March 1990.

lyzed by multiple logistic regression and multivariate analysis, it was found that: (*a*) age had a linear (not U shaped) relation to preeclampsia after adjusting for parity; (*b*) preeclampsia was twice as likely to occur if chronic hypertension was present, controlling for all other variables; (*c*) diabetes **did not have a significant association with preeclampsia** when an independent effect of this risk factor was determined by multivariate methods, controlling for all other factors; and (*d*) heart disease, renal disease, race, and multiple gestation had important independent effects on preeclampsia.

Blood pressure measurements normally decline during 1st trimester and reach a nadir in 2nd trimester followed by a gradual increase to or near preconception levels in 3rd trimester (78). Four criteria have been established by the American College of Obstetricians and Gynecologists for the definition of hypertension in pregnancy (Table 18.2). The diagnosis of chronic hypertension (antedating pregnancy) is suspected if the systolic blood pressure is >130 mm Hg or the diastolic pressure is >80 mm Hg before 3rd trimester. Other findings that strengthen the likelihood of this diagnosis are: (*a*) failure of mean blood pressure to decline normally in late 2nd trimester; (*b*) an elevation of BUN to ≥10 mg/dl, serum creatinine to ≥1 mg/dl, or a reduced creatinine clearance to <100 ml/min.

Pregnant women with severe chronic hypertension and other hypertensive disorders of pregnancy are at increased risk of developing preeclampsia, eclampsia, abruption of the placenta, disseminated intravascular coagulation (DIC), cerebral hemorrhage, hepatic failure, and acute renal failure. The fetus has a higher risk of intrauterine growth retardation and death.

Management of chronic hypertensive pregnant diabetic women is summarized in Table 18.3. Bedrest, often with the addition of an antihypertensive agent to treat a systolic blood pressure consistently >150 mm/Hg and diastolic pressures of >100 mm Hg is the usual treatment. The **goal of therapy** is to control the upper limits of maternal blood pressure and minimize the risk of stroke, abruption of the placenta, and acute renal tubular and cortical necrosis. These untoward events correlate with age of pregnant women and duration of their high blood pressure (79). Most of these complications occur in women over age 30 yr or in those with evidence of end-organ damage. Most women with essential hypertension—about 85%—have uncomplicated and successful pregnancies (80). An adequate blood pressure must be maintained so that uterine perfusion is adequate for fetal growth.

The choice of antihypertensive agents requires experience and a full understanding of their potential side effects (81, 82). Table 18.4 describes the drug therapy of chronic hypertension in pregnancy. Most obstetricians specializing in diabetes care use methyldopa as the first-line drug and agent of choice. The initial dose is 250 mg three or four times per day with a maximum dose of 3000 mg daily. This drug has a long history of safe use and a successful clinical trial including a 7-yr follow-up of infants of mothers who received this treatment. A β-adrenergic inhibitor (and the com-

Table 18.2.
Definition of Hypertension in Pregnancy[a,b]

Systolic blood pressure ≥140 mm Hg
Diastolic blood pressure ≥90 mm Hg
Increase of ≥30 mm Hg in systolic pressure
Increase of ≥15 mm Hg in diastolic pressure

[a]With permission from The American College of Obstetricians and Gynecologists.
[b]Any of these criteria must be present on at least two occasions, separated by at least 6 h.

Table 18.3.
Management of Pregnant Diabetic Women With Chronic Hypertension

Bedrest is the cornerstone of therapy.
Modified (6 h daily plus sleep) or full bedrest when:
Fatigue or headache become prominent maternal symptoms
Fetal growth is at or below the 10th percentile or reaches a plateau
Fetal surveillance tests become worrisome (borderline findings but not diagnostic of fetal distress)
Initiate **antihypertensive medications** when diastolic pressures are *consistently* >100 mm Hg and systolic pressures >150 mm Hg
Adjust antihypertensive medications to keep diastolic pressures between 88 and 95 mm Hg
Monitor laboratory tests and clinical findings for impending **preeclampsia.**

Table 18.4.
Drug Therapy of Chronic Hypertension in Pregnancy[a,b]

Drug	Dose	Adverse Effects and Comments
Agent of choice		
Methyldopa	500–3000 mg in 2–4 divided doses	Safety for mother and fetus (after 1st trimester) is well documented
Second-line agents		
Hydralazine	500–300 mg in 2–4 divided doses	Few controlled trials but extensive experience with few serious adverse effects documented; several reports of neonatal thrombocytopenia
β-adrenergic inhibitors (and the combined α-β-blocker, labetalol)	Dependent on specific agent used	May cause fetal bradycardia and impair fetal responses to hypoxia; risk of intrauterine growth retardation remains unclear
Third-line agents		
Thiazide diuretics	Dependent on agent used	Most controlled studies are in normotensive gravidas; few data in hypertensive pregnancies; implicated in volume depletion, electrolyte imbalance, pancreatitis, and thrombocytopenia
Clonidine	0.1–0.8 mg in 2 divided doses	Limited data
Nifedipine	30–120 mg in 3–4 divided doses	Limited data; may inhibit labor; potential for severe hypotension in patients receiving $MgSO_4$
Prazosin	1–30 mg in 2–3 divided doses	Limited data
Contraindicated		
Angiotensin-converting-enzyme inhibitors	Dependent on agent used	High rates of fetal loss in animals; several cases of neonatal anuric acute renal failure in humans

[a]With permission from Barron WM, Murphy MD, Lindheimer MD. Management of hypertension during pregnancy. In: Laragh JH, Brenner BM (eds). Hypertension. Diagnosis and Management. New York: Raven Press, 1990, pp 1809–1827.
[b]Note that safety during the 1st trimester has not been established for any antihypertensive agent.

bined α-β blocker, labetalol) can be added as a second agent when diastolic pressures are >100 mm Hg (83). In some centers, hydralazine is used as a reasonable second-line agent. Medications should be titrated to keep the patient's diastolic pressure in the range of 90–95 mm Hg and the systolic pressure <160 mm Hg. It is helpful to have the patient check blood pressures daily at home during the interval between office visits. However, care should be taken in increasing the dose of antihypertensive medications. Women who require the addition of a second or third agent more frequently experience poor fetal growth and early onset of preeclampsia.

Diuretics have not proved to be beneficial in chronic hypertension or preeclampsia. Their use has been associated with a number of adverse side effects including severe extracellular volume depletion, azotemia, and electrolyte disturbances. They may affect placental perfusion adversely and have also been associated with neonatal thrombocytopenia and hemorrhage. Maternal risks include hemorrhagic pancreatitis and hyperuricemia. A rise in serum uric acid level is an important diagnostic sign of preeclampsia. Caution is advised concerning routine use of diuretics; the only pregnant women for whom Barron and colleagues prescribe saluretics unhesitatingly are those with pulmonary edema and/or left ventricular failure (82). A broader appraisal of the use of

diuretics in pregnancy by NHBPEP follows below (69). Controversy remains, however, about use of diuretics during pregnancy.

The theoretic concerns about diuretic agents, reported mostly in the 1960s, have to be balanced by the extensive experience in several well-controlled studies with their prophylactic use in **normotensive** pregnant women in whom there was no evidence of excessive perinatal mortality or morbidity (84). A meta-analysis of nine randomized trials comprising over 7000 subjects showed a decrease in the tendency of these women to develop edema and/or hypertension and confirmed the observation that there were no increased adverse effects in the fetus (85). Based on theoretic concerns, diuretics are usually not used as first-line drugs. However, if their use is indicated, they are safe and efficacious agents that can markedly potentiate the response to other antihypertensive agents and are not contraindicated in pregnancy except in settings where uteroplacental perfusion is already reduced, e.g., preeclampsia and intrauterine growth retardation.

Although recent data concerning use of diuretics in pregnant women with hypertension are sparse, the NHBPEP consensus group concluded that gestation does not preclude use of saluretic drugs to reduce or control blood pressure in women (especially those who are salt sensitive) whose hypertension antedates conception or is manifested before 20 weeks' gestation (69). The 1988 report of the Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure recommended smaller doses of diuretics than used previously, thus minimizing metabolic effects (86).

Sodium restriction during pregnancy has also been associated with severe volume depletion, azotemia, and electrolyte disturbances. There are no documented benefits of sodium restriction. However, patients with chronic hypertension who enter pregnancy on a moderately restricted sodium intake need not alter their dietary patterns (82).

Angiotensin convertase inhibitors, e.g., captopril and enalopril, are used with increasing frequency in nonpregnant hypertensive patients. However, during pregnancy, these drugs have been linked to poor fetal growth, fetal anuria, and fetal death (87). They should be discontinued early in pregnancy and restarted **only if potential benefits outweigh documented risks.**

Preliminary information concerning calcium antagonists is encouraging but only limited data are available. The roles of calcium supplementation and low-dose aspirin medication (which decreases thromboxane synthesis while sparing prostacyclin production) to prevent preeclampsia and/or chronic or transient hypertension are under investigation (69).

Finally, the question should be raised whether women with **mild** chronic hypertension during pregnancy should receive any medication at all. Sibai and colleagues (88) have reported their experience in 300 women with mild chronic hypertension at 6–13 weeks' gestation who were randomly allocated to receive methyldopa, labetol, or no medication. In the 263 women followed with serial renal function tests and assessment of fetal status for the duration of pregnancy, there were no differences among groups with respect to superimposed preeclampsia (15.6%, 18.4%, and 16.3%, respectively), abruption of the placenta (2.2%, 1.1%, and 2.3%), or preterm delivery (10%, 12.5%, 11.6%). Furthermore, there were no differences among groups with respect to gestational age at delivery, birth weight, intrauterine growth retardation, or neonatal head circumference. There was one fetal loss in each group. They concluded that, in mild chronic hypertension in pregnancy, treatment does not improve perinatal outcome.

Many of the published studies of antihypertensive agents in mild and severe chronic hypertension in pregnancy have been limited in scope. There remains a critical need for large multicenter clinical trials using the combined services of obstetricians, hypertension specialists, epidemiologists, and statisticians (79).

PREECLAMPSIA

Preeclampsia is a disease peculiar to pregnancy. It is most common in nulliparas, presents usually after gestational week 20, most frequently near term. The criteria for diagnosis are listed in Table 18.5. It may occur earlier in women with trophoblastic disease, such as hydatidiform mole or a fetus with hydrops. Signs helpful in diagnosis are proteinuria, edema (especially if of recent or rapid onset), and any of the following: hemoconcen-

Table 18.5.
Diagnosis of Preeclampsia

Hypertension	Blood pressure >140/90 on 2 occasions, 6 h apart
	Rise in blood pressure of >30 mm Hg systolic and 15 mm Hg diastolic
Proteinuria	≥1 + on standard urine dipstick; this correlates with 30 mg/dl on a random specimen
	≥300 mg urinary protein in a 24-h collection
Edema	Significant nondependent edema or >4-lb weight gain in 1 week

tration, hypoalbuminemia, abnormalities of hepatic function and/or coagulation, and increased serum urate levels. The predictive value of raised serum iron levels, low antithrombin III concentrations and hypocalciuria are under investigation. Any of the following criteria suffice for the diagnosis of hypertension: (*a*) systolic blood pressure increases of 30 mm Hg or greater; (*b*) diastolic blood pressure increases of 15 mm Hg or greater from 1st trimester values. If pregestational blood pressure is unknown, readings of 140/90 mm Hg after 20 weeks' gestation are considered sufficiently elevated to satisfy the blood pressure criterion for preeclampsia. **Many young women will show the blood pressure increase required for a diagnosis of preeclampsia without increasing their pressure to 140/90 mm Hg. Preeclampsia superimposed upon chronic hypertension has a much worse prognosis for mother and fetus than either condition alone.**

Proteinuria is defined as the excretion of 0.3 g or greater in a 24-h specimen. This correlates with a 30 mg/dl ("1+ dip-stick") or greater amount in a random urine determination. Proteinuria is usually a late sign in the course of preeclampsia.

Edema is diagnosed as clinically evident swelling, but fluid retention may also be manifested as a rapid increase of weight without evident swelling. There is a tendency for preeclampsia to be inherited (89). Twin pregnancy increases the risk five times (90).

Eclampsia is the occurrence of seizures in a preeclamptic woman that cannot be attributed to other causes.

Transient hypertension is the development of elevated blood pressure during pregnancy or in the first 24 h postpartum without other signs of preeclampsia or preexisting hypertension. This condition is often predictive of the eventual development of essential hypertension. It is probably the usual basis for the erroneous diagnosis of preeclampsia in multiparas.

A major pathophysiologic feature of preeclampsia is a marked increase in peripheral resistance caused by vasospasm due, in part, to exaggerated vascular responsiveness to circulating angiotensin II and catecholamines. This may represent an imbalance between thromboxane and prostacyclin production. Before therapeutic interventions are imposed, cardiac output is often decreased, pulmonary capillary wedge pressure is normal or low, and intravascular volume is below that of normal pregnant women. Renal hemodynamics also decrease due, to some extent, to glomerular endotheliosus, a characteristic morphologic lesion in the glomerulus. Increased vascular permeability leads to loss of albumin from the intravascular space. Uteroplacental perfusion is often reduced and associated with fetal growth retardation. It is important to recognize the onset of preeclampsia because poor management may result in significant fetal and maternal morbidity. Conversely, a carefully managed diabetic woman with mild preeclampsia near term will experience very little effect on herself or the baby.

Many obstetricians find it useful to define more severe signs and symptoms of preeclampsia (Table 18.6). Lindheimer disagrees with attempts to categorize preeclampsia as mild or severe because this definition may be misleading (79). In essence, he recommends that de novo 3rd-trimester hypertension in a nullipara is sufficient reason for hospitalization, regardless of whether other signs are present, because deterioration and progression from mild to severe forms of preeclampsia can occur suddenly. In the variant of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome; Table 18.7), the initial onset and appearance may be quite benign and misleading with only minimal changes in platelet count, liver function tests and blood pressure, and little or no renal dysfunction. The syndrome can quickly reach life-threatening proportions with transami-

Table 18.6.
Criteria for the Diagnosis of Severe Preeclampsia[a]

Hypertension	Blood pressure > 160/110 mm Hg
Proteinuria	3+ – 4+ on urine dipstick or > 5 g of urinary protein excretion in 24 h
Oliguria	<20 ml/h × 4 h or longer <400 ml/24 h
CNS symptoms	Severe or persistent headache Visual phenomena: blurred vision, scotomata, or scintillations Altered consciousness
Epigastric pain	
Pulmonary edema	

[a]Any of these are sufficient for the diagnosis of severe preeclampsia (see text for expanded discussion on preeclampsia-eclampsia)

nase values increasing to >1000 IU, platelet counts decreasing to <40,000/mm^3, and marked evidence of microangiopathic anemia constituting an emergency that requires termination of pregnancy (91, 92).

A second life-threatening complication of preeclampsia is progression to a convulsive stage, eclampsia. This severe form has been associated with cerebral hemorrhage, cardiovascular collapse, and maternal death. Impending or frank eclampsia requires immediate termination of gestation.

Table 18.7.
Diagnosis of the Syndrome of Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP)

Hemolysis	Abnormal peripheral blood smear Elevated serum bilirubin (≥1.2 mg/dl)
Abnormal liver function	Increased SGOT (AST, aspartate amino transaminase) Increased SGPT (ALT, alanine amino transaminase) Increased lactic dehydrogenase (LDH) to >600 IU/L
Thrombocytopenia	Platelet count <100,000 mm^3

Treatment

In mild preeclampsia, a conservative approach can be taken. Fetal maturity (documented by fetal lung maturity with amniocentesis or certain gestational age >38.5 weeks) is an indication for immediate delivery. However, if the fetus is immature (<37 completed weeks of gestation), observation of the patient, preferably in the hospital, for signs of severe preeclampsia and documentation of fetal lung maturity is appropriate. Intensive fetal and maternal monitoring should be instituted during conservative management of preeclampsia (Table 18.8). **For clinical management, preeclampsia should be overdiagnosed because a major goal in managing preeclampsia is the prevention of eclampsia, primarily through timing of delivery.**

As noted previously, in large epidemiologic studies, diabetes does not have a significant association with preeclampsia when a multivariate analysis of other confounding variables is performed (74). Aside from nulliparity, the most frequent associations are age (after adjusting for parity), chronic hypertension, heart disease, renal disease, race, multiple gestations, genetic factors, and immunologic disorders such as lupus erythematosus (93).

In chronic hypertensive women, it may be difficult to diagnose preeclampsia with certainty but an attempt should be made. Progressive elevations in blood pressure in women with chronic hypertension can be managed conservatively with additional antihyperten-

Table 18.8.
Guidelines for Monitoring Diabetic Women With Mild Preeclampsia and an Immature Fetus

Check maternal vital signs and fetal heart rate every 4 h
Fetal biophysical surveillance daily
Every 3 days: complete blood count and platelet count, liver enzymes, BUN, creatinine, uric acid
Weekly: 24-h urinary protein and creatinine clearance determinations
Weekly: amniotic fluid volume assessment by ultrasound
Every other week: fetal growth assessment by ultrasound

sive medications as long as the fetus is growing and well oxygenated. A previously hypertensive patient is considered to have superimposed preeclampsia when serum uric acid is elevated or platelet counts decrease (94). The onset can be insidious or rapid and may not be recognized until a severe stage. In severe preeclampsia, particular attention should be paid to detection of early signs of the HELPP syndrome described previously (95, 96).

When severe preeclampsia is present, **delivery arrangements should be made immediately.** Sibai and colleagues (97) have reported that conservative management of patients with severe preeclampsia and an immature fetus resulted in a progression to eclampsia in 8%, abruption of the placenta in 10%, and stillbirths in 25% of women. Conservative management of severe preeclampsia is dangerous for both mother and fetus. Even if the fetus is immature, prompt delivery provides the best chance for both mother and baby. The 1990 NIH consensus panel agrees that treatment for preeclampsia when gestation is advanced is delivery of the baby (69). The group also recommends that severe intrapartum hypertension be controlled with intravenous hydralazine, which is successful in most instances. Favorable results have been recorded with parenteral diazoxide, labetalol, and clonidine as well as oral nifedipine. **Nitroprusside should be avoided unless maternal jeopardy is extreme.** Magnesium sulfate remains the drug of choice to prevent or treat eclamptic convulsions. Table 18.9 outlines drug therapy of severe hypertension of pregnancy (82).

The management of severe hypertension during labor and delivery remains controversial among perinatologists, but all agree that this situation requires special precautions and careful use of medications. Management at The University of California San Diego is a modification of the consensus report to the following procedure.

Patients whose blood pressure is consistently above 160/110 mm Hg are considered to be at increased risk for intracranial hemorrhage. However, abrupt and excessive lowering of the blood pressure may precipitate fetal distress. Thus, the target maintenance range for blood pressure in these patients should be 140/90 to 155/105 mm Hg.

The use of hydralazine is recommended as a first-line agent (Table 18.9) and given in 5- to 10-mg doses with 20-30 minutes allowed to lapse between doses to permit the drug to act. Administration of the drug in this fashion permits a gentle but limited decline in blood pressure. More severe and prolonged increases in blood pressure to >160/110 may require a continuous intravenous infusion. This is typically observed at the onset of cesarean section delivery and particularly during endotracheal intubation. Both nitroglycerine and sodium nitroprusside have been used successfully and safely during these periods of transient changes in blood pressure. These drugs are administered as a continuous infusion before and during intubation and then rapidly discontinued. It should be emphasized that continuous infusions of antihypertensive agents require continuous monitoring of blood pressure via arterial catheter and many of these patients will benefit by central hemodynamic monitoring.

Second-line agents in the treatment of intrapartum severe hypertension include the α-β blocker, labetalol, and the calcium channel blocker, nifedipine. There is limited experience with both of these agents, and injudicious administration may precipitate maternal hypotension and fetal distress.

The role of prostaglandins in preeclampsia is not well understood; nor is it known whether the reported metabolic derangements (an imbalance in the production of vasoactive prostaglandins, thromboxane A_2 and prostacyclin) that lead to vasoconstriction of small arteries and activation of platelets are primary or secondary. Table 18.10 compares the relationship of prostacyclin and thromboxane in normal and preeclamptic pregnancies.

Fitzgerald and colleagues (98) have reported that thromboxane metabolite excretion (urinary excretion of thromboxane B_2 metabolites as markers of thromboxane A_2 synthesis) correlates with mean arterial blood pressure, platelet lactate dehydrogenase, and platelet count, all of which are indices of the severity of preeclampsia. These findings are important because they provide a rationale for the use of low doses of aspirin for prevention and treatment of preeclampsia that is still under active investigation. Walsh has reviewed the present status of low-dose aspirin treatment for the imbalance of increased thromboxane and decreased prostacyclin in preeclampsia (99). The use of aspirin as a treatment of primagravid patients at risk for preeclampsia was first re-

Table 18.9.
Drug Therapy of Severe Hypertension in Pregnancy[a,b]

Drug	Dose/Route[c]	Onset of Action	Adverse[d] effects	Comments
Agent of choice				
Hydralazine	5 mg IV/IM, then 5–10 mg every 20–40 min; or constant infusion of 0.5–10 mg/h	IV: 10 min IM: 20–30 min	Headache, flushing, tachycardia, nausea, vomiting	Broad experience of safety and efficacy
Second-line agents				
Diazoxide	30–50 mg IV every 5–15 min	2–5 min	Inhibition of labor; hyperglycemia, fluid retention with repeated doses	Doses of 150–300 mg may cause severe hypotension
Labetalol	20 mg IV, then 20–80 mg every 20–30 min, up to 300 mg; or constant infusion of 1–2 mg/min until desired effect, then stop or reduce to 0.5 mg/min	5–10 min	Flushing, nausea, vomiting, tingling of scalp	Limited experience in pregnancy
Nifedipine	10 mg p.o.; repeat in 30 min if necessary, then 10–20 mg p.o. every 3–6 h	10–15 min	Flushing, headache, nausea, inhibition of labor	May have adverse interaction with $MgSO_4$: limited experience in pregnancy
Relative contraindication				
Nitroprusside	0.5–10 μg/kg/min by constant IV infusion	Instantaneous	Cyanide toxicity, nausea, vomiting	Use only in critical care unit at low doses for shortest time feasible; may cause fetal cyanide toxicity

[a]With permission from Barron WM, Murphy MD, Lindheimer MD. Management of hypertension during pregnancy. In: Laragh JH, Brenner BM (eds). Hypertension. Diagnosis and Management. New York, Raven Press, 1990, pp 1809–1827.
[b]Indicated for acute elevation of diastolic blood pressure to >105 mm Hg; goal is gradual reduction to 90–100 mm Hg.
[c]Abbreviations: IV, intravenously; IM, intramuscularly; p.o., per os (orally).
[d]All agents may cause marked hypotension, especially in severe preeclampsia.

Table 18.10.
Alterations in Serum Thromboxane A_2 and Prostacyclin in Normal Pregnancies and Preeclampsia

	Normal Pregnancy	Preeclampsia	
Platelet activiation with ↑ thromboxane A_2 (a platelet aggregate and vasoconstrictor)	↑	↑	
Serum prostacyclin (endogenous inhibitor of platelet aggregation)	↑	↓	or absent
Altered sensitivity to angiotensin II	–	+	with possible ↓ blood flow to uteroplacental unit and formation of placental thrombi

ported by Beaufils and associates (100). The following year (1986), Wallenburg and coworkers reported their results of a low-dose aspirin trial in 46 women. They used a dose of 60 mg of aspirin a day and found that 2 of 23 women developed symptoms of preeclampsia compared with 12 of 23 women treated with a placebo. Many thousands of women throughout the world with both normal and high-risk pregnancies are enrolled in low-dose aspirin studies.

Initial reports (100–103) and presentations at international meetings have been promising, but the actual number of patients described in the literature is still small. Schiff and colleagues (104) conducted a prospective randomized, double-blind, placebo-controlled study in 69 of 791 pregnant women with an increase in blood pressure and risk factors for preeclampsia. They studied 65 women with either 100 mg of aspirin a day ($N = 34$) or a placebo ($N = 31$). Significantly fewer women in the aspirin group developed preeclampsia. The ratio of serum levels of thromboxane A_2 to serum prostacyclin metabolites decreased in the aspirin group and increased in the placebo group. They concluded that low doses of aspirin in this small preliminary study reduced the incidence of hypertension and preeclampsia without serious maternal or neonatal side effects.

Benigni and colleagues (105) have followed their initial report with a randomized study of daily long-term administration of 60 mg of aspirin in 33 women at risk for preeclampsia (17 study patients and 16 controls treated with a placebo). They found that low-dose aspirin given from the 12th week of gestation to delivery prolonged gestation and increased birth weight.

In sum, chronic hypertension and preeclampsia are frequent and serious complications for normal and diabetic women. These patients must be monitored carefully and treated judiciously. The recent consensus statement from an NIH panel will help clarify and standardize our current approach to this problem. The most interesting and provocative development in this area is the use of low-dose aspirin as **primary prevention** for preeclampsia. Collaborative trials have been designed and are in progress but it is too soon to recommend routine use of aspirin in women at possible risk for preeclampsia until efficacy is determined and the risk/benefit ratio is clearly established as advantageous for the mother and fetus.

PRETERM LABOR

Preterm labor is defined as the presence of uterine contractions resulting in cervical change before fetal maturity occurs. The most widely used definition is six to eight uterine contractions per hour or four contractions in 20 minutes associated with cervical change (106). The incidence of preterm birth in Britain and America has not changed in 25 yr and 6–8% of pregnancies still end in preterm delivery (107).

Pathophysiology and Clinical Observations

Although most spontaneous preterm labors are not due to a recognizable cause, there has been increasing epidemiologic, microbiologic, and biochemical evidence for a link between infection and preterm labor (108, 109). In a prospective New York study, strong associations were reported between preterm birth and a history of pelvic inflammatory disease or use of an intrauterine contraceptive device (110). Other well-recognized conditions associated with preterm labor include low socioeconomic status, low and high maternal age, history of preterm birth, previous abortion, maternal smoking, multiple gestation, hydramnios, antepartum hemorrhage, and chorioamnionitis. In addition, uterine anomalies, such as large fibroids or bicornuate uteri, maternal history of diethylstilbestrol (DES) exposure in utero, and previous cervical surgery (e.g., cone biopsy) are also risk factors for this complication.

In IDDM women, the prevalence of spontaneously occurring preterm labor is unknown because previous studies have been confounded by a high rate of iatrogenic prematurity. At the University of Cincinnati College of Medicine, Mimouni and colleagues abandoned a policy of "early delivery strategy" for diabetic women in the late 1970s (111). This permitted their group to conduct a prospective epidemiologic study from 1978–1986 of the spontaneous preterm labor rate in 181 pregnancies of diabetic women who received insulin. They excluded patients with GDM. The diagnosis of preterm labor was based on evidence of regular uterine contractions documented by external tocodynamometry, cervical dilation of 3 cm or more, and/or progressive effacement of the cervix at 20–37 weeks of gestation. Nondiabetic pregnant women who were cared for by the same obstetricians in university private clinical settings from 1984–1986 served as a comparison group. A high rate of spontaneous preterm labor was found in both the diabetic and comparison groups (31.1% versus 20.2%; with a relative risk for developing preterm labor in diabetic women of 1.64 with a confidence interval of 1.16–2.31). They did not find an association of preterm labor with maternal age, parity, gravidity, diabetic class according to White, presence of renal disease, retinopathy, previous elective abortion, chronic hypertension, preeclampsia, cigarette smoking, vaginal bleeding in 1st trimester or after 20 weeks' gestation, maternal serum magnesium concentrations, or hydramnios. There were only four positive associations with preterm labor: (*a*) premature rupture of membranes; (*b*) history of preterm delivery; (*c*) poor glycemic control in 2nd trimester; and (*d*) urogenital infection.

In a second recent study (1989) of prematurity among 420 insulin-requiring diabetic pregnant women at the Joslin Clinic and The Brigham and Women's Hospital in Boston, Greene and colleagues reported their experience from 1983–1987 (112). There were 110 deliveries (26.2%) before 37 completed weeks of gestation in diabetic women compared with 9% for the general population of Brigham and Women's Hospital in 1985. Their findings differ from those of Mimouni and co-workers in that 33% were the result of hypertension or preeclampsia in women with more advanced White class. They also found a correlation with a history of preterm delivery, duration of diabetes, and male sex of the fetus. In both studies, the comparison groups were not strictly comparable with the study population and multivariate analyses of cases and controls were not performed. Nonetheless, taken together, the two studies, which differed in design and conclusions, affirmed the importance of good control of hyperglycemia, detection and treatment of urogenital infections, and management of chronic hypertension and preeclampsia in diabetic (and nondiabetic) women.

Treatment

Diabetic women with risk factors for preterm labor described previously should have intensive surveillance in addition to treatment of hyperglycemia, hypertension, and urinary tract infections with symptomatic or asymptomatic bacteriuria. Individual instruction should be given about signs and symptoms of preterm labor and warnings that more than four uterine contractions per hour increase the risk of preterm delivery (113). Patients can use this limit as a threshold for contacting their physician. All pregnant diabetic women should have a clinic visit each week and have telephone contact available with the nurse coordinator and their physician 24 h/day.

Once a diagnosis of preterm labor is con-

firmed, the risk of preterm birth should be assessed. This requires a careful review of obstetric dates before considering intervention by medications to inhibit labor. The absolute and relative contraindications for the use of β-sympathomimetic tocolytic agents should also be reviewed (Table 18.11). If fetal lung maturity is likely (based on the review of gestational age by dates, ultrasonography, and physical examination), amniocentesis for a phospholipid profile, gram stain, and culture should be performed. If the fetus is immature, every effort should be made to suppress labor and avoid delivery if there are no contraindications. This topic has been reviewed comprehensively by Main and Main (114).

β-Sympathomimetic tocolytic intravenous drug therapy has become standard practice in the treatment of preterm labor in many centers and it is often followed by oral β-sympathomimetic medication for maintenance of tocolysis. Opinions vary about the indications for and potential benefits of these drugs: King and colleagues (115) have conducted a meta-analysis of controlled trials of β-sympathomimetic therapy for preterm labor. The trials were identified in the Oxford Database of Perinatal Trials, published papers, and unpublished trials in the United States, Canada, and Europe. Adequately controlled trials are few in number; King and associates (115) were able to analyze data from 890 women who participated in 16 methodologically acceptable controlled trials. Meta-analysis demonstrated an unequivocal effect of β-sympathomimetic tocolytic administration in delaying delivery as reflected by a reduction in preterm births and low birth weight infants. However, there was no beneficial effect of this treatment on perinatal mortality or severe neonatal respiratory disorders.

When tocolytic agents are used, the choice of a particular drug depends on the experience of the obstetrician, the difficulty encountered in suppressing contractions, and the degree of prematurity. At present, the only FDA-approved β-sympathomimetic agent for inhibition of preterm labor in the United States is ritodrine. Ritodrine must be used cautiously, particularly in diabetic women, because it increases hyperglycemia appreciably. β-Sympathomimetic therapy for preterm labor has been associated with maternal deaths. Many women experience nausea (20–30%) and 50% develop tachycardia of greater than 120 beats per minute. Pulmonary edema is the most serious nonfatal complication. IDDM women who have had the disorder for more than 10 yr are at special risk for serious fatal cardiovascular complications.

β-Sympathomimetic drugs cross the placenta freely and may cause severe cardiovascular complications in the fetus (116). These include stillbirth, heart failure, disturbances

Table 18.11.
Absolute and Relative Contraindications to the Administration of β-Mimetic Agents in Preterm Labor[a]

Absolute	Relative (Increased Risk)
Maternal cardiac disease	Multiple gestation
Preeclampsia or eclampsia	Preterm rupture of membranes
Significant antepartum hemorrhage	Fever
Chorioamnionitis	Well-controlled diabetes
Fetal mortality or significant abnormality	Chronic hypertension
Significant fetal growth retardation	Women receiving K^+ depleting diuretics
Uncontrolled diabetes mellitus	History of severe migraine headaches
Hyperthyroidism, uncontrolled hypertension, hypovolemia	
Obstetric or medical condition that contraindicates prolongation of pregnancy	

[a]Adapted with permission from Main DM, Main EK. Management of preterm labor and delivery. In: Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York, Churchill Livingstone, 1986, 689–737.

of rate and rhythm, myocardial ischemia or infarction, hydrops, and neonatal death. Prospective studies have documented changes in the interventricular septa. The mechanism of β-sympathomimetic fetal toxicity appears to be an increased myocardial concentration of intracellular calcium leading to overexcitation and cell necrosis. Katz and Seeds caution that benefits should outweigh risks before these potent agents are prescribed (116).

In diabetic women, control of blood glucose during β-sympathomimetic treatment is extremely difficult. Most patients become significantly hyperglycemic during tocolysis (mean blood glucose 200 mg/dl; 100 mmol/L) and require high-dose insulin infusions (up to 3.5 U/h) to maintain even modest levels of glucose control. For these reasons, it is best to avoid these drugs in diabetic women and use another agent.

Other investigators who use β-sympathomimetic drugs in diabetic women under strictly controlled clinical settings have been more optimistic. Miodovnik and associates (117) reported the successful use of these agents in 12 insulin-dependent diabetic women with preterm labor. In this small retrospective study, tocolytic treatment was initiated at a mean gestational age of 31.5 ± 0.9 weeks. Delivery time (35.8 ± 0.5 weeks) was delayed by a mean of 30.5 ± 6.6 days. There were no fetal or infant deaths and neonatal morbidity did not differ from that of infants of 30 IDDM women delivered at term. At the Sansum Medical Foundation, Santa Barbara, California, Jovanovic-Peterson and her colleagues (118) also report favorable outcomes for diabetic women with preterm labor following use of β-sympathomimetic drugs in meticulously controlled clinical circumstances.

Another tocolytic drug, magnesium sulfate ($MgSO_4$), offers the advantage of equivalent efficacy to β-adrenergic agents without hyperglycemic side effects (119). In a comparison of β-sympathomimetic agents and $MgSO_4$, Beall and colleagues (120) concluded that this drug was superior in efficacy because it had fewer maternal and fetal side effects. They discontinued use of the β-sympathomimetic drug, terbutaline, because it was associated with an unacceptably high level of side effects in mothers with no enhanced therapeutic advantage over ritodrine.

In 1988, Lam and co-workers (121) reported the first use of subcutaneous terbutaline administered by a pump for long-term tocolysis. They managed nine nondiabetic women with preterm labor on an ambulatory program. All had failed oral tocolytic treatment and would otherwise have required prolonged hospitalization. In this preliminary feasibility study, women were monitored at home with portable tocodynamometers and visits by nurses. Uterine activity data were transmitted via telephone to the study center and infusion rates of terbutaline adjusted accordingly. The patients received a combination low-dose, continuous basal infusion of terbutaline supplemented with intermittent high-dose boluses. The total daily dose was low (<3 mg/24 h). Treatment was prolonged (9.2 ± 4.3 weeks) and mean gestational age at delivery was 37.3 weeks with no significant complications. There are no other published clinical trials of this technology (as of 1990). In a case report of an IDDM woman treated in this way, diabetic ketoacidosis and insulin resistance occurred (122).

At UCSD, $MgSO_4$ is the first-line agent for suppression of preterm labor in all patients and the drug of choice in diabetic women. The guidelines for use of magnesium sulfate for tocolysis are presented in Table 18.12. An initial intravenous bolus followed by at least 3 g/h is necessary to obtain therapeutic magnesium levels promptly (123). Fluid overload must be avoided; pulmonary edema occurs in patients whose cumulative positive fluid balance exceeds 3000 ml/day (124).

Signs of toxicity with $MgSO_4$ are predictable and related to serum levels of Mg. Patients complain of lethargy and thirst when serum Mg concentrations are greater than 6.0 mg/dl; above 7.0 mg/dl, constipation, urinary retention, and nausea are prominent symptoms. When levels rise above 8.0 mg/dl, deep tendon reflexes cannot be elicited; respiratory depression occurs at and above 9.0 mg/dl. Infusion of $MgSO_4$ should be discontinued if serum Mg values exceed 8.0 mg/dl.

For the occasional woman who continues to have contractions and shows cervical dilatation despite therapeutic levels of serum magnesium, a second agent or (less frequently) changing therapeutic agents can be considered. Indomethacin is very useful in this situation. Courses limited to 48 h in duration, are reported to be safe for the fetus (125, 126). Mo-

Table 18.12.
Guidelines for Use of Magnesium Sulfate in Labor Inhibition

Mix 10 g $MgSO_4$ sulfate in 100 ml 0.5% normal saline
Administer a 4- to 6-g intravenous bolus over 20–30 min
Follow with an infusion rate of 3.0 g/h; continue at this or a higher rate until contractions have diminished in strength and the frequency is less than 4/h
Maintain serum magnesium level between 6 and 8 mg/dl
Maintain drip at a minimum of 2 g/h for at least 48 h after contractions have subsided
Gradually decrease infusion by 0.3–0.5 g/h
Monitor serum $MgSO_4$ levels every 6 h while infusing >2 g $MgSO_4$/h
Avoid fluid overload by limiting *total fluids* to 2400 ml/24 h while infusion rates are above 2.5 g/h; measure total intake and output daily
Do not reduce the infusion rate below 2.0 g/h until labor has been suppressed for at least 48 h

rales and colleagues (127) report that indomethacin and ritodrine hydrochloride are equally effective in inhibiting uterine contractions and delaying delivery. In their study comparing the two drugs, there were no maternal side effects with indomethacin in contrast to their experience with ritodrine hydrochloride that was associated with a 24% incidence of serious cardiovascular and metabolic adverse effects prompting discontinuation of the drug. They reported no difference in outcome of infants who received these two medications and no newborn infant had premature closure of the ductus arteriosus or pulmonary hypertension.

Indomethacin supplementation is employed at our institution to assist in weaning difficult patients from therapeutic levels of $MgSO_4$ to maintenance doses (2 g/h). This second-line therapy should not be used in pregnancies beyond 33 weeks' gestation because of concern about constriction of the ductus arteriosus, nor should it be given in pregnancies in which the fetus has marginal oxygenation, growth retardation, documented cardiac anomalies, or myocardial dysfunction (128).

Calcium channel blockers have been reported to suppress labor with greater efficacy and fewer side effects than β-sympathomimetic drugs (129, 130). A calcium channel blocker (nifedipine) can be added to or substituted for $MgSO_4$ therapy. The principal maternal side effects include flushing and headache. Nifedipine, when used with $MgSO_4$, may precipitate significant hypotension in women with hypovolemia. The potential benefit versus risk of these agents should be weighed carefully before use in diabetic women.

Preterm labor often leads to preterm birth. The respiratory distress syndrome (RDS) occurs in 10–15% of infants who weigh less than 2500 g at birth (131). Infants who weigh less than 1500 g and those below 30 weeks' gestation are most susceptible to RDS and most likely to die from it (132). Liggins and Howie (133) were the first to report a controlled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in preterm infants. A review of this topic has been provided by Papageorgiou and Stern (134).

Should prenatal steroids be used to prevent neonatal respiratory distress and in what circumstances? In the United States, collaborative studies have been in progress since 1976 and two papers describing major outcomes have been published (135, 136). A report of all findings of the trial was issued by the National Institutes of Health (NIH) in 1985 (137). Avery and other participants in a report of an NIH conference in September 1985 have provided an update of the United States experience (138). Overall, the trial was confirmatory in showing a reduction of RDS in the treated group. It was equivocal in showing no effect in the presence of multiple pregnancy and premature rupture of membranes. The question of prenatal use of dexamethasone in twins remained open because none of the trials had sufficient numbers to permit control for confounding factors such as sex of the fetuses and infection. No statistically significant benefit was found in treated male infants of any race. No conclusion was reached concerning the advisability of giving a repeat dose of dexamethasone after 7 days if delivery had not taken place.

The collaborative study did not show a benefit for prenatal dexamethasone in gestations of <28 weeks; however, there were only 36 births of <1-kg birth weight and 24 were from a single center. Follow-up data on infants in

the study will require future trials. The review group noted, however, that current practice among obstetricians was to use corticosteroids in patients who were ≤27 weeks' gestation (135). The abbreviated conclusion of the conference was that antenatal dexamethasone to prevent respiratory distress syndrome was effective under the constraint that >24 h before delivery were required to see an effect beneficial to female infants of >30 weeks' gestation.

In the United Kingdom (U.K.), from mid-1975 to February 1978, 11 hospitals participated in a multicenter prospective, randomized, double-blind trial that compared antenatal treatment with betamethasone phosphate with a placebo for the prevention of RDS (139). This trial, which included 251 women (130 in the betamethasone and 132 in the placebo group), contributed further evidence of the effectiveness of antenatal corticosteroids in prevention of RDS. There was a significant reduction in RDS and neonatal deaths in infants born between 24 h and 6 days after entry into the trial. The largest difference in frequency occurred in the subgroup of infants born before 38 weeks' gestation, within 8 days of trial entry, whose mothers had received at least three injections. The U.K. group recommended that use of betamethasone be restricted to women in whom steroids are not contraindicated because of maternal disease, severe hypertension, or infection including amnionitis. Of course, many diabetic women with preterm labor have these complications in addition to worsening of glycemic control when these medications are prescribed. The brief period of higher maternal glucose levels can be managed easily, however, by additional insulin therapy by constant intravenous infusion for 36–48 h.

In our institution, corticosteroid therapy is rarely used in diabetic pregnancies; a gestational age of >32 weeks and borderline maturity of the amniotic fluid phospholipid profile eliminate the need for steroid treatment in most diabetic women. Most preterm infants of >32 weeks' gestation do not develop RDS.

Long-term studies are in progress to determine late effects of in utero exposure to steroids on children at a later age. Many of the infants so treated in the United States have been lost to follow-up, but no developmental deficiencies have been noted in one 3-yr follow-up study (136). MacArthur and co-workers (140) report similar findings in New Zealand children to age 6 yr and Doyle and colleagues (141) did not detect any adverse effects of antenatal steroid therapy on any relevant aspect of mortality or morbidity over the first 2 yr of life in infants in Melbourne, Australia. In a 10- to 12-yr follow-up of physical development and medical history of children treated antenatally with corticosteroids to prevent RDS, Smolders-de Haas and colleagues (142) report that no differences between corticosteroid and placebo groups were found except that, in the children exposed to corticosteroids, there were significantly more hospital admissions because of infectious diseases during the first years of life.

PREMATURE RUPTURE OF MEMBRANES (PROM)

Rupture of membranes with leakage of amniotic fluid through the cervix before fetal maturity (PROM) complicates 25–30% of preterm deliveries (143). When there is no longer integrity of the amniotic sac, labor follows typically within 24 h in 50% of women, within 3 days in 70%, and in 1 week in 90% (144). The fetus is at risk for intrauterine sepsis, asphyxia, and death from umbilical cord occlusion secondary to a decrease in amniotic fluid volume. The risks to the mother and newborn baby are infection and preterm birth.

Prevention of PROM is preferable to management after it occurs. This is achieved best by careful management of preterm labor, because PROM commonly occurs in periods of increased uterine activity. This complication can occur unexpectedly despite careful efforts at prevention and management must be altered appropriately.

After documentation of ruptured membranes, the timing of labor induction or cesarean section becomes paramount. When it is clear that continued conservative management will increase rather than decrease neonatal morbidity, delivery preparations should begin (Table 18.13). If indications for delivery are not present when PROM occurs, a period of conservative observation should follow. A phospholipid lung profile obtained from a vaginal pool of amniotic fluid permits documentation of presence or absence of phosphotidylglycerol (PG). In the absence of PG, using the percentage of phosphotidylinositol helps

Table 18.13.
Indications for Prompt Delivery in Women With Premature Rupture of Membranes

Fetal distress
Documentation of maturity by amniotic fluid phospholipid profile
Intrauterine infection or active herpes infection
Unstable fetal lie: back-up, transverse or footling breech

project the anticipated time of pulmonary maturity and the relative risk of RDS can be estimated from the lecithin/sphingomyelin (L/S) ratio. The use of the amniotic fluid phospholipid profile to determine timing of delivery is illustrated and discussed in Chapter 21.

Fetal distress is an indication for prompt delivery even if fetal lung maturity can not be documented. Early recognition of fetal compromise from oligohydramnios or sepsis is facilitated by monitoring the fetal heart rate (FHR) twice daily. Late decelerations, lack of accelerations, or significant variable deceleration should be evaluated by a fetal biophysical profile (145) (Section VII, p. 215). We assess amniotic fluid volume using the Amniotic Fluid Index (AFI), a four-quadrant assessment of amniotic fluid volume, every 1–2 days (146, 147). A plot of the AFI by gestational age is shown in Figure 18.1. AFI values of <50 mm are associated with meconium staining and fetal distress (148). Delivery should be considered when the AFI is <50 mm for several days.

Expectant management of PROM may be associated with the presence or development of amnionitis. Early detection of this complication can be difficult and requires close monitoring. A major neonatal threat is Group B Streptococcal infection (GBS) (149). This organism is associated with rapidly progressive sepsis; risk of neonatal death is at least 50% (150). All patients with PROM should have a cervical and vaginal culture for GBS as soon as this diagnosis is apparent. We begin antibiotic treatment immediately after cultures are obtained and continue until results are known. If a positive cervical GBS culture is

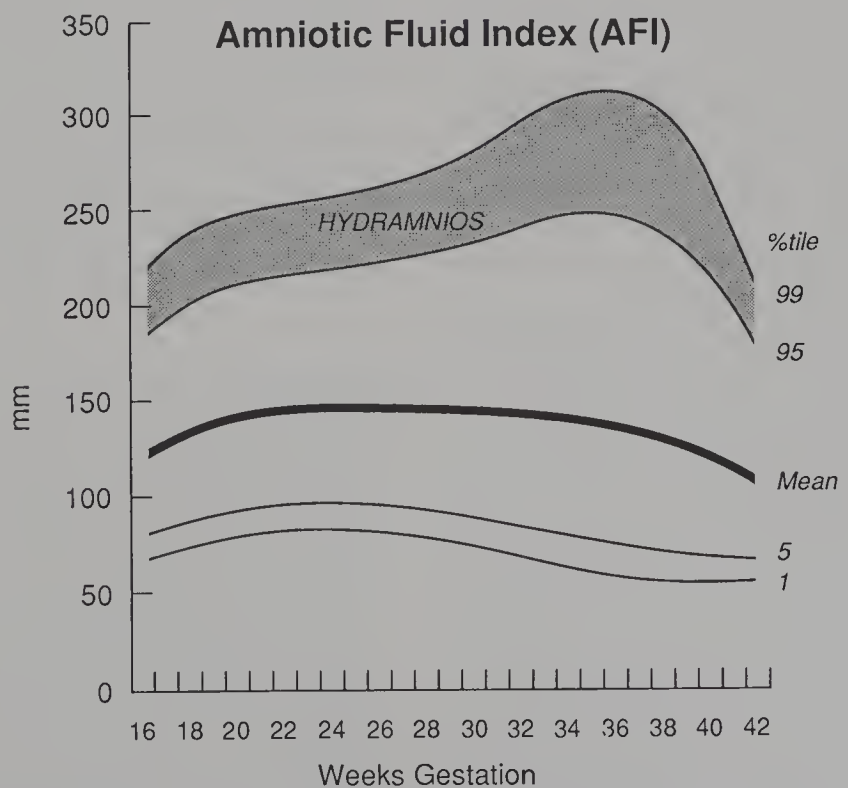


Figure 18.1. The amniotic fluid index represents the sum (mm) of four pockets from each quadrant of the uterus determined by measurements during ultrasonography. An index that exceeds the 95th percentile indicates hydramnios. The mean (50th percentile) is indicated by the *heavy black line*. Values characteristic of hydramnios are shown in the *dotted area*.

confirmed, the patient should be delivered promptly unless the fetus is very immature.

The onset of amnionitis may be asymptomatic or associated with maternal fever (≥100°F, 37.8°C), leukocytosis (>20,000), uterine tenderness, labor, fetal distress, or a combination of these signs and symptoms. Confirmatory findings include demonstration of pathogenic organisms on a gram stain of unspun amniotic fluid, foul odor, a positive amniotic fluid culture, or a biophysical profile (BPP) score of less than 6 (see p. 215 for scoring of BPP). Broad-spectrum antibiotic therapy should be initiated promptly and the patient delivered (151).

Use of glucocorticoids in the presence of PROM is controversial (135, 136). The largest and best-controlled studies in the United States (135, 152) have failed to demonstrate a beneficial effect of these agents when membranes are ruptured. Corticosteroids are usually not administered to diabetic women with PROM because they may exacerbate intrauterine infection and worsen glycemic control.

HYDRAMNIOS

Hydramnios is the accumulation of excessive amniotic fluid volume in the uterus. The clinical definition of hydramnios varies, e.g., an estimate of >2000 ml of amniotic fluid recorded at delivery (153) and various measurements of amniotic fluid pocket depths observed on ultrasound (147, 154).

In normal pregnancies, there is a wide range of amniotic fluid volumes. The three major determinants of volume are: (*a*) movement of water and solutes across the membranes; (*b*) physiologic regulation by the fetus by swallowing and urine production; and (*c*) maternal influences on transplacental fluid movement (155). The frequency of hydramnios varies from 1–2% in normal subjects to 5–18% among diabetic women with an overall incidence of about 16% (156). This complication is more frequent in diabetic women with poor glucose control. Severe prolonged maternal hyperglycemia results in fetal hyperglycemia; this may stimulate a fetal diuresis to excrete an excessive solute load. In addition, hydramnios is associated with congenital malformations of the central nervous system and gastrointestinal tract. These are more common in diabetic women who were in poor control at conception and during embryogenesis.

In practice, hydramnios is usually diagnosed when any single vertical pocket of amniotic fluid is deeper than 80 mm (equivalent to the 97th percentile) or when the sum of four pockets from each quadrant of the uterus (AFI exceeds 250 mm, 95th percentile) (146, 154). Ideally, ultrasound measurements of amniotic fluid volume should be referenced against appropriate normal values for gestational age (Fig. 18.1). Carlson and colleagues (157) designed a prospective study using an AFI ≥ 24 cm (>2 SD above the mean) to detect hydramnios in 112 nondiabetic women. Although all subjects were reported to have hydramnios on ultrasonography, only 49 met the authors' criterion for significant hydramnios (AFI ≥ 24 cm). Their definition detected all fetuses with serious structural defects or death.

The diagnosis of hydramnios is important because of its association with fetal anomalies and preterm labor (158). A rapid increase in fundal height may indicate excessive amniotic fluid and should prompt a thorough ultrasound examination by a skilled examiner. Esophageal atresia should be ruled out by careful evaluation of the fetal stomach (159). Abdominal wall defects, such as gastroschisis and omphalocele, can also lead to hydramnios and should be excluded by ultrasonographic scrutiny of the umbilical cord insertion site on the fetal abdomen. Fetal hydrops and hydramnios also occur in conjunction with fetal cardiac anomalies, which are observed more frequently in diabetic women (160).

Table 18.14.
Investigation of Hydramnios in Pregnant Diabetic Women

Measure amniotic fluid volume using the four-quadrant technique
High-definition ultrasonography to rule out:
Esophageal atresia
Omphalocele and gastroschisis
Fetal cardiac anomaly and hydrops
Anencephaly and spina bifida
Evaluate and improve maternal glycemic control
Educate the patient about signs of preterm labor
Schedule frequent office visits to detect early cervical change

Mamopoulos and colleagues (161) have treated 15 women with polyhydramnios and symptoms related to excess amniotic fluid with indomethacin therapy begun at 27.4 ± 2.79 weeks' gestation and discontinued at 32.9 ± 1.8 weeks. The patients received 2.0–2.2 mg/kg body weight of indomethacin per day either orally or in the form of rectal suppositories. No treatment was given after 35 weeks' gestation and the drug was administered no longer than 4 weeks. Most of the reduction of amniotic fluid occurred in the 1st week with a small but steady further decrease during treatment. All women were delivered at 38 weeks' gestation and their infants had a mean weight of 3543 ± 586.3 g. There were no adverse effects of indomethacin observed in newborn babies or at follow-up at 3, 6, and 12 months later.

Management of women with hydramnios is summarized in Table 18.14. Once significant fetal structural defects have been excluded, the focus should shift to prevention of preterm labor. Enhanced patient awareness of uterine contractions is the most important first step. Careful instruction about the signs and subtle sensations of contractions associated with preterm labor is essential. The patient should be seen weekly with frequent examinations of the cervix. Hospital admission should be considered in all patients with advanced dilation of the cervix.

As additional studies become available, prostaglandin inhibition may emerge as a useful therapy for treatment of hydramnios. However, the use of indomethacin to reduce amniotic fluid volume remains experimental because of the potential for adverse effects on ductus arteriosus flow and renal hemodynamics.

References for Section VI

1. Wilson DE. Excessive insulin therapy: Biochemical effects and clinical repercussions. Current Concepts of counter-regulation in Type I diabetes. Ann Intern Med 1983;98:219-227.
2. Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD. Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. Am J Med 1980; 68:105-112.
3. Jovanovic L, Braun CB, Druzin ML, Peterson CM. Protocols for Managing Diabetes in Pregnancy. A Guide for Physicians and Allied Health Care Professionals. Indianapolis, IN:Bio-Dynamics, A Boehringer Mannheim Corp, 1982.
4. Chez RA, Curcio FD III. Ketonuria in normal pregnancy. Obstet Gynecol 1987;69:272-274.
5. Churchill JA, Berendes HW, Nemore J. Neuropsychological deficits in children of diabetic mothers. Am J Obstet Gynecol 1969;105:257-268.
6. Churchill JA, Berendes HW. Intelligence of children whose mothers had acetonuria during pregnancy. In: Perinatal factors affecting human development. Washington, DC: Pan American Health Organization, Scientific Publication No. 185, 1969.
7. Stehbens JA, Baker GL, Kitchell M. Outcome at ages 1, 3 and 5 years of children born to diabetic women. 1977;127:408-413.
8. Naeye RL, Chez RA. Effects of maternal acetonuria and low pregnancy weight gain on children's psychomotor development. Am J Obstet Gynecol 1981;139:189-193.
9. The Collaborative Study on Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood Manual. Bethesda, MD: United States Department of Health, Education, and Welfare, 1966.
10. Coetzee EJ, Jackson WPU, Berman PA. Ketonuria in pregnancy—with special reference to calorie-restricted food intake in obese diabetics. Diabetes 1980;29:177-181.
11. Algert S, Shragg P, Hollingsworth DR. Moderate caloric restriction in obese women with gestational diabetes. Obstet Gynecol 1985;65: 487-491.
12. Freinkel N. Review. Diabetic embryopathy and fuel mediated organ teratogenesis: Lessons from animal models. Horm Metabol Res 1988;20:463-475.
13. Barrett EJ, DeFronzo RA. Diabetic ketoacidosis: Diagnosis and treatment. Hosp Pract 1984; April:90-104.
14. Carroll P, Matz R. Uncontrolled diabetes mellitus in adults: Experience in treating diabetic ketoacidosis and hyperosmolar nonketotic coma with low-dose insulin and a uniform treatment regimen. Diabetes Care 1983;6:579-585.
15. Foster DW. Banting Lecture: From glycogen to ketones—and back. Diabetes 1984;33:1188-1199.
16. Androgué HJ, Wilson H, Boyd AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982; 307:1603-1610.
17. Walker M, Marshall SM, Alberti KGMM. Clinical aspects of diabetic ketoacidosis. Diabet Metab Rev 1989;5:651-663.
18. Capps N, Jessamine J, Slater S. Diabetic ketoacidosis: A complex mixed acid-base disorder. Scott Med 1986;31:182-183.
19. Zonszein J, Baylor P. Diabetic ketoacidosis with alkalosis—A review. West J Med 1988; 149:217-219.
20. Kitabachi AE. Low-dose insulin therapy in diabetic ketoacidosis: Fact or fiction? Diabet Metab Rev 1989;5:337-364.
21. Turnbridge WMG. Deaths due to diabetic ketoacidosis. Quart J Med 1981;50:502-504.
22. Fowler AA, Hamman RF, Good JT, Benson KN, Baird M, Eberle DJ, Petty TL, Hyers TM. Adult respiratory distress syndrome: Risk with common predispositions. Ann Intern Med 1983; 98:593-597.
23. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988;113:10-14.
24. Paton RC. Hemostatic changes in diabetic coma. Diabetologia 1981;21:172-177.
25. Matz R. Hyperosmolar non-acidotic diabetic coma. Pract Diabetol 1984;May/June:10-12.
26. Campbell IW, Munro JF, Duncan LJP. Hyperglycemic hyperosmolar nonketotic metabolic decompensation in diabetes. Scott Med J 1974;19:177-182.
27. Unger RH, Foster DF. Diabetes mellitus. In: Wilson JD, Foster DW (eds). Williams' Textbook of Endocrinology, 7th ed. Philadelphia: WB Saunders, 1985:1018-1080.
28. Levine SN, Sanson TH. Treatment of hyperglycaemic hyperosmolar nonketotic syndrome. Drugs 1989;38:462-472.
29. Jervel J, Moe N, Skjaeraasen J, Blystad W,

Egge K. Diabetes mellitus and pregnancy: Management and results at Rikshospitalet, Oslo 1970-1977. Diabetologia 1979;16:151-155.
30. Lorenzi M, Goldbaum MH, Spencer CM, Cheney C. Improved diabetic control and retinopathy. N Engl J Med 1983;308:1600.
31. The KROC Collaborative Study Group: Blood glucose control and the evolution of diabetic retinopathy and albuminuria. N Engl J Med 1984;311:365-372.
32. Van Ballegooie E, Hooymans JMM, Timmerman Z, Reitsma WD, Sluiter WJ. Schweitzer NM, Doorenbos H. Rapid deterioration of diabetic retinopathy during treatment with continuous subcutaneous insulin infusion. Diabetes Care 1984;7:236-242.
33. Brinchmann-Hansen O, Dahl-Jørgensen K, Hanssen KF, Sandvik L. Effects of intensified insulin treatment on various lesions of diabetic retinopathy. Am J Ophthalmol 1985; 100: 644-653.
34. Lauritzen T, Frost-Larsen K, Larsen H-W, Deckert T, Steno Study Group. Effect of one year near normal blood glucose levels on retinopathy in insulin-dependent diabetics. Lancet 1983;1:200-204.
35. Helve E, Laatikainen L, Merenmies L, Koivisto VA. Continuous insulin infusion therapy and retinopathy in patients with type I diabetes. Acta Endocr (Copenh) 1987;115:313-319.
36. Dandona P, Bolger JP, Boag F, Fonesca V, Abrams JD. Rapid development and progression of proliferative retinopathy after strict diabetic control. Br Med J 1985;290:895-896.
37. Soubrane G, Canivet J, Coscas G. Influence of pregnancy on the evolution of background retinopathy: preliminary results of a prospective fluorescein angiography study. In: Ryan SJ, Dawson AK, Little HL (eds). Retinal diseases. New York: Grune and Stratton, 1985:15-20.
38. Phelps RL, Sakol P, Metzger BE, Jampol LM, Freinkel N. Changes in diabetic retinopathy during pregnancy. Correlation with regulation of hyperglycemia. Arch Ophthalmol 1986;104: 1806-1810.
39. The KROC Collaborative Study Group. Diabetic retinopathy after two years of intensified insulin treatment. Followup of the KROC Collaborative Study. JAMA 1988;260:37-41.
40. Jovanovic-Peterson L. Sansum Medical Research Foundation, Santa Barbara, CA. Personal Communication, 1990.
41. Elman KD, Welch RA, Frank RN, Goyert GL, Sokol RJ. Diabetic retinopathy in pregnancy: A review. Obstet Gynecol 1990;75:119-127.
42. Sinclair SH, Nesler C, Foxman B, Nichols CW, Gabbe S. Macular edema and pregnancy in insulin-dependent diabetes. Am J Ophthalmol 1984;97:154-167.
43. Schmitz A, Hansen HH, Christensen T. Kidney function in newly diagnosed Type 2 (non-insulin-dependent) diabetic patients, before and during treatment. Diabetologia 1989;32:434-439.
44. Mogensen CE, Schmitz A, Christensen CK. Comparative renal pathology relevant to IDDM and NIDDM patients. Diabet Metab Rev 1988;5:453-483.
45. Fajans SJ. Maturity-onset diabetes of the young (MODY). Diabet Metab Rev 1989; 5(7):579-606.
46. White P. Pregnancy and diabetes. In: Marble A, White P, Bradley RF, Krall LP (eds). Joslin's Diabetes Mellitus, 11th ed. Philadelphia: Lea & Febiger, 1971, 581-599.
47. Driscoll S. The pathology of pregnancy complicated by diabetes. Med Clin North Am 1965;49:1053-1067.
48. Knowles HC, Guest GM, Lampe J, Kessler M, Skillman TG. The course of diabetes treated with an unmeasured diet. Diabetes 1965;14: 239-273.
49. Sims EAH. The kidney in pregnancy. In: Strauss MB, Welt LG (eds). Diseases of the kidney, 2nd ed. Boston: Little, Brown, 1971:1155-1205.
50. Early LE, Gottschalk CW. Circulatory, metabolic and toxic effects on the kidney. In: Early LE, Gottschalk CW (eds). Strauss and Welt's Diseases of the Kidney, 3rd ed. Boston: Little, Brown, 1979:1330-1331.
51. Lindheimer MD, Katz AI. Kidney disease. In: Lindheimer MD, Katz AI (eds). Kidney function and disease in pregnancy. Philadelphia: Lea & Febiger 1977:166-167.
52. Hare JW, White P. Pregnancy in diabetes complicated by vascular disease. Diabetes 1977;26: 953-955.
53. Kitzmiller JL, Brown ER, Phillippe M, Stark AR, Acker D, Kaldany A, Singh S, Hare JW. Diabetic nephropathy and perinatal outcome. Am J Obstet Gynecol 1981;141:741-751.
54. Reece EA, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, Hobbins JC. Diabetic nephropathy: Pregnancy performance and fetomaternal outcome. Am J Obstet Gynecol 1988;159:56-66.
55. McCance DR, Traub AI, Harley JMG, Hadden DR, Kennedy L. Urinary albumin excretion in diabetic pregnancy. Diabetologia 1989;32:236-239.
56. Biesenbach G, Zazgornik J. Incidence of transient nephrotic syndrome during pregnancy in diabetic women with and without pre-existing microalbuminuria. Br Med J 1989;299:366-367.
57. Airaksinen KEJ, Ikaheimo MJ, Salmela PI, Kirkinen P, Linnalvoto MK, Takkunen JT. Impaired cardiac adjustment to pregnancy in Type I diabetes. Diabetes Care 1986;9:376-383.
58. Nylund L, Lunell N-O, Lewander R, Persson B, Sarby B, Thornstrom S. Ureteroplacental blood flow in diabetic pregnancy: measurements with indium 113m and a computer-linked gamma camera. Am J Obstet Gynecol 1982;144:298-302.
59. Hilsted J, Galbo H, Christensen NJ, Parving HH, Benn J. Hemodynamic changes during graded exercise in patients with diabetic autonomic neuropathy. Diabetologia 1982;22:318-323.
60. Reece EA, Egan JF, Coustan DR, Tamborlane

W, Bates SE, O'Neill TM, Fitzpatrick JG. Coronary artery disease in diabetic pregnancies. Am J Obstet Gynecol 1986;154:150-151.
61. Deleted in proof.
62. Ewing DJ, Clarke BF. Review article. Diabetic autonomic neuropathy: present insights and future prospects. Diabetes Care 1986;9:648-665.
63. Sawers JS, Todd WA, Kellett HA, Miles RS, Allan PL, Ewing DJ, Clarke BF. Bacteriuria and autonomic nerve function in diabetic women. Diabetes Care 1986;9:460-464.
64. Vinik A, Mitchell B. Clinical aspects of diabetic neuropathies. Diabet Metab Rev 1988;4:223-253.
65. Greene DA, Sima AAF, Pfeifer MA, Albers JW. Diabetic neuropathy. Annu Rev Med 1990;41: 303-317.
66. Committee on Health Care Issues, American Neurological Association. Does improved control of glycemia prevent or anelioriate diabetic neuropathy? Ann Neurol 1986;19:288-290.
67. Winegrad AI. Banting Lecture 1986. Does a common mechanism induce the diverse complications of diabetes? Diabetes 1986;36:396-406.
68. Sima AAF, Nathaniel V, Brill V, McEwen TAJ, Greene DA. Histopathological heterogeneity of neuropathy in insulin-dependent and non-insuln-dependent diabetes, and demonstration of axoglial dysfunction in human diabetic neuropathy. J Clin Invest 1988;81:349-364.
69. National High Blood Pressure Education Program (NHBPEP) working group report on high blood pressure in pregnancy. March 1990. Am J Obstet Gynecol 1990; 163:1691–1712.
70. Hughes EC (ed). Obstetric-Gynecologic Terminology. Philadelphia: FA Davis, 1972:422-423.
71. American College of Obstetricians and Gynecologists: Management of preeclampsia. ACOG Technical Bulletin, February 1986; No. 91.
72. World Health Organization Study Group: The Hypertensive Disorders of Pregnancy. WHO Technical Report Series No. 758. Geneva, World Health Organization, 1987.
73. Maikranz P, Lindheimer DM. Hypertension in pregnancy. Med Clin North Am 1987;71:1031-1043.
74. Guzick DS, Klein JR, Tyson JE, Lasky RE, Gant NF, Rosenfeld CR. Risk factors for the occurrence of pregnancy-induced hypertension. In Zuspan FP, Symonds EM (eds). Clinical and Experimental Hypertension. Part B. Hypertension in Pregnancy. New York: Marcel Dekker, 1987;B6(2):281-297.
75. Lufkin EG, Nelson RL, Hill LM, Melton JL, O'Fallon WM, Evans AT. An analysis of diabetic pregnancies at Mayo Clinic, 1950-1979. Diabetes Care 1984;7:539-547.
76. Gabbe SG, Mestman JH, Freeman RK, et al. Managment of the outcome of pregnancy in diabetes mellitus, Classes B to R. Am J Obstet Gynecol 1977;129:723-732.
77. Kitzmiller JL, Cloherty JP, Younger MD, et al. Diabetic pregnancy and perinatal morbidity. Am J Obstet Gynecol 1978;131:560-580.
78. Chesley LC. Hypertension in pregnancy: Definitions, familial factor and remote prognosis. Kidney Int 1980;18:234-240.
79. Lindheimer MD, Katz AI. Current concepts. Hypertension in pregnancy. N Engl J Med 1985;313:675-680.
80. Chesley LC. Hypertensive Disorders in Pregnancy. New York, Appleton-Century-Crofts, 1978.
81. Fletcher AE, Bulpitt CJ. A review of clinical trials in pregnancy. In: Rubin PC (ed). Hypertension in Pregnancy. New York: Elsevier, 1988:186-201.
82. Barron WM, Murphy MD, Lindheimer MD. Management of hypertension during pregnancy. In: Laragh JH, Brenner BM (eds). Hypertension. Diagnosis and Management. New York:Raven Press, 1990:1809-1827.
83. Olofsson P, Montan S, Sartor G, Sjoberg NO. Effects of beta 1-adrenoceptor blockade in the treatment of hypertension during pregnancy in diabetic women. Acta Med Scand 1986;220: 321-328.
84. Kraus GW, Marchese JR, Yen SSC. Prophylactic use of hydrochlorthiazide in pregnancy. JAMA 1966;198:1150-1154.
85. Collins R, Yusuf S, Peto R. Overview of randomized trials of diuretics in pregnancy. Br Med J 1985;290:17-23.
86. The 1988 Joint National Committee. The 1988 report of the Joint Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch Int Med 1988;148:1023-1038.
87. Editorial. Are ACE inhibitors safe in pregnancy? Lancet 1989;2:482-483.
88. Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyldopa or labetol in chronic hypertension during pregnancy. Am J Obstet Gynecol 1990;162:960-967.
89. Chesley LC, Cooper DW. Genetics of hypertension in pregnancy: Possible single gene control of preeclampsia and eclampsia in the descendents of eclamptic women. Br J Obstet Gynecol 1986;93:898-908.
90. Hinselmann H. Allegmeine krankheitslehre. In Hinselmann H (ed). Die Eklampsie. Bonn: Cohen, 1924:1-87.
91. Manas KJ, Welsh JD, Rankin RA, Miller DD. Hepatic hemorrhage without rupture in preeclampsia. N Engl J Med 1985;312:424-426.
92. Sibai BH, Taslimi MM, El Nazer A, Amon E, Mabie BC, Ryan GM. Maternal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol 1986;155:501-509.
93. Kilpatrick DC, Gibson F, Liston WA, Livingstone J. Association between susceptibility to preeclampsia within families and HLA DR4. Lancet 1989;2:1063-1065.
94. Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma uric acid measurements in predicting fetal death in hypertensive pregnancy. Lancet 1976;1:1370-1373.
95. Weinstein L. Syndrome of hemolysis, elevated

liver enzymes and low platelets: A severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982;142:159-167.
96. Goodlin RC. Hemolysis, elevated liver enzymes and low platelets syndrome. Obstet Gynecol 1984;64:449-450.
97. Sibai BM, Taslimi M, Abdella TN, Brooks TF, Spinnato JA, Anderson GD. Maternal and perinatal outcome of conservative management of severe pre-eclampsia in midtrimester. Am J Obstet Gynecol 1985;152:32-37.
98. Fitzgerald DJ, Rocki W, Murray R, Mayo G, Fitzgerald CA. Thromboxane A_2 synthesis in pregnancy-induced hypertension. Lancet 1990;335:1:751-754.
99. Walsh SW. Low-dose aspirin: Treatment for the imbalance of increased thromboxane and decreased prostacyclin in preeclampsia. Am J Perinatol 1989;6:124-132.
100. Beaufils M, Uzan S, Donsimori R, Colau JC. Prevention of preeclampsia by early antiplatelet therapy. Lancet 1985;1:840-842.
101. Wallenburg HC, Dekker GA, Makovitz JW, Rotmans P. Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primagravidae. Lancet 1986;1:1-3.
102. Elder MG, de Swiet M, Robertson A, Elder MA, Floyd E, Hawkins DF. Low-dose aspirin in pregnancy. Lancet 1988;1:410.
103. Trudinger B, Cook C-M, Thompson R, Giles W, Connelly A. Low-dose aspirin improves fetal weight in umbilical placental insufficiency. Lancet 1988;2:214-215.
104. Schiff E, Peleg E, Goldenberg M, et al. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A_2 to prostacyclin in relatively high risk pregnancies. N Engl J Med 1989;321:351-356.
105. Benigni A, Gregorini G, Frusca T, et al. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. N Engl J Med 1989;321:357-362.
106. Lauersen N, Merkatz I, Tejani N, et al. Inhibition of premature labor: A multicenter comparison of ritodrine and ethanol. Am J Obstet Gynecol 1977;127:837-845.
107. Drife J. Infection and preterm birth. Br Med J 1989;96:1128-1132.
108. Skoll A, Moretti ML, Sibai BM. The incidence of positive amniotic fluid cultures in patients with preterm labor with intact membranes. Am J Obstet Gynecol 1989;161:813-816.
109. Romero R, Sitori M, Oyarzun E, et al. V. Prevalence, microbiology and clinical significance of intraamniotic infection in women with preterm labor and intact membranes. Am J Obstet Gynecol 1989;161:817-824.
110. Toth M, Witkin SS, Ledger W, Thaler H. The role of infection in the etiology of preterm birth. Obstet Gynecol 1988;171:723-726.
111. Mimouni F, Miodovnik M, Siddiqui TA, Berk MA, Wittekind C, Tsang RC. High spontaneous premature labor rate in insulin-dependent diabetic pregnant women: An association with poor glycemic control and urogenital infection. Obstet Gynecol 1988;72:175-180.
112. Greene MF, Hare JW, Krache M, et al. Prematurity among insulin-requiring diabetic women. Am J Obstet Gynecol 1989;161:106-111.
113. Katz M, Newman RB, Gill PJ. Assessment of uterine activity in ambulatory patients at high risk of preterm labor and delivery. Am J Obstet Gynecol 1986;154:44-48.
114. Main DM, Main EK. Managment of preterm labor and delivery. In: Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill-Livingstone, 1986:689-737.
115. King JF, Grant A, Keirse MJNC, Chalmers I. Beta-mimetics in preterm labour: An overview of the randomized controlled trials. Br J Obstet Gynaecol 1988;95:211-222.
116. Katz VL, Seeds JW. Fetal and neonatal cardiovascular complications from β-sympathomimetic therapy for tocolysis. Am J Obstet Gynecol 1989;161:1-4.
117. Miodovnik M, Peros N, Holroyde JC, Siddiqi TA. Treatment of premature labor in insulin-dependent diabetic women. Obstet Gynecol 1985;65:621-627.
118. Jovanovic-Peterson L. Personal communication of unpublished results, 1990.
119. Elliot JP. Magnesium sulfate as a tocolytic agent. Am J Obstet Gynecol 1984;147:277-284.
120. Beall MH, Edgar BW, Paul RH. A comparison of ritodrine, terbutaline and magnesium sulfate for the suppression of preterm labor. Am J Obstet Gynecol 1985;153:854-859.
121. Lam F, Gill P, Smith M, Kitzmiller JL, Katz M. Instruments and methods. Use of the subcutaneous terbutaline pump for long-term tocolysis. Obstet Gynecol 1988;72:810-813.
122. Tibaldi JM, Lorber DL, Nerenberg A. Diabetic ketoacidosis and insulin resistance with subcutaneous terbutaline infusion: A case report. Am J Obstet Gynecol 1990;163:509-510.
123. Petrie RH. Tocolysis using magnesium sulfate. Semin Perinatol 1981;5:266-273.
124. Elliot JP, O'Keefe DF, Greenberg P, Freeman RK. Pulmonary edema associated with magnesium sulfate and betamethasone administration. Am J Obstet Gynecol 1979;134:717-720.
125. Niebyl JR, Blake DA, White RD, et al. The inhibition of premature labor with indomethacin. Am J Obstet Gynecol 1980;136:1014-1019.
126. Niebyl JR, Witter FR. Neonatal outcome after indomethacin treatment for preterm labor. Am J Obstet Gynecol 1986;155:747-749.
127. Morales WJ, Smith SG, Angel JL, O'Brien WF, Knuppel RA. Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: A randomized study. Obstet Gynecol 1989;74:567-572.
128. Mari G, Moise KJ Jr, Deter RL, Kirshon B, Carpenter RJ. Doppler assessment of the renal blood flow velocity waveform during indometh-

acin therapy for preterm labor and polyhydramnios. Obstet Gynecol 1990;75:199-201.
129. Read MD, Welby DR. The use of a calcium antagonist (nifedipine) to suppress preterm labor. Br J Obstet Gynecol 1986;93:933-937.
130. Ferguson JE, Dyson DC, Schutz T, Stevenson DK. A comparison of tocolysis using nifedipine or ritodrine: Analysis of efficacy and maternal, fetal and neonatal outcome. Am J Obstet Gynecol 1990:163:105-111.
131. Avery ME. Corticosteroids: The case for their use. In: Elder MG, Hendricks CH (eds). Preterm Labour. London: Butterworth, 1981:176-186.
132. Roberton NRC. Advances in respiratory distress syndrome. Br Med J 1982;284:917-918.
133. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for the prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515-525.
134. Papageorgiou AN, Desgranges MF, Masson M, Colle E, Shatz R, Gelfrand MM. The antenatal use of betamethasone in the prevention of respiratory distress syndrome: Benefits and potential risks for the mother and the infant. J Perinat Med 1986;14:75-86.
135. Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. Am J Obstet Gynecol 1981; 141:276-287.
136. Collaborative Group on Antenatal Steroid Therapy. Effects of antenatal dexamethasone administration in the infant: Long-term follow up. J Pediatr 1984;104:259-267.
137. Prevention of respiratory distress syndrome: Effect of antenatal dexamethasone administration. Washington DC: National Institutes of Health, Publication no. 85-2695, August 1985.
138. Avery ME, Aylward G, Creasy R, Little AB, Stripp B. Update on prenatal steroid for prevention of respiratory distress. Report of a conference—September 26-28, 1985. Am J Obstet Gynecol 1986;155:2-5.
139. Gamsu HR, Mullinger BM, Donnai P, Dash CH. Antenatal administration of betamethasone to prevent respiratory distress syndrome in preterm infants: Report of a UK multicentre trial. Br J Obstet Gynaecol 1989;96:401-410.
140. MacArthur G, Howie R, Dezoete J, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. Pediatrics 1982;70:99-105.
141. Doyle LW, Kitchen WH, Ford GW, et al. Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. J Pediatr 1986;108:287-292.
142. Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: A 10-12 year follow-up. Pediatrics 1990;86:65-70.
143. American College of Obstetricians and Gynecologists. Premature rupture of membranes. Technical Bulletin #115, April 1988.
144. Johnson JW, Daikoku NH, Niebyl JR, Johnson TRB, Khouzami VA, Witter FR. Premature rupture of the membranes and prolonged latency. Obstet Gynecol 1981;57:547-556.
145. Golde SH, Montoro M, Good-Anderson B, et al. The role of nonstress tests, fetal biophysical profile, and contraction stress tests in the outpatient management of insulin requiring diabetic pregnancies. Am J Obstet Gynecol 1984; 148:269-273.
146. Moore TR, Cayle JE. The amniotic fluid index in normal human pregnancy. Am J Obstet Gynecol 1990;162:1168-1173.
147. Moore TR. Superiority of the four-quadrant sum over the single-deepest pocket technique in ultrasonographic identification of abnormal amniotic fluid volumes. Am J Obstet Gynecol 1990; 163:762:767.
148. Rutherford SE, Phelan JP, Smith CV, Jacobs N. The four quadrant assessment of amniotic fluid volume: An adjunct to antepartum fetal heart rate testing. Obstet Gynecol 1987;70:353-356.
149. Boyer KM, Gottoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986;314:1669-1673.
150. Dillon HC, Khare S, Gray BM. Group B streptococcal carriage and disease: A 6 year prospective study. J Pediatr 1987;110:31-36.
151. Gibbs RS, Blanco JD. Premature rupture of the membranes. Obstet Gynecol 1982;60:671-679.
152. Garite TJ, Freeman RK, Linzey EM, Braly PS, Dorchester WL. Prospective randomized study of corticosteroids in the management of premature rupture of the membranes and the premature gestation. Am J Obstet Gynecol 1981; 141:508-515.
153. Queenan JT, Thompson W, Whitfield CR, Shah SI. Amniotic fluid volume in normal pregnancies. Am J Obstet Gynecol 1972;114:34-38.
154. Chamberlain PF, Manning FA, Morrison I, Harman CR, Lange IR. Ultrasound evaluation of amniotic fluid volume. II. The relationship of increased amniotic fluid volume to perinatal outcome. Am J Obstet Gynecol 1984;150:250-254.
155. Brace RA. Amniotic fluid dynamics. In: Creasy RK, Resnik R (eds). Maternal-Fetal Medicine: Principles and Practice. Philadelphia: WB Saunders, 1989:128-135.
156. Cousins L. Obstetric complications. In: Reece EA, Coustan DR (eds). Diabetes Mellitus in Pregnancy. New York: Churchill-Livingstone, 1988:461.
157. Carlson DE, Platt LD, Medearis AL, Hobenstein J. Quantifiable polyhydramnios: Diagnosis and management. Obstet Gynecol 1990; 75:989-993.
158. Leucht W, Rabe D, Hendrik HJ, Grischke EM, Schmidt W. Sonographic evaluation of the amount of amniotic fluid. I. polyhydramnios—

significance for the course of pregnancy and labor. Geburtshilfe-Frauenheilkd 1986;46:157-161.
159. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. Obstet Gynecol Surv 1986;41:325-335.
160. Rowland TW, Hubbell JP, Nadas AS. Congenital heart disease in infants of diabetic mothers. J Pediatr 1973;83:815-820.
161. Mamopoulos M, Assimakopoulos E, Reece EA, Andereou A, Zheng X-Z, Mantalenakis S. Maternal indomethacin therapy in the treatment of polyhydramnios. Am J Obstet Gynecol 1990; 162:1225-1229.

SECTION

VII

Fetal Obstetric Complications and Fetal Surveillance

Thomas R. Moore

Pregnancy complicated by diabetes represents a perturbation of normal metabolic adjustments that occur during gestation, as described in Section II. In addition, if complications, such as hypertension or preeclampsia, ensue in normal or diabetic pregnancies, uterine blood flow may be compromised with reduction of fetal growth. Placental infarction with inadequate transfer of nutrients may also limit fetal growth or result in fetal death.

During pregnancy, the fetus engages in three major activities: (*a*) Maintenance of metabolic homeostasis through the steady-state consumption of oxygen and energy substrates (glucose, lipids, and amino acids); (*b*) growth through accretion of bone, soft tissue, and fat; under normal conditions, the rate of transfer of nutrients to the fetus is of such a high order that it triples in size during the last 12 weeks of pregnancy; and (*c*) motor and neurobehavioral development. The fetus develops adaptive responses, reflexes, and behaviors that will assist in the transition to extrauterine life.

The goals of fetal management during a diabetic pregnancy are to minimize the degree of abnormality of the fetal environment by normalization of maternal physiology and to monitor the fetus and its milieu to detect problems early and intervene before substantial morbidity or fetal loss occur.

In some diabetic pregnancies, there is an altered pattern of oxygen delivery to the fetus during uterine contractions with labor. This may impede oxygen transfer in the intervillous space and the fetus can experience relative hypoxia following each uterine contraction. The poorly compensated fetus with a cardiac anomaly, for example, may be unable to withstand these physiologic alterations successfully.

Difficulties of another sort may occur during fetal passage through the birth canal. A macrosomic fetus of a poorly controlled hyperglycemic mother characteristically has truncal obesity with a large thorax and shoulders. This abnormal central deposition of fat can pose a problem if, following delivery of the head, the size of the fetal shoulders and abdomen exceeds the dimensions of the mother's pelvis. These difficult deliveries can result in permanent neurologic injury.

CHAPTER

19

Fetal Complications

SPONTANEOUS ABORTION

Spontaneous abortion or miscarriage is defined as death of the embryo or fetus before 20 weeks' gestation. Approximately half of all conceptions are unrecognized; among those that are apparent, 10–15% are lost during 1st trimester and an additional 2% later in pregnancy (1). Approximately half of spontaneous abortions occur in association with fetal chromosomal or structural anomalies, with the cause of the remainder unknown. The contributions of maternal vascular disease, immunologic factors, and an abnormal metabolic milieu to fetal loss are not well understood. Fetal structural anomalies and placental or uterine microvascular and macrovascular disease also contribute to an excessive fetal loss rate.

There is evidence from a number of centers documenting a significant increase in spontaneous abortions among diabetic women in poor control (2–5). Preconception counseling has had a positive effect and resulted in fewer early fetal losses (4). In IDDM of more than 15 years' duration, vascular disease and hypertension may alter vascular supply to and within the uterus, resulting in blighting of the embryo.

Mills and colleagues have reported the early results of a prospective multicenter Diabetes in Early Pregnancy Study (DIEP) (5). In this research project that stressed early detection (before 10 days' gestation) and management of diabetic pregnancies, they followed 386 IDDM and 432 control subjects from five institutions. Early pregnancy losses among diabetic (16.1%) and control women (16.2%) were not different. After adjustment for known risk factors, the rate was still not significantly different in diabetic women in good control. Among those who had poorer control, however, there was an increase in risk of spontaneous abortion of 3.1% for each standard deviation above the normal range of 1st trimester glycosylated hemoglobin concentration. These observations can be used persuasively in preconception counseling. On the other hand, patients in early pregnancy who have elevated glycohemoglobin values should be reassured that the increased risk of miscarriage is modest.

Women who have an elevated glycohemoglobin concentration should have early pregnancy surveillance by ultrasonography. We document the presence of the fetal heart at a 1st trimester visit in all women with elevated glycohemoglobin values and follow closely the subsequent growth of the embryo. Control of hyperglycemia during early gestation and the potential risks of severe hypoglycemia during this period are discussed in Sections I and IV.

FETAL DEATH AND PERINATAL ASPHYXIA

Neonatal outcome for infants of diabetic mothers (IDM) has improved markedly since the introduction of insulin in 1922 and intensive perinatal and newborn care in the 1970s. This has resulted in an impressive decline in perinatal mortality (Section I; Fig. 1.1). The currently reported perinatal and infant mortality rates among diabetic women cared for in perinatal centers approach those of nondiabetic women. Nevertheless, fetal demise and intrapartum asphyxia after 20 weeks' gestation continue to occur.

An association of fetal death with poor maternal glycemic control has been recognized for decades; only recently has the probable pathophysiology been elucidated. Fetal hyperglycemia in poorly controlled diabetic women can lead to progressive fetal hypoxemia, acidosis and, eventually, death. Pathologic changes in the fetal heart rate (decreased variability, late decelerations) have been recorded by several

groups of investigators during periods of poor maternal glycemic control and ketonemia (6–12). Thus, poor diabetic control remains a risk factor for fetal and neonatal loss despite the technological advances of perinatology and neonatology.

Edelberg and co-workers studied the effect of maternal hyperglycemia on fetal biophysical status following maternal glucose infusion using the glucose clamp technique (13). Fetal activity was monitored by ultrasound. They reported a significant decrease in fetal movements when maternal glucose levels were raised to 120 mg/dl (6.6 mmol/L). Patrick and colleagues have confirmed the close association between decreased human fetal movements and fetal acidemia in the last 10 weeks of pregnancy (14). Other investigators, utilizing doppler wave-form analysis of fetal umbilical blood flow, have shown an increase in placental vascular resistance when maternal glucose levels were elevated (15). These findings support the hypothesis that oxygen delivery to the fetus is adversely affected by poor maternal glucose control and ketoacidosis.

The implications of the above experimental observations for management of diabetic pregnancies are: (*a*) excellent control of maternal metabolic status throughout pregnancy may minimize the risk of fetal hypoxia, (*b*) women with poor control of hyperglycemia in later pregnancy should be viewed with concern and undergo more intensive fetal surveillance.

PRETERM BIRTH

Early delivery of infants of diabetic mothers (IDM) with a gestational age of <37 weeks remains a problem in diabetic pregnancies with respect to preterm labor and PROM (Section VI). Maternal complications, such as preeclampsia, a sharp decline in renal function, or placental insufficiency may require early timing of delivery. Iatrogenic preterm births are uncommon now that ultrasound examinations make possible more accurate dating of pregnancies and fetal biophysical profiles give a better assessment of fetal well-being. Amniocentesis for the evaluation of fetal pulmonary maturation has also been helpful in women in poor diabetic control and those with poor dating criteria for gestational age.

CHAPTER

20

Fetal Surveillance

Concern for a prospective fetus begins before conception (Section I) and continues throughout pregnancy. Once pregnancy has occurred, there is an array of techniques to detect a fetus in jeopardy. A recommended sequence for fetal evaluation during diabetic pregnancy in IDDM and NIDDM women is outlined in Table 20.1.

DETECTION OF CONGENITAL MALFORMATIONS

The role of preconception counseling and metabolic control of hyperglycemia for prevention of congenital malformations has been discussed comprehensively in Section I. Once pregnancy is established, early detection of fetal malformations is of paramount importance. The goal of early fetal surveillance is to provide anxious diabetic mothers and their partners with reassuring information about the structural integrity of the baby. When major malformations are detected, alternatives for decision-making need to be presented carefully and in detail to both parents.

Women with NIDDM are at special risk for fetal malformations because they are frequently asymptomatic and often have unrecognized diabetes. They usually enter prenatal care long after embryogenesis is complete. Among many low income older women with NIDDM, access to modern diabetic care is unavailable or limited. In the United States, this group represents a large pool of one million women of childbearing age at high risk for major and minor fetal malformations.

Women with "truly gestational diabetes," e.g., evoked by pregnancy, are not at risk for diabetic embryopathy but, of course, are not exempt from the myriad of other causes of birth defects (chromosomal, drug related, infections, and others). Thus, a fetal anatomic survey by ultrasonography should be performed in all diabetic women during examinations for fetal growth as pregnancy progresses.

Accurate documentation of date of conception, or the 1st day of the last normal menstrual period is possible in many but not all women. A sonographic survey of the embryo at 9–10 weeks' gestation provides highly accurate gestational dating (± 3 days). Fog-Pedersen and colleagues have reported a delay in early fetal growth in women with poor diabetic control (16). In some pregnancies in their Copenhagen clinic, this has been a risk marker for congenital malformations. Of interest, in their studies early fetal growth delay has been followed by poorer postnatal psychomotor development.

At 16 ± 2 weeks', a maternal serum α-fetoprotein (MSAFP) screening test should be performed to rule out the possibility of a neural tube defect. This test is recommended to all pregnant women but is especially important in IDDM and NIDDM women because the frequency of neural tube malformations is increased more than ten times that in those with poor diabetic control (17). A normal MSAFP value indicates a lower risk of undetected spina bifida by a factor of 100. The result of the screening test should be available when high resolution sonography is performed at 20–22 weeks' gestation. An abnormal MSAFP screening test is an indication to measure α-fetoprotein concentration in the amniotic fluid.

At the high-resolution ultrasonographic examination at 20–22 weeks', targeted imaging of fetal anatomy including the cranium and its contents, spinal axis, heart, abdominal contents, kidneys, bladder, genitalia, umbilical cord insertion, and limb morphology should be conducted. This study should be performed by an experienced sonographer with equipment

Table 20.1.
Fetal and Neonatal Assessment of Pregnant Diabetic Women and Their Infants

Time (week of gestation)	Tests and Procedures
8–12	**Fetus** Ultrasonography for dating of pregnancy and measurement of early growth; serial growth observations if fetus appears under- or overgrown during subsequent examination of the mother
15–16	Maternal serum α-fetoprotein level (MSAFP)
20–22	**IDDM, NIDDM** High-resolution real-time ultrasonographic examination to detect possible developmental anomalies Amniotic fluid α-fetoprotein measurement if MSAFP was abnormal Fetal echocardiography if initial maternal HbA1c concentration was elevated;[a] in some centers, this procedure is performed in all women with diabetes antedating conception
26	Sonographic assessment of fetal growth
28–Delivery	Maternal instruction for counting fetal movements
32	Follow-up longitudinal assessment of fetal growth by ultrasound
34–40	**Monitor fetal well-being** Biophysical testing: 2 times weekly NST *or* weekly CST *or* weekly biophysical profile (See text for description and expanded discussion)
36	Sonographic estimation of fetal weight
Delivery	Timing, type, and mode of delivery are planned by the perinatologist
37–38.5	Amniocentesis and delivery for patients in poor control
38.5–40	Delivery without amniocentesis for patients in good control with good dating criteria
Birth and Neonatal period	Macro- and microscopic examination of the placenta; diabetic control, lactation instruction, plans for postpartum diabetic care and contraception should be discussed before hospital discharge
	Newborn infant Physical examination, including Dubovitz assessment and evaluation of developmental abnormalities if present Metabolic assessment in special care nursery for: hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, and/or hyperviscosity, hyperbilirubinemia, and respiratory distress syndrome

[a]Check local hospital laboratory for normal values.

that provides high resolution. In obese women and in poorly positioned fetuses, inadequate fetal assessment is common. In these situations, every attempt should be made for a second examination before 24 weeks' gestation. Fetal echocardiography performed by an experienced pediatric fetal cardiologist should be performed in all women with abnormal HbA1c concentrations at conception, during the first 8 weeks of pregnancy or at the first prenatal visit. Normal reference values for HbA1c values vary in different institutions and this range should be checked with the local laboratory. In some institutions, fetal echocardiography is performed in all women who are known to have had diabetes before conception. If a fetal cardiologist is not available, a four-chamber view of the heart during high-resolution cardiac ultrasonography will detect 90% of major cardiac malformations.

EVALUATION OF ABNORMAL FETAL GROWTH

Macrosomia and Fetal Dystocia

The multitude of complex factors that contribute to normal and abnormal fetal growth have not been fully elucidated. The problem is difficult because the fetus represents a type of tissue culture experience that reflects the influence of genetic inheritance, the fetal intravenous umbilical diet, and placental endocrine, autocrine, and paracrine factors (18). For the individual fetus, the final outcome at birth represents the interplay and modulation of all intrauterine events from conception to birth.

It is difficult to differentiate the growth of fetuses of diabetic and nondiabetic mothers by ultrasound before early 3rd trimester. Individual fetal growth patterns, however, can be followed serially from early gestation onward. Deviations from normal can be documented and plotted on fetal growth curves. Abnormal increments in abdominal circumference are an indication of fetal macrosomia and truncal obesity (19). Figure 20.1 illustrates ultrasonographic findings in an overgrown fetus of a mother with GDM.

Reece and colleagues, in an ultrasound study of measurements of the fetal head, have reported normal growth velocities in diabetic women similar to those of normals, despite an advanced degree of maternal vascular disease

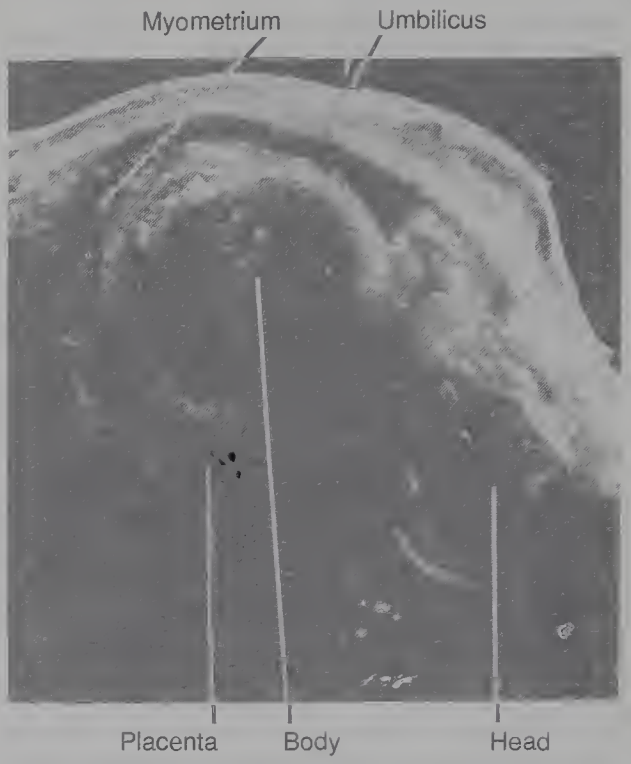


Figure 20.1. Longitudinal scan through the mid-abdomen of a woman with GDM at 36 weeks. Ultrasonographic documentation of macrosomia. The 107-mm body is disproportionately large when compared with the 89-mm biparietal diameter of the head.

(20). Landon and colleagues (21) confirmed the cranial and femur growth measurements observed by Reece. In addition, they differentiated diabetic from normal fetuses by abdominal circumference growth beginning at 32 weeks' gestation (diabetic: 1.36 cm/week versus 0.901 cm/week in normals, $p < .001$). Their method employed a cutoff value of a growth velocity of 1.2 cm/week from 32–39 weeks and identified macrosomic infants with 84% specificity and 85% sensitivity.

Enormous effort has been expended using ultrasonography to describe and validate a regression formula to predict accurately the birth weights of normal and diabetic babies (22, 23). Polynomial formulas employ a combination of biometric measurements (head, abdominal circumference, and limb length) to predict fetal weight in grams. Unfortunately, small errors in individual measurements have an exaggerated effect on such predictions that limit their accuracy and validation (24). For this reason, no single formula has been sufficiently accurate to identify reliably the large or small infants of normal or diabetic mothers. Despite methodologic problems, it is important

to try to identify an overgrown or undergrown fetus before delivery.

Shinozuka and colleagues at the University of Tokyo have devised two new formulas to improve the accuracy of fetal weight estimation by ultrasound measurement that is applicable especially to low birth weight infants, including those with intrauterine growth retardation (24). In a prospective study of 657 pregnancies, they showed a high correlation between estimated weights and actual birth weights with a small range of error (15%) in nearly 90% of infants who weighed between 450 g and 4800 g at gestational ages from 21–41 weeks. An error of ± 10–15% is thought to be inevitable because of the variance of values obtained through ultrasonographic measurements; especially those of soft tissue, such as anteroposterior trunk diameter (APTD) and transverse trunk diameter (TTD) that are of this magnitude.

Figure 20.2 describes the principle for the Shinozuka formula for fetal weight estimation. Ultrasonographic measurements of the fetuses included biparietal diameter (BPD), APTD, TTD, spine length (SL), and femur length (FL).

Figure 20.3 shows the impressive correlation obtained by the Shinozuka formula for estimated weights by ultrasound and actual birth weights. Birth weights were measured immediately after delivery and the actual volumes of the heads and trunks with all four limbs were measured within 2 days after delivery. A separate formula was devised for newborn data. The correlation coefficient of estimated weights and actual birth weights was 0.920. This study was performed by several residents and specialists. The formula for the ultrasound techniques is available in a computer program. This methodology has not been applied to diabetic pregnancies because they are so few at the University of Tokyo (personal communication from Dr. Shinozuka).

Growth trends in the fetus are characterized in most obstetric settings in the United States by a minimum of three ultrasonographic examinations performed in the 3rd trimester (typically at 28, 32, and 36 weeks). Three data points permit a more accurate assessment of fetal growth than one or two observations. At the University of California San Diego, serial ultrasonographic examinations are performed every 3–4 weeks during 3rd trimester; fetal weight is calculated according to the formula of Warsof (25) (Fig. 20.4). This method is reasonably accurate as a predictor of fetal weight. We pay close attention to the percentiles of abdominal circumference and calculated weight. If both are consistently greater than the 90th percentile on two or more 3rd trimes-

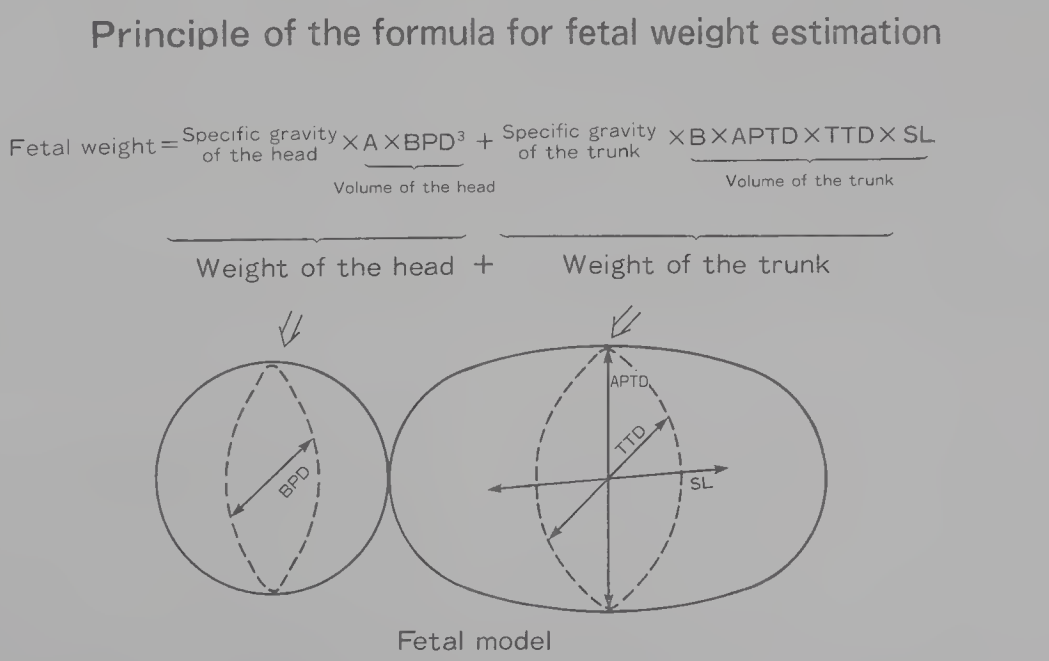


Figure 20.2. Principle of the Shinozuka formula for estimation of fetal weight. BPD^3 (biparietal diameter) and anterposterior trunk diameter (APTD) x transverse trunk diameter (TTD) x spine length (SL) were used as three-dimensional parameters of the head and trunk, respectively. Coefficients A and B are the ratios of the volumes and parameters of each part. The trunk includes all four limbs. With permission from Norio Shinozuka, MD, University of Tokyo.

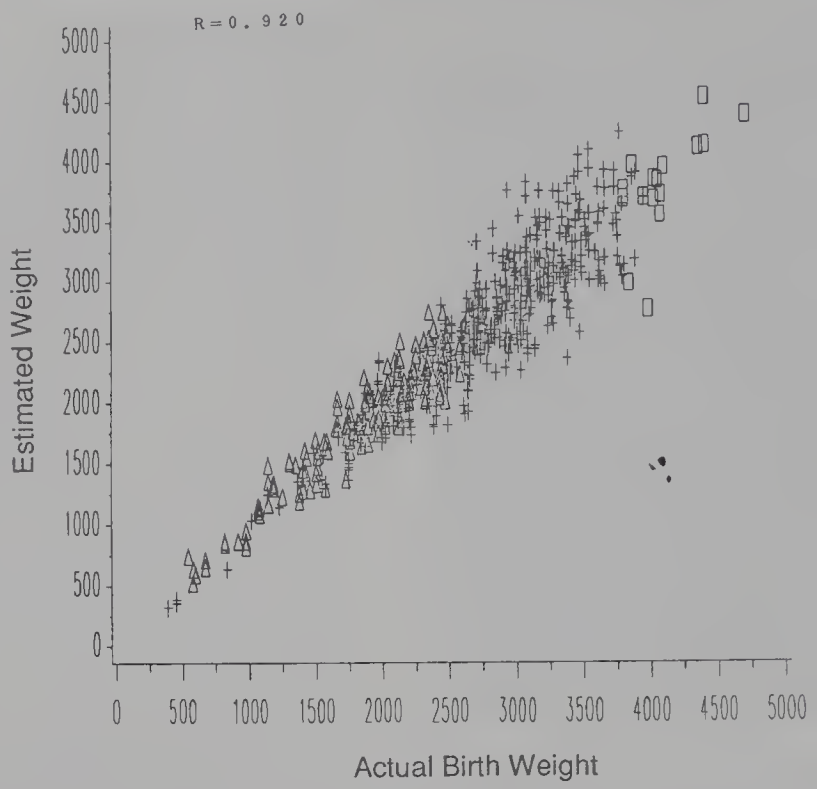


Figure 20.3. Correlation between estimates of fetal weights by ultrasound and actual birth weights by the Shinozuka formula. Key: △, light-for-dates; +, appropriate for dates; ‡, heavy-for-dates. With permission from Norio Shinozuka, MD, University of Tokyo.

ter examinations, the likelihood of macrosomia is very high (26).

In some women who have late entry into prenatal care, only a single ultrasonographic examination and abdominal measurements of uterine height on physical examination may be available to evaluate the possibility of fetal macrosomia. Hadlock and co-workers (26) have suggested that calculation of a ratio of femur length to abdominal circumference (FLAC) would be helpful because it is relatively constant at 22 ± 2% throughout the latter half of pregnancy. Unfortunately, this calculation is not sufficiently sensitive nor specific for clinical management.

Elliot and colleagues have proposed a macrosomia index, calculated by subtraction of the biparietal diameter from the chest diameter (27). In their experience, an index of 1.4 cm or greater was associated with shoulder dystocia in 25% of patients. This is not an encouraging figure and their macrosomia index has not had wide application because ultrasonographic measurement of the chest diameter is difficult and subject to a high degree of variation.

The main goal of antenatal detection of macrosomia is to avoid birth injury. In poorly controlled IDDM, NIDDM, and even well-controlled GDM women, fetal shoulder and abdominal widths can become excessive and result in extremely difficult vaginal deliveries (28). Shoulder dystocia is a complication defined as difficulty in delivery of the fetal body after expulsion of the fetal head. This obstetric emergency occurs in 0.3–0.5% of vaginal deliveries among normal pregnant women and is much higher in diabetic women. The incidence of shoulder dystocia rises tenfold to 3% among infants weighing 4000 g or more. In some reports of diabetic women with infants of >4000 g, 16% sustained shoulder dystocia (29–30). The higher incidence in IDM is attributed to abnormal fat patterning in utero with truncal obesity in both **normal weight** and macrosomic babies (19).

The clinical characteristics that signal increased risk of shoulder dystocia include: (*a*) protracted active phase of labor; (*b*) prolonged second stage of labor (pushing for more than 2 h); (*c*) use of midforceps. The majority of shoulder dystocia complications occur without warning. A long second stage of labor, prolonged deceleration phases, and excessive birth weight contribute to the risk of shoulder dystocia, but only 16% of cases with subsequent trauma can be predicted by this multifactorial model (31). Acker and colleagues recommend

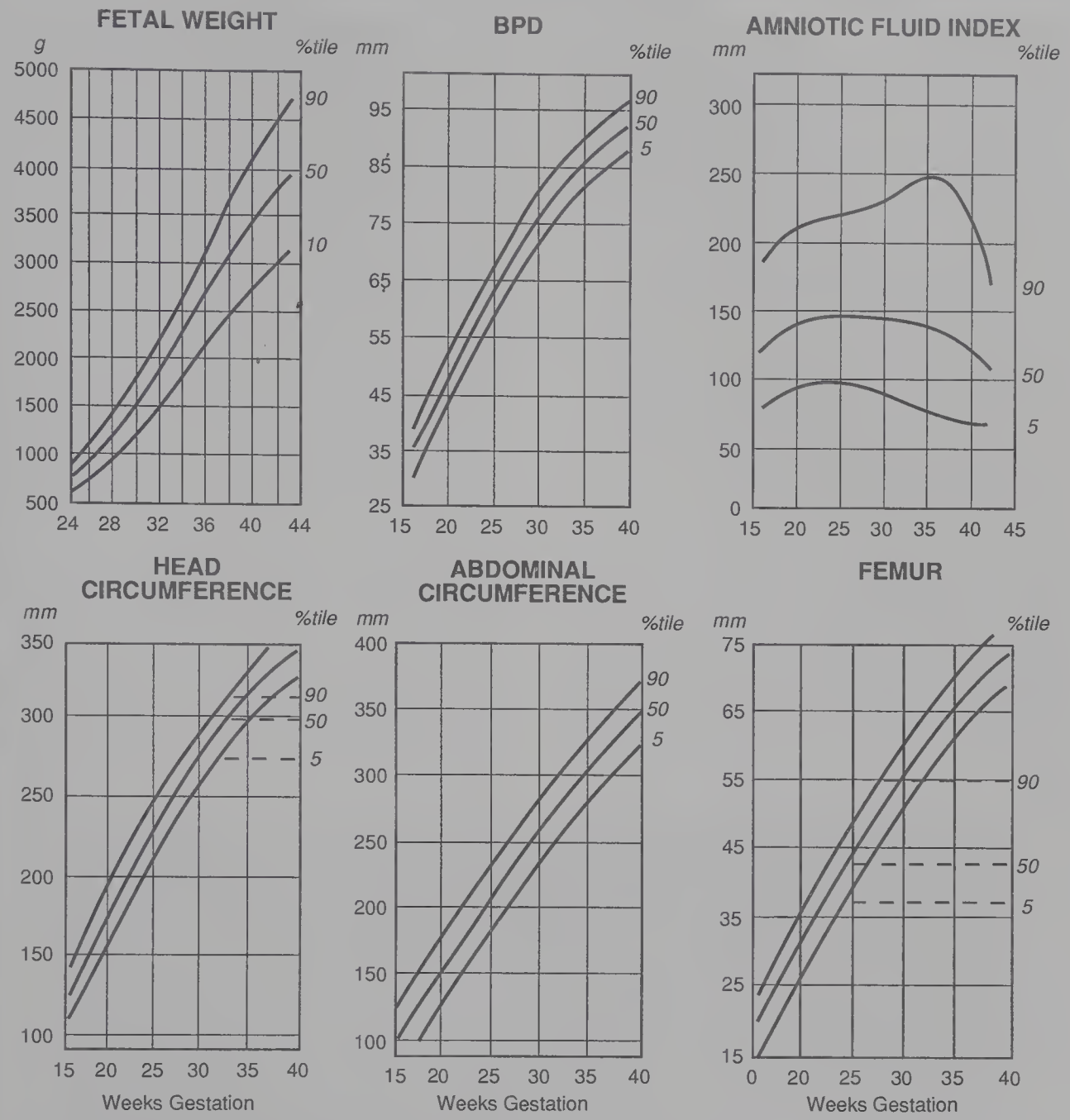


Figure 20.4. Fetal growth record and amniotic fluid index for longitudinal sonographic examinations at the University of California San Diego. Fetal weight is calculated by the formula of Warsof and associates (25).

cesarean section delivery for all diabetic women whose estimated fetal weight is >4000 g because of their higher risk for dystocia (32). Other experienced obstetricians prefer to assess each pregnancy individually and plan the mode of delivery accordingly (33).

In summary, fetal macrosomia in diabetic pregnancy is often but not always predictable by performing serial ultrasonographic examinations. An estimate of the trend of fetal weight and an assessment of abdominal growth compared with those of normal women are useful guidelines. In our institution, all infants with a predicted birth weight ≥4300 g are delivered by cesarean section unless there are compelling reasons to make an alternative decision. A discussion of the pathophysiology of macrosomia in infants of diabetic mothers is presented in Section X.

Intrauterine Growth Retardation (IUGR)

Intrauterine growth retardation is usually defined as a birth weight or fetal growth measurements below the 10th percentile when cor-

Table 20.2.
Diagnostic Clues for the Detection of Fetal Growth Retardation

Accurate assessment of gestational age
A single ultrasound examination is less accurate than longitudinal analysis of fetal growth
Helpful sonographic parameters:
Head/abdominal ratio ↑
Femur length/abdominal circumference ratio ↑
Ponderal index ↓
Plot biometric observations against normal curves
Longitudinal plot of fetal weight and abdominal circumference
Assess amniotic fluid volume
Assess biophysical profile

rected for gestational age. Fetuses with poor intrauterine growth are at risk for increased rates of perinatal asphyxia and death.

A diagnosis of IUGR requires an accurate assessment of gestational age and several ultrasonographic examinations. Diagnostic clues for the detection of IUGR are shown on Table 20.2. A study of pulsed doppler blood flow of the uterine artery and fetal circulatory system may also be helpful (34). Fok and colleagues (35) have correlated umbilical artery doppler velocimetry with arterial lesions in the placentas of small-for-dates pregnancies. They studied the placentas of 14 growth-retarded fetuses from mothers with abnormal umbilical artery velocimetry at 36–40 weeks' gestation and compared them with placentas of 15 appropriately grown fetuses with normal wave forms. They found that a large percentage of arterial vessels in the placentas from the growth-retarded fetuses showed abnormal changes in the vessel wall. The percentage of abnormal vessels correlated significantly with the resistance index on doppler velocimetry and provided an anatomic basis for elevated resistance to blood flow in small-for-dates pregnancies.

Good obstetric dating criteria and longitudinal observations on three or more occasions also permit the useful measurement of fetal growth pattern and determination of several types of fetal growth disorder (asymmetric or symmetric) with some degree of certainty. A plot of estimated fetal weight on intrauterine growth charts provides the best method of as-

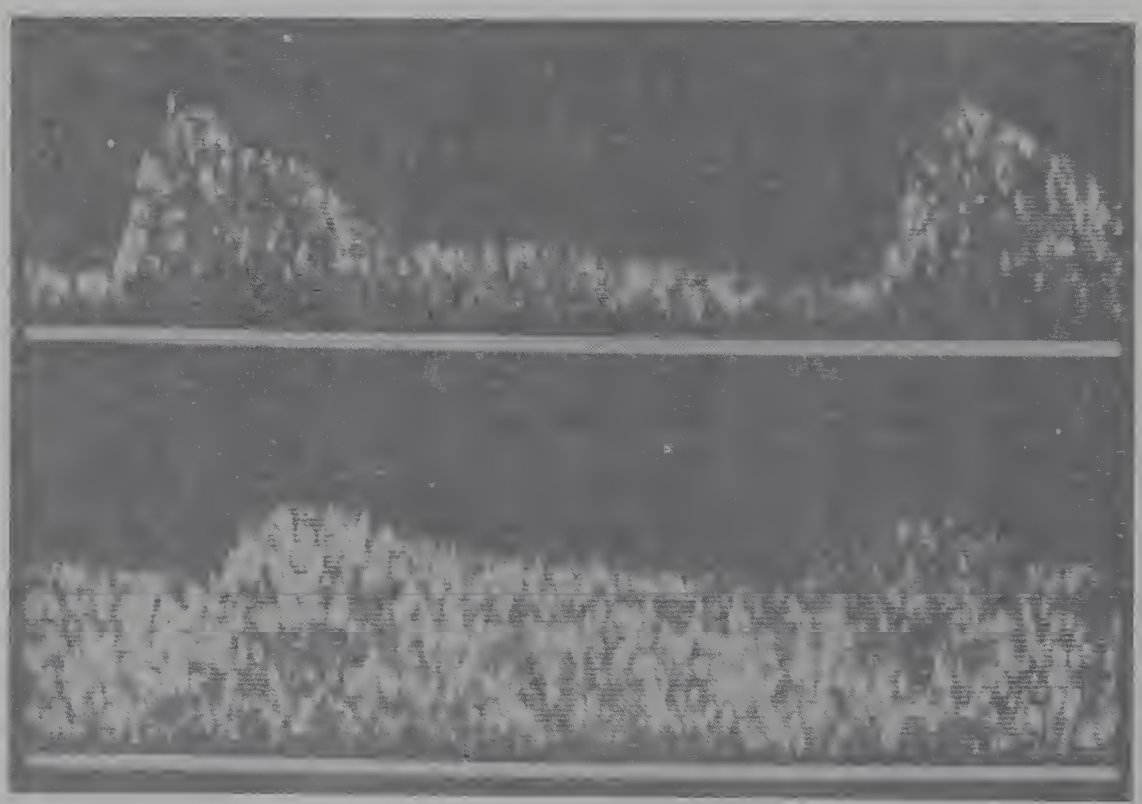


Figure 20.5. *Top,* Abnormal doppler wave form from the uteroplacental circulation at first examination (16–22 weeks) with a high resistance pattern and elevated resistance index of 0.65. *Bottom,* Normal doppler wave form resistance pattern with a resistance index of 0.36. Courtesy of Dr. S.A. Steel and her colleagues at St. George's Hospital, London, U.K.

sessment of the fetal growth profile (36). National United States growth curves are available as well as those with validated data at high altitudes and at sea level (37–40). Figure 20.5 shows the University of California San Diego longitudinal record for plotting fetal growth and the amniotic fluid index (AFI). The severity of IUGR and the possible urgency for obstetric intervention must be evaluated with care.

Amniotic fluid volume declines markedly in late stages of growth retardation (41). Oligohydramnios is a sign of diminished placental function and a potential cause of fetal death secondary to umbilical cord compression. It is useful to monitor this complication by measurement of the four-quadrant sum of vertical pockets of amniotic fluid (AFI) at each sonographic evaluation (42, 43). An AFI value of <75 mm total should be viewed with suspicion. Measurements <50 mm should prompt immediate evaluation for delivery.

A fetus that grows steadily along a low-growth profile curve and shows active movements, breathing, and adequate amniotic fluid will likely do well over the short term. In careful observation of these pregnancies, however, signs of cessation of growth and changes in amniotic fluid volume may occur as a harbinger of impending fetal jeopardy. In fetuses with **symmetric IUGR,** sonographic examinations for fetal malformations should be performed at more frequent intervals.

A preterm fetus at 28–34 weeks' gestation with **asymmetric growth** and diminished amniotic fluid should be monitored weekly or more often. Normal fetal movement and satisfactory serial biophysical profiles provide reassurance that the pregnancy continues toward maturity (46). Maternal bedrest is recommended to improve placental blood flow and fetal nutrient supply. Sonographic evidence of growth arrest should prompt evaluation for delivery.

In summary, accurate diagnosis and management of fetal growth abnormalities requires sophisticated clinical skills and ultrasonographic expertise. Simple measurements of fetal head size by ultrasonography are not sufficient. Attention should be paid to all aspects of the fetal environment. These include underlying maternal problems, the dynamics of measurements of all aspects of fetal growth, and changes in the volume of amniotic fluid.

Table 20.3.
Fetal Biophysical Profile[a,b]

Reactive nonstress test
At least two episodes of fetal heart rate acceleration of >15 beats/min and ≥15 sec in duration associated with fetal movement in 20 min
Fetal breathing movements
At least one episode of sustained fetal breathing movements ≥30 sec in duration in 30 min of observation
Fetal tone
At least one episode of active extension with return to flexion of fetal limbs or trunk in 30 min of observation
Fetal movement
At least three discrete limb or body movements in 30 min of observation
Amniotic fluid volume
At least one pocket of amniotic fluid that measures 1 cm in the ventral plane

[a]Modified from Manning et al. Fetal assessment based on fetal biophysical profile scoring: Experience in 12,620 referred high-risk pregnancies. I. Perinatal mortality by frequency and etiology. Am J Obstet Gynecol 1985;151:345.
[b]Two points are awarded for each parameter when the above criteria are fulfilled. No points are given if the criteria are not met.

BIOPHYSICAL PROFILE (BPP)

An oxygen-deficient fetus in extremis typically moves infrequently or sluggishly (43). The biophysical profile (BPP) is a useful adjunct for the evaluation of fetal well-being in these pregnancies (44, 45). Many obstetricians also prefer to assess a BPP if a nonstress test (NST) is not reactive. Table 20.3 is a modification of the original profile developed by Manning (44). The presence of normal fetal breathing movements, gross body movements, fetal tone, and amniotic fluid volume are each given a score of 2 with 2 additional points for a reactive NST. A score of 8–10 is reassuring while a score of 6 or less may indicate a fetus in jeopardy.

Several investigators have described their extensive experience with the BPP. Golde and colleagues (48) reported that 430 of 434 tests performed after a **reactive** NST in diabetic women were associated with BPP scores of 8 or higher. When the NST was nonreactive (25 women), 25 consecutive BPP tests were normal while four had scores lower than 8. All patients, even those with low scores, had a good perinatal outcome.

In a study by Dicker and co-workers (49), a normal BPP predicted normal Apgar scores in 99% of patients. Johnson and colleagues (50) performed BPP assessments in 50 IDDM women twice weekly and weekly tests in 188 women with GDM. There were no stillbirths and only 8 of 238 (3.3%) tests were abnormal. Neonatal morbidity was significantly higher in infants whose mothers had positive tests. This study was reassuring because it demonstrated that the BPP can be used successfully for fetal surveillance with few interventions, thereby prolonging pregnancy beyond 37 weeks' gestation in most women.

ELECTRONIC FETAL MONITORING

IDDM Women

Antenatal fetal heart rate tests (46) are used extensively to monitor fetal well-being in women with IDDM and NIDDM during 3rd trimester. The choice of test and interval between tests vary in different countries and medical centers. In the United States, there is no unanimity of opinion among obstetricians in excellent perinatal centers. External electronic fetal heart rate monitoring is accomplished by applying a doppler transducer to the maternal abdomen.

Nonstress Test (NST)

An NST is a noninvasive recording from these instruments that correlates fetal activity with changes in baseline fetal heart rate during a defined time interval. At the University of California San Diego, a reactive NST suggesting fetal well-being is defined as two fetal cardiac accelerations of 15 beats per minute lasting 15 seconds concomitant with fetal movement during 20 minutes of observation.

A majority of perinatal centers in the United States use the NST as the primary biophysical test. However, a multicenter comparison of the NST and the contraction stress test (CST) documented a significantly lower risk of antepartum death with monitoring by a CST (1.1 versus 7.8/1000 births, $p < .05$) (47).

How effective are NST tests in diabetic pregnancies? Keegan and Paul (51) noted that the NST failed to predict two perinatal deaths in 342 pregnancies when the test was performed weekly. A subsequent study by Golde and coworkers (47) in which the NST was administered twice weekly to 107 women with IDDM reported no perinatal losses. In reports by Olofsson and colleagues (52, 53), NST and CST were compared retrospectively in 99 diabetic pregnancies. These studies documented no difference in the predictive value of a reassuring test performed weekly, but the CST was superior with fewer false-positive tests that precipitated unwarranted intervention.

In Landon and Gabbe's review of seven clinical studies of NSTs that included 426 patients with diabetes tested weekly, six antepartum deaths were documented, a significantly higher fetal death rate than that seen in other high-risk situations (46). Their summary of data from 13 series in the literature reported 49 deaths within 1 week of a reactive NST result. Twenty-six of these were due to acute causes, such as placental abruption or umbilical cord prolapse. Of the 23 deaths attributed to chronic processes, 10 occurred in women with diabetes. Experience in various centers has led to the recommendation that the NST should be performed **twice weekly** if used in diabetic pregnancies.

Contraction-Stress Test (CST); Oxytocin Challenge Test (OCT)

If an NST is nonreactive, a CST (oxytocin challenge test, OCT) should be performed. Oxytocin is administered intravenously by an infusion pump (initial dose, 0.44 mU/min) and carefully titrated to a rate sufficient to produce three uterine contractions in a 10-minute interval. The OCT evaluates the heart-rate response to uterine contractions in the fetus at risk for uteroplacental insufficiency.

The interpretation of the OCT test is defined as follows: **negative**—absence of persistent, late decelerations of the fetal heart rate after uterine contractions; **suspicious**—occasional late decelerations of the fetal heart rate after uterine contractions; **positive**—late fetal heart rate decelerations after each uterine contraction.

A negative OCT test is reassuring and usually indicates that the fetus is not in immediate jeopardy. False-negative tests have been reported, especially in diabetic pregnancies. Positive OCTs have been associated with intrapartum fetal distress (50).

The incidence of abnormal perinatal outcomes including mortality, fetal distress in labor, low Apgar scores, and reduced birth weight is higher in patients with a positive

Table 20.4.
Antepartum Surveillance of Diabetic Pregnancies[a]

Technique	Abnormal Results (T)	False-Negative Results (%)	False-Positive Results (%)[a]
Contraction stress test	10	1	50
Nonstress test	10	1	75–90
Fetal movement	5–15	1	60
Biophysical profile	2	1	20

[a]Published with permission from Landon MB, Gabbe SG. Antepartum fetal surveillance and delivery timing in diabetic pregnancies. Clin Diabet 1990;8:33–46.

OCT. Landon and Gabbe (46) note that the incidence of **false-positive** OCT results in pregnancies complicated by diabetes and other high-risk conditions has been significant, ranging from 40–60% (Table 20.4). For this reason, they advise that elective intervention in a preterm pregnancy complicated by diabetes should be undertaken only when several tests suggest fetal compromise or fetal pulmonary maturation has been documented.

Available information indicates that the OCT and BPP can be performed weekly to monitor fetal risk. In IDDM women, tests should be performed weekly from 34 weeks' gestation onward unless fetal growth retardation, significant maternal hypertension, or oligohydramnios require monitoring earlier in pregnancy. In some centers, the BPP has replaced the OCT for fetal surveillance. Obstetric intervention for abnormal fetal testing is performed in less than 5% of pregnancies (excluding fetal malformations and noncooperative patients). The frequency of intrauterine deaths in diabetes centers (but not in nontertiary hospitals or rural centers) is now 5.1/1000 (46).

Are American women tested excessively and can the costs, even in diabetic pregnancies, be justified? The answer to this question awaits the completion of the diabetes in pregnancy trials now in progress and a comparison of results with those of prospective studies in Canada, Scandinavia, Europe, the United Kingdom, and Australia where fetal electronic monitoring is often less intensive.

NIDDM Women

No data for fetal surveillance have been published in NIDDM pregnancies. These older, often heavier, and frequently hypertensive women always require insulin during gestation and are likely to be in worse control than IDDM in early 3rd trimester. They are at higher risk for preeclampsia, preterm birth, and macrosomic infants. At present, no separate guidelines for monitoring women with NIDDM have been established. Fetal electronic monitoring and decisions for obstetric intervention are based upon the diagnosis of diabetes and the complications that occur during the course of gestation.

GDM Women

Opinions differ concerning the necessity for surveillance of fetuses of women with GDM. In some centers, management varies for women who are treated only by diet in contrast to those who require insulin. Landon and Gabbe (46), following a review of 69 of their patients who were diet controlled and 28 who required insulin, no longer initiate antepartum surveillance in GDM women who have normal fasting and postprandial glucose values unless they have hypertension, preeclampsia, or a history of a previous stillbirth. Those who require insulin are followed in the same manner as IDDM and NIDDM patients, with twice weekly NSTs beginning at week 32. Maternal counts of fetal movement are monitored from 28 weeks' gestation onward.

Our approach differs from that of Landon and Gabbe with the intensity of antepartum testing in GDM before 40 weeks' gestation based on glycemic control. Women with occasional postprandial blood glucose values higher than 120 mg/dl (6.6 mmol/L), who are not receiving insulin, have fetal heart rate testing with an NST each week because of the association of hypoxemia and hyperglycemia. In general, most GDM women, whether diet controlled or receiving insulin, begin fetal movement counts at 28 weeks and have weekly NSTs from 36–40 weeks. There are no large prospective studies of fetal surveillance in these two groups of GDM patients.

Because women with true gestational carbohydrate intolerance (reversible immediately

postpartum) have normal HbA1c values and rarely have a blood glucose value of >150 mg/dl (8.3 mmol/L), is there any real justification for expensive and cumbersome NST and OCT tests? In GDM pregnancies with complications, the decision to test is straightforward. In the absence of good prospective epidemiologic studies in GDM, many obstetricians in the United States are more comfortable with and feel reassured by fetal electronic monitoring of GDM patients. The efficacy of intense fetal monitoring of GDM women remains an open question.

MATERNAL COUNTS OF FETAL MOVEMENT

A mother's perception of fetal activity is the oldest and most widely used form of monitoring fetal well-being. It is simple, cheap, requires no equipment, and can be done at home. There are, however, large inter- and intrapatient variations in fetal movement and no normal frequency and pattern has been established (54).

About 60% of all perinatal deaths occur beyond 28 weeks' gestation and, of these, there is no obvious cause in about 70% (55). Fetal deaths may be preceded by reduction or cessation of fetal movement by a day or more. In the early 1980s, Neldam published two studies of a small, controlled trial and showed that routine formal counting of fetal movement was associated with a significantly lower rate of antepartum death among normally formed babies weighing more than 1500 g when compared with infants of mothers who only informally noted fetal activity (56, 57). A nonrandomized cohort study of 20,000 women failed to confirm such a benefit (58).

Grant and colleagues (59) evaluated a routine recommendation to women to count fetal movements daily using a modified Cardiff count-to-ten chart (60). All women were instructed by specially trained midwives. This is the most widely used system in the U.K. and their collaborative study included the Oxford Perinatal Epidemiology Unit, The Department of Obstetrics and Gynecology in the General Hospital in Malm, Sweden, and the Maternit Universitaire de la Citadelle Liege, Belgium. They enrolled 68,000 women who were randomly allocated to a policy of routine counting or to standard care that might involve selective use of formal counting or informal noting of movements. The large sample size was necessary because the rate of late fetal deaths in the participating countries was estimated at the time of the trial to be only about 4/1000 total births. In this setting, antepartum death rates for normally formed singletons were similar in the two groups regardless of cause of fetal death or risk status. Despite the counting policy, most of the fetuses were dead by the time the mothers received medical attention. The study did not rule out a beneficial effect of fetal movement counting but, at best, the policy would have to be used by about 1250 women to prevent unexplained antepartum late fetal death.

In Canada, Connors and associates (54) recruited 146 women for a study of maternally perceived fetal activity from 24 weeks' gestation to term in both normal and high risk pregnancies. The periodicity of fetal activity perceived by mothers correlated well with ultrasonic observations. They too confirmed the variability of fetal movement counts and the need to take periodicity into account when maternally perceived fetal activity is used as a screen for fetal well-being. Their data suggested that the patient should be observed for a consecutive period up to a maximum of 2 h; if no fetal activity is perceived by 2 h of observation, further evaluation of well-being should be considered. They reported no stillbirths in either group of patients. In the at-risk group, one fetus had fetal hypoxemia that was suspected before labor and delivery. A real-time scan of twins at 37 weeks' showed persistent bradycardia. An emergency cesarean section was performed and monoamniotic twins with significant cord entanglement were delivered. One twin had severe birth asphyxia and subsequently died. The second twin showed no birth asphyxia. There had been no change in this patient's fetal movement counts to suggest fetal compromise. The investigators concluded that the extreme variability of maternally perceived fetal movement counts makes it difficult to determine a normal range of fetal activity. Thus, it would be difficult to use movement counts as the only objective assessment of fetal well-being.

Moore and Piacquadio (43) have conducted a prospective study of women who were mostly dependents of active duty Navy personnel based at San Diego Naval Medical Center.

During a 7-month control period with no fetal movement screening program, there were 2519 deliveries with a fetal mortality rate of 8.7/1000 births. After a pilot study that required patients to record the elapsed time required to note 10 fetal movements to validate a fetal movement protocol, they conducted an investigation of 1864 women over a 6-month period. Patients were instructed to request further fetal evaluation if 10 movements were not perceived within a 2-h counting period. During the active study phase, the number of antepartum fetal electronic monitoring tests increased 13%; interventions for fetal compromise prompted by inadequate fetal activity trebled, and fetal mortality among women with decreased movement was 10/1000 births. The overall fetal mortality rate in study patients was 2.1/1000 births.

Enthusiasm for maternal fetal movement counting varies in different health care settings. In the Diabetes in Pregnancy Clinic at the University of California, San Diego, we have a multiracial (White, Mexican-American, Asian, American Indian, and Pacific Islander) population of low socioeconomic status. Many women do not speak English and some are illiterate. From both a medical and economic standpoint, these are high-risk pregnancies with increased risks for mothers and babies. In 1988, we initiated a program of fetal movement counting because it is inexpensive and, more importantly, involves each diabetic woman directly in her own care (43). A change

Table 20.5.
Daily Fetal Movement Record

Name _____

Birthdate _____

Hospital # _____

Counting fetal movements is one way that you may play an important role in checking the health of your baby. By counting and recording the number of movements made by your baby once each day at the same time, you create a profile of your baby's activity during the final weeks of your pregnancy. An ideal time for counting is following dinner. Select a quiet place.

Please bring this record with you each time you visit the doctor's office, clinic or hospital.

Date	Time First Movement Felt	Time 10th Movement Felt	Total Time
EXAMPLE 11/4/88	6:50	7:28	38 minutes

in the pattern of fetal movement or requiring more than 2-h to feel 10 movements alerts her to the immediate urgency to find transportation to the hospital for a more comprehensive fetal assessment. Our patient numbers are too small for an accurate analysis of the efficacy of fetal movement counting apart from other measures of fetal surveillance. However, in a county where the fetal mortality rate per 1000 varies from 5.6 for Whites to 10.19 for Blacks, 6.34 for Asians, and 5.36 for Mexican-Americans, it seems worthwhile to explore all avenues that may help in management of expensive obstetric problems of diabetic pregnancies.

Table 20.5 is a chart of the fetal movement record we use at UCSD. Maternal counting begins at 28 weeks' gestation.

Doppler Ultrasound Flow Velocity Tests

Doppler ultrasound was first described to investigate the fetal circulation in 1977 by Fitzgerald and Drumm (61). Since then the technique has had extensive use in pregnancies complicated by intrauterine growth retardation (IUGR) (35, 62–64), hypertension (65–68), and diabetes (69, 70). McParland and Pearce (67) have provided a comprehensive historical review of doppler blood flow studies in pregnancy and Pearce and colleagues (71) have published reference ranges and sources of variation for indices of pulsed doppler flow velocity wave forms from the utero placental and fetal circulation.

In diabetic pregnancies, there are two high-risk circumstances where doppler wave forms have been reported to be helpful: in hypertension and in IUGR. Al-Ghazali and colleagues (65) have examined two vessels, the fetal aorta and the umbilical artery, in 32 women with complicated pregnancies that resulted in IUGR. They were able to identify three groups of patients: (*a*) In six pregnancies, normal doppler flow in both arteries resulted in a good outcome at birth. These babies are presumably healthy but have a low-growth potential. (*b*) The second group of 11 pregnancies had abnormal flow in both arteries and all infants had subsequent morbidity problems. Six mothers had severe proteinuric preeclampsia and the remaining five had fetuses with severe growth retardation. (*c*) In the third group of 12 pregnancies, umbilical artery flow was abnormal but uterine artery tracings were normal. Seven fetuses had severe IUGR and five women had preeclampsia. The authors explain the normal uterine artery readings in the seven fetuses with severe IUGR by the fact that the primary defect was on the fetal side of the placenta and not maternal in origin. In the study by Al-Ghazali and associates, doppler assessment of high-risk pregnancies was of clinical value because when all indices were normal the outcome was likely to be good. The most reliable predictor of morbidity was the umbilical artery tracing; only 2 of 28 pregnancies with abnormal tracings had a normal outcome.

In a report of doppler wave forms in women with hypertension by Cameron and co-workers (66), patients were grouped according to the severity of their hypertension, e.g., chronic hypertension, mild or severe preeclampsia. They found that doppler assessment offered no significant value in women with chronic hypertension or mild preeclampsia. In women with severe preeclampsia, however, doppler changes may precede those of the biophysical profile or nonstress test. Both systolic and di-

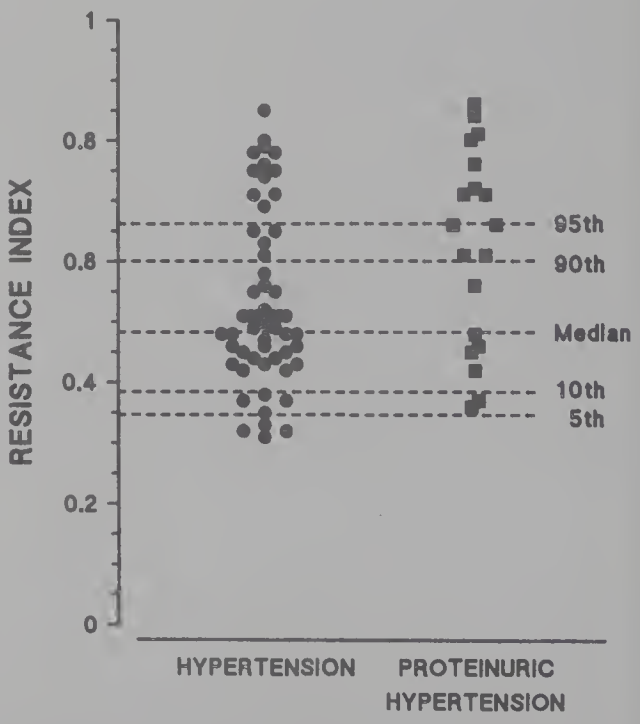


Figure 20.6. Maximum resistance index in patients with hypertension or proteinuric hypertension. The centile range is derived from maximum resistance index in all normotensive patients. See text for description. Courtesy of Dr. S.A. Steel and her colleagues at St. George's Hospital, London, U.K.

astolic flow velocities in the fetal aorta must be considered and abnormalities of these may precede those seen in the descending aorta.

Fok and colleagues (35), as mentioned earlier, have provided the first anatomic evidence that correlated elevated resistance to blood flow in placentas from growth-retarded fetuses with doppler velocimetry. Thus, determination of the extent of vessel involvement from doppler velocimetry permits a qualitative assessment of total placental function. This is a valuable adjunctive method of antenatal testing to assess fetal well-being.

Preeclampsia and IUGR are both associated with impaired perfusion of the intervillous space (34), antenatal fetal asphyxia, high perinatal morbidity and mortality. Present methods of fetal surveillance include fetal movement charts, NSTs, and ultrasonographic biophysical profiles. However, warning signs from use of these methods may inadequately antedate fetal distress. Doppler ultrasound examination provides a more direct estimation of blood flow in the fetoplacental unit and an earlier indication of impending fetal hypoxia (66). Steel and colleagues have screened 1198 nulliparous women in early pregnancy (mean 18 weeks) by recording doppler ultrasound wave forms from the uteroplacental circulation (68). The results of 114 women were available for analysis. In 18 women (12%), there were persistently abnormal wave forms in repeat ultrasound scans at 24 weeks that were regarded as a positive result. In these patients, hypertension was significantly more frequent (29/118; 25% versus 45/896; 5%). Hypertension associated with abnormal wave forms was more likely to be severe and accompanied by proteinuria (12; 10%) and IUGR (15; 13%) compared with 0.8% and 0%, respectively, in women with normal wave forms.

Figure 20.5 shows an abnormal doppler wave form from the uteroplacental circulation at first examination. Wave forms were standardized by means of a resistance index calculated by taking mean of three wave forms with a high signal-to-noise ratio. A resistance index of 0.58 is an appropriate cut-off point that maintains maximum sensitivity with an acceptable false-positive rate. Figure 20.6 shows the highest resistance index of women in whom hypertension and proteinuric hypertension developed, plotted against centile ranges for the highest resistance index from the population without hypertension. They noted that the higher the resistance index, the greater the likelihood of complicated hypertension.

In sum, the development of doppler ultrasound has moved beyond the initial stage of development to a second stage of application for efficacy in high-risk patients. It is now to a final stage of a clinical trial to incorporate the technique into standard management of patients in a concealed/revealed fashion in order to determine whether knowledge of the new tests resulted in improved outcome (67, 72).

References for Section VII

1. Simpson JL. Fetal wastage. In: Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill Livingstone 1986:651-673.
2. Miodovnik M, Skillman C, Holroyde JC, Butler JB, Wendel JS, Siddiqi T-A. Elevated maternal glycohemoglobin in early pregnancy and spontaneous abortion among insulin-dependent diabetic women. Am J Obstet Gynecol 1985; 153:439-442.
3. Sutherland HW, Pritchard CW. Increased incidence of spontaneous abortion in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1986;155:135-138.
4. Dicker D, Feldberg D, Samuel N, Yeshaya A, Karp M, Goldman JA. Spontaneous abortion in patients with insulin-dependent diabetes mellitus: The effect of preconceptional diabetic control. Am J Obstet Gynecol 1988;158:1161-1164.
5. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med 1988;319: 1617-1623.
6. Miodovnik M, Lavin JP, Harrington DJ, Leung MS, Seeds AE, Clark KE. Cardiovascular and biochemical effects of infusion of beta hydroxybutyrate into the fetal lamb. Am J Obstet Gynecol 1982;144:594-600.
7. Teramo K, Ammala P, Ylinen K, Raivio KO. Pathologic fetal heart rate associated with poor metabolic control in diabetic pregnancies. Obstet Gynecol 1983;61:559-565.
8. Teramo KA, Widness JA, Clemons GK, Volltilainen P, McKinlay S, Schwartz R. Amniotic fluid erythropoietin correlates with umbilical plasma erythropoietin in normal and abnormal pregnancy. Obstet Gynecol 1987;69:10-16.
9. Kariniemi V, Forss M, Siegberg R, Ammala P. Reduced short term variability of fetal heart rate in association with maternal hyperglycemia during pregnancy in insulin dependent diabetic women. Am J Obstet Gynecol 1983; 147:793-794.
10. Phillips AF, Rosenkrantz TS, Raye J. Consequences of perturbations of fetal fuels in ovine pregnancy. Diabetes 1985;34:(Suppl 2):32-35.
11. Hughes AB. Fetal heart rate changes during diabetic ketosis. Acta Obstet Gynecol Scand 1987;66:71-73.
12. Miodovnik M, Mimouni F, Berk M, Clark KE. Alloxan-induced diabetes mellitus in the pregnant ewe: metabolic and cardiovascular effects on the mother and her fetus. Am J Obstet Gynecol 1989;160:1239-1244.
13. Edelberg SC, Dierker L, Kalhan S, Rosen MB. Decreased fetal movements with sustained maternal hyperglycemia using the glucose clamp technique. Am J Obstet Gynecol 1987;156:1101-1105.
14. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. Am J Obstet Gynecol 1982;142:363-371.
15. Bracero LA, Jovanovic L, Rochelson B, Bauman W, Farmakides G. Significance of umbilical and uterine artery velocimetry in the well controlled pregnant diabetic. J Reproduc Med 1989;34: 273-276.
16. Fog-Pedersen J, Mølsted-Pedersen L, Møller S. Ultrasound studies of fetal growth. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate metabolism in Pregnancy and the Newborn. IV. London: Springer-Verlag, 1989: 83-93.
17. Milunsky A, Alpert E, Kitzmiller JL, Younger MD, Neff RK. Prenatal diagnosis of neural tube defects. VIII. The importance of serum alpha fetoprotein screening in diabetic pregnant women. Am J Obstet Gynecol 1982;142:1030-1032.
18. Freinkel N, Metzger BE. Pregnancy as a tissue culture experience: The critical implications of maternal metabolism for fetal development. In: CIBA Foundation Symposium 63 (new series): Pregnancy Metabolism, Diabetes and the Fetus. Amsterdam: Excerpta Medica, 1979:23-28.
19. Ogata ES, Sabbagha R, Metzger BE, Phelps RL, Depp R, Freinkel N. Serial ultrasonography to assess evolving fetal macrosomia. Studies in 23 pregnant diabetic women. JAMA 1980;243: 2405-2408.
20. Reece EA, Winn HN, Smikle C, et al. Sonographic assessment of growth of the fetal head in diabetic pregnancies compared with normal gestations. Am J Perinatol 1990;7:18-22.
21. Landon MB, Mintz MC, Gabbe SG. Sonographic evaluation of fetal abdominal growth: predictor of the large for gestational age infant in pregnancies complicated by diabetes mellitus. Am J Obstet Gynecol 1989;160:115-121.
22. Shepherd MJ, Richards VA, Berkowitz RL, Warsof SL, Hobbins JC. An evaluation of two equations for predicting fetal weight by ultrasound. Am J Obstet Gynecol 1982;142:47-54.

23. Tamura RK, Sabbagha RE, Dooley SL, Vaisrub N, Socol ML, Depp R. Real-time ultrasound estimations of weight in fetuses of diabetic gravid women. Am J Obstet Gynecol 1985;153:57-60.
24. Shinozuka N, Okai T, Kohzuma S, et al. Formulas for fetal weight estimation by ultrasound measurements based on neonatal specific gravities and volumes. Am J Obstet Gynecol 1987; 157:1140-1145.
25. Warsof SL, Gohari P, Berkowitz RL, Hobbins JC. The estimation of fetal weight by computer-assisted analysis. Am J Obstet Gynecol 1977; 128:881-892.
26. Hadlock FP, Deter RL, Harrist RB, Roecker E, Dark SK. A date independent predictor of intrauterine growth retardation: Femur length/ abdominal circumference ratio. AJR 1982; 141:979-984.
27. Elliott JP, Garite TJ, Freeman RK, McQuown DS, Patel JM. Ultrasonic prediction of fetal macrosomia in diabetic patients. Obstet Gynecol 1982;60:159-162.
28. Hollingsworth DR, Ney D, Fujimoto J, Milewski M, Murphy H. Further obervations in lean and obese women with gestational diabetes during a 400-kilocalorie meal tolerance test. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate Metabolism in Pregnancy and the Newborn. IV. London: Springer-Verlag, 1989: 245-256.
29. Al Najashi S, al Suleiman SA, el Yahia A, Rahman MS, Rahman J. Shoulder dystocia—a clinical study of 56 cases. Aust NZ J Obstet Gynaecol 1989;29:129-132.
30. McFarland LV, Raskin M, Daling JR, Benedetti TJ. ERB/Duchenne's palsy: A consequence of fetal macrosomia and method of delivery. Obstet Gynecol 1986:783-788.
31. Gross SJ, Shime J, Farine D. Shoulder dystocia: Predictors and outcome. A five year review. Am J Obstet Gynecol 1987;156:334-336.
32. Acker DB, Sachs BP, Friedman EA. Risk factors for shoulder dystocia. Obstet Gynecol 1985; 66:762-768.
33. O'Leary JA, Leonetti HB. Shoulder dystocia: Prevention and treatment. Am J Obstet Gynecol 1990;162:5-9.
34. Fleischer A, Schulman H, Farmakides G, et al. Umbilical artery velocity waveforms and intrauterine growth retardation. Am J Obstet Gynecol 1985;151:502-505.
35. Fok RY, Pavlova Z, Benirschke K, Paul RH, Platt LD. The correlation of arterial lesions with umbilical artery doppler velocimetry in the placentas of small-for-dates pregnancies. Obstet Gynecol 1990;75:578-583.
36. Gabbe S. Intrauterine growth retardation. In: Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill-Livingstone, 1986:769-785.
37. Lubchenco LO, Hansman C, Dressler M, et al. Intrauterine growth as estimated from liveborn birth weight data at 24–42 weeks gestation. Pediatrics 1963;32:793-800.
38. Lubchenco LO, Searls DT, Brazie JT. Neonatal mortality rate: Relationship to birth weight and gestational age. J Pediatr 1972;81:814-822.
39. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. Am J Obstet Gynecol 1976;126:555-564.
40. Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashieo M. Fetal growth and perinatal viability in California. Am J Obstet Gynecol 1982;59:624-632.
41. Manning FA, Hill LM, Platt LD. Qualitative amniotic fluid volume determination by ultrasound: Antepartum detection of intrauterine growth retardation. Am J Obstet Gynecol 1981;139:254-258.
42. Rutherford SE, Phelan JP, Smith CV, et al. The four quadrant assessment of amniotic fluid volume: An adjunct to antepartum fetal heart rate testing. Obstet Gynecol 1987;70:353-356.
43. Moore TR, Piacquadio K. A prospective evaluation of fetal movements screening to reduce the incidence of antepartum fetal death. Am J Obstet Gynecol 1989;160:1075-1080.
44. Manning FA, Morrison I, Lange IR, Harman CR, Chamberlain PF. Fetal assessment based on fetal biophysical profile scoring: Experience in 12,620 referred high-risk pregnancies. I. Perinatal mortality by frequency and etiology. Am J Obstet Gynecol 1985;151:343-350.
45. Platt LD, Walla CA, Paul RH, et al. A prospective trial of the fetal biophysical profile versus the nonstress test in the management of high-risk pregnancies. Am J Obstet Gynecol 1985; 153:624-633.
46. Landon MB, Gabbe SG. Antepartum fetal surveillance and delivery timing in diabetic pregnancies. Clin Diabet 1990;8:33-46.
47. Freeman RK, Anderson G, Dorchester W. A prospective multi-institutional study of antepartum fetal heart rate monitoring. I. Risk of perinatal mortality and morbidity according to antepartum fetal heart rate results. Am J Obstet Gynecol 1982;143:771-777.
48. Golde S, Montoro M, Good-Anderson B, et al. The role of NST, fetal biophysical profile and CST in the outpatient management of insulin-requiring diabetic pregnancies. Am J Obstet Gynecol 1984;148:269-273.
49. Dicker D, Feldberg D, Yeshaya A, Peleg D, Karp M, Goldman JA. Fetal surveillance in insulin-dependent diabetic pregnancy: Predictive value of the biophysical profile. Am J Obstet Gynecol 1988;159:800-804.
50. Johnson JM, Lange IR, Harman CR, Torchia MG, Manning FA. Biophysical profile scoring in the management of diabetic pregnancy. Obstet Gynecol 1988;72:841-846.
51. Keegan KA, Paul RH. Antepartum fetal heart rate testing. IV. The non-stress test as a primary approach. Am J Obstet Gynecol 1980;136:75-80.
52. Olofsson P, Sjoberg NO, Solum T, Svenningsen NW. Changing panorama of perinatal and infant mortality in diabetic pregnancy. Acta Obstet Gynecol Scand 1984;63:467-472.
53. Olofsson P, Sjoberg NO, Solum T. Fetal surveil-

lance in diabetic pregnancy. II. The nonstress test versus the oxytocin challenge test. Acta Obstet Gynecol Scand 1986;65:357-360.
54. Connors G, Natale R, Nasello-Paterson C. Maternally perceived fetal activity from twenty-four weeks' gestation to term in normal and at risk pregnancies. Am J Obstet Gynecol 1988; 158:294-299.
55. Scottish Health Service Common Services Agency, Information and Statistics Division. Scottish stillbirth and neonatal death report 1987: Edinburgh: Common Services Agency, 1988.
56. Neldam S. Fetal movements as an indicator of fetal well-being. Lancet 1980;1:1222-1224.
57. Neldam S. Fetal movements as an indicator of fetal well-being. Dan Med Bull 1983;30:274-280.
58. Lobb MO, Beazley JM, Haddad NG. A controlled study of daily fetal movement counts in the prevention of stillbirths. J Obstet Gynaecol 1985; 2806:87-91.
59. Grant A, Valentin L, Elbourne D, Alexander S. Routine fetal movement counting and risk of antepartum late death in normally formed singletons. Lancet 1989;2:345-349.
60. Pearson JF. Fetal movement recording: A guide to fetal well-being. Nurs Times 1979;75:1639-1641.
61. Fitzgerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: A new method. Br Med J 1977;2:1450-1451.
62. Erskine RLA, Ritchie JWK. Umbilical artery blood flow characteristics in normal and growth retarded fetuses. Br J Obstet Gynecol 1985;92:605-610.
63. Brar HS. The use of Doppler ultrasound to assess intrauterine growth retardation in the fetus. Semin Perinatol 1988;12:40-51.
64. Berkowitz GS, Mehalek KE, Chitkara U, Rosenberg J, Cogswell C, Berkowitz RL. Doppler umbilical velocimetry in the prediction of adverse outcome in pregnancies at risk for intrauterine growth retardation. Obstet Gynecol 1988;71:742-746.
65. Al-Ghazali W, Chapman MG, Allan WD. Doppler assessment of the cardiac and uteroplacental circulations in normal and complicated pregnancies. Br J Obstet Gynecol 1988;95:575-580.
66. Cameron AD, Nicholson SF, Nimrod MB, Harder JR, Davies DM. Doppler waveforms in the fetal aorta and umbilical artery in patients with hypertension in pregnancy. Am J Obstet Gynecol 1988;158:339-345.
67. McParland P, Pearce JM. Review article. Doppler blood flow in pregnancy. Placenta 1988; 9:427-450.
68. Steel SA, Pearce JM, McParland P, Chamberlain GVP. Early doppler ultrasound screening in prediction of hypertensive disorders of pregnancy. Lancet 1990;335:1548-1551.
69. Bracero L, Schulman H, Fleischer A, Farmakides G, Rochelson B. Umbilical artery velocimetry in diabetes and pregnancy. Obstet Gynecol 1986;68:654-658.
70. Landon MB, Gabbe SG, Bruner JP, Ludmir J. Doppler umbilical artery velocimetry in pregnancy complicated by insulin-dependent diabetes mellitus. Obstet Gynecol 1989;73:961-965.
71. Pearce JM, Campbell S, Cohen-Overbeek T, Hackett G, Hernandez J, Royston JP. Reference ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulation. Br J Obstet Gynaecol 1988;95:248-256.
72. Trudinger BJ, Cook CM, Giles WB, et al. Umbilical artery flow velocity waveforms in high-risk pregnancy—randomized controlled trial. Lancet 1987;1:188-190.

SECTION

VIII

Intrapartum Management of Labor and Delivery

Thomas R. Moore

During the 3rd trimester, in preparation for delivery, there are three major aspects of patient care for diabetic women: (*a*) regulation of maternal glycemia, (*b*) assessment of fetal well-being, and (*c*) determination of fetal pulmonary maturation.

Management of labor and delivery in a diabetic mother requires knowledge about previous obstetric history. This should include the gestational ages, mode of delivery, complications, ease or difficulty of previous births, and birth weights of previous children. Intrapartum management may be complicated by the presence of hypertension, preeclampsia-eclampsia, preterm labor, premature rupture of membranes, infections, an over- or undergrown fetus, hydramnios, or variable control of hyperglycemia during late gestation.

Diabetic women with preeclampsia, whose labor must be induced for maternal indications, frequently become severely ill without warning. In addition, diabetes is associated with a higher risk, with or without prolonged labor, of chorioamnionitis, and other infections. Their infections are often more severe and pose a higher risk for fetal sepsis.

Diabetic pregnancy is a poor setting for prolonged labor, slow cervical dilation, high doses of oxytocin, or midforceps delivery. The timing and mode of delivery should be carefully planned well in advance unless complications ensue that require immediate delivery. Most perinatal centers have a high rate of cesarean section delivery of about 50% in IDDM and NIDDM women.

CHAPTER

21

Timing and Mode of Delivery

A critical issue in diabetic pregnancy is planning the timing of delivery (1, 2). Although it has been common practice in the past to perform amniocentesis and deliver diabetic women at 37 weeks' gestation, experience in perinatal centers since 1980 indicates that, with meticulous antepartum fetal assessment procedures, delivery can be delayed frequently until nearly 40 weeks' gestation without an increase in morbidity for the mother or morbidity or mortality for the infant.

In diabetic women in good control and with normal antepartum surveillance tests, delivery should be delayed until fetal pulmonary maturation occurs. Term or near-term delivery permits ripening of the cervix and improves the chances of vaginal delivery. The considerations for delivery at term must be balanced with the risk of a larger baby or an unexpected fetal demise as the due date approaches. In the United States, Landon and Gabbe (2) plan elective induction of labor at 38–40 weeks' in well-controlled diabetic women without vascular disease. An amniocentesis may be performed to document fetal maturity, but this procedure is often not necessary when there is accurate gestational dating and there has been good diabetic control.

Coustan points out that the convergence of advancing perinatal technology and our improved understanding of the relationship between maternal diabetic control and a good pregnancy outcome now permit the obstetrician to individualize decision making so that the majority of women can proceed to term or near term before planned delivery (1). The approach used at Brown University for timing and delivery of diabetic women is presented in Table 21.1 (1). It should be noted that, in the Coustan scheme, the White class of maternal diabetes does not enter into clinical decision-making concerning timing of delivery. In general, perinatal risks increase when any type of diabetic pregnancy goes much beyond term; most obstetricians are reluctant to allow women with diabetes including those with GDM, to continue their pregnancies much beyond the estimated date of confinement (EDC).

The uncomplicated diabetic pregnancy at 40 weeks' gestation with the maternal cervix unfavorable for induction can present a dilemma. One option is to use prostaglandin E gel or laminaria for cervical ripening. The efficacy of this procedure has not been demonstrated unequivocably but this approach is often used to alleviate anxiety of both the patient and the obstetrician. Except in the presence of macrosomia or if there has been a previous delivery by cesarean section, the option of cesarean section without labor is almost never chosen (1).

Primary prevention of perinatal complications is possible when diabetic women are euglycemic throughout pregnancy (fasting blood glucose values <100 mg/dl; 5.5 mmol/L, other values consistently <120–130 mg/dl; 6.6 mmol/L–7.2 mmol/L) and with normal HbA1c values during 3rd trimester. In Ireland, Drury and colleagues (3) followed 129 diabetic pregnancies and limited antepartum fetal testing to women with hypertension (12 patients), suspected IUGR (3 patients), and reduced fetal movement (3 patients). These complicated pregnancies represented only 14% of diabetic deliveries. Women with GDM were not included in the study and 85% of deliveries were between 38 and 40 weeks' gestation. The cesarean section rate was 20% and perinatal mortality rate, excluding congenital anomalies incompatible with life, was 2.3%.

ASSESSMENT OF FETAL PULMONARY MATURATION

Preterm birth of infants of diabetic mothers remains a persistent problem even with excellent maternal control of hyperglycemia be-

Table 21.1.
Guidelines for an Approach to Decisions for Timing, of Delivery in Diabetic Women[a]

Decision	Examples
Immediate delivery even without documentation of fetal lung maturity	Maternal or fetal compromise puts the life of either at significant risk
	Proven severe fetal compromise at a time when fetal survival after delivery is considered possible (26 weeks' gestation at Brown University)
	Maternal eclampsia or severe preeclampsia when maternal well-being is compromised by continuing the pregnancy and little improvement in fetal outcome is anticipated
Delivery as soon as fetal lung maturity can be documented when there is a significant maternal or fetal problem, but neither pose an immediate risk	Poor or undocumented maternal metabolic control, preeclampsia, worsening of pre-existing hypertension, IUGR, strongly suspected fetal macrosomia, previous classical cesarean section, or equivocal antepartum assessment of fetal condition
Patients who do not fulfill any of the above criteria; elective delivery is **considered** at 38 weeks' gestation	Cervix is clinically "ripe" and fetal lung maturity has been documented by studies on amniotic fluid
	Unfavorble cervix: amniocentesis not attempted because fetal lung maturity would not lead to induction of labor under these circumstances
	If after 38 completed weeks of gestation, oligohydramnios precludes successful amniocentesis, this is taken as an indication to proceed with delivery without amniotic fluid studies
	Repeat cesarean sections are performed at 38 weeks if lung maturity is documented

[a]Adapted from Coustan DR. Delivery: Timing, Mode and Management. In: Reece EA, Coustan DR (eds). Diabetes Mellitus in Pregnancy. Principles and Practice. New York, Churchill Livingstone, 1988;525–533.

cause maternal complications may require delivery before term. The main causes are preeclampsia, a decline in renal function, and uteroplacental insufficiency. When clear obstetric indications for preterm delivery are present, an assessment of fetal lung maturity is critical (Fig. 21.1).

Kulovich and Gluck (4, 5) originally reported a delay in normal timing of pulmonary maturation in diabetic pregnancies. They described a longer interval before appearance of the amniotic fluid phospholipid compound, phosphatidylglycerol (PG). Their observations were in amniotic fluid samples from an unselected population of poorly controlled diabetic women in the general community and they were not correlated with degree of diabetic control, confirmation of gestational age, or type of diabetes (IDDM, NIDDM, or GDM).

Other investigators have reported different observations. Landon and colleagues (6) stratified IDDM patients by mean maternal glucose level and reported that fetal lung maturity occurs later in pregnancies with **poor glycemic control** (mean glucose level >110 mg/dl; 6.1 mmol/L) irrespective of type of diabetes. Fadel

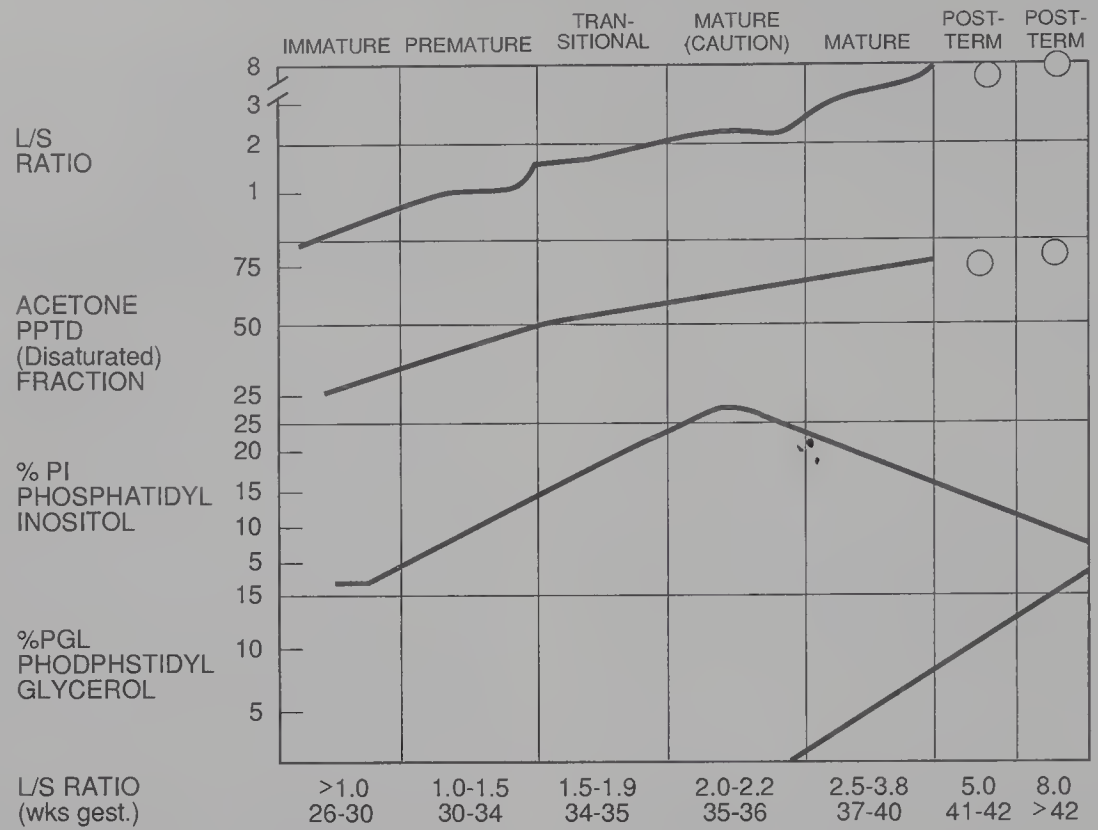


Figure 21.1. Kulovich-Gluck form used to report the lung profile (4, 5). The four amniotic fluid lipid determinations are plotted on the ordinate and the weeks of gestation are plotted on the abscissa (as well as the L/S ratio and an internal standard). When these are plotted, they fall with a very high frequency into a given grid that identifies the stage of development of the lung, as shown in the upper part of the form. The term "mature (caution)" refers to patients other than those with diabetes who can be delivered if necessary at this time. Patients with diabetes can be delivered with safety when the values fall in the "mature" grid. Reprinted with permission from Regents of the University of California, 1977.

and co-workers (7) obtained amniotic fluid for fetal maturity studies in 287 healthy and 198 diabetic women. Each diabetic patient was matched with a control subject of the same race, sex of newborn infant, and gestational age at amniocentesis. The regression lines of nonhypertensive, hypertensive, and all diabetic women were not different from those of their respective matched control subjects. Also, there was no difference in the proportion of mature lecithin phosphorus concentrations at different weeks between diabetic and normal women. They interpreted their failure to find a significant influence of diabetes on fetal lung maturation to a probable improvement in diabetic control, which resulted in normalization of the fetal metabolic environment.

In a study from Finland, Ylinen (8) reported amniotic fluid phospholipid concentrations in 227 3rd trimester specimens and HbA1c values in 889 maternal blood specimens. In 115 IDDM singleton pregnancies without fetal malformations or stillbirths, they found that fetuses of diabetic mothers whose HbA1c was 8.5% or higher during pregnancy remained PG negative more often than those in pregnancies with mean HbA1c values below 8.5% at 37 and 38 completed weeks of gestation. Their results and recent studies of others suggest that **maternal hyperglycemia** or other metabolic disturbances associated with hyperglycemia are the cause of delayed fetal lung maturation among IDDM women.

In diabetic women in less than ideal control, it is not safe to assume that there is no risk for neonatal respiratory distress syndrome (RDS) until at least 38.5 completed weeks of gestation. Any delivery planned before this time for other than the most urgent fetal and maternal indications should be preceded by documentation of pulmonary maturity by amniocentesis. The documentation of a lecithin/sphingomyelin (L/S) ratio of >2.0 is insufficient reassurance. An amniotic fluid concen-

tration of phosphotidylglycerol of 3% and a decline in phosphotidyl/inositol (PI) indicate a mature lung profile (Fig. 21.1). Amniocentesis should also be performed for confirmation of fetal maturity if obstetric dates are uncertain or the patient has been in poor diabetic control throughout pregnancy.

CONTINUOUS FETAL HEART RATE MONITORING

For the past two decades, techniques have been available for continuous fetal heart rate monitoring during labor and delivery and measurements of fetal scalp blood pH values. Although there has been some disagreement about the place of this technology in normal and abnormal pregnancies, there has been a rapid proliferation of monitoring in both the United Kingdom (9) and the United States.

One problem with fetal heart rate monitoring has been the high degree of inter- and intraobserver variation (10, 11). Visual analysis of tracings, even by experienced professionals, presents difficulties in recognition of erroneous or doubtful decelerations or accelerations. Dawes and colleagues have addressed these problems and the errors caused by fetal heart rate monitors in a study of 1000 consecutive fetal heart rate tracings from 349 patients (12). They documented erroneous or doubtful decelerations in 111 (11%) tracings when they used the computer technique of autocorrelation to process ultrasound signals from the fetal heart to derive the best estimate of pulse interval. Their use of a computer to measure variables permitted an accuracy not attainable from visualization of strips and allowed a consistent judgment to be made when information was deficient. The system also made it possible, for the first time, to judge the functions of fetal monitors by measuring their limitations objectively. In evaluating continuous fetal heart rate monitoring, more comprehensive outcome measurements than neonatal mortality are necessary to assess the long-term efficacy of the technique.

In the United States, monitors are used during labor and delivery in about 75% of births. A number of studies have failed to show that monitoring reduces perinatal mortality or the incidence of neurologic developmental disorders. Prentice and Lind (13) have examined eight prospective randomized controlled trials designed to assess the value of fetal heart rate monitoring during labor. None suggested any improvement over surveillance by intermittent auscultation. Rates of cesarean section and forceps delivery were higher in the continuously monitored group. In a randomized trial involving 13,079 newborn children conducted by the Oxford National Epidemiology Unit at the Radcliffe Infirmary, Oxford, and the National Maternity Hospital in Dublin, intensive monitoring had little, if any protective effect against cerebral palsy (14).

In an important United States multicenter randomized clinical trial of 93 children born prematurely, whose heart rates were monitored electronically during delivery, and 96 prematurely born infants whose heart rates were periodically monitored by auscultation, there was no improvement in perinatal outcomes among the infants who had fetal electronic monitoring (15). Moreover, the procedure was associated with about a threefold risk of cerebral palsy compared with the conventional practice of auscultation in which a nurse uses a stethoscope to check the unborn infant's heart rate every few minutes during labor and delivery.

In addition, Shy and colleagues (15) showed that the development of cerebral palsy was correlated with the duration of abnormal heart rates before delivery. The heart rate of a normal fetus may slow during uterine contractions. Very slow heart rates or failure of the heart rate to rise promptly to the normal range following a contraction may signal a potentially dangerous lack of oxygen. In this study, the average time that elapsed between detection of an abnormal heart rate and delivery was longer in the electronically monitored group (104.5 minutes) than in the group monitored manually by stethoscope (60.5 minutes). They suggest that the physicians who used fetal electronic heart rate monitoring may have delayed the decision to perform a cesarean section either because they were falsely reassured by the technology or because they did not believe the results were reliable. Although the American College of Obstetricians and Gynecologists previously recommended fetal electronic monitoring for all high-risk patients, they issued a statement in 1990 that auscultation is equally acceptable (16). In most American hospitals, however, the shortage of nurses has made frequent checks of fetal heart

rate impossible. For this reason, fetal electronic monitoring is likely to continue, because it is preferable to not checking the baby's heart rate at all (16).

Freeman (17) commented on the Shy paper in an editorial by summarizing all the clinical trials of electronic fetal monitoring dating from optimistic retrospective reports in the 1970s to the more recent prospective reports from 1979–1987 (18–21). The hoped-for benefit from electronic fetal monitoring has not been confirmed because controlled trials were not carried out before this form of technology became applied universally.

Diabetic women exemplify all recognized risks for intrapartum fetal hypoxia, fetal acidosis, fetal death, low Apgar scores, and childhood developmental problems despite improved maternal glucose control; a strong case can be made for a large prospective, randomized trial that emphasizes both specially trained nurses and monitors. Such a trial would be informative; otherwise, the answers concerning the best methods for monitoring labor and delivery in diabetic women will elude us for a long time. Meanwhile, and in the absence of specially trained nursing personnel in **constant attendance** during deliveries of diabetic women, it is both prudent and justifiable to utilize continuous fetal heart monitoring. Every effort should be made to avoid incorrect interpretations of the tests that can lead to interventions for preterm delivery. Nor should we forget that it has been the combined approach of control of hyperglycemia with use of self-monitoring of blood glucose levels at home plus the advances in technology in perinatal medicine that is responsible for the optimistic outcome of these pregnancies today.

CESAREAN SECTION

Despite efforts in the United States in recent years to reduce the rate of delivery by cesarean section (CS), about half of diabetic women are delivered by this route. In California, in a state-sponsored program from 1986–1988, 1817 deliveries in diabetic women were analyzed (22). The statistics did not include all diabetic women, adjust for type of diabetes by NDDG criteria, or take into account control of maternal hyperglycemia. In this survey, CS delivery rate varied from 38–56%. The most common indications for operative delivery were fetal distress, failed induction of labor, arrest of cervical dilatation, and repeat CS. A major concern for the prevention of birth injuries in infants of diabetic mothers (IDM) has contributed to the high rate of CS in all clinical settings. In the United States, rates for CS exceed those in the United Kingdom and other European nations with long established national diabetes in pregnancy programs. Current American guidelines for fetal, maternal, and obstetric contraindications to a trial of labor are indicated in Table 21.2 (23), and relative contraindications for spontaneous vaginal delivery are shown in Table 21.3. These conditions must be assessed carefully and managed on a case by case basis.

Table 21.2.
Contraindications to a Trial of Labor[a]

Previous uterine incision secondary to uterine disease
Extensive myomectomy
Cephalopelvic disproportion resulting from abnormalities of pelvic bones
Malpresentation of the fetus, e.g., shoulder, complete, or footling breech
Invasive cervical carcinoma
Central or total placenta previa
Active or culture proven genital herpes infection

[a]In general, any contraindication to spontaneous labor and vaginal delivery is a contraindication for induction of labor. (Adapted from text by O'Brien WF, Cefalo RC. In: Gabbe SG, Niebyl JR, Simpson, JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill Livingstone, 1986;370–371.

INDUCTION OF LABOR

In diabetic pregnancy, the decision for induction of labor is sometimes made for obstetric reasons at a time when cervical maturation

Table 21.3.
Relative Contraindications for Normal Spontaneous Delivery in Diabetic Women

Breech presentation
More than one previous cesarean section
Questionable fetal macrosomia
Severe preeclampsia and an unfavorable cervix for induction of labor
Grand multiparity and uterine overdistension secondary to multiple gestation
Hydramnios

is not fully complete. In this circumstance, labor is often prolonged or less successful than spontaneous labor with full cervical dilation. For this reason, cervical length and consistency, dilation, and position of the presenting part should always be determined.

Women with unfavorable Bishop scores (Table 21.4) (24) are sometimes thought to be candidates for preinduction cervical ripening. When the Bishop score is 4 or less, preinduction intracervical or intravaginal prostaglandin administration may be effective (25). This is achieved by instillation of prostaglandin E_2 in an appropriate vehicle into the endocervical canal or posterior vaginal fornix. Women who are prescribed this type of cervical ripening may experience strong uterine contractions for the first 1–3 h following administration of the prostaglandin. Fetal distress, abnormal fetal heart rate patterns, and fetal death have been documented (26). For this reason, administration of prostaglandin gel should always be conducted in a hospital setting with continuous fetal monitoring for at least 2 h following instillation. The procedure can be repeated once in the next 4–8 h. Studies of labor induction using this technique have demonstrated an overall improvement in Bishop score. Although some investigators have noted a shortening of labor and reduced cesarean section rate, this has not been a universal finding.

Administration of oxytocin over a 1- to 3-day period may also induce cervical readiness for labor and development of the lower uterine segment. This is typically done by preparing the patient for labor, administering oxytocin intravenously to achieve contractions every 4 minutes and continuing the drug until 8:00 or 10:00 at night. At the end of each day, if the cervix has not reached complete effacement or dilation to 3 cm, oxytocin is discontinued and the patient is allowed to rest overnight. This technique has the advantage of permitting the membranes to remain intact during the cervical ripening phase. The disadvantage in women with IDDM, NIDDM, and GDM is that the patient is not permitted to take food or fluids by mouth during this prolonged induction period. In IDDM and NIDDM women, a constant intravenous infusion of insulin with an adequate glucose supply is necessary. Because of the requirement in this setting to continue the insulin drip for 2–3 days, many obstetricians avoid this "serial induction" technique in diabetic women for whom it is an especially stressful and unpleasant experience.

An alternative approach is used by Samuels and Landon (26). In general, they recommend that a patient who fails to demonstrate significant cervical change after 6–8 h of oxytocin stimulation is best delivered by cesarean section. They rarely perform serial induction of labor. In women whose labor is clearly established, their practice is to continue close external or internal electronic monitoring of the fetal heart rate. Analgesics or anesthesia are usually prescribed and the blood sugar is maintained in the normal range.

The decision to perform a CS delivery for failed induction of labor should be based on obstetric criteria. This decision is made when the patient has had an adequate latent phase of labor (contractions every 3 minutes of moderate or strong intensity) and failed to achieve complete cervical effacement. The length of time for entry into the active phase of labor should be individualized. The work of Friedman and colleagues (28) suggests that 97% of

Table 21.4.
Bishop Score[a]

Criteria	0	1	2	3
Position of cervix	Posterior	Mid	Anterior	
Consistency of cervix	Firm	Medium	Soft	
Effacement (%)	0–30	40–50	60–70	>80
Dilation (cm)	0	1–2	3–4	>5
Position of head	Negative 3 station (3 cm above iliac spines)	Negative 2 station	Negative 1 station	+1 station

[a]A score of 9 or more is favorable for induction. With permission from Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266–268.

primiparous women should enter the active phase of labor after 20 h with a shorter period for multiparous women (16 h).

Other indications for a CS after the active phase of labor has been established include: (*a*) fetal distress (persistent late decelerations or severe variable decelerations) and, when possible, confirmation of fetal acidosis by measurement of pH from a capillary blood sample obtained from the fetal scalp; (*b*) arrest of dilation with failure of the cervix to dilate for 2 consecutive hours despite adequate contractions; and (*c*) arrest of fetal descent with failure of the vertex to descend into a deliverable station after 2–3 h of adequate maternal bearing-down efforts.

Caution is indicated in diabetic women with marginally macrosomic infants with slow progress in labor, a prolonged second stage, and oxytocin stimulation. In these patients, the use of forceps or vacuum to assist in delivery of the fetal head poses a marked danger of shoulder dystocia, Erb's palsy or other neurologic injury, asphyxia, or fracture of the clavicle.

At delivery of diabetic mothers, a skilled pediatric team should stand by even if labor has been spontaneous or induced without difficulty. An initially vigorous infant may develop respiratory distress insidiously or hypoglycemia may occur while the newborn baby is still in the delivery room. Most pediatric services have clear guidelines to monitor IDM for hypoglycemia, metabolic problems, respiratory distress, major malformations, and hypertrophic or congestive cardiomyopathy. Neonatal problems of IDM are discussed in Section X.

Following delivery of the baby, the obstetrician should turn attention to the third stage of labor to avoid postpartum hemorrhage and ensure appropriate uterine involution. Women who have received prolonged oxytocin therapy or whose uteri have been overdistended by a macrosomic infant are at increased risk for postpartum hemorrhage in the delivery room and in the first hours postpartum. Vigorous fundal massage, administration of intravenous oxytocin and, in appropriate instances, injection of intramuscular prostaglandin F_2 will assist in keeping the uterus firm.

CHAPTER

22

Management of Diabetes During Labor and Delivery

After the onset of labor, control of maternal plasma glucose levels is often erratic. The problem becomes more difficult when labor is prolonged or a cesarean section is necessary. Labor and delivery suites tend to be very busy places. The staff responsible for the care of a diabetic patient may change throughout the course of the day and night. Thus, it is helpful to have a simple method to record the course of labor, metabolic status, and treatment throughout this period. Figure 22.1 is a flowsheet that has been devised to provide this information on a single page of the chart.

The control of plasma glucose levels during labor and delivery is much easier when insulin is administered as a continuous low-dose infusion during the peripartum period. The patient is hospitalized 1 day before delivery. She follows her usual schedule for diet, insulin administration, and activity.

Table 22.1 is a simplified protocol adapted from Coustan (1) for the management of diabetes during labor and delivery in IDDM and NIDDM women. Table 22.2 is a guideline for infusion of insulin and glucose during labor and delivery. The treatment is coordinated with the anesthesiologist to prevent overhydration and excessive glucose administration during delivery.

Coustan employs a simple procedure for diabetic control for elective cesarean sections (1). The patient follows her usual meal and insulin plan on the day and evening before surgery. If she has been in good control, her fasting blood glucose on the morning of surgery should be normal. An intravenous line is inserted and normal saline without glucose is infused. Her cesarean section should be the first operation on the morning schedule and begin at an early hour so that no perturbations in glucose metabolism have yet occurred. If she is not in good control and is hyperglycemic on the morning of surgery (fasting blood glucose >120 mg/dl; 6.6 mmol/L), the suggested guidelines on Table 22.1 should be followed. Once the baby is delivered, glucose with or without insulin can be infused as needed.

Women with gestational diabetes, unless they have unrecognized NIDDM that required large doses of insulin during pregnancy, require little or no insulin during labor and delivery. The flowsheet described earlier (Fig. 22.1) is useful to monitor their progress. Small doses of rapid-acting insulin injected subcutaneously are given as necessary to maintain euglycemia.

Although a normal maternal plasma glucose level during delivery does not reverse fetal pancreatic β-cell hypertrophy that may have occurred over the previous 9 months, infants delivered by the method described previously have much less difficulty in maintaining a normal neonatal level of plasma glucose (29, 30).

Jovanovic and Peterson (31) use a somewhat different protocol for management of labor and delivery, and aim to maintain maternal glucose values at 70–90 mg/dl (3.8–5.0 mmol/L) during induction of labor in well-controlled insulin-dependent patients. The usual dose of NPH intermediate-acting insulin is given at bedtime and insulin is withheld on the morning of induction of labor. An intravenous line is placed and normal saline is infused. Once active labor is achieved or the blood glucose level falls below 70 mg/dl, the infusion solution is changed to dextrose at a rate of 2.55 mg/kg/min. The blood glucose level is checked at intervals and the dextrose infusion rate is

LABOR AND DELIVERY FLOWSHEET FOR DIABETIC PATIENTS

Name: _____
Birthdate: _____
Hosp # _____

ADMISSION: DATE _____ TIME _____

DATE	TIME (h)	IV INSULIN INFUSION (Rate, insulin, glucose/h) or SUB Q INSULIN (Type and U)	BLOOD GLUCOSE (mg/dl)	INTAKE IV + ORAL (kcal)	(cc)	OUTPUT (cc)	TPR B/P	WBC HCT	BLOOD CHEMISTRY	COMMENT: DIL, EFFAC, L/S Ratio Complications, Other Meds, Insulin Reactions, etc.
TOTAL (8 H)		INSULIN (units)	I & O	kcal	cc	cc				
			INTAKE & OUTPUT							

Figure 22.1. Labor and delivery flowsheet for diabetic patients.

Table 22.1.
Management of Diabetes During Labor and Delivery in Women with IDDM or NIDDM[a,b,c]

Decision	Examples
One day before induction of labor	
	Usual insulin dose and meal plan to maintain euglycemia
Morning of induction	
	Withhold insulin and breakfast
	Baseline fasting blood glucose
	Initiate labor and delivery flowsheet (Fig. 22.1)
	Start intravenous infusion of 5% dextrose in 0.5% normal saline at 125 ml/h using an infusion pump
Measure blood glucose hourly with meter at bedside	
	For glucose level >110 mg/dl (6.1 mmol/L) add 10 U regular insulin to 1000 ml D5/0.5N saline and continue infusion rate of 125 ml/h (1.25 U insulin/h); **keep infusion rate constant**
	Insulin adjustments are made hourly if necessary by doubling or halving the insulin concentration to maintain blood glucose at 70–120 mg/dl (3.8–6.6 mmol/L)

[a]This clear and concise protocol is adapted from Coustan DR. Delivery, Timing, Mode and Management. In: Reece EA, Coustan DR. Diabetes Mellitus in pregnancy. Principles and Practice. New York: Churchill Livingstone 1988:525–533.

[b]For spontaneous labor, follow the same procedure. Insulin requirement will be less if the patient has taken intermediate-acting insulin in the previous 12 h. Patients with fever or infection will require higher doses (insulin-infusion "Guideline", Table 22.2).

[c]Obese NIDDM women who have required >100U of insulin a day prepartum, and patients with fever, infection, or other complications will require higher insulin doses.

changed accordingly. If the blood glucose rises to >140 mg/dl (7.7 mmol/L), 2 U rapid acting insulin are given subcutaneously each hour until the blood glucose is <140mg/dl (7.7 mmol/L). When elective cesarean sections are planned, the bedtime dose of NPH insulin is repeated at 8:00 AM on the day of surgery and every 8 h if surgery is delayed. Glucose infusions are started if the blood glucose falls below 70 mg/dl (3.8 mmol/L).

In later studies, Jovanovic and Peterson (32) used glucose-controlled insulin infusions to define glucose and insulin requirements during first stage of labor induced by oxytocin in 52 IDDM women. In these circumstances, insulin requirements decreased to zero during active stage 1 labor while glucose infusion rate was constant. In six women with spontaneous labor, the decrement in insulin requirement was similar. Insulin was required during second stage of labor.

Golde and colleagues (33), however, found that half their patients required insulin infusions of 0.6–1.2 U or more per hour throughout labor. Thus, although some women with diabetes require no insulin during active labor, others need insulin to maintain normoglycemia. Our experience is similar to that of Golde and associates (33). We have found that women who require insulin during labor are most likely to be IDDM patients in poor glycemic control or **NIDDM women** who are obese with variable and, sometimes, marked degrees of insulin resistance. These differences underscore the importance of individualization of the management of pregnant diabetic woman during labor and delivery. Blood glucose levels should be checked hourly at the bedside and the insulin dose should be adjusted accordingly.

In summary, there are several ways to manage insulin therapy and maternal caloric intake during labor and delivery. We prefer the constant insulin infusion method because it provides more even control of maternal plasma glucose values and is easier to implement and supervise on a busy labor and delivery suite.

Table 22.2.
Guidelines for Insulin and Glucose Infusion During Labor and Delivery in IDDM and NIDDM[a]

Fluids by Infusion Pump	Capillary Glucose mg/dl	Capillary Glucose mmol/L	Insulin U/h
5% dextrose in	<80	4.4	0.0
0.5% normal	80–100	4.4–5.5	0.5
saline, constant	101–140	5.6–7.7	1.0
rate: 125 ml/h	141–180	7.8–1.0	1.5
	181–220	10.1–12.2	2.0
	>220	>12.2	2.5

[a]These guidelines will need to be adjusted for each patient.

References for Section VIII

1. Coustan DR. Delivery: Timing, mode and management. In: Reece EA, Coustan DR (eds). Diabetes Mellitus in Pregnancy. Principles and Practice. New York: Churchill Livingstone, 1988:525-533.
2. Landon MB, Gabbe SG. Antepartum fetal surveillance and delivery timing in diabetic pregnancies. Clin Diabet 1990;8:33-46.
3. Drury MI, Stronge JM, Foley ME, MacDonald DW. Pregnancy in the diabetic patient. Timing and mode of delivery. Obstet Gynecol 1983; 62:279-282.
4. Kulovich MV, Hallman MB, Gluck L. The lung profile. I. Normal pregnancy. Am J Obstet Gynecol 1979;135:57-63.
5. Kulovich MV, Gluck L. The lung profile II. Complicated pregnancy. Am J Obstet Gynecol 1979;135:67-70.
6. Landon MB, Gabbe SG, Piana R, Mennuti MT, Main EK. Neonatal morbidity in pregnancy complicated by diabetes mellitus: Predictive value of maternal glycemic profiles. Am J Obstet Gynecol 1987;156:1089-1095.
7. Fadel HE, Saad SA, Nelson GH, Davis HG. Effect of maternal-fetal disorders on lung maturation. I. Diabetes mellitus. Am J Obstet Gynecol 1986;155:544-553.
8. Ylinen K. High maternal levels of HbA1c associated with delayed fetal lung maturation in insulin-dependent pregnancies. Acta Obstet Gynecol Scand 1987;66:263-266.
9. Wheble AM, Gillmer MDG, Spencer JAD, Sykes GS. Changes in fetal monitoring practice in the UK: 1977-1984. Br J Obstet Gynaecol 1989;96: 1140-1147.
10. Trimbos JB, Keirse MJNC. Observer variability in assessment of antepartum cardiotocograms. Br J Obstet Gynaecol 1978;85:900-906.
11. Borgatta L, Shrout PE, Divon MY. Reliability and reproducibility of nonstress test readings. Am J Obstet Gynecol 1988;159:554-558.
12. Dawes GS, Moulden M, Redman CWG. Limitations of antenatal fetal heart rate monitors. Am J Obstet Gynecol 1990;162:170-173.
13. Prentice A, Lind T. Fetal heart rate monitoring during labour—too frequent intervention, too little benefit? Lancet 1987;2:1375-1377.
14. Grant A, Joy M-T, O'Brien N, Hennessy E, MacDonald D. Cerebral palsy among children born during the Dublin randomized trial of intrapartum monitoring. Lancet 1989;2:1233-1236.
15. Shy KK, Luthy DA, Bennett JC, et al. Effects of electronic fetal-heart-rate monitoring, as compared with periodic auscultation, on the neurologic development of premature infants. N Engl J Med 1990;322:588-593.
16. Research activities. Agency for Health Care Policy and Research (AHCPR), Rockville, MD; No 128, April, 1990.
17. Freeman R. Editorial. Intrapartum fetal monitoring—a disappointing story. N Engl J Med 1990;322:624-626.
18. Haverkamp AD, Orleans M, Langendoerfer S, McFee J, Murphy J, Thompson HE. A controlled trial of the differential effects of intrapartum fetal monitoring. Am J Obstet Gynecol 1979; 134:399-412.
19. Parer JT. Fetal heart rate monitoring. Lancet 1979;2:632-633.
20. Langendoerfer S, Haverkamp AD, Murphy J, et al. Pediatric follow-up of a randomized controlled trial of intrapartum fetal monitoring techniques. J Pediatr 1980;97:103-107.
21. Luthy DA, Shy KK, van Belle G, et al. A randomized trial of electronic fetal monitoring in preterm labor. Obstet Gynecol 1987;69:687-695.
22. California Department of Health Services, Maternal and Child Health Branch. Status Report of the Sweet Success California Diabetes and Pregnancy Program 1986–1988. July 15, 1989.
23. OBrien WF, Cefalo RC. Labor and delivery. In: Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York: Churchill Livingstone, 1986:371-372.
24. Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266-268.
25. Shepherd JH, Knuppel RA. The role of prostaglandins in ripening of the cervix and inducing labor. Clin Perinatol 1981;8:49-55.
26. Quinn MA, Murphy AJ. Fetal death following extraamniotic prostaglandin gel: report of two cases. Br J Obstet Gynaecol 1981;88:650-655.
27. Samuels P, Landon MB. Medical Complications. In Gabbe SG, Niebyl JR, Simpson JL (eds). Obstetrics. Normal and Problem Pregnancies. New York, Churchill Livingstone 1986:900.
28. Friedman EA, Sachtleben MR. Dysfunctional labor. I. Prolonged latent phase in the nullipara. Obstet Gynecol 1961;17:135-148.
29. West TET, Lowy C. Control of blood glucose during labor in diabetic women with combined glucose and low dose insulin infusion. Br Med J 1977;1:1252-1254.
30. Yeast JD, Porreco RP, Ginsberg HA. The use of continuous insulin infusion for the peripartum

management of the diabetic pregnancy. Am J Obstet Gynecol 1978;131:861-864.
31. Jovanovic L, Peterson CM. Optimal insulin delivery for the pregnant diabetic patient. Diabetes Care 1982;5(Suppl):24-37.
32. Jovanovic L, Peterson CM. Insulin and glucose requirements during the first stage of labor in insulin-dependent women. Am J Med 1983; 75:607-612.
33. Golde SH, Good-Anderson B, Montoro M, Artal R. Insulin requirements during labor: A reappraisal. Am J Obstet Gynecol 1982;144:556-559.

SECTION

IX

Postpartum Management of IDDM, NIDDM, and GDM: Transitional Care

Dorothy R. Hollingsworth

Following delivery, an **immediate** decrease in insulin requirement occurs. This is related to the abrupt loss of the placenta, which has synthesized high levels of peptide and steroid hormones throughout pregnancy. These substances are diabetogenic and have actions that are antagonistic to those of insulin. Thus, immediate maternal metabolic adjustments occur following birth. The postpartum course is smoother for diabetic women who have been carefully controlled throughout labor and delivery with a low-dose constant insulin infusion.

CHAPTER

23

Blood Glucose Control

IDDM WOMEN

The care of IDDM patients after delivery is difficult on busy obstetrical services. Different physicians and nursing staff members may be responsible for medications and treatment and they may not be familiar with the details of the medical history and antenatal course of the patients. The hospital record is often cumbersome and it may be difficult to coordinate laboratory values with fluid intake and their relation to labor and delivery. This period can be simplified if a one-page summary flowsheet is attached to the front of the chart (Fig. 23.1). This is especially useful for women who have a long labor, cesarean section, or complications during delivery or the postpartum period.

In IDDM patients, particularly those who have had a cesarean section, the easiest management in the transitional immediate postpartum period is to continue the low-dose insulin infusion during the 1st postoperative day or until normal oral intake is ensured. Alternatively, plasma glucose levels can be assessed before meals (6 AM, 12 noon, 6 PM) and at bedtime with a meter at the bedside. Small doses of rapid-acting insulin are administered subcutaneously before each meal to cover elevated levels of plasma glucose. There is a very real danger of **overinsulinization** of patients during this period and "sliding scale" insulin orders based on tests of random urine specimens or plasma glucose values should never be left for nursing staff or covering physicians to carry out.

Each insulin dose in the immediate postpartum period (1–3 days) should be determined judiciously based on the patient's plasma glucose level, clinical course, and intake of nutrients. Little or no insulin may be required during the 1st postpartum day. This period is a brief, mild honeymoon that begins immediately after delivery and lasts 48–72 h.

The mild honeymoon is not apparent in many women who have had complications, a cesarean section with already present chorioamnionitis, postoperative fever, endometritis, and infections in the incision or urinary tract.

Breast feeding is encouraged and there is no contraindication to lactation in IDDM women. Some women experience hypoglycemia during breast feeding unless they have a snack beforehand. Caloric intake may be modestly increased or insulin may be decreased. The recommended maternal dietary adjustments for lactation are discussed in Section IV. Although difficult with a new baby, each mother should be encouraged to have three meals at regular times with midmorning, midafternoon, and bedtime snacks. If this can be worked out, it is soon possible to return to a maintenance insulin program.

After 1–3 days, the patient can be restarted on twice daily injections of intermediate- and rapid-acting insulin. The selection of the insulin dose has to be individualized. Because many women are in poor diabetic control at the onset of pregnancy, the prepregnancy dose of insulin may be a poor guideline. However, in patients who were in excellent control before conception, on home monitoring and with normal HbA1c concentrations, it is appropriate to return to about two thirds the previous prepregnancy insulin dose.

The first morning after vaginal delivery, one half of the last predelivery intermediate-acting insulin dose and 4–6 units of regular insulin may be sufficient before breakfast and dinner. Glucose monitoring should be resumed by the patient and insulin adjusted again on day 3. Ideally, glucose levels should range between

POSTPARTUM FLOWSHEET FOR DIABETIC PATIENTS

Name: _____
Birthdate: _____
Hosp # _____

DELIVERY: DATE _____ TIME _____ ☐ Vaginal ☐ CS

DATE	TIME (h)	IV INSULIN INFUSION (Rate, insulin, glucose/h) or SUB Q INSULIN (Type and U)	BLOOD GLUCOSE (mg/dl)	INTAKE IV + ORAL (kcal)	INTAKE IV + ORAL (cc)	OUTPUT (cc)	TPR B/P	WBC HCT	BLOOD CHEMISTRY	COMMENT: Complications, Infection, Insulin Reactions, etc. Rx.
TOTAL (12 h)		INSULIN (units)	I & O	kcal	cc	cc				
			INTAKE & OUTPUT							

Figure 23.1. Composite flow chart to record the clinical course and treatment of diabetic women in the immediate postpartum period.

70 and 150 mg/dl (3.8–8.3 mmol/L), but this may not be possible with the excitement of a new baby or if a urinary tract infection or endometritis is present. Lactation decreases insulin requirements. Before hospital discharge, each IDDM woman should be instructed to make an appointment with her diabetologist within 1 week and reminded to have an annual (around the time of each birthday) pelvic examination with a Papanicolaou smear of the cervix, retinal examination, and renal assessment.

NIDDM WOMEN

In NIDDM patients, an even greater decrease in insulin requirement is noted following delivery. During the first few postpartum days, no exogenous insulin may be necessary. Plasma glucose levels should be monitored by strips or a meter at the bedside before each meal. If these values exceed 150 mg/dl (8.3 mmol/L), 2–4 U of rapid-acting insulin are usually adequate, but some patients will require as much as 8–10 U. The course of the individual patient will depend upon whether delivery was vaginal or by cesarean section, complications, food intake, and activity.

The postpartum diabetic honeymoon is unfortunately short lived for both IDDM and NIDDM patients. Within 48–72 h, glucose tolerance worsens and higher doses of insulin are often necessary. Hospital discharge usually coincides with this period of increased glucose intolerance, hyperglycemia, and the onset of lactation. Home blood glucose monitoring should be resumed.

In women with psychosocial problems and limited financial resources, home visits by public health nurses and weekly medical clinical appointments are helpful. Supervision of diabetic care should revert to the patient's usual medical care physician or clinic by 1 week postpartum. A decision is made to continue insulin or shift to oral hypoglycemic agents.

After discharge from the hospital, most diabetic patients become more casual about their control because of the added responsibility of a new baby and irregular hours of eating and sleeping. In follow-up metabolic studies of diabetic patients at 6–12 weeks postpartum, marked **underinsulinization** is common and many women are in worse control than at any time during pregnancy.

NIDDM women present a special problem because they may be asymptomatic with marked elevations of plasma glucose and lipid values. They may discontinue administration of insulin altogether and often do not seek medical supervision. This group of generally older and obese women is at increased risk for hypertension and micro- and macrovascular disease. Special efforts are needed to provide them with preventive medical care. Because these women are so easily lost from the health care system, plans for continuation of their medical care should be formulated during the 3rd trimester of pregnancy. Many NIDDM women have no regular physician and arrangements need to be made before delivery for a postpartum appointment with a diabetes clinic or physician within 1 week or 10 days after discharge from the hospital.

GDM (REVERSIBLE CARBOHYDRATE INTOLERANCE EXPERIENCED DURING PREGNANCY)

These women require **no** insulin immediately postpartum. A preventive medicine approach should be taken with a careful explanation of GDM, describing the importance of a proper retrospective diagnosis and future health measures.

At hospital discharge, each GDM patient should be instructed to return for her 6-week postpartum visit after fasting from 8:00 PM onward on the previous night. She should have an adequate diet containing 150 kcal of carbohydrate in the 3 preceding days. At the postpartum obstetric clinic visit, venous blood is drawn for a fasting plasma glucose level. She should then be given a cola drink containing 75 g of glucose following which a plasma of glucose determination is repeated at 2 h.

This procedure coordinated with regular postpartum obstetric care permits reclassification of each woman following delivery according to World Health Organization (WHO) criteria as (*a*) **normal** with previously mildly impaired glucose tolerance during pregnancy; (*b*) having **impaired** glucose tolerance; or (*c*) **diabetes** (Table 23.1) (1, 2).

These women are usually in good health and do not require frequent or expensive medical testing or care. Their usual annual health examination is a routine pelvic examination and a Papanicolaou smear of the cervix by their gynecologist. Because they are at higher risk

Table 23.1.
Definition of Diabetes Mellitus by World Health Organization (WHO) Criteria[a]

	Normal[b]		Impaired		Diabetes	
Time	mg/dl	mmol/L	mg/dl	mmol/L	mg/dl	mmol/L
Fasting	<140	<7.8	<140	<7.8	≥140	≥7.8
2h	<140	<7.8	140–198	7.8–11	≥198	≥11.1

[a]With permission from WHO Expert Committee on Diabetes Mellitus: Second Report. WHO Tech Rep Ser 1980;646;9–14; and Report of a WHO Study Group. Diabetes Mellitus. WHO Tech Rep Ser 1985;727:9–17.
[b]The terminology "normal" is not used by WHO. In the postpartum redefinition of gestational diabetes, we use the term to mean the absence of impaired glucose tolerance or diabetes.

for subsequent development of NIDDM or IDDM, we recommend that, for convenience of remembering, they have their gynecologic examination around the time of their birthday each year and request a **random** blood glucose determination at this appointment. An abnormally high result (>150 mg/dl; 8.3 mmol/L) should lead to further investigation and treatment by a diabetologist.

Clinical investigations during the past several years have revealed two gaps in the care of women with diabetes: (*a*) the postadolescent-prepregnancy period when young women leave home and become independent but may not find a new physician; and (*b*) the postpartum period when maternal diabetes tends to be ignored and all attention is focused on the new infant.

CHAPTER

24

Lactation

LACTATION

There is a paucity of information for diabetic women concerning breast feeding; several recent articles have added new insights on this neglected topic. Lawrence (3) has provided guidelines for lactation in IDDM women and Ferris and Reece (4) have written an excellent overview of lactation for IDDM women. No information is available concerning breast feeding or the composition of human milk in NIDDM or GDM women.

In a case-control study, Ferris and colleagues (5) followed 30 diabetic mothers and a matched comparison group from birth to 6 weeks postpartum. More than half of each group (53% and 57%) intended to breast feed but fewer diabetic women actually did and more stopped nursing in the 1st week. The primary reason was that many infants of diabetic mothers (IDM) spent variable periods in the special neonatal unit for observation for possible hypoglycemia. Of interest, however, is that by 1 week postpartum as many diabetic mothers as those in the comparison group were nursing. Initially, there were no differences in feeding problems between groups; between 2 and 6 weeks, two IDDM patients developed mastitis. By 6 weeks postpartum, fasting plasma glucose levels were lower in nursing mothers (82 ± 40 mg/dl; 4.6 ± 2.2 mmol/L) versus mean values in women who stopped nursing (145 mg/dl; 8.1 ± 2.1 mmol/L) and IDDM mothers who chose to bottle feed (120 ± 30 mg/dl; 6.7 ± 1.7 mmol/L). The daily caloric intake of nursing mothers necessary to sustain lactation was 31 kcal/kg of ideal maternal weight.

A detailed analysis of breast milk from an IDDM woman by Bitman and colleagues (6) has shown that, with the exception of lipids, there was no difference in milk composition of the IDDM mother compared with normal women. In the IDDM mother, there was a higher proportion of free fatty acids (FFA) but it was not clear whether this represented lower rates of fatty acid activation or lower activity of acyltransferases within the mammary gland. Medium-chain fatty acids (C10–C14) were also lower. No information is available concerning whether there are biochemical differences in breast milk from IDDM women versus NIDDM women or the effect of maternal diet, insulin doses, and degree of control of hyperglycemia.

There has been some uncertainty about insulin requirements during lactation and the risk of maternal hypoglycemia. Davies and coworkers (7) have studied 24 consecutive IDDM pregnancies. Breast feeding was established in 18 women and continued by 16 at the 6-week postpartum visit. All women had been placed on their prepregnancy insulin dose following delivery; five who nursed had hypoglycemia while in the ward. Subsequently, IDDM required a reduction of insulin dose of 11.6 U (95% confidence interval of 8.9–14.3 U; $p < 0.001$) by 1 week after delivery, compared with a reduced insulin dose of 5.2 U in women who were bottle feeding. These investigators recommend a postpartum reduction of 27% of the insulin dose in IDDM women who plan to breast feed compared with predelivery requirements.

Diabetic women who plan to nurse their babies should have detailed instruction about lactation and supervision of breast feeding before hospital discharge. In addition, they should have specific dietary instructions (Section IV) to increase carbohydrate intake before

nursing and cautionary advice concerning the complications of mastitis and lactation associated hypoglycemia.

THYROID DYSFUNCTION AFTER DELIVERY

Women with IDDM are at higher risk for autoimmune thyroid disorders. The most common problem is chronic Hashimoto's thyroiditis, which may or may not be associated with goiter. All pregnant IDDM women should be screened for this problem with antenatal tests for serum T_4, free thyroxine index, sensitive TSH assay, and the presence of thyroid microsomal autoantibodies.

Women with chronic thyroiditis may have a rebound recurrence of the disorder 2–5 months postpartum. Unless suspected, the symptoms of fatigue and failure to lose weight gained during pregnancy may be attributed to the usual tiredness and normal changes that occur with a new baby. Because the symptoms are depressing and debilitating and because hypothyroidism is so easy to treat, physicians should be alert to the possibility of this diagnosis in the postpartum period.

CHAPTER

25

Contraceptive Dilemmas for Postpartum Diabetic Women

No form of contraception is successful unless it is agreeable to **both** partners; this can sometimes be a religious, ethnic, or cultural problem. All current opinions indicate that we are years away from an ideal contraceptive for both nondiabetic and diabetic women and there is nothing in sight for men.

GUIDELINES FOR DIABETIC WOMEN BASED ON CURRENT INFORMATION (1990)

This topic is reviewed extensively in this section because there is uncertainty and controversy about the most ideal and least hazardous form of contraception for diabetic women. General advice is not adequate because young women with IDDM under 30 years of age without hypertension or macro- or microvascular complications and who do not smoke are very different from older IDDM women with these problems or older NIDDM women or previous GDM patients with obesity, hyperlipidemia, insulin resistance, or hypertension.

Barrier and Spermicidal Methods

In many clinics, there has been renewed interest in the use of the diaphragm along with a spermicidal cream or jelly. Barrier and surgical sterilization methods of birth control result in the least perturbation of metabolic factors and have the lowest risk of complications. Use of a diaphragm with or without additional protection of a spermicide or a condom by the male partner is the best method of contraception for diabetic women who have not yet completed their families. The reasons for these methods as a first choice are several: (*a*) Diabetic women and those with a history of GDM are at higher risk for hyperlipidemia, macro- and microvascular disease, hypertension, and obesity. (*b*) From a preventive medicine standpoint, use of barrier methods represents a method of primary prevention of later cardiovascular disease. The reassuring prospective studies of Stampfer and colleagues (9) that show a lack of association of risks associated with past use of oral contraceptives in **normal** women may not apply to women with diabetes.

Barrier methods of contraception have the additional advantage of reducing the rate of transmission of sexually transmitted diseases (*Chlamydia trachomatis,* syphilis, bacteria, gonorrhea, genital herpes, and HIV-1). The incidence of cervical neoplasia is also lower among women in couples using diaphragms or condoms (10, 11) probably because of decreased transmission of the human papilloma virus (12).

The practical problem that arises is that many diabetic women dislike or refuse to consider using a diaphragm and their partners may not be enthusiastic about or willing to use condoms. Their major concerns are the higher risks for unplanned pregnancies and loss of spontaneity in their sex lives. These are not insoluble problems. A proper discussion of barrier methods requires considerably more time than writing a prescription for an oral contraceptive. In addition, many obstetricians and paramedical personnel have not had a great deal of experience in the technique of skillful fitting of a diaphragm, which may require experimentation with several models, and follow-up for necessary changes of type of diaphragm should repeated urinary tract infections occur secondary to urethral compression.

The psychological disadvantage of associating contraceptive activity with sexual intercourse can be avoided by some ingenuity in

preplanning its insertion. There is considerable variation among women in the frequency and times and places of engaging in sexual intercourse. For example, some women put in their diaphragm when they brush their teeth in the morning; others bathe and insert theirs in the late afternoon before dinner some hours before planned, unplanned, or no sexual activity. It is handy to have two diaphragms and women without regular partners or those with unstable sex lives or unexpected opportunities for sex can carry one in their purses.

In England and in Europe, many women prefer using a cervical cap because it can be left in place longer and is more comfortable than a poorly fitted diaphragm. There are no reports of use of a cervical cap in diabetic women, but it has many obvious physical and psychological advantages. In the United States, the Prentif cavity-rim cervical cap has been approved for general use (8). A spermicide should be applied inside the cap and it can be left on the cervix for 48 h. Caps come in four sizes. Physicians, obstetricians, and paramedical workers who provide this service need special training in the technique to ensure efficacy and pregnancy prevention. There have been no clinical trials of the cervical cap in North America. Thus, there are no data from control studies concerning patient acceptance, reliability, and side effects.

For couples who choose to try a barrier and/or spermicidal form of birth control, a frank discussion should take place **in advance** that recognizes sexual activity is often impulsive, unplanned, or unexpected. This form of contraception is subject to failure if a diaphragm or condom is not in place or if there is a method failure. It is far easier to discuss possible **alternatives** of an unplanned pregnancy (abortion, prenatal care, or possible adoption) at a time when decisions are likely to be more rational and less emotional.

Surgical Control of Fertility

Diabetic women who have completed childbearing overwhelmingly choose this method of contraception. Even smooth pregnancies without complications require a tremendous effort and frequently difficult behavioral modifications. If a planned or repeat cesarean section is the mode of delivery, women desiring tubal ligation have signed consent papers in advance to have the procedure. Others having vaginal deliveries, and their partners, also give considerable thought to this option. Alternatively, there may be a decision requested by the male partner for a vasectomy. For all couples, thoughtful counseling by the physician with an explanation of current figures on reversibility of tubal ligation and vasectomy procedures is a necessary part of contraceptive planning and transitional postpartum care.

Oral Contraceptives

This section considers the risks and benefits of oral contraceptives (OCs) in considerable detail because, in most obstetric settings, diabetic women who are nulliparous or those who have not elected to have a tubal ligation following delivery most often select this contraceptive option. This is true even when there are clearly increased risks for cardiovascular disease because a repeat pregnancy may be considered a greater immediate hazard. The whole issue of birth control for women with diabetes needs to be examined in well-designed prospective epidemiologic studies because previous clinical trials have not addressed this subset of women.

In **nondiabetic women** who do not have well-recognized risk factors for cardiovascular disease (Table 25.1), recent epidemiologic studies indicate that use of OC formulations containing <50 μg of estrogen by healthy nonsmoking women, including those in the group 35 ± 4 yr of age is not associated with an increased risk of arterial cardiovascular disease, specifically, myocardial infarction and cerebrovascular accidents (13). Similar optimistic data regarding the use of low-dose OC formulations by healthy women have been reported from a large cohort study in Britain (14).

The steroid components of OCs have been progressively decreased without an increase in side effects or risk of unplanned pregnancy. In 1989, the FDA required removal from the market of OCs with an estrogen content of greater than 50 μg/tablet. There are 35 OC prepara-

Table 25.1.
Risk Factors for Cardiovascular Disease in Users of Oral Contraceptives

Hypertension
Diabetes
Hypercholesterolemia
Women older than 35 yr who smoke

tions currently available in the United States. All of the newer products contain ethinyl estradiol as the estrogen component. The only other estrogen, mestranol, which is inactive alone and must be converted to active ethinyl estradiol in the body, is available in older products.

Side effects associated with the estrogen component of OCs, even in low-dose formulations, include nausea, breast tenderness, fluid retention, and depression. Studies of a number of risk factors involving OCs indicate that the use of newer products using doses of ethinyl estradiol in the 30- to 35-μg range offer very low failure rates and a significantly lower side effect rate. Cardiovascular risks commonly associated with the estrogen component, including venous thrombosis and pulmonary embolism, appear to be significantly reduced by the use of OCs with less than 50 μg of ethinyl estradiol. It is recommended that only OCs with 35 μg of estrogen or less be prescribed.

At present, a controversy remains concerning the possible association of OC use and cancer of the breast. Several studies have indicated that risk of breast cancer increases in women who use OCs for more than 4–8 yr before age 25 yr or their first full-term pregnancy (15, 16). Other investigators and a Centers for Disease Control (CDC) study in the United States have not found such relationships (17, 18). More than 20 epidemiologic studies have shown no overall association between use of OCs and breast cancer (19).

Several reports from Europe in 1988 and 1989 (20–22) have described a significantly increased risk of breast cancer in women younger than age 45 if they used OCs for many years. In the study by Stadel and Schlesselman (20), the increased risk was limited to nulliparous women with onset of menarche before age 13 (20). Kay and Hannaford (21) found an increased risk limited to former users of OCs who had only one child and were between the ages of 30 and 34 yr.

In southern Sweden during the 1960s, women began using OCs at a young age. In a case-control study, Olsson and colleagues (23) studied the relationship between the use of OCs and development of breast cancer in the early 1980s. In a multivariate analysis, an early starting age of OC use emerged as a determinant of breast cancer.

Meirik and co-workers (22) have reanalyzed a Swedish-Norwegian case-control study of 473 women less than 45 yr old, with newly diagnosed invasive breast cancer first detected in 1984–1985, and 722 age-matched control women to evaluate if nulliparous women who had used OCs were at particular risk for breast cancer. In their Scandinavian study, the relative risk of cancer of the breast for nulliparous women who used OCs for 8 yr or more was 4.1 (95% confidence interval, 1.4–13.1) and parous women with the same duration of use had a relative risk of 1.7 (0.7–4.2) when compared with nulliparous and parous women who had never used OCs. Parous women who had used OCs for 2 yr or more after their first full-term pregnancy had a relative risk of 3.0 (1.3–7.4). This study is important because it indicates that, at least in this data set, total duration of OC use appears to be a risk factor for premenopausal breast cancer. Of special interest, nulliparous women had a higher relative risk estimate after 8 yr of OC use than parous women after 12 yr of use. Thus, a full-term pregnancy may possibly modify any increased risk of breast cancer associated with OCs. Stadel and colleagues (24) have also reported that a high-risk group of nulliparous women with early menarche may be particularly susceptible to breast cancer risk following long-term exposure to OCs.

Three new studies reviewed by a Food and Drug Administration (FDA) committee (1989) raised the possibility of an increased relative risk of breast cancer among women less than 45 yr of age who present with the disease (25). One study found a risk ratio of approximately 2, irrespective of duration of OC use. It seems unlikely that the existence of such a large overall risk could have been missed by other studies in the United States. This report was followed by letters to the editor of the *American Journal of Epidemiology* by several other investigators who have questioned the methodology of studies in the FDA review (26–28). Controls were selected in a different manner in the studies of 1986 and 1989 by Miller and associates, which reported such a marked difference in risk for cancer of the breast (null risk ratio in 1986 and risk ratio of 2.0 in 1989). In reply, Rosenberg and associates (29) denied any real differences in methodology, but could not exclude the possibility of bias in their most recent study. In sum, relevant studies of the

association of OCs with breast cancer report results that are inconsistent. Biases in the selection of controls or in reporting of past history could be present or the association of OCs with breast cancer could be genuine.

After 30 yr of human use of OCs, we still do not know for certain if they are associated with a risk of breast cancer. The International Committee for Research in Reproduction (19) endorses the unanimous decision of the FDA's committee not to recommend any change in use or prescription of OCs at this time and issues a plea that resources be made available to explore further the relevant existing data sets. At the same time, this committee believes that users and providers of OCs should be aware that uncertainties exist and that additional research is being conducted. Mortality and morbidity associated with breast cancer more than justify a significant and urgent expansion in basic and epidemiologic research into the etiology of this devastating disease. One goal should be to present achievable changes in life-style that could reduce the incidence of breast cancer, e.g., protection through lactation. Another goal should be to understand the role of exogenous hormones, with the possibility of developing formulations of systemically active agents that might have a protective effect.

Taken together, the numerous studies cited previously raise concern about use of OCs at a young age. The possible risk association of breast cancer with low-dose OCs cannot yet be evaluated epidemiologically because the latent period since they were introduced (less than 30 yr) is too short for analysis.

Three studies have been reported to show that women who used OCs for more than 5 yr have a significantly higher risk of cervical cancer than do control groups (30–32). Other studies, which have taken confounding factors into account, did not find such an association (33–36). OCs have a protective effect against endometrial and ovarian cancers (37–39).

Other side effects can also occur with OC use. Some women experience hypertension on low dose formulations of estrogen (40) but those who receive progestins without estrogen do not have an increase in blood pressure over time (41). Blood pressure should be monitored in all women on OCs (13).

Most studies of metabolic alterations associated with triphasic OCs have been conducted in normal women for short periods of time and focused on changes in HDL cholesterol levels. Study comparisons are difficult because of differences in protocols, schedules of blood sampling and laboratory methodology that have led to controversy, and difficulties in interpretation of results. In the study by Lussier-Cacan and associates (42), subjects were followed for a full year of treatment that included weekly blood samples in each of two different treatment cycles, in addition to posttherapy samples. They observed transient but no remarkable alterations in total cholesterol, LDL cholesterol, or HDL cholesterol. There were, however, significant increases in triglycerides (both total and lipoprotein fractions) during treatment that fell to baseline levels within one posttreatment cycle (Fig. 25.1). Very low density lipoprotein (VLDL) cholesterol and apolipoproteins AI, AII, and B also rose during the study.

Ball and co-workers (43), in a 6-month study, have compared the effects of two triphasic OCs: levonorgestrel (EE/LN) or a new progestagen, gestogene (SHG451g), not yet on the market, for six pill cycles. Exclusion criteria included abnormal body weight of 25% above or below ideal for height, diabetes, alcoholism, diastolic blood pressure >90 mm Hg, smoking more than 10 cigarettes per day, a family history of hyperlipidemia, or drugs known to affect lipid metabolism. The treatment regimen is shown in detail on Table 25.2.

In this trial, a number of side effects were reported (16 on EE/LN; 11 on SHD 4156) that were similar in each group. They included nausea, headaches, breast tenderness, and breakthrough bleeding. Five women (5% on EE/LN; 18% on SHD415G), including one woman with persistent headaches, withdrew from the study. There were no significant effects of either preparation on carbohydrate metabolism, a finding that is in agreement with other reports of lose-dose triphasic OCs (44–46). There were, however, small but significant increases in total cholesterol, triglycerides (TG), LDL cholesterol, and the ratio of total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol. In addition, coagulation factors VII and fibrinogen increased significantly in both groups. Antithrombin III, an important inhibitor of coagulation, decreased significantly from baseline. Overall, coagulation alterations in the Ball study were in agreement

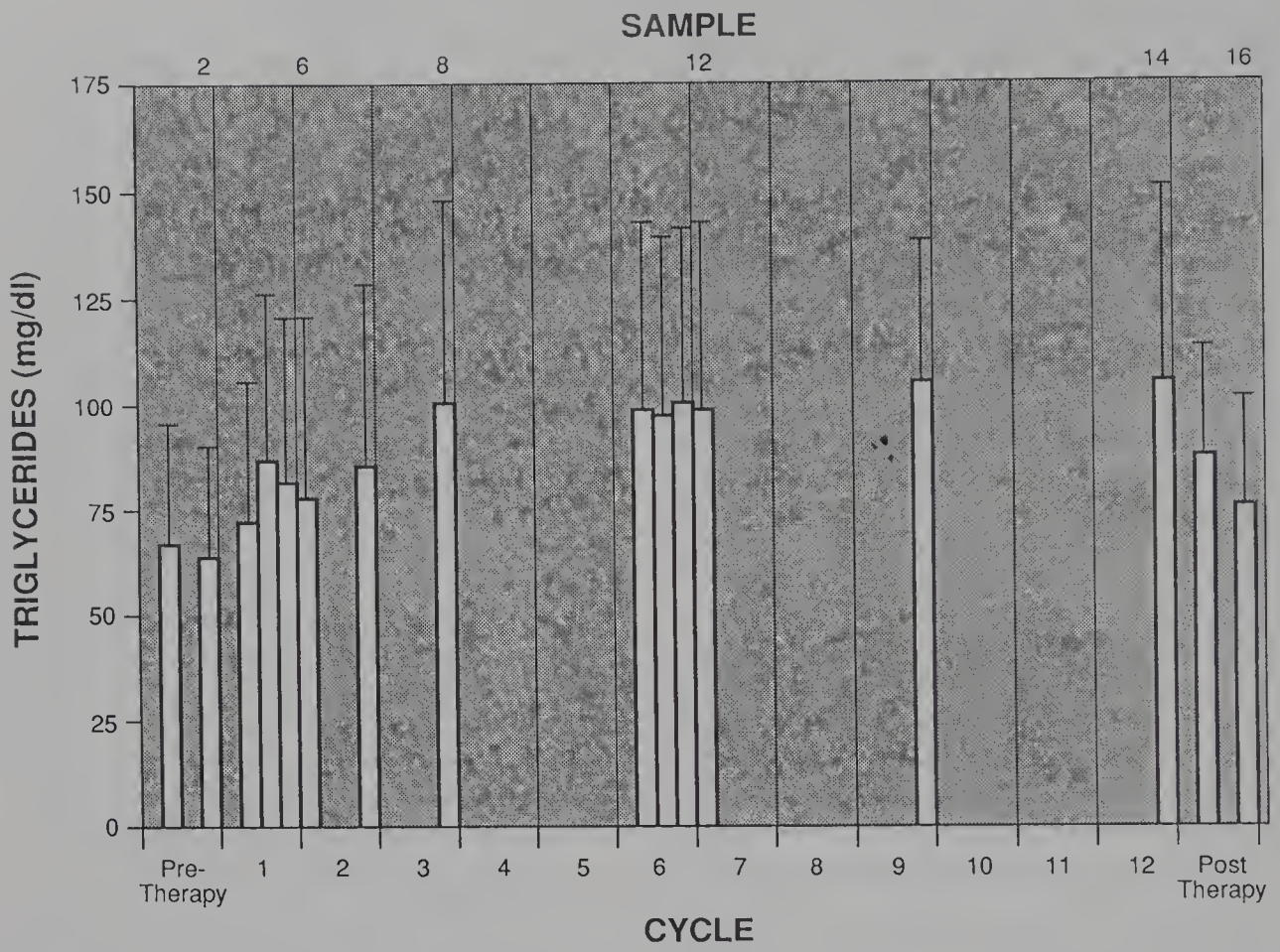


Figure 25.1. Plasma triglyceride levels (means±SEM) before, during, and after OC therapy. Except for samples 3, 6, and 16, all values are significantly different from baseline: samples 5 and 15; $p<0.0005$ and all others: $p<0.001$. Published with permission of Lussier-Cacan S, Nestruck AC, Arslanian H, et al. Influence of triphasic oral contraceptive preparation on plasma lipids and lipoproteins. Fertil Steril 1990;53:28–34.

with other OC studies that suggest a prothrombotic change.

Sex hormone-binding globulin levels in the Ball study increased two- to threefold. The metabolic effects of these triphasics in **normal** women are much less than those of older formulation OCs that contained higher amounts of estrogen but are still apparent. The implications of a slight increase in lipoprotein levels and moderate changes in coagulation factors, both potential risk factors for cardiovascular disease, remain uncertain for the long term (47). Several other studies have also reported elevations of TG levels and other lipoproteins with all the common triphasic preparations now in use (48–50).

Singh and Nattrass (51) have reported, for the first time, that the use of a low-dose estrogen (30–35 μg ethinyl estradiol) with either levonorgestrel or norethisterone as the pro-

Table 25.2.
Treatment Regimen for a Trial of Two Triphasic Contraceptives with Different Progestagens[a]

Menstrual Cycle	Days 1–6	Days 7–11	Days 12–21	Days 21–28	Total Dose per cycle
EE/LN(N = 21)					
Ethinyl estradiol (μg)	30	40	30	0	680
Levonorgestrel (μg)	50	75	125	0	1875
SHD 415G (N = 22)					
Ethinyl estradiol (μg)	30	40	30	0	680
Gestodene (μg)	50	70	100	0	1650

[a]Adapted from Ball MJ, Ashwell E, Jackson M, Gillmer MDG. Comparison of two triphasic contraceptives with different progestogens: Effects on metabolism and coagulation proteins. Contraception 1990;41:363–376.

gesterone component, induces in vivo insulin resistance in the metabolism of free fatty acids (FFA) and ketones (Fig. 25.2). This was predominantly a **progesterone** effect and is a metabolic change that is well documented during pregnancy. Although the implications of these findings may or may not be of significance in normal women, these metabolic effects could contribute to postreceptor insulin resistance in obese NIDDM women, those with a previous history of GDM, and those with familial problems of hyperlipidemia.

Very few studies have been published on the effects of OCs on lipid metabolism in IDDM, NIDDM, or previous GDM women. All reports in the literature except those of Skouby (52) are from studies with combined compounds that contained at least 50 μg of ethinyl estradiol and 250–1000 μg of a progestogen. All report increased serum lipid levels. Pyorala and associates (53) have reported no influence of "progesterone only" preparations (norethisterone and lynestrenol) on plasma TG and cholesterol values in women with previous GDM. They did not measure FFA or assess insulin resistance.

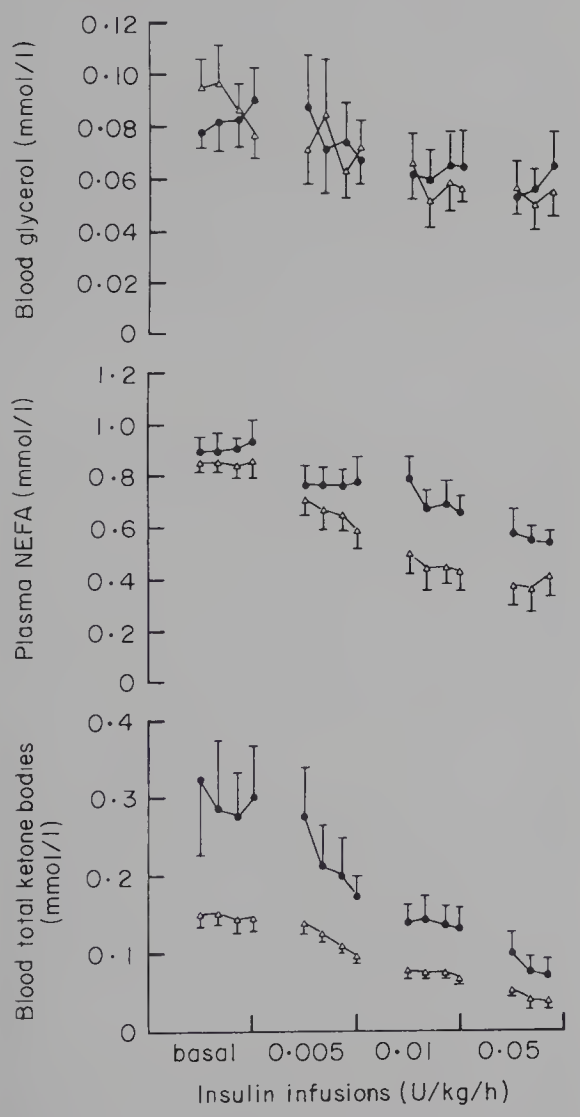


Figure 25.2. Mean (SEM) blood glycerol, plasma FFA, and blood total ketone bodies concentrations during incremental insulin infusion in eight women taking OCs preparations (●-●) and eight women in the luteal phase of the menstrual cycle (△). Adapted with permission from Singh BM, Nattrass M. Use of oral contraceptive preparations alters insulin sensitivity of fatty acid and ketone metabolism. Clin Endocrinol 1989;30:561–570.

Atherosclerotic-prone IDDM, NIDDM, GDM women and women with a positive family history of coronary artery disease may be at higher risk for changes in plasma lipid and lipoprotein levels with use of even low dose estrogen-variable progestogen content contraceptives. Skouby (52) has examined the effects of four oral low-dose contraceptive agents on glucose and lipid metabolism in IDDM women and those women with a previous history of GDM. None of the subjects experienced difficulty with glucose control or lipid/lipoprotein metabolism when taking nonalkylated estrogen/norethisterone and triphasic ethinyl/levonoryestrel preparations. However, **low-dose ethinyl estradiol/norethisterone combinations resulted in small but significant increases in plasma TG and VLDL cholesterol levels.** Treatment with norethisterone alone as "mini-pills" might be considered an appropriate alternative form of contraception, except that more information is needed to assess their effect on insulin resistance, FFAs, and ketones.

No observations were made by Skouby (52) in NIDDM women who frequently have elevated levels of TG and decreased HDL cholesterol values. Elevated TG concentrations in these women reflect enhanced hepatic production of VLDL-TG in response to elevated levels of FFA and decreased catabolism (54). He reported no differences in plasma lipid/lipoprotein levels in women with normal weight and previous GDM but he made no observations in obese GDM women.

As mentioned previously, side effects of OC agents do occur with triphasic low-dose formulations, but are less frequent and severe than those reported in previous decades with pills containing higher doses of estrogen. They include nausea, vomiting, edema, weight gain, headaches, hypertension, depression, decreased libido, amenorrhea (failure of with-

drawal bleeding), and intermenstrual bleeding. These side effects are not usually reported spontaneously and do not appear to be much of a problem in routine clinic visits. Although these side effects are reversible and not ordinarily considered serious they do negatively affect compliance and efficacy of this method of birth control.

Droegemuller and colleagues (55) note that while OCs have the highest theoretical efficacy of all reversible forms of contraception, they have an actual failure rate equivalent to that of some barrier methods. A major reason for discontinuation is the nuisance of intermenstrual bleeding. In a triphasic randomized clinical trial in North Carolina this group compared Ortho-Novum 7-7-7, Tri-Levien, and Tri-Norinyl. Women on Ortho-Novum 7-7-7 had the highest incidence of intermenstrual bleeding (63%) followed by Tri-Levien (44%) and Tri-Norinyl (33%). Control subjects on other formulations with higher amounts of ethinyl estradiol had no breakthrough bleeding and a 4% incidence of spotting.

Inadvertent pregnancies also occur in low-dose OC users. Kovacs and associates studied 209 inadvertent pregnancies in Australian women (56). In Australia, at least 25% of women of reproductive age use the pill. They compared percentage of pill types with market usage over the same period and found that the most common problems were missed pills, late pills, drug ingestion, and gastrointestinal upsets. Surprisingly, the triphasic pills were represented more frequently than would have been expected from their share of the market and were comparatively less effective.

In women who do not wish to breast feed, OCs can be started by 2 weeks postpartum. The amount of breast milk is decreased with OCs containing less than 50 μg of estrogen (57). Progestin-only OCs do not decrease breast milk and are the formulation of choice for women who wish to nurse and to use an OC. Lactation in diabetic women is discussed on pp. 244–245.

Intrauterine Devices (IUDs)

In the United States, there are only two FDA-approved intrauterine devices, the copper T380A and a progesterone-releasing T-shaped model. There are a number of reasons why **diabetic women should not use IUDs.** They are more susceptible to infection than nondiabetic subjects; this could play a role in the high failure rate of IUDs in IDDM and NIDDM women. The major contraindication, however, is the high risk of pregnancy in diabetic women with IUDs.

In a study by Gosden and colleagues (58) at the Royal Infirmary in Edinburgh, Scotland, 11 of 30 (36.6%) of IDDM women fitted with IUDs became pregnant within 1 yr. In contrast, the pregnancy rate for nondiabetic women fitted with the same types of IUDs by the same consultant gynecologists over a similar time period was 4/100 women years (4%). The IUDs were examined by a scanning electron microscope with x-ray microprobe analysis to measure the amount of copper eroded from the wire, extent of encrustation on the wire, and composition of the deposit. In 40% of IUDs from diabetic women, deposits contained sulfur and chloride compared with only 15.3% of IUDs from normal women. In normal women, deposits on IUDs consisted mainly of calcium. Figure 25.3 compares an analysis of an IUD removed from a normal woman with that of an IUD removed from a diabetic woman. Both had copper 7 devices. The results for diabetic patients demonstrated that the high sulfur plus chloride and low calcium response was not attributable to pregnancy; erosion and deposition were linked in IUDs from diabetic but not normal women.

IUD use in both normal and diabetic women may cause menorrhagia, cramping, or expulsion of the device. IUDs are contraindicated in all women with a history of salpingitis, nulliparous women under age 25 yr, and all women with multiple sexual partners. **In diabetic women, the added risk for pregnancy is the strongest contraindication for use of an IUD.** In Edinburgh, the first clinic to implement preconception counseling for diabetic women, the policy of contraception for all diabetic women includes the progesterone-only pill and barrier methods (59). The Scottish findings differ from those of Wiese from Denmark who reported only four pregnancies in 118 diabetic women during the 1st yr of use of "antigon" IUDs (60). However, there was a very high expulsion rate in this series with 14 devices (12%) expelled in the 1st yr.

Other Methods (8)

Periodic abstinence of sexual intercourse with calendar rhythm methods is associated

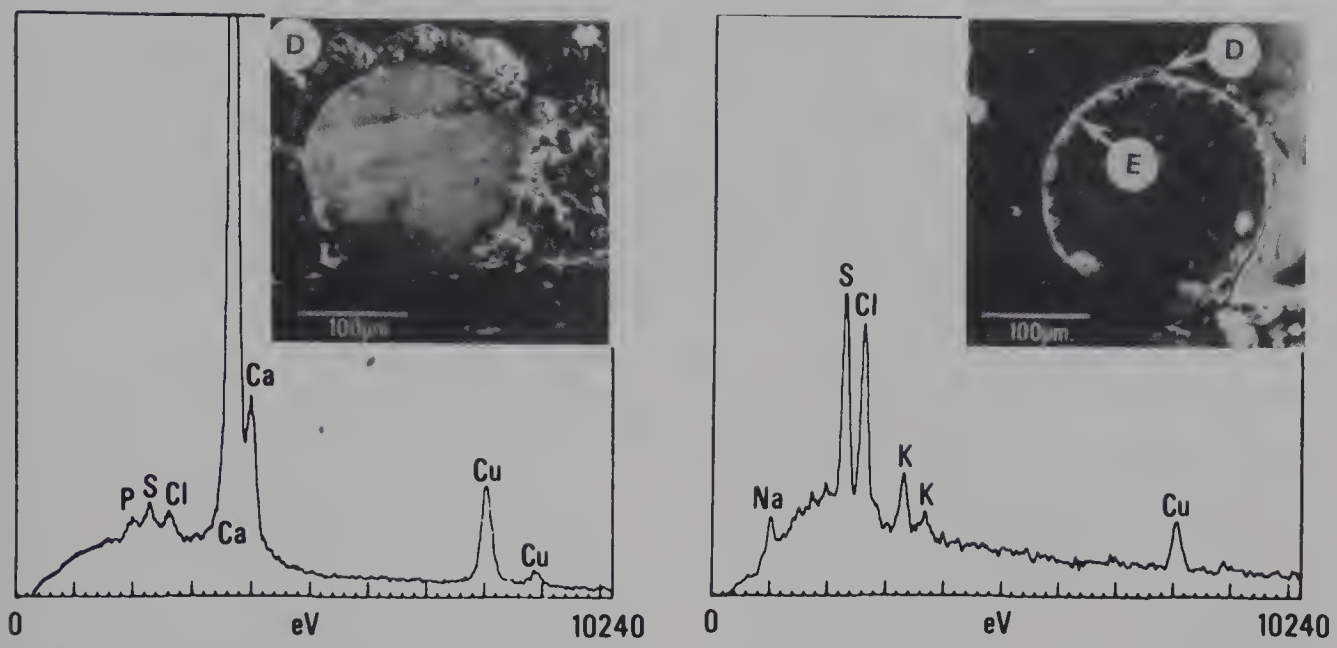


Figure 25.3. X-ray microanalysis of spectra and micrographs of copper 7 devices removed from a normal and a diabetic woman. *Left,* Copper 7 device removed from a normal woman. The analysis showed the deposit (*D*) to consist mainly of calcium with little evidence of erosion. *Right,* Copper 7 device removed from a diabetic woman. Analysis of the IUD showed a deposit (*D*) consisting mainly of sulphur and chloride but with an erosion layer (*E*). Abbreviations: *P:* phosphorus; *S:* sulphur; *Cl:* chloride; *Ca:* calcium; *Cu:* copper; *K:* potassium; *Na:* sodium. With permission from Gosden et al. Intrauterine contraceptive devices in diabetic women. Lancet 1982;1:530–535.

with high pregnancy rates of 14.4–47/100 menstrual years. "Natural family planning methods" that rely on temperature changes, alterations in cervical mucus, and symptothermal methods require high motivation and training and an inevitable loss of spontaneity for sexual activity. In addition, these approaches necessarily require avoidance of sexual intercourse for many days of each menstrual cycle.

In summary, diabetic women, more than most others, face a difficult contraceptive dilemma. The best methods, with the least side effects, are barrier techniques with careful instruction and follow-up. These are the methods of choice for women who wish to have additional children. Couples who select barrier techniques should consider in advance whether a personal or method failure wouldresult in a wanted or unwanted pregnancy or a decision for an adoption or abortion. Of course, a woman may change her mind.

Women who have completed their families will, most often, choose tubal ligations for themselves or their partners will opt for vasectomy. Either of these decisions will require counseling and a discussion about chances for reversibility should a change of heart occur.

OCs have a high degree of reliability for prevention of pregnancy, but only if there is excellent compliance in addition to patience with troublesome side effects. Diabetes, hypertension, hyperlipidemia, cardiovascular disease, depression, and migraine may significantly increase the risk/benefit ratio with this method. There are method failures with low-dose triphasic formulations and intermenstrual bleeding is a nuisance. The higher frequency of cardiovascular disease in diabetic women and still uncertain and emerging possible epidemiologic evidence of an association of OCs with cancer of the breast and cervix further dampen enthusiasm for this method. On the other hand, many young IDDM women without diabetic complications will not use barrier methods and, for them, a trial of low-dose triphasic preparations or a progestagen only pill may be reasonable in the short term because this approach is a better, safer, and certainly an easier alternative than a diabetic pregnancy.

Intrauterine devices may be associated with more frequent infections in diabetic women; the more serious problem is that they are less effective and result in a higher rate of pregnancies in diabetic women compared with nondiabetic women.

Thus, women with IDDM, NIDDM, or previous GDM and their partners have to make somewhat more complicated decisions postpartum than others about future reproductive plans and the several forms of contraception. The problem is more difficult because of shortened hospital stays after the birth of a baby, often hasty advice without much counseling on busy labor and delivery services or at the 6-week postpartum visit, and, perhaps less individualized attention that may not include the partners of diabetic women.

References for Section IX

1. WHO Expert Committee on Diabetes Mellitus: Second report. WHO Tech Rep Ser 1980;646:9-14.
2. Report of a WHO Study Group. Diabetes Mellitus. WHO Tech Rep Ser 1985;727:9-17.
3. Lawrence RA. Breastfeeding: A Guide for the Medical Profession. St. Louis:CV Mosby Co., 1985.
4. Ferris AM, Reece EA. Postpartum management and lactation. In: Reece EA, Coustan DR (eds). Diabetes Mellitus in Pregnancy. Principles and Practice. New York:Churchill Livingstone 1988;623-633.
5. Ferris AM, Dalidowitz CK, Ingardia CH, et al. Lactation outcome in insulin-dependent diabetic women. J Am Dietet Assoc 1988;88:317-322.
6. Bitman J, Hamosh M, Hamosh P, et al: Milk composition, and volume during onset of lactation in a diabetic mother. Am J Clin Nutr 1989;50:1364-1369.
7. Davies HA, Clark JDA, Dalton KJ, Edwards OM. Insulin requirements of diabetic women who breast feed. Br Med J 1989;298:1357-1358.
8. Mishell DR. Medical progress. Contraception. N Engl J Med 1989;320:777-787.
9. Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH. A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. N Engl J Med 1988; 319:1313-1317.
10. Wright NH, Vessey MP, Kenward B, McPherson K, Doll R. Neoplasia and dysplasia of the cervix and contraception: A possible protective effect of the diaphragm. Br J Cancer 1978;38:273-279.
11. Harris RW, Brinton LA, Cowdell RH, et al. Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. Br J Cancer 1980;42:359-369.
12. Celentano DD, Klassen AC, Weisman CS, Rosentheim NB. The role of contraceptive use in cervical cancer: The Maryland cervical cancer case-control study. Am J Epidemiol 1987; 126:592-604.
13. Mishell DR. Use of oral contraceptives in women of older reproductive age. Am J Obstet Gynecol 1988;158:1652-1657.
14. Mant D, Vllard-Mackintosh L, Vessey MP, Yeates D. Myocardial infarction and angina pectoris in young women. J Epidemiol Community Health 1987;41:215-219.
15. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: Possible modifying effect of formulation and age of use. Lancet 1983;2: 926-930.
16. McPherson K, Coope PA, Vessey MP. Early oral contraceptive use and breast cancer: Theoretical effects of latency. J Epidemiol Community Health 1986;40:289-294.
17. Skegg PC, Spears GF, Kaldor JM. Oral contraceptives and breast cancer: A national study. Br Med J 1986;293:723-726.
18. Centers for Disease Control. Long-term oral contraceptive use and the risk of breast cancer. JAMA 1983;249:1591-1595.
19. Letter. International Committee for Research in Reproduction. Oral Contraceptives and Breast Cancer. From Paris, France (E.E. Baulieu); Rome, Italy (G. Benagiano); Leuven, Belgium (I. Brosens); Sheffield, England (I.D. Cooke); Houston, Tex (J.W. Goldzieher); West Berlin, West Germany (J.W. Hammerstein); Utrecht, the Netherlands (A. Haspels); Geneva, Switzerland (E. Johannisson); Tel Aviv, Israel (B. Lunenfeld); Tokyo, Japan (M. Mizuno); and Research Triangle Park, NC (M. Potts). JAMA 1989; 262:206-207.
20. Stadel BI, Schlesselman JJ. Oral contraceptives and breast cancer. Lancet 1986;2:922-923.
21. Kay CR, Hannaford PC. Breast cancer and the pill—a further report from the Royal College of General Practitioners' oral contraception study. Br J Cancer 1988;58:675-680.
22. Meirik O, Farley TMM, Lund E, Adami H-O, Christoffersen T, Bergsjo P. Breast cancer and oral contraceptives: Patterns of risk among parous and nulliparous women—further analyses of the Swedish-Norwegian material. Contraception 1989;39:471-475.
23. Olsson H, Moller TR, Ranstam J. Early oral contraceptive use and breast cancer among premenopausal women: Final report from a study in southern Sweden. J Natl Cancer Inst 1989; 81:1000-1004.
24. Stadel BV, Lai S-H, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. Contraception 1988;38:287-299.
25. Miller DR, Rosenberg L, Kaufman DW, Stolley P, Worshauer ME, Shapiro S. Breast cancer before age 45 and oral contraceptive use: New findings. Am J Epidemiol 1989;129:269-280.
26. Petitti DB. Letter. Am J Epidemiol 1989; 130:1254.
27. Vandenbroucke JP, Atsma WJ. Letter. Am J Epidemiol 1989;130:1254-1255.

28. Spirtas R. Letter. Am J Epidemiol 1989; 130:1255-1256.
29. Rosenberg L, Shapiro S, Miller DR. Letter. The authors reply. Am J Epidemiol 1989;130:1256-1257.
30. Vessey MP, Lawless M, McPherson K, Yeates D. Neoplasia of the cervix uteri and contraception: A possible adverse effect of the pill. Lancet 1983;2:930-934.
31. WHO collaborative study of neoplasia and steroid contraceptives. Invasive cervical cancer and combined oral contraceptives. Br Med J 1985;290:961-965.
32. Brinton LA, Reeves WC, Brenes MM, et al. Oral contraceptive use and risk of invasive cervical cancer. Int J Epidemiol 1990;19:4-11.
33. Celetano DD, Klassen AC, Weisman CS, Rosenheim NB. The role of contraceptive use in cervical cancer: The Maryland cervical cancer case-control study. Am J Epidemiol 1987;126:592-604.
34. Clarke EA, Hatcher J, McKeown-Eyssen GE, Lickrish GM. Cervical dysplasia: Association with sexual behavior, smoking and oral contraceptive use? Am J Obstet Gynecol 1985;151:612-616.
35. Irwin KL, Rosero-Bixby L, Oberle MW, et al. Oral contraceptives and cervical cancer risk in Costa Rica. JAMA 1988;259:59-64.
36. Hellberg D, Valentin J, Nilsson S. Long-term use of oral contraceptives and cervical neoplasia: An association confounded by other risk factors? Contraception 1985;32:337-346.
37. Centers for Disease Control. Combination oral contraceptive use and risk of endometrial cancer. JAMA 1987;257:796-800.
38. The reduction in risk of ovarian cancer associated with oral-contraceptive use: The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. N Engl J Med 1987;316:650-655.
39. Villard-Mackintosh L, Vessey MP, Jones L. The effects of oral contraceptives and parity on ovarian cancer trends in women under 55 years of age. Br J Obstet Gynaecol 1989;96:783-788.
40. Khaw K-T, Peart WS. Blood pressure and contraceptive use. Br Med J 1982;285:403-407.
41. Wilson ES, Cruickshank J, McMaster M, Weir RJ. A prospective controlled study of the effect on blood pressure of contraceptive preparations containing different types and dosages and progestogen. Br J Obstet Gynaecol 1984;91:1254-1260.
42. Lussier-Cacan S, Nestruck AC, Arslanian H, et al. Influence of triphasic oral contraceptive preparation on plasma lipids and lipoproteins. Fertil Steril 1990;53:28-34.
43. Ball MJ, Ashwell E, Jackson M, Gillmer MDG. Comparison of two triphasic contraceptives with different progestogens: Effects on metabolism and coagulation proteins. Contraception 1990; 41:363-376.
44. Vermeulen A, Thiery M. Metabolic effects of the triphasic oral contraceptive trigynon. Contraception 1982;26:505-513.
45. Spellacy WN, Ellingson AB, Kotlik A, Tsibris JCM. Prospective study of carbohydrate metabolism in women using a triphasic oral contraceptive containing norethindrone and ethinyl estradiol for three months. Am J Obstet Gynecol 1988;159:877-879.
46. Bowes WA, Katta LR, Droegemueller W, Bright TG. Triphasic randomized clinical trial: Comparison of effects on carbohydrate metabolism. Am J Obstet Gynecol 1989;161:1402-1407.
47. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions: Associations between triglyceride and coronary heart disease. N Engl J Med 1980;302:1383-1389.
48. Marz W, Gross W, Gahn G, Romberg G, Taubert H-D, Kuhl H. A randomized crossover comparison of two low-dose contraceptives: Effects on serum lipids and lipoproteins. Am J Obstet Gynecol 1985;153:287-293.
49. Van Der Vange N, Kloosterboer HJ, Haspels AA. Effects of seven low dose combined oral contraceptives on high density lipoprotein subfractions. Br J Obstet Gynaecol 1987;94:559-567.
50. Patsch W, Brown SA, Gotto AM, Young RL. The effect of triphasic oral contraceptives on plasma lipids and lipoproteins. Am J Obstet Gynecol 1989;161:1396-1401.
51. Singh BM, Nattrass M. Use of combined oral contraceptive preparations alters insulin sensitivity of fatty acid and ketone metabolism. Clin Endocrinol 1989;30:561-570.
52. Skouby SO. Oral contraceptives: Effects on glucose and lipid metabolism in insulin-dependent diabetic women and women with previous gestational diabetes. Danish Med Bull 1988;35:157-167.
53. Pyorala T, Vahapassi J, Huhtala M. The effect of lynestrenol and norethindrone on the carbohydrate and lipid metabolism in subjects with gestational diabetes. Ann Chir Gynaecol 1979; 68:69-74.
54. Nikkila EA, Huttunen JK, Enholm C. Postheparin plasma lipoprotein lipase and hepatic lipase in diabetes mellitus. Relationship to plasma triglyceride metabolism. Diabetes 1977; 26:11-27.
55. Droegemueller W, Katta LR, Bright TG, Bowes WA Jr. Triphasic randomized clinical trial: Comparative frequency of intermenstrual bleeding. Am J Obstet Gynecol 1989;161:1407-1411.
56. Kovacs GT, Riddoch G, Duncombe P, et al. Inadvertent pregnancies in oral contraceptive users. Med J Austral 1989;150:549-551.
57. Lonnerdal B, Forsum E, Hambralus L. Effect of oral contraceptives on the composition and volume of breast milk. Am J Clin Nutr 1980;33:816-824.
58. Gosden C, Ross A, Steel J, Springbett A. Intrauterine contraceptive devices in diabetic women. Lancet 1982;1:530-535.
59. Steel JM, Duncan LJP. Contraception for the insulin dependent diabetic. Diabetes Care 1980; 3:557-560.
60. Wiese J. Intrauterine contraception in diabetic women. Fertil Steril 1977;28:422-425.

SECTION

X

Infants of Diabetic Mothers

Dorothy R. Hollingsworth

Diabetic mothers in poor control have infants with a higher prevalence of neonatal problems than those of normal women. Improvement of maternal metabolic control and the new technological advances in perinatal and neonatal care since the mid-1970s have resulted in a marked decrease in morbidity for infants of diabetic mothers (IDM). In many diabetic pregnancies, a high standard of perinatal care for high risk pregnancies is not available. This section presents a summary of problems and complications that may be encountered in IDM.

The physician responsible for care of the diabetic mother must coordinate plans for the infant well in advance of delivery. The pediatrician should be aware of the mother's prenatal course, type of diabetes, treatment and complications, and be in attendance at delivery. This collaboration permits anticipation and immediate treatment of fetal and neonatal complications.

CHAPTER

26

Perinatal Mortality and Morbidity

MORTALITY

Women with IDDM account for approximately 5/1000 pregnancies. Because there is no national surveillance of pregnancies in diabetic women, national trends in the rates of perinatal mortality and congenital malformations associated with maternal diabetes cannot be monitored (1).

The Centers for Disease Control (CDC) have reported data from 225 United States, Canadian, and European hospitals, published from 1940–1988, of pregnancies of women with IDDM. The reports evaluated the relationship of congenital malformations and perinatal mortality in such pregnancies (2). These data were compared with published hospital-based data for all women for the same years. The only reports included were those that had identified women with IDDM and had calculated the perinatal mortality rate and/or the proportion of perinatal mortality from congenital malformations for women with IDDM.

From 1940 through 1988 in the United States, Canada, and many European countries, the perinatal mortality rate for IDM had decreased from 250–300/1000 births to 30–50/1000.

This substantial decline in perinatal mortality in IDM has not been matched by a lessening of the problem of congenital malformations, which have emerged as the most common cause of death for IDM in the United States, accounting for approximately 50% of all perinatal deaths. The genesis of congenital malformations among infants of IDDM is not well understood; other factors may be involved in addition to glycemic control (3). A comprehensive discussion of fetal malformations in IDM is presented in Section I.

Connell and colleagues (4) have reported a population-based study of incidence, referral for care, and perinatal mortality in diabetic pregnancies from 1979–1980 in Washington State. They found an incidence rate of 2.1/1000 total births in women with **preexisting** diabetes mellitus. Of these, 25% had NIDDM. The perinatal mortality rate was 108/1000 births, eight times the state perinatal mortality rate. Only 45% of all births to diabetic women occurred in the five tertiary centers in the state; 39% were in hospitals that had fewer than six deliveries of diabetic women per year. Congenital malformations accounted for 43% of the 28 perinatal deaths. Fetal losses between 20 and 27 weeks' gestation were responsible for another 21%. These data from a population-based study give a more realistic view of an unselected, statewide population encompassing over 125,000 births during a 2-yr period. For various reasons, the investigators say the number of **NIDDM women** is, most likely, an underestimate. Nevertheless, the perinatal mortality of infants of **NIDDM women** was almost five times that of the general population and these infants also appeared to be at increased risk for fatal congenital malformations. Other population-based studies (5, 6) have not differentiated between diabetes that **antedated** pregnancy and GDM.

In selected studies from diabetes centers in the United States in the late 1970s, perinatal mortality among IDM had been reduced to less than 5% (7, 8); this optimistic outcome was not matched in the unselected population-based study reported for Washington state, where perinatal mortality exceeded 10%, or for South Carolina with 102 perinatal deaths in IDM per 1000 births per year.

It has been difficult to evaluate and compare outcomes of pregnancy in diabetic women because of lack of standardized criteria and methods for assessing programs in different geographic locations and because of different

types of settings for clinical care. There are no national or local registries for all women with diabetes, all pregnant women with diabetes, or infants born to mothers with diabetes. The cost of such registries has delayed their implementation, but several states are beginning to develop such programs.

Braveman and colleagues (9) at University of California, San Francisco, in conjunction with the Centers for Disease Control (CDC), have evaluated both primary sources of information collected by programs (registration forms, flowsheets, labor and delivery records) and secondary data information collected by other agencies, such as vital statistics, computerized hospital discharge abstracts, and third party billing data for setting up a registry. These are important steps to determine the number of diabetic women of childbearing age. Once registeries are established, it will be possible to calculate rates of selected maternal and infant outcomes for various types and settings of obstetric care. A registry would also define a target population for concerted efforts to provide preconception counseling and referral to appropriate health care services.

MORBIDITY

Infants of IDDM, NIDDM, and GDM women have more perinatal problems than those of normal mothers (8). These complications, which are discussed in greater detail later in this section, have usually been attributed to poor maternal control of hyperglycemia and iatrogenic or emergency preterm delivery. Infant morbidity remains a problem despite the decline in mortality rate to 3–5%. Figure 26.1 illustrates the common problems of neonatal morbidity by gestational age in IDM.

Landon and co-workers (10) have assessed the relationship between glycemic control and perinatal outcome in a relatively uniform population of White class B through D pregnant IDDM diabetic women. All patients used home blood glucose monitoring with a minimum of four determinations daily. They divided their population in two groups based on mean cap-

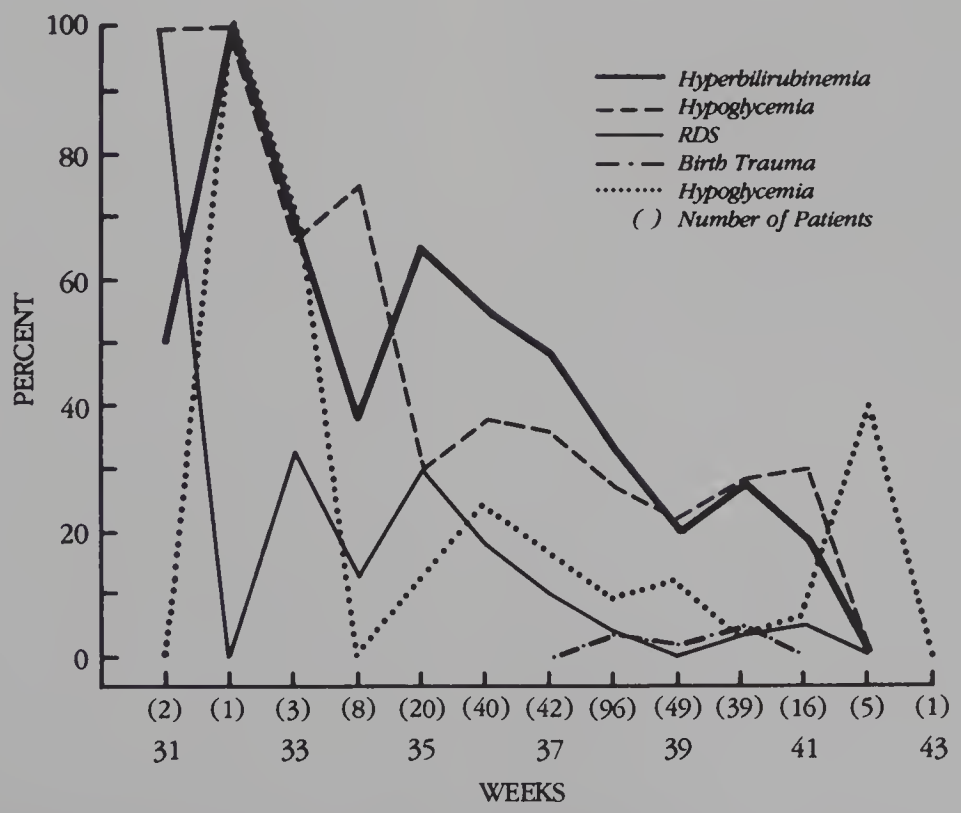


Figure 26.1. Prevalence of common problems of neonatal morbidity by gestational age in infants of diabetic mothers (IDM). With permission from Gabbe S. Semin Perinatol Vol 2, 1978.

illary blood glucose values (<110 mg/dl; 6.1 mmol/L) versus those above this level. The mean for the first group (43 patients) was 96.8 ± 7.1 mg/dl (5.5 ± 0.4 mmol/L) while the second group had a mean of 126 ± 9 mg/dl (7.0 ± 0.5 mmol/L).

They were able to correlate a significant positive effect of maternal glycemic control with perinatal outcome for the incidence of neonatal hypoglycemia, macrosomia, and respiratory distress syndrome.

Duffty and Lloyd (11) have reported their Aberdeen experience with 46 infants of IDDM mothers during 1986 and 1987. Thirteen babies (28%) had no neonatal problems whatsoever and 14 had only mild problems that would not normally have needed admission. Two-thirds of the infants were discharged to the postnatal wards within 48 h and only 5 (11%) required intensive care. The most common problems, like those of other centers, were macrosomia (26%), hypoglycemia (39%), respiratory disorders (9%), and hypocalcemia (9%).

CHAPTER

27

Perinatal Complications

Problems associated with morbidity in newborn IDM are positively correlated with prematurity. The most common complications for these infants, excluding congenital malformations, are pulmonary and metabolic. Figure 26.1 shows the prevalence of common problems of neonatal morbidity from age 31–43 weeks' gestation.

MACROSOMIA

Macrosomia, shoulder dystocia, and birth injuries have been discussed earlier in Section VII.

IDM often appear fat and have the characteristic appearance of an IDM even when birth weight is normal. Figure 27.1 shows the infant of an obese NIDDM mother who gained 24 lb on a 2400 kcal/day diabetes diet and was in good diabetic control throughout pregnancy. The interesting feature of this photograph is that although the birth weight was normal (3000 g at delivery at 37 weeks), the infant was fat, plethoric, Cushingoid, and had the typical appearance of an IDM. Birth weight alone is not an accurate measurement of macrosomia in IDM. Because it is not practical or possible to measure fat cell size and number in these infants, relative obesity and macrosomia can be assessed most easily by simple skin fold measurements (12).

Massively obese women who develop GDM and gain excessive amounts of weight during pregnancy are at greatest risk for severely macrosomic infants. Figure 27.2 shows the grossly obese (weight 6260 g; length, 54 cm; head circumference, 28 cm) newborn male infant of a 41-yr-old woman who weighed 250 lb (114 kg) at conception with her 12th pregnancy. At 18 weeks' gestation, she had a normal 3-h oral glucose tolerance test—plasma glucose values: fasting 100 mg/dl (5.5 mmol/L); 1 h, 170 mg/dl (9.4 mmol/L); 2 h, 160 mg/dl (8.8 mmol/L); 3 h, 140 mg/dl (7.7 mmol/L). At 22 weeks' gestation, the fasting plasma glucose level was elevated to 110 mg/dl (6.1 mmol/L), but tests before lunch (110 mg/dl; 6.1 mmol/L) and 2 h after lunch (80 mg/dl; 4.4 mmol/L) were normal. No treatment aside from dietary advice was given.

At 33 weeks' gestation, the fasting plasma glucose was 132 mg/dl (7.3 mmol/L) and a 2-h postbreakfast value was 155 mg/dl (8.6 mmol/L). A sonogram at 36 weeks' showed scalp edema and a biparietal diameter of 10.0 cm. The mother gained a total of 57 lb (30 kg; normal = 10–12 kg) during pregnancy. The huge infant was delivered vaginally without an episiotomy and with no problems. The placental weight was 870 g (normal 539 ± SD 121 g). The infant was hypoglycemic (Dextrostix glucose values, 25–45 mg/dl; 1.4–2.5 mmol/L) and treated with early feeding (1st h of life) and intravenous glucose. A central hematocrit of 68 necessitated a partial exchange transfusion. Hypocalcemia with a serum Ca value of 7.2 mg/dl was treated with calcium supplementation. Following discharge from the nursery, the baby did well and had no further problems. At 10 weeks of age, the infant remained above the 95th percentile for weight.

This pregnancy illustrates the severe neonatal problems that can be associated with pregnancy-evoked carbohydrate intolerance in women who are markedly overweight and then gain excessive additional weight. Ideally, a GDM woman with this course should be prescribed strict dietary control, limitation of weight gain to the recommended amount for an obese pregnant woman, and rapid-acting insulin before each meal in an attempt to limit infant birth weight and lessen neonatal metabolic problems. This approach was successful in the infant shown in Figure 27.1 but did not

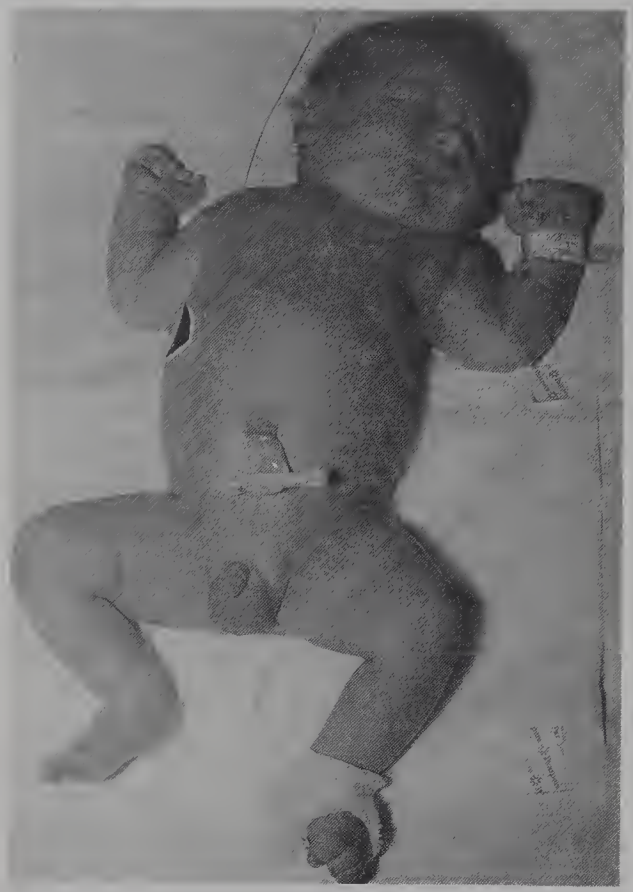


Figure 27.1. Normal weight (3000 g) but plethoric, Cushingoid IDM at 37 weeks' gestation. The mother had NIDDM and gained 24 lb (10.9 kg) on a 2400 kcal/day diabetic diet during pregnancy. With permission from Hollingsworth DR, Cousins L. In Milunsky A, Friedman EA, Gluck L (eds): Advances in Perinatal Medicine. New York, Plenum Publishing, vol 20. 1982;245–320.

prevent an obese appearing infant with the typical phenotype of an IDM.

The problem of excessive fetal growth in utero is complex and may reflect the end result of an abnormal mixture of fuels delivered to the fetus. Shortly after the discovery of insulin, Dubrueil and Anderodias (13) made the observation that fetuses of diabetic mothers had increased pancreatic islet cell tissue. Other investigators subsequently reported that β cells of IDM showed both hypertrophy and hyperplasia (14, 15) and had an increased amount of insulin (16). Pedersen (17) later proposed the hypothesis that maternal hyperglycemia results in fetal hyperglycemia, which causes hypertrophy of fetal islet tissue, hypersecretion of insulin, and fetal macrosomia.

The Pedersen hypothesis has been extended by Freinkel and Metzger (18) who have examined the role of other nutrients that provide a substrate mixture for the fetus (Fig. 27.3). In this hypothetical model, decreased availability of maternal insulin results in both overproduction and underutilization of glucose. Major changes occur in all maternal nutrients with higher levels of plasma glucose, lipids, selected amino acids, and ketones. Placental structure and/or function may be altered, permitting an abnormal mixture of fuels to the fetus. In addition to excessive fetal insulin production, Freinkel and Metzger suggest that other fetal growth factors not yet identified

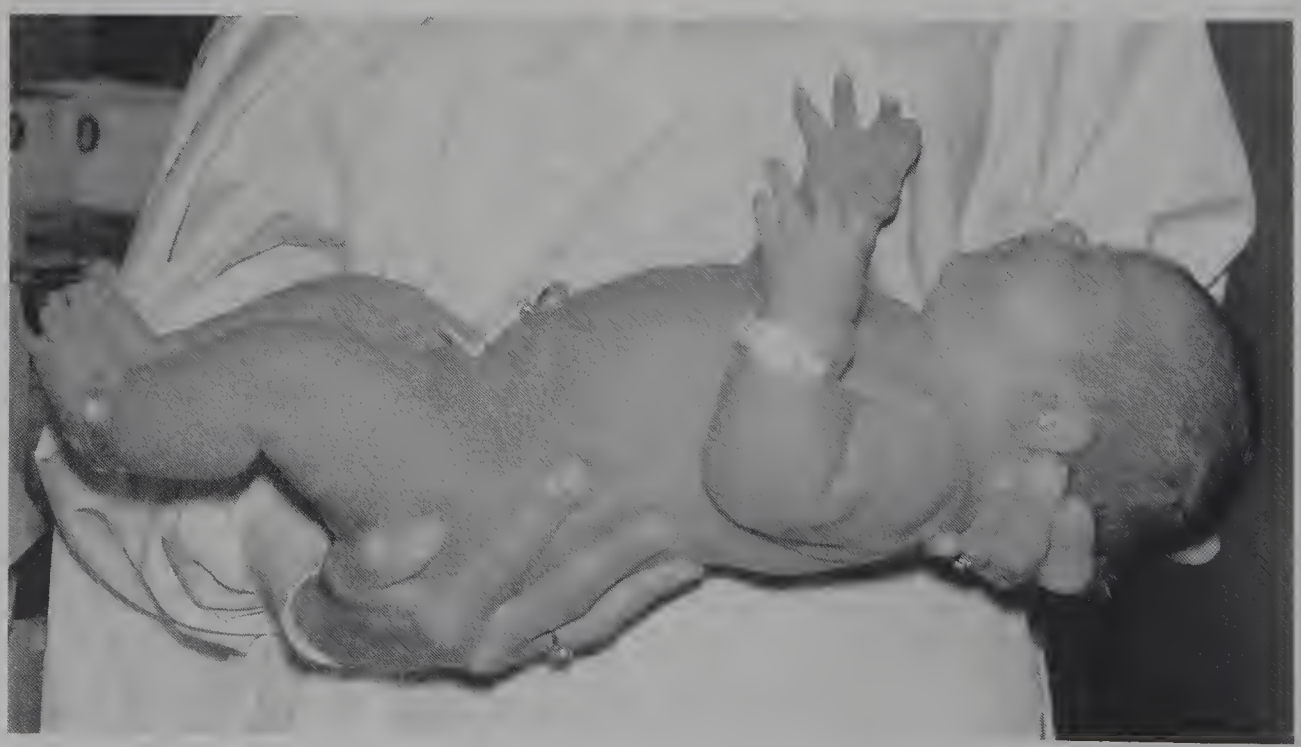


Figure 27.2. A 6260-g term infant of a massively obese woman with mild untreated GDM and excessive weight gain (57 lb; 30 kg) during pregnancy. See text for description.

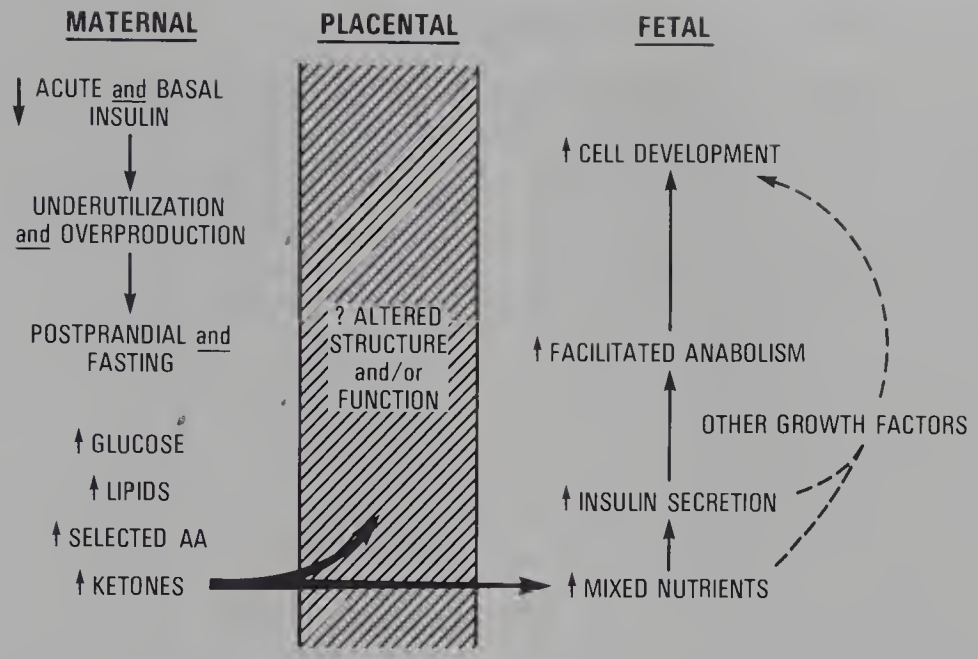


Figure 27.3. Modification of the Pedersen hypothesis of excessive fetal growth in diabetic pregnancies. With permission from Freinkel N, Metzger BE. Pregnancy Metabolism, Diabetes and the Fetus. Amsterdam: Excerpta Medica, 1979. See text for description.

may contribute to development of facilitated anabolism and increased cell development. The possible role of insulin-like growth factors (IGF-I and IGF-II) and others in fetal growth has been reviewed by Brinsmead and Liggins (19), Giordano and colleagues (20), and Guyda and co-workers (21).

What is known about development of the fetal pancreas? Microscopically, the fetal pancreas (about 20–25 somites) is visible from the fourth week after conception (22). Pancreatic insulin is present at 7–10 weeks' gestation at a concentration of 300 U/mg at 10.5–15.5 weeks', and approximately 4000 U/mg at 16–25 weeks'. In vitro studies indicate that the β cell is functional from 14–24 weeks' gestation and responds to amino acids, ions such as Ca^{2+} and factors that raise intracellular cyclic AMP, such as theophylline and glucagon.

In vitro studies of human fetal islets have shown that they have not responded at all to glucose or have responded poorly. However, organ cultures and other methods have shown that human fetal β cells can release insulin in response to glucose stimulation (23, 24). Thus, there is strong evidence to suggest that insulin may be a physiologic regulator of glucose metabolism and fetal growth (25).

Otonkoski and colleagues (26) have performed dynamic studies of insulin secretion using a technique of perifusion of pancreatic islet-like cell clusters from fetal pancreases at different stages of gestation. Their experiments indicated that the human fetal β cell is responsive to glucose as early as the 17th to 20th week of gestation. They also demonstrated, in a secretory dynamic study of the fetus of an IDDM mother at 22.5 weeks' gestation, a prompt early insulin response, which suggested precocious functional maturation of the β cells.

These new studies (1988) open the question of the physiologic impact of early glucose sensitivity. It is reasonable to postulate that it may be important in fetal growth because fetal insulin production is regulated by the maternal supply of nutrients (27, 28). Sensitivity to glucose levels may occur quite early in fetuses of diabetic mothers and, if it does, a pattern for macrosomia may be set much earlier than previously thought.

Placental synthesis of human chorionic somatomammotropin (hCS) influences maternal nutrient supply. Decidual production of prolactin and a biosynthetic precursor for adrenocorticotropic hormone, lipotropin, and β endorphin, may also play a role in modulating fetal growth. In the latter half of pregnancy, the fetus has a well-integrated hypothalamic-pituitary axis with a well-developed middle lobe of the pituitary, which synthesizes growth-promoting peptides. Thus, fetal growth and size at birth reflect the final neuroendocrine-metabolic pathway of an integrated three-compartmental system: maternal, placental, and fetal.

In summary, the occurrence of macrosomia is complex and probably represents fetal hypernutrition of all nutrients in addition to other growth factors. Accumulating evidence indicates that fetal hyperglycemia may not be the sole etiologic stimulus for endogenous fetal hyperinsulinemia. In humans, glucose is only one of the substrates involved in the stimulation of insulin production. The role of amino acids, especially those that are insulinogenic, has not been established for the fetus of human diabetic mothers. Further studies of hormone-substrate-cell interaction are necessary to define the cell biology of diabetic fetopathy.

In insulin-treated women, transplacental passage of antibody-bound insulin has been reported in pregnant IDDM women by Menon and colleagues (29). They suggest that the transferred antibody-bound insulin has biologic activity and may be a determinant of fetal macrosomia independent of maternal blood glucose levels.

RESPIRATORY DISTRESS SYNDROME (RDS) AND TRANSIENT TACHYPNEA OF THE NEWBORN

Until the 1980s, RDS was the most common and serious morbidity problem for IDM. The improvement in maternal prenatal management of diabetes and new techniques in obstetrics for timing and mode of delivery have resulted in a dramatic decline in RDS from 31% to 3% in diabetic pregnancies (30).

Curet and colleagues (31) have followed 108 diabetic pregnancies in an ambulatory program aimed at close control of blood glucose levels. The prevalence of RDS in their patients was not different from that in nondiabetic women. They found that pulmonary fetal maturity progressed at a normal rate in all diabetic pregnancies with careful metabolic control without increased risk of RDS. Hallman and Teramo (32) have confirmed the predictive accuracy of the lecithin/sphingomyelin (L/S) ratio, and phosphatidylglycerol (PG) analysis. They were able to detect RDS, transient tachypnea, symptomatic pneumothorax, and persistence of fetal circulation by amniotic fluid determinations of phospholipids. PG concentrations improved the predictive value of both the mature L/S ratio (2 or more) and nonmature L/S ratio (less than 2).

A mild form of RDS without hyaline membrane disease, transient tachypnea of the newborn, may occur with retained lung fluid following delivery by cesarean section. Infants with polycythemia and hyperviscosity may also have transient respiratory distress or tachypnea that resolves in a few days.

NEONATAL HYPOGLYCEMIA

The hyperinsulinemic fetus of a diabetic mother is at special risk for low plasma glucose levels after birth. This complication is usually much milder and less frequent in infants whose insulin-dependent mothers are well controlled during pregnancy and euglycemic throughout a labor and delivery that is carefully monitored by constant low-dose insulin infusion administered intravenously. This approach combined with early feeding (in the 1st h of life) may eliminate the necessity for a neonatal intravenous infusion of glucose. The use of bolus infusions of hypertonic glucose stimulates the hypertrophied fetal pancreatic β cells excessively and tends to perpetuate a cycle of hyperinsulinemia and hypoglycemia.

Hypoglycemia in the neonate may not be apparent on physical examination and has to be documented by measurement of low levels of blood glucose. Suggestive physical signs include twitching, jitteriness, hypotonia, apnea, or seizures. These signs may be absent or apparent only with careful observation.

Management of neonatal hypoglycemia should begin with measurement of blood glucose in the baby while still in the delivery room or certainly within the first half hour. Cowett has stated that the most important factor is to deliver these infants in a facility that can deal with all the potential problems (33). In his institution (Women and Infants Hospital, Providence, Rhode Island, Brown University), all infants born to women known to be diabetic, e.g., GDM, IDDM, and NIDDM women, are admitted to the intensive care unit for at least 6 h. Glucose is monitored first at 30 minutes of age and, then, frequently throughout the first 6-h period. At that point, if the babies are stable, they are transferred to the regular nursery but considered **high risk** and managed accordingly.

For high-risk IDM there is as much concern about hyperglycemia as hypoglycemia, especially in the prematurely born neonate. When infusions of glucose at 4–6 mg/kg/minute are started, which is the basic glucose production rate, the intravenous infusion has to be mon-

itored carefully to maintain **euglycemia** and to prevent extremes. The new infusion pumps are very accurate and glucose measurements should be made at the cribside with a glucose analyzer or glucose meter. Glucose oxidase strips are not sufficiently accurate for monitoring these infants. Management of IDM requires nursing expertise and a capable in-house staff—a very different level of complexity and intensity than in the average nursery (34).

Because there may be possible long-term sequellae of neonatal hypoglycemia, treatment is advised for both symptomatic and asymptomatic infants with blood glucose levels <35 mg/dl (1.9 mmol/L). Early oral feeding may be the only treatment required. If a repeat blood glucose determination is <45 mg/dl (2.5 mmol/L), intravenous administration of glucose is necessary.

Oh (35) does not recommend subcutaneous injections of glucagon because of the risk of rebound hyperglycemia nor does he recommend epinephrine because of possible untoward cardiovascular side effects and lactic acidosis in infants who may already have cardiopulmonary difficulties. In a few infants, hypoglycemia may persist beyond 24–28 h. In these instances, he recommends the use of glucocorticoids.

Infants with prolonged severe, intractable hypoglycemia that does not respond to glucose infusion or glucocorticoids present a serious diagnostic problem. The various possibilities include nesidioblastosis (β-cell hyperplasia of unknown cause), islet cell or other insulin-producing tumor, hypopituitarism, or hypoadrenalism.

Two studies have emphasized the importance of maintaining blood glucose concentrations above 46.8 mg/dl (2.6 mmol/L) in newborn babies and children (36–38). Aynsley-Green and Eyre (37) have raised the possibility that "safe" blood glucose concentrations may be higher than 46.8 mg/dl (2.6 mmol/L) in those with other conditions that compromise neural function or cerebral autoregulation. Chucas and colleagues (38) have reported adverse neurodevelopmental outcomes following moderate neonatal hypoglycemia in premature infants. In a study of evoked brainstem auditory responses by Koh and collagues (39), responses were normal before episodes of hypoglycemia and became abnormal associated with a fall in blood glucose levels. When normoglycemia was restored, evoked potentials remained abnormal in four children for 1 h, 1.5 h, 16 h, and 2 days in the absence of factors such as asphyxia, acidosis, hyperbilirubinemia, intracranial hemorrhage, or aminoglycoside treatment, all factors recognized to influence evoked potentials.

The long-term result of mild or severe neonatal hypoglycemia is under investigation. Low blood glucose values in neonates should be recognized and treated promptly, because prolonged hypoglycemia is clearly associated with central nervous system abnormalities in children and older individuals.

NEONATAL HYPOCALCEMIA

Derangements in mineral metabolism are frequent in IDM (40–44). There is increasing evidence that the disturbance in calcium metabolism is linked to maternal and fetal magnesium (Mg) deficiency created by an increased maternal Mg excretion that occurs in diabetes mellitus (42–44). No differences have been demonstrated in diabetic women compared with nondiabetic women with respect to levels of calcitonin or phosphorus in the mother, fetus, or neonate (43).

Low levels of serum calcium (<7 mg/dl) have been recognized in as many as 50% of IDM during the first 3 days of life. Tsang and colleagues (40, 41) have studied this problem extensively. They have reported normal levels of parathyroid hormone in cord blood of IDM, indicating normal fetal parathyroid function. Decreased parathyroid function in IDM after birth was associated with decreased levels of serum calcium and increased serum phosphorus values. These changes in infants of IDDM mothers did not evoke an increase in serum parathyroid hormone. The resulting "functional hypoparathyroidism" is aggravated by birth asphyxia and iatrogenic prematurity (42).

Maternal serum-ionized Ca correlates positively with cord-ionized Ca. In a report of Tsang et al. (41), higher values of maternal ionized Ca were related to greater postnatal depression of serum Ca in infants and decreased parathyroid function. Increased parathyroid hormone levels were not demonstrated in maternal serum. Neonatal hypocalcemia is usually treated with administration of calcium by oral or intravenous routes. In IDMs, neonatal hypocalcemia refractory to standard in-

travenous calcium therapy can be corrected by magnesium supplementation.

NEONATAL HYPOMAGNESEMIA

Magnesium (Mg) plays an important role in neonatal calcium metabolism (42, 44). The recommended daily allowance of Mg during pregnancy is 450 mg but, in most women, this intake is not met (45). Decreasing serum Mg concentrations are observed during pregnancy that may reflect, to some extent, hemodilution rather than true deficiency (46). In pregnant rats fed Mg-deficient diets, there is a high rate of spontaneous abortion, intrauterine growth retardation, and malformations (47, 48).

In normal neonates, serum Mg concentrations range from 1.6–2.8 mg/dl with 35% of Mg bound to proteins.

Tsang and colleagues (41) followed 56 diabetic mothers and their infants prospectively from birth and noted that 38% of IDM had a serum Mg level of <1.5 mg/dl on at least one occasion during the first 3 days of life. Decreased levels of serum Mg were related to low maternal age and gravidity, severity of maternal diabetes, and prematurity. Neuromuscular irritability in infants was not correlated with decreased serum Mg alone or with decreased ionized or total Ca. In IDM, decreased serum Mg levels were associated with decreased maternal serum Mg, decreased ionized and total Ca, increased serum phosphorus levels, and decreased parathyroid function. The significance of hypomagnesemia in IDM is unknown.

HYPERBILIRUBINEMIA

The risk of hyperbilirubinemia is higher in IDM than in normal infants. Prematurity is a major contributing factor in some infants. Infants of mothers with NIDDM are at greater risk for polycythemia. In these newborns, increased destruction of red blood cells contributes to the risk of jaundice. There are multiple etiologic causes for hyperbilirubinemia in IDM and, often, the cause cannot be defined precisely. Treatment of this problem is usually by phototherapy, but exchange transfusions may be necessary if bilirubin levels are markedly elevated.

The incidence of hyperbilirubinemia (49, 50) in IDM remains relatively high despite modern methods of perinatal management of maternal diabetes. Contributing factors include impairment of hepatic conjugation of bilirubin because of prematurity and the influence of polycythemia. However, treatment of polycythemia by partial exchange transfusion does not prevent jaundice in IDM (51). Stevenson and colleagues (49) have reported that IDM have a relatively delayed clearance of bilirubin implicating impairments in the uptake of bilirubin into hepatocytes, conjugation, or excretion.

Jahrig and co-workers (50) have assessed neonatal jaundice in 357 IDM and 20 healthy newborns at term. IDM at term had prolonged and higher concentrations of serum bilirubin compared with controls (Fig. 27.4). Hyperbilirubinemia was not simply related to macrosomia (birth weight) but was correlated with an increased birth weight/length ratio (central obesity, "heavy-for-length infants"). Despite identical cord blood insulin levels of IDM, the shorter, fatter IDM had significantly lower blood glucose concentrations immediately after birth. White classes of diabetes had no influence on the course of hyperbilirubinemia.

Stevenson (49) and Peevy and associates (52) speculate that IDM are heterogeneous with respect to pathogenesis of hyperbilirubinemia and certain adverse metabolic consequences cannot be prevented by simply normalizing maternal blood glucose levels.

Although IDM with hyperbilirubinemia are a high-risk population, it is not known whether

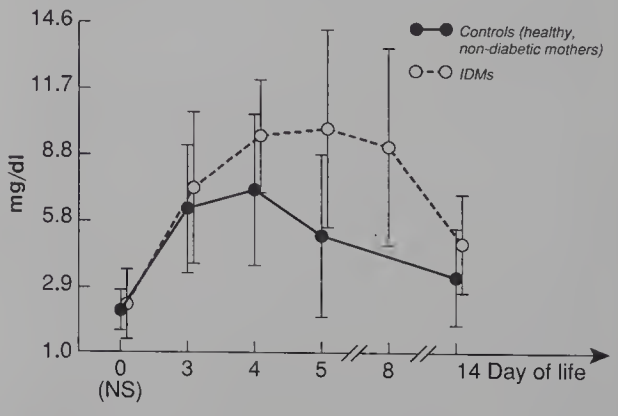


Figure 27.4. Bilirubin serum concentration in the first 2 weeks of life in full-term infants of healthy nondiabetic mothers (●-●) and IDM (o-o). The factor for converting conventional units (mg/dl) to SI units is 17.1. Adapted with permission from Jahrig et al. Neonatal jaundice in infants of diabetic mothers. Acta Paediatr Scand (Suppl) 1989;360:101–107.

there is a relationship between moderate elevations in bilirubin and morbidities later in life. A National Institutes of Child Health and Human Development Randomized, Controlled Trial of Phototherapy for Neonatal Hyperbilirubinemia has been conducted to determine whether phototherapy used to control neonatal serum bilirubin levels is safe and is as effective in preventing brain injury as exchange transfusion (53). The study, conducted at six neonatal care centers, randomly assigned 1339 newborn infants to phototherapy or control groups by the following subgroups: (*a*) birth weight <2000 g; (*b*) birth weight 2000–2499 g and bilirubin level >171 μmol/L (10 mg/dl); or (*c*) birth weight s 2500 g and bilirubin level >222 μmol/L (13 mg/dl). Phototherapy was administered for 96 h and exchange transfusion was used to control hyperbilirubinemia at the same predetermined levels in both groups. Neurological and developmental examinations were conducted at 1 and 6 yr of age, with follow-up rates of 83% and 62%, respectively. The two groups did not differ in mortality or diagnosed medical conditions. The phototherapy and control groups had similar rates of cerebral palsy (5.8% versus 5.9%), other motor abnormalities including clumsiness and hypotonia (11.1% versus 11.4%), and sensorineural hearing loss (1.8% versus 1.9%). The Wechsler Intelligence Scale for Children-Revised Scores overall were not significantly different for the two groups (Verbal, 96.8 versus 94.8; Performance, 95.8 versus 95.1 for phototherapy and control groups, respectively). Phototherapy effectively controlled neonatal hyperbilirubinemia without evidence of adverse outcome at 6 yr of age and was at least as effective as management with exchange transfusion alone.

POLYCYTHEMIA AND HYPERVISCOSITY

Neonatal polycythemia is defined as venous hematocrit (from a peripheral vein) ≥65% (±2 SD above the mean hematocrit in normal newborns) (54). Hyperviscosity is measured by a microviscometer; most infants with hyperviscosity are polycythemic but either condition can be present without the other. In a prospective study of IDM, the incidence of polycythemia has been reported to be 12% (55, 56).

Other infants at risk for polycythemia and hyperviscosity are those with perinatal asphyxia, intrauterine growth retardation (IUGR), the recipient in twin-to-twin transfusion, babies with a large placental transfusion because of delay in clamping the cord, and infants with Beckwith's syndrome (macrosomia, hypoglycemia, umbilical hernia, and macroglossia) (57). Infants at risk should be checked in the first hours of life for prompt detection and therapeutic decisions.

The possible mechanisms for development of polycythemia include increased erythropoiesis in response to hypoxia and an increased level of erythropoietin (58–60). Widness and associates (61) have reported a direct relationship of antepartum glucose control and fetal erythropoitin levels in IDDM pregnancies. Oh's proposed pathogenesis for the multiple prenatal, intrapartum, and postnatal events that can lead to polycythemia and hyperviscosity is shown schematically in Figure 27.5 (57). An abrupt increase in blood volume by acute intrauterine or postnatal placental transfusion results in physiologic compensatory events and hemoconcentration (Fig. 27.6). The consequences of these events are: (*a*) a marked increase in hematocrit resulting in polycythemia and hyperviscosity in some infants; (*b*) transudation of fluid from the intravascular into the extravascular (primarily interstitial) compartments; and (*c*) persistence of a high red blood cell volume.

Clinical manifestations may or may not be present in polycythemic IDM. When apparent, they include plethora, jitteriness, irritability, lethargy, seizures, and apnea. Tachypnea and respiratory distress may occur and, rarely, congestive heart failure may develop. Polycythemic IDM are at higher risk for feeding problems and for necrotizing enterocolitis (62, 63).

The treatment of asymptomatic infants with polycythemia and hyperviscosity is controversial because of the lack of good data from controlled studies. Oh recommends that management of asymptomatic infants be individualized based on the level of the venous hematocrit (≤70%), accuracy in determining whether an infant is symptomatic, and the postnatal age because during the first 6–12 h after birth, the hematocrit generally rises due to fluid shifts from the intravascular compartment (57).

In infants with symptoms treated with partial exchange transfusion, better neurologic and developmental outcomes are reported (64).

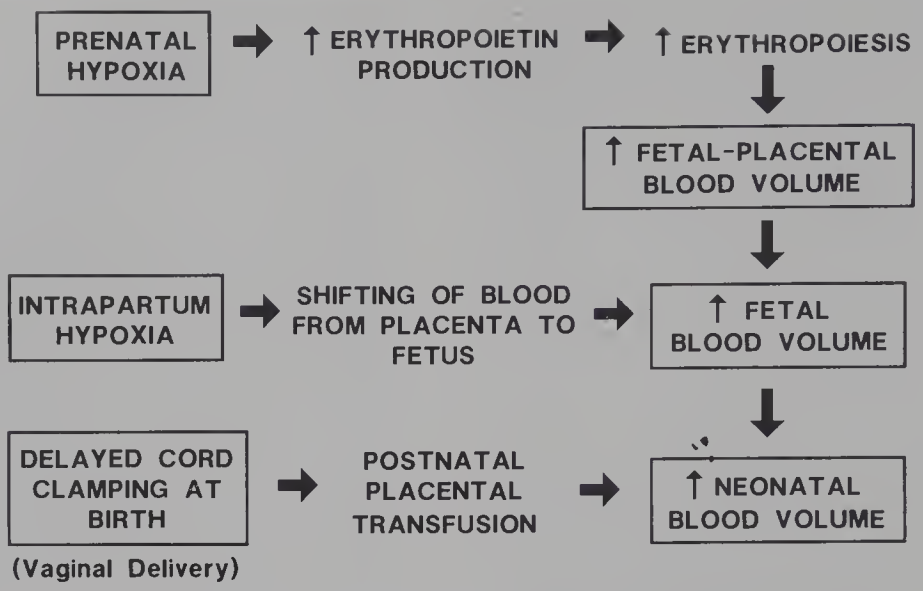


Figure 27.5. Polycythemia and hyperviscosity: Proposed pathogenesis (I). With permission from Oh W. Neonatal polycythemia and hyperviscosity. Pediatr Clin North Am 1986;33:523–532. See text for descriptions.

In a follow-up report of infants with neonatal hyperviscosity and polycythemia, Black and colleagues (64) re-evaluated 49 children at age 7 yr. Of these, 21 infants had received a partial exchange transfusion, while 28 were given symptomatic care. Small, but statistically significant improvements were noted in the group that received the exchanges. The question remains unsettled as to whether the risks of partial plasma exchange transfusion are warranted in otherwise asymptomatic infants. The risk/benefit ratio of the exchange procedure is not fully established and this therapy has been associated with a variety of neonatal problems. No study has attempted to evaluate outcome at any age with a multivariate analysis for each of the pregnancy and neonatal problems that may be associated with neonatal polycythemia and hyperviscosity. The amount of blood volume exchange with colloid or crystalloid during a partial exchange depends on the hematocrit. The formula for calculation is (57):

$$\text{Blood volume to be exchanged} = \frac{\text{Observed HCT} - \text{Desired HCT (55\%)}}{\text{Observed HCT}} \times \text{blood volume} \times \text{body weight (kg)} \times (100 \text{ mg/kg})$$

Plasmanate is used most commonly for the exchange.

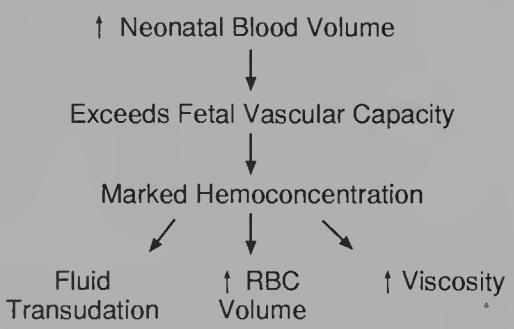


Figure 27.6. Polycythemia and hyperviscosity. Proposed pathogenesis (II). With permission from Oh W. Neonatal polycythemia and hyperviscosity. Pediatr Clin North Am 1986;33:523–532. See text for descriptions.

HYPERTROPHIC AND CONGESTIVE CARDIOMYOPATHY

In some macrosomic, plethoric infants of poorly controlled diabetic mothers, a thickened myocardium and significant asymmetric septal hypertrophy has been described (66). The pathogenesis of hypertrophic cardiomyopathy in IDM is unclear, although it is recognized to be associated with poor maternal metabolic control and fetal hyperinsulinemia. The fetal myocardium is particularly sensitive to insulin during gestation, and Susa and colleagues (67) have reported a 100% increase in cardiac mass in fetal hyperinsulinemic rhesus monkeys.

IDM who manifest cardiomegaly and signs of congestive heart failure may have either congestive or hypertrophic cardiomyopathy.

This condition is often asymptomatic and unrecognized. Echocardiograms show a hypercontractile, thickened myocardium, often with septal hypertrophy disproportionate to the size of ventricular walls. The ventricular chambers are often smaller than normal and there may be anterior systolic motion of the mitral valve producing left ventricular-outflow tract obstruction.

Way and colleagues (68) have followed 11 IDM with hypertrophic cardiomyopathy for 30–40 months. All infants presented with **cardiorespiratory distress** and were found to have disproportionate septal hypertrophy on echocardiogram. Four infants had a cardiac catheterization; three had subaortic obstruction. The natural history of hypertrophic cardiomyopathy appears to be benign with a resolution of symptoms within 2–4 weeks and septal hypertrophy within 2–12 months. Most infants need only supportive care. If pharmacologic intervention is necessary, propanolol is the drug of choice.

IDM may also have congestive cardiomyopathy without hypertrophy. On echocardiogram, the myocardium is overstretched and poorly contractile. This condition is often rapidly reversible with correction of neonatal hypoglycemia, hypocalcemia, and polycythemia; it responds to digoxin or diuretics or both. In contrast, treatment of hypertrophic cardiomyopathy with an ionotropic or diuretic agent tends to decrease further the size of the ventricular chambers and leads to obstruction of blood flow. Echocardiographic examination of IDM with enlarged hearts is recommended to detect and treat clinically silent cardiomyopathy.

CONGENITAL MALFORMATIONS

Problems associated with developmental defects have emerged as the most important cause of neonate mortality in IDM. Table 27.1 is a list of the most common congenital defects

Table 27.1.
Congenital Malformations in Infants of Diabetic Mothers

Central nervous system
Anencephalus
Encephalocele
Meningomyelocele
Skeletal and spinal
Sacral agenesis
Spina bifida
Heart
Transposition of great vessels
Ventricular septal defect
Atrial septal defect
Situs inversus
Single ventricle
Hypoplastic left ventricle
Kidney
Agenesis
Cystic kidney
Ureteral duplication
Gastrointestinal tract
Small left side of colon
Situs inversus
Anal/rectal atresia
Lungs
Hypoplasia

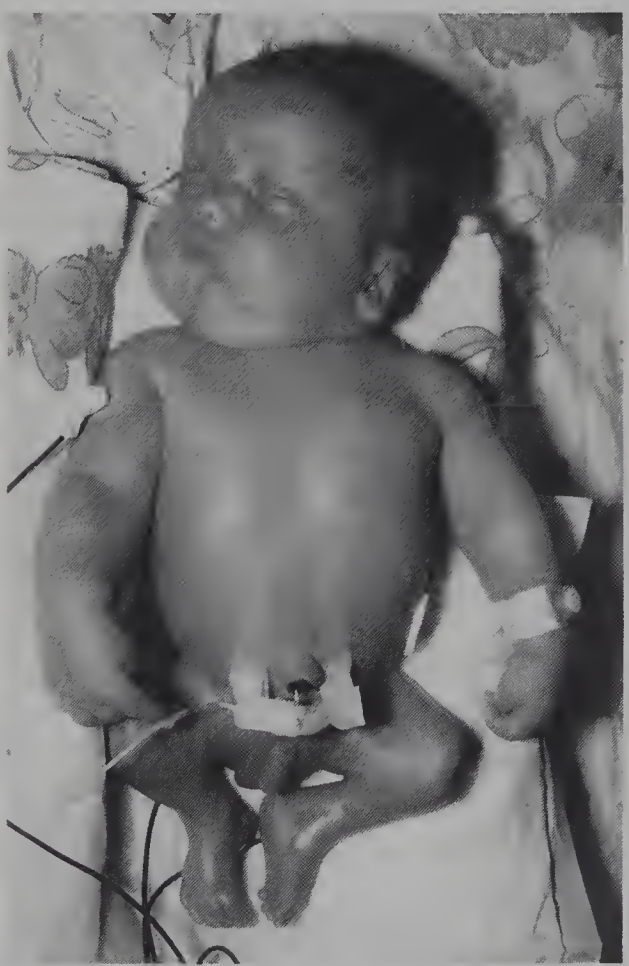


Figure 27.7. Newborn infant with sacral agenesis syndrome, flexion contractures, and hypoplasia of the lower extremities. The mother had IDDM and a HbA1c concentration of 13.5% when first seen for prenatal care at 12 weeks' gestation.

reported in diabetic pregnancies. In all reviews, the number of significant malformations is underreported since many abnormalities do not have clinical signs or symptoms in the early perinatal period. No specific congenital defect is peculiar to diabetes but malformations are more severe and cardiovascular and central nervous system defects are overrepresented. Congenital heart disease is more often fatal in IDDM than control groups. Grix and associates (69) have described in detail the patterns of multiple malformations in IDM.

The severe malformation, sacral agenesis syndrome (Fig. 27.7), with agenesis of the sacrum and lumbar spine and hypoplasia of the lower extremities is almost never seen except in IDM. Davis and Campbell (70) have reported an unusually high incidence (40%) of IDM who have a narrowed colon from the splenic fixture to the anus (neonatal small left colon syndrome). This disorder is spontaneously reversible in the 1st week of life.

Poor maternal control of diabetes at conception is associated with a higher incidence of congenital malformations in infants of IDDM and NIDDM women but not those of women with "truly gestational diabetes" (e.g., occurrence >20 weeks' gestation, normal HbA1c concentration, and reversible postpartum). Because this topic is intimately associated with preconception and early postconception events, the major discussion of the subject and most recent data (1990) are presented in Section I.

CHAPTER

28

Long-Term Observations of Children of Diabetic Mothers

A retrospective view of children born to mothers with diabetes during pregnancy presents a confusing picture. Although these mothers all have glucose intolerance, IDDM and NIDDM women have metabolic problems associated with different genetic disorders. In addition, the fetal intrauterine environment of each infant has been influenced by maternal complications including hyperglycemia or hypoglycemia, ketosis, documented or undocumented hypoxia, and abnormal concentrations of amino acids and lipids. In some women, repeated infections and hypertension are additional complications. Data collected before the 1970s do not reflect the recent improvements in perinatal care and delivery methods. Thus, it is difficult to assess the role of individual factors in present retrospective studies. Prospective studies with modern perinatal and neonatal care will provide a better view of infants of mothers with different types of diabetes.

NEURODEVELOPMENTAL STUDIES

Yssing (71) reported the long-range findings in 740 Danish children born from 1946–1966 with a birth weight of >1000 g who survived the neonatal period. The follow-up period extended from 1.5–26 yr. The main abnormal findings were postneonatal (>10 days of age) mortality of 4%, congenital malformations (11%), and cerebral dysfunction (36%). In 130 children (18%), a major cerebral handicap of definite clinical significance was recorded. Cerebral palsy and epilepsy were noted in 3% of the total series which represented a prevalence three to five times higher than the normal population.

In a more recent study, Petersen and her associates (72) in Copenhagen, have reported their findings in 99 consecutive IDDM women and 101 nondiabetic women who had an ultrasonographic examination to assess early fetal growth. There was early intrauterine growth delay in 42 diabetic and 3 nondiabetic mothers. All children available for study were evaluated by the Denver Developmental Screening test at 4–5 yr of age. Only 23 of 34 (68%) children of diabetic mothers with early intrauterine growth delay had normal test scores compared with 46 of 50 (92%) children of diabetic mothers with normal intrauterine growth. The children failed in personal-social development, gross motor development, and, particularly, in language and speech development. Children of diabetic mothers with normal early fetal growth had scores very similar to those of nondiabetic mothers of whom 76 of 86 (88%) tested had normal scores.

Brain development in the fetus, neonate, and infant is extremely complex and basic knowledge in this field stems mainly from experimental work in animals. Herschkowitz (73) has reviewed the eight interrelated but distinguishable events recognized in structural brain development: *(1)* neuronal induction; *(2)* neuroblast proliferation; *(3)* neuronal migration; *(4)* neuronal selective aggregation; *(5)* neuronal differentiation and formation of specific patterns of connection; *(6)* neuronal death; *(7)* selective synapse elimination; and *(8)* myelination. The basic mechanisms regulating these developmental events are genetically determined but, at any stage of development, epigeneic and environmental factors modulate genetic regulation. Do perturbations in early fetal growth and an abnormal maternal metabolic environment have later sequellae, such as behavioral terato-

genesis (74) in IDM? These questions are, of course, of great importance for all children, but unanswered at present.

Petersen (75) has also studied 90 children born from 1980–1983 to IDDM women and 115 in a comparison group. She found that the General Cognitive Index (IQ) of IDM differed significantly from the mean of normal birth weight children of nondiabetic mothers in the comparison group. Some of the differences might be explained by a difference in social class distribution. Nevertheless, 14.5% of children of diabetic mothers were intellectually subnormal and, excluding three children from poor social backgrounds, the percentage was 10.5%. Peterson and others have not found any relationship between IQ of IDM and maternal White class and metabolic compensation. Like Yssing's previous studies (71), this follow-up found low birth weight (preterm birth or IUGR) infants were at greatest risk. Children of IDDM mothers remained at risk for psychomotor problems. Poor performance in three noncognitive fields (the grooved pegboard test, the McCarthy Motor, and the Qualitative Motor Development Score) suggested a neurologic immaturity or sequellae to some adverse influence on the development of the fetal brain.

In the Swedish experience reported by Persson and Gentz (76), at age 5 yr, 53 children of IDDM mothers had normal physical and neurologic development (13 infants lost to follow-up and, accordingly, not examined had more perinatal complications including malformations than the follow-up group). Social class and data from infants of nondiabetic mothers were not evaluated. No obvious relationship was found among the variables of acetonuria during pregnancy, infant birth weight, blood glucose during first hours after birth, and neonatal complications and subsequent IQ of the children. These studies were in agreement with those of Hadden and colleagues (77), Cummins and Norrish (78), and Reid and Russell (79) whose studies in children of mothers with GDM were more optimistic than those in older studies (71, 80, 81).

The differences in outcome of children with IDDM may reflect differences in study protocols and perhaps differences in maternal complications during gestation. In the Belfast study of Hadden and associates (77), several trends were noted beyond age 4 yr that did not reach statistical significance. These children appeared to miss school and to have a somewhat lower academic achievement in teachers' assessments than the control group.

GROWTH PATTERNS AND SUBSEQUENT RISK OF DIABETES

Oppermann and colleagues (82), in a study of GDM and macrosomia, found that large babies were more prone to become or stay obese in later life. Farquhar (83) followed 231 children of "truly diabetic women" in Edinburgh and compared their birth weights with weight 1–19 yr later. He employed a weight/height index using the 50th percentile for height and weight as 100/100 = 1.0. At birth, two thirds of the infants had an index of 1.0 or greater. Subsequent findings showed a clear trend toward heavy babies becoming heavy children. Pima Indian women with NIDDM also have excessive obesity in their offspring (84). Insensitivity to insulin has been reported in offspring of NIDDM (85).

Improved control of maternal diabetes during pregnancy will enable better correlations to be made for the assessment of relative risks of genetic factors, maternal metabolic abnormalities, and neonatal and childhood obesity. Prospective studies that include skin fold measurements at birth may provide a better index of neonatal obesity than birth weight alone and should be helpful in defining the relative risk of long-term obesity in infants of mothers with IDDM, NIDDM, and GDM.

Children of IDDM are at higher risk for developing insulin-dependent diabetes. Many studies have been conducted throughout the world to assess the risk for development of diabetes in IDM. Estimates vary depending upon whether glucose tolerance tests were performed. White (86) reported that in the United States 9% of infants were diabetic by adolescence and 14% had borderline glucose tolerance. In Denmark, Yssing (71) detected diabetes in 1%, borderline diabetes in 15.9%, and an abnormal oral glucose tolerance test in 18.4%. All reports suggest the risk for developing diabetes is far greater in IDM than the normal population. It will be important in future studies to compare the outcome in children of mothers with IDDM, NIDDM, and GDM. Amendt and colleagues (87) have found a high percentage of abnormal or borderline glucose tolerance tests in IDM, and Persson

and associates (88) report a frequency of IDDM of 3% in offspring of IDDM mothers.

It is extremely difficult to assess subsequent risk of diabetes in IDM because of the lack of a genetic marker for any type or subtype of maternal diabetes. From the experience in well-studied Pima Indians who have NIDDM, the risk for diabetes in children of mothers with this type of diabetes is likely to be much higher than for children of IDDM mothers. Pettitt and associates (89) suggest that the intrauterine environment is an important determinant for congenital susceptibility to NIDDM.

In summary, diabetic mothers who are in poor control at conception are at much higher risk for infants with congenital malformations and higher morbidity and mortality. There has been a dramatic fall in perinatal complications of IDM, which reflects better maternal metabolic control throughout pregnancy, prevention of premature births, improved methods of labor and delivery, and the availability of neonatal intensive care nurseries. The relationship of maternal diabetes of various types upon the growth patterns and risk of diabetes in their children has not been established but will be of importance in these families.

References for Section X

1. Perinatal Mortality and Congenital Malformations in Infants Born to Women with Insulin-Dependent Diabetes Mellitus—United States, Canada, and Europe, 1940–1988. JAMA 1990; 264:437–441.
2. Morbidity and Mortality Weekly Report (MMWR) 1990;39:363–365.
3. Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemia control during organogenesis. N Engl J Med 1988; 318:671–676.
4. Connell FA, Vadheim C, Emanuel I. Diabetes in pregnancy: A population-based study of incidence, referral for care and perinatal mortality. Am J Obstet Gynecol 1985;151:598–603.
5. Jervell J, Bjerkedal T, Moe N. Outcome of pregnancies in diabetic mothers in Norway, 1967–1976. Diabetologia 1980;18:131–134.
6. Wheeler FC, Gollmar CW, Deeb LC. Diabetes and pregnancy in South Carolina: Prevalence, perinatal mortality, and neonatal morbidity in 1978. Diabetes Care 1982;5:561–565.
7. Gabbe S, Mestman JH, Freeman RK, et al. Management and outcome of pregnancy in diabetes mellitus class B to R. Am J Obstet Gynecol 1977;129:723–732.
8. Kitzmiller JL, Cloherty JP, Younger MD, et al. Diabetic pregnancy and perinatal morbidity. Am J Obstet Gynecol 1978;131:560–580.
9. Braveman P, Showstack J, Browner W, Selby J, Teutsch S, Sepe S. Special article. Evaluating outcomes of pregnancy in diabetic women. Diabetes Care 1988;11:281–286.
10. Landon MB, Gabbe SG, Piana R, Mennuti MT, Main EK. Neonatal morbidity in pregnancy complicated by diabetes mellitus: Predictive values of maternal glycemic profiles. Am J Obstet Gynecol 1987;156:1089–1095.
11. Duffty P, Lloyd DJ. The infant of the diabetic mother. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate Metabolism in Pregnancy and the Newborn IV. London: Springer-Verlag 1989:327–332.
12. Whitelaw A. Subcutaneous fat in newborn infants of diabetic mothers: An indication of quality of diabetic control. Lancet 1977;1:15–18.
13. Dubrueil G, Anderodias J. Ilots de Langerhans glands chez un nouveaune issu mere glycosurique. C R Soc Biol 1920;83:1490–1493.
14. Cardell BS. Hypertrophy and hyperplasia of pancreatic islets in newborn infants. J Pathol Bacteriol 1953;66:335–346.
15. Driscoll SG, Benirschke K, Curtis GW. Neonatal deaths among infants of diabetic mothers. Am J Dis Child 1960;100:818–835.
16. Steinke J, Driscoll SG. The extractable insulin content of pancreas from fetuses and infants of diabetic and control mothers. Diabetes 1965; 14:573–578.
17. Pedersen J. Diabetes and pregnancy. Blood sugar of newborn infants. Copenhagen:Danish Science Press, 1952.
18. Freinkel N, Metzger BE. Pregnancy as a tissue culture experience: The critical implications of maternal metabolism for fetal development. In: Pregnancy Metabolism, Diabetes and the Fetus. CIBA Foundation Symposium 63 (New Series) Excerpta Medica, Amsterdam, 1979, pp 3–28.
19. Brinsmead MW, Liggins GC. Somatomedins and other growth factors in fetal growth. In: Scarpelli EM, Cosmi EV (eds). Reviews in Perinatal Medicine. New York:Raven Press, 1979;3:207–242.
20. Giordano G, Van Wyk JJ, Minuto F. Somatomedins and Growth. New York:Academic Press, 1979.
21. Guyda HJ, Posner BI, Rappaport R. Insulin like growth factors. In: Collu R, Ducharme JR, Guyda H (eds). Pediatric Endocrinology. New York:Raven Press, 1981:205–229.
22. Sperling MA, Devaskar S. Insulin action in the placental fetal unit. In: Drazin B, Melmed S, LeRoith D (eds). Molecular and Cellular Biology of Diabetes Mellitus. Vol. 2. New York:Alan R. Liss Inc. 1989;203–217.
23. Hoffman L, Mandel TE, Carter WM, Koulmanda M, Martin FIR. Insulin secretion by fetal human pancreas in organ culture. Diabetologia 1982; 23:426–430.
24. Maitland JE, Parry DG, Turtle JR. Perfusion and culture of human fetal human pancreas. Diabetes 1980; 29(Suppl 1):57–63.
25. Reddy S, Elliot RB. Reviews. Ontogenic development of peptide hormones in the mammalian fetal pancreas. Experientia 1988;44:1–9.
26. Otonkoski T, Andersson S, Knip M, Simell O. Maturation of insulin response to glucose during human fetal and neonatal development. Studies with perifusion of pancreatic isletlike cell clusters. Diabetes 1988;37:286–291.
27. Milne RDG. Growth and development of the endocrine pancreas. In: Davis JA, Dobbing J (eds). Scientific Foundations of Pediatrics. London:Heinemann 1981:701–713.

28. Hill DJ, Milner RDG. Insulin as a growth factor. Pediatr Res 1985;49:879–886.
29. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC. Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus. Its role in fetal macrosomia. N Engl J Med 1990;323:309–315.
30. Frantz ID III, Epstein MF. Fetal lung development in pregnancies complicated by diabetes. In: Merkatz IR, Adam PAJ (eds). The Diabetic Pregnancy: A Perinatal Perspective. New York:Grune & Stratton 1979;227–233.
31. Curet LB, Olson RW, Schneider JM, Zachman RD. Effect of diabetes mellitus on amniotic fluid lecithin/sphingomyelin ratio and respiratory distress syndrome. Am J Obstet Gynecol 1979;135:10–13.
32. Hallman M, Teramo K. Measurement of lecithin/sphingomyelin ratio and phosphatidyl glycerol in amniotic fluid: An accurate method for the assessment of fetal lung maturity. Br J Obstet Gynaecol 1981;88:806–813.
33. Cowett RM. Infant of the diabetic mother. In Gabbe S, Oh W (eds). Report of the 93rd Ross Conference on Pediaric Research. Columbus OH:Ross Laboratories, 1987;26–40.
34. Hay WW. Infant of the diabetic mother. In Gabbe S, Oh W (eds). Report of the 93rd Ross Conference on Pediaric Research. Columbus, OH:Ross Laboratories: 1987;38–39.
35. Oh W. Neonatal care and long-term outcome of infants of diabetic mothers. In: Merkatz IR, Adam PAJ (eds). The Diabetic Pregnancy: A Perinatal Perspective. New York:Grune & Stratton 1979:195–205.
36. Anonymous. Brain damage by neonatal hypoglycemia. (Editorial) Lancet 1989;1:882–883.
37. Aynsley-Green A, Eyre JA. Letter. Lancet 1989;2:447.
38. Chucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. Br Med J 1988;297:1304–1308.
39. Koh THHG, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycemia. Arch Dis Child 1988;63:1353–1358.
40. Tsang RC, Kleinman LI, Sutherland JM, Light IJ. Hypocalcemia in infants of diabetic mothers. J Pediatr 1972;80:384–395.
41. Tsang RC, Brown DR, Steicher JJ. Diabetes and calcium: calcium disturbances in infants of diabetic mothers. In Merkatz IR, Adam PAJ (eds). The Diabetic Pregnancy: A Perinatal Perspective. New York:Grune & Stratton, 1979:207–225.
42. Mimouni F, Tsang RC. Diabetes in pregnancy: Perinatal magnesium metabolism. Infant of the diabetic mother. In Gabbe S, Oh W (eds). Report of the 93rd Ross Conference on Pediatric Research. Columbus, OH:Ross Laboratories, 1987;124–129.
43. Cruikshank DP, Pitkin RM, Varner MW, Williams GA, Hargis GK. Calcium metabolism in diabetic mother, fetus and newborn infant. Am J Obstet Gynecol 1983;145:1010–1016.
44. Shaul PW, Mimouni F, Tsang RC, Specker BL. The role of magnesium in neonatal calcium homeostasis. Pediatr Res 1987;22:319–323.
45. Ashe JR, Schofield FA, Gram MR. The retention of calcium, iron, phosphorus and magnesium during pregnancy: The adequacy of prenatal diets with and without supplementation. Am J Clin Nutr 1979;32:286–291.
46. Pitkin RM. Calcium metabolism in pregnancy and the perinatal period. A Review. Am J Obstet Gynecol 1985;151:99–109.
47. Dancis J, Springer D, Cohlan SQ. Fetal homeostasis in maternal malnutrition: II. Magnesium deprivation. Pediatr Res 1971;5:131–136.
48. Hurley LS, Cosens C, Theriault LL. Teratogenic effects of magnesium deficiency in rats. J Nutr 1976;106:1254–1260.
49. Stevenson DK. Bilirubin metabolism in the infants of the diabetic mothers: An overview. Infant of the diabetic mother. In Gabbe S, Oh W. (eds). Report of the 93rd Ross Conference on Pediatric Research. Columbus, OH:Ross Laboratories, 1987;109–117.
50. Jahrig D, Jahrig K, Stiete S, Beyersdorff E, Poser H, Hopp H. Neonatal jaundice in infants of diabetic mothers. Acta Paediatr Scand Suppl 1989;360:101–107.
51. Gamsu HR. Neonatal morbidity in infants of diabetic mothers. J Royal Soc Med 1978;71:211–222.
52. Peevy KJ, Landaw SA, Gross SJ. Hyperbilirubinemia in infants of diabetic mothers. Pediatrics 1980;66:417–419.
53. Scheidt PC, Bryla DA, Nelson KB, Hirtz DG, Hoffman MA, and principal invesigators. Phototherapy for neonatal hyperbilirubinemia: Six-year follow-up of the National Institutes of Child Health and Human Development Clinical Trial. Pediatrics 1990;85:455–463.
54. Gross GB, Hathaway WE, McGaughey HR. Hyperviscosity in the neonate. J Pediatr 1973; 82:1004–1021.
55. Mimouni F, Miodovnik M, Siddiqi TA, Butler JB, Holyroyde J, Tsang RC. Neonatal polycythemia in infants of diabetic mothers. Obstet Gynecol 1986;68:370–372.
56. Mimouni F, Tsang RC, Hertzberg VS, Miodovnik M. Polycythemia, hypomagnesemia, and hypocalcemia in infants of diabetic mothers. Am J Dis Child 1986;140:798–800.
57. Oh W. Neonatal polycythemia and hyperviscosity. Pediatr Clin North Am 1986;33:523–532.
58. Oh W. Pathophysiology of polycythemia in infants of diabetic mothers. Infant of the diabetic mother. In Gabbe S, Oh W (eds). Report of the 93rd Ross Conference on Pediatric Research. Columbus, OH:Ross Laboratories, 1987;133–141.
59. Widness JA, Susa JB, Garcia JF, et al. Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic rhesus fetuses. J Clin Invest 1981; 67:637–642.
60. Widness JA, Garcia JF, Oh W, et al. Cord serum erythropoietin values and disappearance rates after birth in polycythemic newborns. Pediatr Res 1982;16:218A.
61. Widness JA, Teramo KA, Clemons GK. Direct relationship of antepartum glucose control and

fetal erythropoietin in human type I (insulin-dependent) diabetic pregnancy. Diabetologia 1990;33:378–383.
62. Leake RD, Thanopoulos B, Nieberg R. Hyperviscosity syndrome, associated with necrotizing enterocolitis. Am J Dis Child 1975;129:1192–1194.
63. Hakanson DO, Oh W. Necrotizing enterocolitis and hyperviscosity in the newborn infant. J Pediatr 1977;458–461.
64. Black VD, Lubchenco LO, Koops BL, Polard RL, Powell AP. Neonatal hyperviscosity: Randomized study of effect of partial exchange transfusion on long-term outcome. Pediatrics 1985; 75:104–105.
65. Black VD, Camp BW, Lubchenco LO, et al. Neonatal hyperviscosity association with lower achievement and IQ scores at school age. Pediatrics 1989;83:662–667.
66. Schwartz JB, Warburton D, Gordon LS. Massive hypertrophic cardiomyopathy in infant of a diabetic mother. J Perinatol 1986;6:350–355.
67. Susa JB, McCormick KL, Widness JA, et al. Chronic hyperinsulinemia in the fetal rhesus monkey. Effects on fetal growth and composition. Diabetes 1979;28:1058–1063.
68. Way GL, Wolfe RR, Eshaghpour E, Bender RL, Jaffe RB, Ruttenberg HD. The natural history of hypertrophic cardiomyopathy in infants of diabetic mothers. J Pediatr 1979;95:1020–1025.
69. Grix A Jr, Curry C, Hall BD. Patterns of multiple malformations in infants of diabetic mothers. In: Prenatal Diagnosis and Mechanisms of Teratogenesis: Part A of Annual Review of Birth Defects, 1981. March of Dimes Birth Defects Foundation (Birth Defects: Original Article Series), New York:Alan R. Liss Inc, 1982: 18(3A):55–77.
70. Davis WS, Campbell JB. Neonatal small left colon syndrome. Am J Dis Child 1975;129: 1024–1027.
71. Yssing M. Long-term prognosis of children born to mothers diabetic when pregnant. In: Camerini-Davalos RA, Cole HS (eds). Early Diabetes in Early Life. New York:Academic Press, 1975:575–586.
72. Petersen MB, Pedersen SA, Greisen G, Pedersen JF, Mølsted-Pedersen L. Early growth delay in diabetic pregnancy: Relation to psychomotor development at age 4. Br Med J 1988;296:598–600.
73. Herschkowitz N. Brain development in the fetus, neonate and infant. Biol Neonate 1988;54:1–19.
74. Werboff J, Gottlieb JS. Drugs in pregnancy: Behavioral teratology. Obstet Gynecol Surv 1963;18:420–423.
75. Petersen MB. Status at 4–5 years in 90 children of insulin-dependent diabetic mothers. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate Metabolism in Pregnancy and the Newborn. London:Springer-Verlag, 1989:353–361.
76. Persson B, Gentz J. Follow-up of children of insulin-dependent and gestational diabetic mothers. Neuropsychological outcome. Acta Pediatr Scand 1984;73:349–358.
77. Hadden DR, Byrne E, Trotter I, Harley JMG, McClure G, McAukey RR. Physical and psychological health of children of Type I (insulin-dependent) diabetic mothers. Diabetologia 1984; 26:250–254.
78. Cummins M, Norrish M. Follow-up of children of diabetic mothers. Arch Dis Child 1980; 55:259–264.
79. Reid JA, Russell G. Qualitative assessment of children of known gestational diabetic mothers. In: Sutherland HW, Stowers JM, Pearson DWM (eds). Carbohydrate Metabolism in Pregnancy and the Newborn. Berlin:Springer-Verlag 1979: 462–477.
80. Bibergeil H, Godel E, Amend T. Diabetes and pregnancy. Early and late prognosis of children of diabetic mothers. In: Camerini-Davalos RA, Cole HS (eds). Early Diabetes in Early Life. New York:Academic Press, 1975:427–434.
81. Haworth JC, McRae RN, Dilling L. Prognosis of infants of diabetic mothers in relation to neonatal hypoglycemia. Dev Med Child Neurol 1976;18:471–479.
82. Oppermann W, Guliucci C, O'Sullivan MJ, Hanover B, Camerini-Davalos RA. Gestational diabetes and macrosomia. In: Camerini-Davalos RA, Cole HS (eds). Early Diabetes in Early Life. New York:Academic Press, 1975:455–468.
83. Farquhar JW. Prognoses for babies born to diabetic mothers in Edinburgh. Arch Dis Child 1969;44:36–47.
84. Pettit DJ, Baird HR, Aleck KN, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 1983;308:242–245.
85. Leslie RDG, Ganash A, Volkmann HP, Hanning I, Alberti KGMM. Insensitivity to insulin in offspring of non-insulin dependent diabetic patients. Diab Nutr Metab 1988;3:235–237.
86. White P. Childhood diabetes, its course and influence of the 2nd and 3rd generations. Diabetes 1960;9:345–355.
87. Amendt P, Michaeles D, Hildmann W. Clinical and metabolic studies in children of diabetic mothers. Endokrinologie 1976;67:351–361.
88. Persson B, Gentz J, Moller E. Follow-up of children of insulin dependent (Type I) and gestational diabetic mothers. Growth pattern, glucose tolerance, insulin response and HLA types. Acta Pediatr Scand 1984;73:778–784.
89. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. Diabetes 1988;37:622–628.

SECTION

XI

Conclusion

In this revised guide for the management of abnormal carbohydrate tolerance during pregnancy, the problem has been approached as a complex metabolic experiment of nature that involves not only elevated maternal plasma glucose levels, but all metabolic fuels that comprise the fetal diet in utero. In this scheme, a large, complex new endocrine gland, the placenta, develops de novo and plays a central role in both the delivery and modulation of maternal fuels to the fetus. IDDM and NIDDM are presented as two entirely different metabolic diseases that unfortunately share the label diabetes in common. GDM is a serious and heterogeneous disorder that requires more precise definition in individual lean and obese women.

Our future knowledge of pregnancy complicated by diabetes will involve well-designed prospective clinical and laboratory investigations to provide a better understanding of the maternal, fetal, and placental compartments. For individual diabetic women, the best approach to successful pregnancy requires: (*a*) preconception counseling and optimal diabetic control before conception, (*b*) meticulous management of diabetic control during pregnancy by a diabetes team in a regional perinatal center, (*c*) prompt attention to the diagnosis and treatment of both trivial and serious complications of pregnancy, (*d*) careful timing and appropriate mode of delivery, (*e*) good diabetic control in the intra- and postpartum periods, (*f*) attendance of a pediatrician at the delivery who is knowledgeable in the assessment and management of infants of diabetic mothers, and (*g*) the proximity of a neonatal intensive care nursery.

The care of pregnant diabetic patients is an exciting challenge for physicians and paramedical personnel. In this setting, the role of the obstetrician is expanded and he or she becomes the pediatrician for the unborn child, internist for the mother, and mental health counselor for the family.

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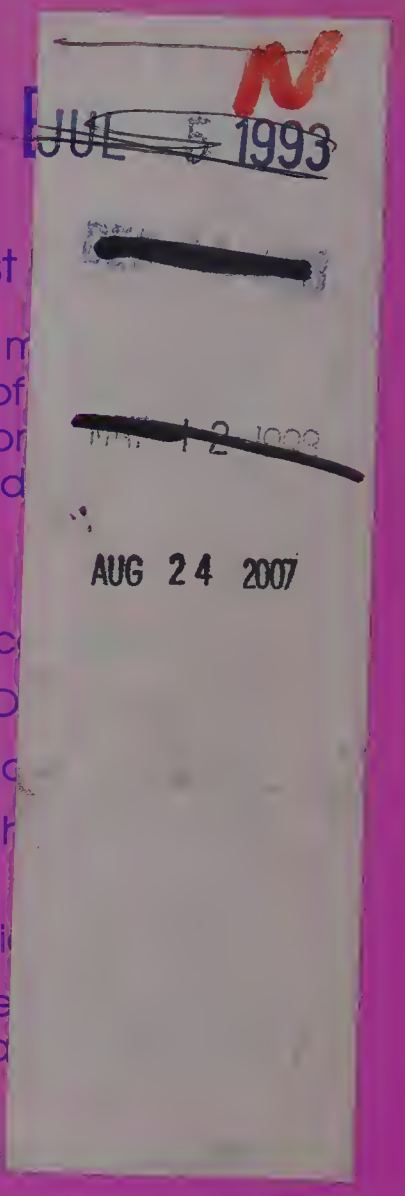

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