Health Professional's Guide *to* Nutrition, Diabetes, and Pregnancy

Alyce Thomas, RDN, FAND, Editor

eat right. Academy of Nutrition and Dietetics

CHICAGO, IL

Academy of Nutrition and Dietetics
120 S. Riverside Plaza, Suite 2190
Chicago, IL 60606

Health Professional's Guide to Nutrition, Diabetes, and Pregnancy

ISBN 978-0-88091-190-0 (print)
ISBN 978-0-88091-122-1 (eBook)
Catalog Number 190021 (print)
Catalog Number 190021e (eBook)

The views expressed in this publication are those of the authors and do not necessarily reflect policies and/or official positions of the Academy of Nutrition and Dietetics. Mention of product names in this publication does not constitute endorsement by the authors or the Academy of Nutrition and Dietetics. The Academy of Nutrition and Dietetics disclaims responsibility for the application of the information contained herein.

10 9 8 7 6 5 4 3 2 1

For more information on the Academy of Nutrition and Dietetics, visit www.eatright.org.

Library of Congress Cataloging-in-Publication Data

Names: Thomas, Alyce M., editor.
Title: Health professional's guide to nutrition, diabetes, and pregnancy / Alyce Thomas, RDN, editor.
Description: First edition. | Chicago, IL : Academy of Nutrition and Dietetics, [2021] | Includes bibliographical references and index.
Identifiers: LCCN 2021000499 (print) | LCCN 2021000500 (ebook) | ISBN 9780880911900 (paperback) | ISBN 9780880911221 (ebook)
Subjects: LCSH: Diabetes in pregnancy. | Pregnancy--Nutritional aspects. | Diabetes in pregnancy--Case studies.
Classification: LCC RG580.D5 H38 2021 (print) | LCC RG580.D5 (ebook) | DDC 618.3/646--dc23
LC record available at https://lccn.loc.gov/2021000499
LC ebook record available at https://lccn.loc.gov/2021000500

Contents

SECTION 3 Medication Use in Diabetes and Pregnancy

SECTION 4 Case Studies

SECTION 5 Appendixes

List of Boxes, Tables, and Figures

BOXES

TABLES

FIGURES

Frequently Used Terms and Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitors
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AFP	α-fetoprotein
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
ARB	angiotensin receptor blockers
ASCVD	atherosclerotic cardiovascular disease
BB	β-2 receptor agonists
BMI	body mass index
BP	blood pressure
BPP	biophysical profile
CCB	calcium channel blocker
CDCES	certified diabetes care and education specialist
CGM	continuous glucose monitoring
CI	confidence interval
COC	combined oral contraceptives
COX	cyclooxygenase
CSII	continuous subcutaneous insulin infusion
DASH	Dietary Approaches to Stop Hypertension
DKA	diabetic ketoacidosis

DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetane
DPP	Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
DRI	Dietary Reference Intake
DSMES	diabetes self-management education and support
EER	Estimated Energy Requirements
eGFR	estimated glomerular filtration rate
FBG	fasting blood glucose
FDA	US Food and Drug Administration
GCT	glucose challenge test
GDM	gestational diabetes mellitus
GI	gastrointestinal
GLP-1	glucagon-like peptide
GLUT	glucose transport molecule
GWG	gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA1c	hemoglobin A1c
hCG	human chorioinic gonadotropin
hct	hematocrit
HDL	high-density lipoproteins
hgb	hemoglobin
hPL	human placental lactogen
IgG	immunoglobulin G
Inh A	inhibin A
IUD	intrauterine device
IUGR	intrauterine growth restriction

LDL	low-density lipoproteins
LGA	large-for-gestational-age
LGI	low-glycemic index
MDI	multiple daily injections
MFMU	National Institute of Child Health and Human Development Maternal-Fetal Medicine Units
MNT	medical nutrition therapy
NAM	National Academy of Medicine
NCP	Nutrition Care Process
NPH	Neutral Protamine Hagedorn
NSAID	nonsteroidal anti-inflammatory drugs
NST	nonstress test
OGTT	oral glucose tolerance test
OR	odds ratio
Pap smear	Papanicolaou test
PCP	primary care physician
PROM	premature rupture of membranes
PUQE	Pregnancy-Unique Quantification of Emesis/Nausea
RDA	Recommended Dietary Allowance
RDN	registered dietitian nutritionist
RR	ratio risk
SGLT2	sodium-glucose cotransporter-2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UACR	urine albumin-to-creatinine ratio
uE3	unconjugated estriol

About the Editor

Alyce Thomas, RDN, FAND, began taking an interest in diabetes and pregnancy during her dietetic internship at the Montreal Diet Dispensary (MDD). At that time, the MDD internship was unique in its focus on community and prenatal nutrition. She was trained in the Higgins method of nutritional intervention; the success of the MDD in decreasing the risk of low birth weight babies inspired the creation of the Special Supplemental Program for Women, Infants, and Children (WIC).

Alyce's work continued after her internship as the Social Planning Nutritionist for the City of Halifax, Nova Scotia, and after moving to the United States, as a WIC Coordinator/Nutritionist. While working as a Nutrition Services Coordinator in Jersey City, NJ, Alyce jumped at the opportunity to return to her first love of high-risk pregnancy. She became a nutrition consultant for the Northern New Jersey Maternal Child Health Consortium and eventually for the Department of Obstetrics and Gynecology at St Joseph's Health in Paterson, NJ, where she continues to support nutrition and health needs during pregnancy.

Alyce is an active member of the Academy of Nutrition and Dietetics and has held many leadership positions, including Chair of the Diabetes Dietetic Practice Group and the Women's Health Dietetic Practice Groups, Chair of the Evidence-Based Practice Committee, and Professional Issues Delegate in the House of Delegates. Her activities with the Academy of Nutrition and Dietetics also include serving as a member of the Academy of Nutrition and Dietetics Evidence-Based Criteria Development Task Force, Honors Committee, and the Evidence-Based Analysis Gestational Diabetes Mellitus and Obesity, Reproduction and Pregnancy workgroups.

Her appointments include the Eunice Kennedy Shriver's National Institute of Child Health Development Advisory Council, the Diabetes Leadership Council, the New Jersey Governor's Council on the Prevention of Developmental Disabilities, and the Sweet Success Extension Program Advisory Council. In 2011, Alyce was appointed to the National Institutes of Health–Consensus Development Panel on Diagnosing Gestational Diabetes.

Alyce has written and contributed to numerous publications, including serving as coauthor of the *American Dietetic Association Guide to Gestational Diabetes Mellitus*; coauthor of chapters in the American Association of Diabetes Educator's *The Art and Science of Diabetes Self-Management Education: A Desk Reference for Healthcare Professionals*; *Diabetes in Black America: Public Health and Clinical Solutions to a National Crisis*; *Pediatric Nutrition*, 3rd edition; and the Academy of Nutrition and Dietetics *Gestational Diabetes Mellitus Toolkit*.

Contributors

Antonia Carbone, PharmD, CDCES, BCACP
Ambulatory Care Clinical Pharmacist, Overlook Medical Center; Clinical Associate Professor of Pharmacy Practice, Fairleigh Dickinson University of Pharmacy and Health Sciences
Florham Park, NJ

Maria Duarte-Gardea, PhD, RDN, LD
Chair and Professor, Department of Public Health Sciences,
The University of Texas at El Paso
El Paso, TX

Celeste Durnwald, MD
Associate Professor, Maternal Fetal Medicine, Department of Obstetrics and Gynecology
Director, Penn Perinatal Diabetes Program
Director, High Risk Clinic at the Helen O. Dickens Center for Women's Health, Hospital of the University of Pennsylvania
Philadelphia, PA

Neda Ghaffari, MD
Assistant Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and RS, University of California
San Francisco, CA

Diana M. Gonzales-Pacheco, DCN, RDN
Assistant Professor, Assistant Director Dietetic Internship, University of New Mexico
Albuquerque, NM

Donna Jornsay, MS, BSN, CPNP, CDCES, BC-ADM, CDTC
Diabetes Program Manager/Clinical Specialist, Mills-Peninsula Medical Center
Burlingame, CA

Christine Lam, PharmD, BCPS, BCACP, CDCES, BCGP
Assistant Professor, Department of Pharmacy Practice, University of the Incarnate Word Feik School of Pharmacy; Adjunct Assistant Professor, Department of Family and Community Medicine, Ambulatory Care Pharmacist, UT Physician Geriatric and Palliative Care Center
San Antonio, TX

Breanna S. Oberlin, MS, RD, CD, CDCES
Swedish Maternal Fetal Specialty Center and Swedish Bariatric, Metabolic, and Endocrinology Center
Seattle, WA

Elif Özdener-Poyraz, PharmD, BCACP, CDCES, AAHIVP
Assistant Professor of Pharmacy Practice, Fairleigh Dickinson University School of Pharmacy and Health Sciences
Florham Park, NJ

Diane M. Reader, RDN, CDCES
Manager, Diabetes Professional Education, International Diabetes Center
Minneapolis, MN

Alyce Thomas, RDN
Nutrition Consultant, Department of Obstetrics and Gynecology, St. Joseph's Health
Paterson, NJ

Reviewers

Denise Andersen, MS, RDN, LD, CLC*
Business Consultant, Private Practice
Mendota Heights, MN

Marina Chaparro, RDN, CDE, MPH
Registered Dietitian, Certified Diabetes Educator and Spokesperson, Nutrichicos
Miami, FL

Aldo Khoury, MD, FACOG
Director, Maternal Fetal Medicine, Department of Obstetrics and Gynecology, St. Joseph's University Medical Center
Paterson, NJ

Chris Pelto, RN, CDE
Diabetes Educator, Swedish Medical Center
Seattle, WA

Lacie Peterson, MS, RDN, BC-ADM, CDCES, FADCES, FAND
Dietetic Internship Director, Clinical Associate Professor, Utah State University
Taylorville, UT

David L. Principe, MD, FACOG
Perinatalogist, Department of Obstetrics and Gynecology, St. Joseph's University Medical Center
Paterson, NJ

Sara (Mandy) Reece, PharmD, CDCES, BC-ADM, FAADE
Vice Chair and Associate Professor of Pharmacy Practice, School of Pharmacy, Philadelphia College of Osteopathic Medicine
Suwanee, GA

Judy Simon, MS, RDN, CD, CHES
Clinical Dietitian, University of Washington Medical Center
Seattle, WA

Malgorzata Slugocki, PharmD
Assistant Professor of Pharmacy Practice, Fairleigh Dickinson University School of Pharmacy
Florham Park, NJ

Usha Sriram, MD
Director, ACEER Health and DIWWAAAS
Adyar, Chennai, India

Ruth Toiba, PhD, RD, CDCES
Diabetes Educator, Dr. Ruth Diabetes Watchers, Inc,
Davie, FL

* Reviewer Denise Andersen, MS, RDN, LD, CLC, died May 20, 2018. The Academy of Nutrition and Dietetics and the authors and editor of the book are grateful for her contributions.

Foreword

With both the prevalence of diabetes and age of pregnant individuals increasing in the United States, more persons enter pregnancy with diabetes or are diagnosed with gestational diabetes. With diabetes impacting a growing number of pregnancies, it is essential to have accurate, clear information to manage the care of these individuals. Under the expert leadership of Alyce Thomas, RDN, FAND, the Academy of Nutrition and Dietetics has created *The Health Professional's Guide to Nutrition, Diabetes, and Pregnancy*. This work builds on a prior publication that focused solely on gestational diabetes, and the expanded content now addresses the critical need for information directed at persons with diabetes entering pregnancy as well as diabetes that develops during pregnancy.

Ms. Thomas assembled experts to author the chapters, creating a stand-alone edition for the practitioner. Beginning with an overview of diabetes in pregnancy, the text provides a foundation to understand the complexity and breadth of the conditions. The chapters on management are comprehensive and provide clear, concise guidance—they not only provide details on what to do but also a clear understanding of the pathophysiology underlying the recommendations. Importantly, there is also guidance on medications, both for the treatment of diabetes and common conditions in pregnancy.

A gem of the text is the case studies, providing real-life situations, including the workup, analysis, and guidance. These case studies bring the recommendations to life—demonstrating clearly the implementation and outcomes. This level of detail and management throughout gestation will be invaluable to the practitioner.

I commend the Academy of Nutrition and Dietetics for the foresight to commission this work and to Alyce Thomas's leadership for creating such a comprehensive text. As a maternal fetal medicine physician, I care for persons with diabetes in pregnancy—and, personally, as a woman who had gestational diabetes in three pregnancies—I appreciate the importance of the material in this text. *The Health Professional's Guide to Nutrition, Diabetes, and Pregnancy* is an excellent addition to the literature for practitioners.

Catherine Y. Spong, MD
Professor and Vice Chair, Department of Obstetrics and Gynecology
Chief, Division of Maternal-Fetal Medicine.
University of Texas Southwestern Medical Center
Gillette Professorship in Obstetrics and Gynecology

Preface

The first book published by the Academy of Nutrition and Dietetics on nutrition, diabetes, and pregnancy, *The American Dietetic Association Guide to Gestational Diabetes*, focused solely on gestational diabetes mellitus (GDM). In this expanded edition, care of pregnant persons with preexisting diabetes—type 1 and type 2—is now included. Although GDM is one of the most common complications in pregnancy and continues to comprise most cases of diabetes in pregnancy, more persons with type 1 and type 2 diabetes are becoming pregnant, and health professionals need to know the similarities and the differences in managing *all* persons with diabetes during their pregnancies. In other words, "one size does not fit all," and neither should all diabetes in pregnancy be managed the same way.

The *Health Professional's Guide to Nutrition, Diabetes, and Pregnancy* provides a resource for those involved in the care of pregnant persons with diabetes. It is intended for registered dietitian nutritionists, registered dietetic technicians, diabetes care and education specialists, physicians, nurses, pharmacists, and other allied health professionals. To better address the full spectrum of care, the authors of this edition include registered dietitian nutritionists, physicians, a nurse, and pharmacologists. Most are CDCESs (Certified Diabetes Care and Education Specialists), and all are considered experts in their respective fields, which gives this book an interdisciplinary and global perspective on diabetes and pregnancy.

The chapters in this book are divided into five main sections:

- **Overview of Diabetes and Pregnancy (Chapters 1 through 3):** Chapter 1 includes a discussion on the current demographics of diabetes and pregnancy and a historical overview of diabetes and pregnancy management. Chapter 2 describes the major physiological changes in energy metabolism in normal pregnancy and in pregnancies complicated with diabetes. This chapter also provides a discussion on how hyperglycemia may affect fetal growth and development. Culture and health literacy are two important areas that impact diabetes care, and both are addressed in Chapter 3.
- **Diabetes Management From Preconception Through Postpartum (Chapters 4 through 6):** Chapter 4 begins with preconception care of persons with type 1 and type 2 diabetes

mellitus. A successful pregnancy begins with preconception counseling and care, which are critically important with preexisting diabetes. Any preexisting comorbid conditions should be managed closely to help improve pregnancy outcomes. Chapter 5 describes the management of pregnancy and diabetes. Rather than separating chapters for preexisting diabetes and GDM, antepartum care is addressed in this single chapter, highlighting when applicable any differences in management. The last chapter in this section, Chapter 6, discusses postpartum care and diabetes.

- **Medication Use in Diabetes and Pregnancy** (**Chapters 7 and 8**)**:** Medication use in pregnancy is always an important topic because of the possible maternal and fetal adverse effects. This section was separated into two chapters: Chapter 7 focuses on diabetes medications, and Chapter 8 discusses nondiabetes medications used in pregnancy, such as tocolytic agents and antihypertensive medications.
- **Case Studies:** A case study is presented for each type of diabetes to help illustrate how to address common issues of care in pregnancy and diabetes.
- **Appendixes:** The appendixes contain nutrition guidelines, sample forms, and other nutrition-related information that will be useful to the reader.

A special thank you is due to all authors for their tremendous effort in making this book a reality and I want to acknowledge each of their contributions. Celeste Durnwald, MD, authored the medical aspects of the normal physiology of pregnancy in Chapter 2 and addressed preconception, antepartum, and postpartum medical care of type 2 diabetes mellitus and GDM in Chapters 4, 5, and 6. She also cowrote with Neda Ghaffari, MD, the content on type 1 diabetes mellitus preconception, antepartum, and postpartum medical care in these chapters. Donna Jornsay, MS, BSN, CPNP, CDCES, BC-ADM, CDTC, is an experienced diabetes care and education specialist in perinatal nursing. Her skillful techniques are evident in her excellent summary on glucose monitoring in Chapter 4 and antenatal testing in Chapter 5. Medical nutrition therapy, which is the cornerstone of diabetes and pregnancy management, and is woven throughout the book was authored by Diana M Gonzales-Pacheco, DCN, RDN, and Breanna S. Oberlin, MS, RD, CD, CDCES. Diane M. Reader, RDN, CDCES, contributed to the interconception and prevention of type 2 diabetes in persons with histories of GDM in Chapter 6. Chapters 7 and 8, addressing medications, were expertly written by

Elif Özdener-Poyraz, PharmD, BCACP, CDCES, AAHIVP; Christine Lam, PharmD, BCPS, BCACP, CDCES, BCGP; and Antonia Carbone, PharmD, CDCES, BCACP. Maria Duarte-Gardea, PhD, RDN, LD, coauthored with me Chapter 3 on cultural aspects and health literacy and also contributed to the case studies.

It is my hope this *Health Professional's Guide to Nutrition, Diabetes, and Pregnancy* will become a valuable resource tool for those who, like me, have a passion for prenatal care, and especially those with diabetes.

Alyce Thomas, RDN, FAND

Acknowledgments

No man is an island to himself, and neither is working on a major project. There are many people to acknowledge for the contribution to this book, which had been a dream of mine for a long time. First, I would like to thank the Academy of Nutrition and Dietetics and especially Betsy Hornick, Acquisitions and Development Manager, who began this journey with me. I will always remember her "checking in" emails that became a source of inspiration when things were not going as expected. Erin Fagan Faley, the Academy of Nutrition and Dietetics Production and Digital Content Development Manager, joined the team as we neared production, and her skills were invaluable in shaping the many notes and pages into a manuscript. Also, a heartfelt thanks to Amy Neil, Medical Editor, whose talent for editing guided the manuscript in another direction, which was not exactly my initial vision but was so helpful in shaping the book to where we are both pleased with the finished product.

I am also grateful for the assistance provided by two of St. Joseph's University Medical Center's library staff, Madeleine Taylor and Jessica Escobar. Their ability to quickly retrieve articles was outstanding. I could not have done this without you!

Also, thank you to all the reviewers, copy editors, and everyone else who contributed to this project. You are why I am so proud of this book.

And last but not least, a special thank you to my husband Lee who has been my biggest cheerleader and fan and the one I could count on to see the light at the end of the tunnel when I thought the tunnel was plugged up. Thank you for always having my back.

Publisher's Note on Gender-Inclusive Language

The Academy of Nutrition and Dietetics encourages diversity and inclusion by striving to recognize, respect, and include differences in ability, age, creed, culture, ethnicity, gender, gender identity, political affiliation, race, religion, sexual orientation, size, and socioeconomic characteristics in the nutrition and dietetics profession.[1]

As part of our commitment to diversity and inclusion, all new and updated editions of professional books and practitioner resources published by the Academy of Nutrition and Dietetics will transition to the use of inclusive language. With recognition and respect for all people who are or may become pregnant, this first edition of the *Health Professional's Guide to Nutrition, Diabetes, and Pregnancy* uses gender-inclusive language to refer to individuals who experience pregnancy. Referring only to women in relation to pregnancy excludes a diverse group of transgender and nonbinary people who have health and nutrition needs similar to but distinct from those of cisgender women.[2]

Although this edition does not specifically address the care of transgender men during pregnancy due to limited research, there is growing recognition of the need for inclusion of transgender and nonbinary individuals in reproductive care, and gaps in available research are being identified.[3,4] Similarly, the complication of diabetes in transgender pregnancy has received very little attention in the literature; however, there is awareness of the need for additional study on the effects of hormone therapy on insulin resistance and the risk for diabetes.[5,6] As research continues to explore the unique health and nutrition needs of transgender people, especially during pregnancy and lactation, nutrition and health practitioners can increase their knowledge and understanding by reviewing resources that provide guidance for person-centered care of gender-diverse individuals.[7-10] Appendix A defines relevant terminology related to gender, including cisgender, gender identity, nonbinary, and transgender.

The use of inclusive language is consistent with the American Medical Association's AMA Manual of Style as well as other health professional groups and government organizations, including the National Institute of Child Health and Human Development, the American College of Obstetrics and Gynecology, the American College of Nurse Midwives, and the Midwives Alliance of North America.[11-14] The Academy of Nutrition and Dietetics will continue to evolve to adopt consensus best practices related to nutrition care of gender-diverse individuals that maximize inclusivity and improve equitable and evidence-based care.

1. Diversity and Inclusion Statement. Academy of Nutrition and Dietetics website. Accessed July 16, 2021. www.eatrightpro.org/practice/practice-resources/diversity-and-inclusion
2. Moseson H, Zazanis N, Goldberg E, et al. The imperative for transgender and gender nonbinary inclusion: beyond women's health. *Obstet Gynecol*. 2020;135(5):1059-1068. doi:10.1097/AOG.0000000000003816
3. MacLean LR. Preconception, pregnancy, birthing, and lactation needs of transgender men. *Nurs Women Health*. 2021;25(2):129-138.
4. Besse M, Lampe NM, Mann ES. Experiences with achieving pregnancy and giving birth among transgender men: a narrative literature review. *Yale J Biol Med*. 2020;93(4):517-528.
5. Shadid S, Abosi-Appeadu K, De Maertelaere A, et al. Effects of gender-affirming hormone therapy on insulin sensitivity and incretin responses in transgender people. *Diabetes Care*. 2020;43(2):411-417. doi:10.2337/dc19-1061
6. Spanos C, Bretherton I, Zajac JD, Cheung AS. Effects of gender-affirming hormone therapy on insulin resistance and body composition in transgender individuals: A systematic review. *World J Diabetes*. 2020;11(3):66-77. doi:10.4239/wjd.v11.i3.66
7. Rozga M, Linsenmeyer W, Cantwell Wood J, Darst V, Gradwell EK. Hormone therapy, health outcomes and the role of nutrition in transgender individuals: A scoping review. *Clinical Nutrition ESPEN*. 2020;40:42-56. doi:10.1016/j.clnesp.2020.08.011
8. Hahn M, Sheran N, Weber S, Cohan D, Obedin-Maliver J. Providing patient-centered perinatal care for transgender men and gender-diverse individuals: a collaborative multidisciplinary team Approach. *Obstet Gynecol*. 2019;134:959-963.
9. Rahman R, Linsenmeyer WR. Caring for transgender patients and clients: nutrition-related clinical and psychosocial considerations. *J Acad Nutr Diet*. 2019;119(5):727-732. doi:10.1016/j.jand.2018.03.006CTICE
10. Fergusson P, Greenspan N, Maitland L, Huberdeau R. Towards providing culturally aware nutritional care for transgender people: key issues and considerations. *Can J Diet Pract Res*. 2018;79(2):74-79. doi:10.3148/cjdpr-2018-001.
11. JAMA Network. *AMA Manual of Style*. 11th ed. Oxford University Press; 2020; 543-544.
12. Committee on Gynecologic Practice and Committee on Health Care for Underserved Women. Health care for transgender and gender diverse individuals. *Obstet Gynecol*. 2021;137(3):e75-e88. Accessed May 13, 2021. www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2021/03/health-care-for-transgender-and-gender-diverse-individuals
13. Editorial: Inclusive Language Promotes Equity: The Power of Words. *J Midwifery Womens Health*. 2021;66(1):7-9. doi:10.1111/jmwh.13225
14. Midwives Alliance of North America. Use of inclusive language. MANA website. Accessed May 13, 2021. https://mana.org/healthcare-policy/use-of-inclusive-language

SECTION 1

Overview of Diabetes and Pregnancy

CHAPTER

1

Diabetes and Pregnancy: Demographics and History

Alyce Thomas, RDN, FAND

CHAPTER OBJECTIVES

- Describe the prevalence of diabetes in pregnancy.
- Discuss the historical treatment of diabetes during pregnancy.
- Identify the evolution of medical nutrition therapy in the treatment of diabetes during pregnancy.
- Define diabetes and the types of diabetes.

Prevalence and Demographics of Diabetes in Pregnancy

The prevalence of diabetes in the United States is increasing.[1] As of 2020, the Centers for Disease Control and Prevention (CDC) estimated that diabetes (including type 1, type 2, and gestational diabetes mellitus) affects 13% of the US adult population (34.1 million people), depending on the diagnostic criteria used. See Box 1.1 for the definition and types of diabetes. In 20% to 23% of these individuals (6.3 to 8.4 million people), diabetes is undiagnosed (Box 1.2).[2] Prediabetes, an asymptomatic abnormal state in which blood glucose levels are higher than normal—but not high enough for a diagnosis of diabetes—affects 34.5% of US adults aged 18 years or older.[1] The diagnostic criteria for prediabetes are not uniform across various international professional organizations, yet prediabetes is recognized as a state of high risk for developing diabetes.[3] Diabetes is the seventh leading cause of death in the United States after heart disease, cancer, accidents, stroke, and Alzheimer disease.[4] However, research from the National Health and Nutrition Examination Survey and the National Health Interview Survey suggests diabetes has a higher mortality rate. Based on this analysis and the proportion of deaths in which diabetes is the underlying cause, this places the condition as the third leading cause of death in the United States.[5]

BOX 1.1

Definition and Types of Diabetes[6,7]

Diabetes is defined as a group of metabolic diseases characterized by hyperglycemia resulting from a defect in insulin secretion, insulin action, or both.

Diabetes classification

According to the American Diabetes Association's Standards of Care, diabetes can be classified into four general categories:

- type 1 diabetes: diabetes caused by autoimmune β-cell destruction, usually leading to absolute insulin deficiency
- type 2 diabetes: diabetes caused by a progressive loss of β-cell insulin secretion, frequently with the background of insulin resistance)
- gestational diabetes mellitus (GDM), diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation
- specific types of diabetes due to other causes (such as monogenic diabetes syndromes), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as after organ transplantation).

NOTE: Prediabetes is not included in the classification of diabetes. It is defined by an impaired fasting glucose, impaired glucose tolerance, glycosylated hemoglobin A1c (HbA1c) of 5.7% to 6.4% (39 to 47 mmol/mol), or a combination of these.

BOX 1.2

Prevalence of Diabetes in Adults in the United States[1]

34.1 million adults (18 years of age and older) with diabetes (13% of US population)

- 26.8% million diagnosed
- 7.3 million undiagnosed
- 5.2% with type 1 diabetes
- 34.5% had prediabetes

Prevalence of diabetes by race/ethnicity

- 14.7% American Indians/ Alaska Natives
- 11.7% Non-Hispanic Blacks
- 12.5% Hispanic
- 9.2% Non-Hispanic Asians
- 7.5% Non-Hispanic Whites

The true prevalence of diabetes in pregnancy, both preexisting and gestational diabetes mellitus (GDM), is unknown. According to the CDC, the prevalence of preexisting diabetes is 0.9% and GDM is 6.0%.[8] Blacks, Hispanics, American Indian, Asians, and Pacific Islanders are at higher risk of developing diabetes (including GDM) than are non-Hispanic Whites.[9]

Diabetes during pregnancy can have detrimental effects. In persons who have preexisting diabetes, uncontrolled blood glucose levels are associated with an increased risk of birth defects, macrosomia,

miscarriage, and preeclampsia. While GDM is considered a milder form of diabetes, it is associated with an increased risk of jaundice, macrosomia, and respiratory challenges in the infant and an increased risk for developing type 2 diabetes later in life. A detailed discussion of potential complications is found in Chapter 2.

Historical Background

Preinsulin Era

The management of diabetes during pregnancy has undergone many changes throughout the years. With preexisting diabetes, intensive blood glucose control before and continuing throughout pregnancy has led to decreased perinatal morbidity and mortality.[10-13] Yet nearly 100 years ago, before the first clinical use of insulin to treat diabetes (1922), this was not the case. Very few cases of diabetes during pregnancy were recorded. Many with diabetes experienced amenorrhea and generally were thought to be infertile. If a person with diabetes became pregnant, the mortality rate during pregnancy was approximately 50%, with the major cause of death attributed to ketoacidosis or diabetic coma.[14-16] Because of this high mortality rate, persons with diabetes were encouraged to avoid or terminate any pregnancy.[17] Those with diabetes not only died during pregnancy but could also succumb to diabetes complications as long as 2 years postpartum. (The records do not indicate if these individuals had preexisting or gestational diabetes.)

In 1824, a 22-year-old German woman became one of the first recorded cases of gestational diabetes in pregnancy.[18] According to this case report, she did not experience diabetes in her first three pregnancies but developed polyuria, polydipsia, and glycosuria during her fourth pregnancy. These conditions disappeared after delivery but reappeared during her fifth pregnancy. Treatment included bloodletting, a high-protein diet, and beer to relieve her thirst. Unfortunately, at 36 weeks' gestation, she delivered a 12-pound stillborn with shoulder dystocia.[19,20]

Nearly 60 years later, Matthew Duncan, an obstetrician from Edinburgh, Scotland, used data compiled from cases of diabetes complicating pregnancy and noted only 22 pregnancies in 15 participants‡. The outcomes of these cases were 13 fetal deaths and nine perinatal deaths within 1 year postpartum.[21,22] One of Duncan's observations was that diabetes might occur during pregnancy but was absent soon after delivery. He also noted that these infants tended to be larger than the

‡ Study participants were described as women. Gender was not further specified. Please see pages xix to xx and Appendix A for more on gender-inclusive terminology. This note applies to all appearances of the ‡ symbol in this chapter.

average newborn and that diabetes could recur later in life.[22] In 1915, Elliott P. Joslin, founder of the Joslin Diabetes Center (Boston, MA), observed similar features where diabetes symptoms disappeared after delivery but recurred during subsequent pregnancies and sometimes progressed to type 2 diabetes.[23]

Early Insulin Use and Pregnancy

The first clinical use of insulin in pregnancy in 1923[24] led to a subsequent decline in perinatal mortality[25] but did not provide any positive effect on the fetus.[26] Many of these infants were stillborn or survived with major congenital anomalies (eg, congenital heart disease, cerebral palsy, intellectual disability). They also were observed to be much larger than infants born to those without diabetes.[27,28] Because no decrease in the perinatal mortality rate was achieved, persons with diabetes were advised to avoid becoming pregnant.[29] Those who chose to continue the pregnancy were usually admitted to a hospital during the last month of pregnancy and underwent cesarean delivery at 38 weeks' gestation or earlier to prevent late-term fetal demise.[15,26,28]

During this time, persons with diabetes who had a live birth often experienced difficulty in breastfeeding their infants. McIlroy and colleagues suggested those with diabetes avoid breastfeeding due to possible deficiencies in their milk supply.[29] It is now understood that inadequate milk production can be due to consequences of premature birth (eg, inability of infant to suck, lack of opportunity to establish breastfeeding), a frequent outcome of diabetes in pregnancy.[30]

Distinction Between Preexisting Diabetes and Gestational Diabetes Mellitus

In 1931, Rowe and colleagues observed a relationship between glycemia and glycosuria during pregnancy.[31] Richardson and Bitter believed pregnancy placed a strain on the glucose metabolizing apparatus.[32] Damage to the kidney tubules, which caused excretion of larger amounts of microscopic sugar crystals, was thought to be a possible cause. Their 1932 study of 247 participants[‡] was conducted to determine why glycosuria occurred in pregnancy and whether this was a serious condition.[32] Eight percent of the participants in the study showed a blood glucose curve analogous to that of diabetes mellitus or of decreased carbohydrate tolerance (gestational diabetes). Glycosuria was observed in 42% of the participants after delivery, but 50% showed little to no trace of glucose in their urine

12 days postpartum. The cause of the glycosuria in pregnancy was thought to be either hyperglycemia in the presence of a normal renal threshold similar to that of diabetes mellitus or a lower renal threshold with normal blood glucose levels.

Diabetes that occurred during pregnancy often was referred to as "mild" or "transitory" diabetes. In 1946, a review article by Eastman reported that there were no differences in treatment modalities for those with diabetes occurring during pregnancy than for those with preexisting diabetes.[33] By 1954, Hoet and Lukens observed that some pregnancies caused abnormal carbohydrate metabolism (characterized by a hyperglycemic glucose tolerance curve).[34] The curve became abnormal around the fourth month of gestation but disappeared or diminished with delivery, whether or not glycosuria was present. The fetal mortality rate was proportionate to the increased severity of the abnormal carbohydrate metabolism. In their article, Hoet and Lukens suggested that correcting the abnormal carbohydrate metabolism using insulin would reduce fetal and infant mortality. They hoped that, in the future, the use of exogenous insulin to correct hyperglycemia during pregnancy would not only improve survival but also would result in normal fetal growth and development. Reis and colleagues—and later, Hagbard and Svanborg—observed that diabetes developing during pregnancy was of shorter duration and less severe than preexisting diabetes.[35,36] In most people, the symptoms disappeared, and oral glucose tolerance test results were normal after delivery and lactation. Reis and colleagues observed that most participants[‡] who had mild diabetes during pregnancy were older and obese.[35]

By 1960, "temporary diabetes" referred to the condition in which women produced large babies and tended to develop diabetes mellitus later in life.[37] In studies from the mid-20th century, persons with prediabetes had a fetal loss rate of 20% to 67%, and those with preexisting diabetes whose pregnancies ended with live births had a higher rate (20%) of large-for-gestational-age babies.[36,38,39] John O'Sullivan, one of the first researchers to use the term *gestational diabetes,* defined it as "unsuspected, asymptomatic diabetes ... occurring during pregnancy."[40]

Classification of Diabetes in Pregnancy

Priscilla White, MD, of the Joslin Diabetes Center was the first physician to classify diabetes in pregnancy based on the age of onset, its duration, and the presence or absence of vascular complications.[41] White's system used various letters of the alphabet to categorize fetal risk (classes A through E) and perinatal risk (class F), as shown in Box 1.3.[42]

BOX 1.3

White's Classification of Diabetes in Pregnancy (Original)[42]

Class A	Diagnosis of diabetes made when glucose tolerance test results deviated slightly from normal. No insulin was required with little dietary regulation.
Class B	Diabetes onset occurred at age 20 years or older, and duration was shorter than 10 years, with no vascular disease.
Class C	Diabetes duration was 10 to 19 years, or its onset occurred at age 10 to 19 years, or vascular disease was minimal.
Class D	Diabetes duration was 20 years or longer, or onset occurred before age 10 years, or evidence of vascular disease was notable.
Class E	Calcified pelvic arteries were seen on radiograph.
Class F	All women[a] with nephritis.

[a] Women was the original wording in the classification.

The classification system was revised by White in 1965,[43] 1978,[44] and finally by Hare and White in 1980.[45] Each revision added classes due to the increasingly recognized complexity of diabetes and pregnancy. The last version included the addition of retinopathy, hypertension, arteriosclerotic heart disease, and prior renal transplantation. Gestational diabetes was classified as a separate category; the lettering system was used only for preexisting diabetes (Box 1.4).[45]

BOX 1.4

White's Classification of Diabetes in Pregnancy (Final)[45]

Gestational diabetes	Abnormal results of oral glucose tolerance test, but euglycemia maintained by diet alone or may require insulin
Class A	Managed by diet alone, any duration, or onset age
Class B	Onset age 20 years or older and duration less than 10 years
Class C	Onset age 10 to 19 years or duration 10 to 19 years
Class D	Onset age younger than 10 years, duration longer than 20 years, background retinopathy, or hypertension (not preeclampsia)
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Nephropathy with proteinuria above 500 mg/d
Class RF	Criteria for both Classes R and F coexist
Class H	Arteriosclerotic heart disease clinically evident
Class T	Prior renal transplantation

BOX 1.5

Proposed Classification System for Diabetes in Pregnancy[49]

Gestational diabetes	Diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes
Type 1 diabetes	Diabetes resulting from β-cell destruction, usually leading to absolute insulin deficiency • without vascular complications • with vascular complications
Type 2 diabetes	Diabetes resulting from inadequate insulin secretion in the face of increased insulin resistance • without vascular complications • with vascular complications
Other types of diabetes	Examples: genetic in origin, associated with pancreatic disease, or drug-induced or chemically induced

The American College of Obstetricians and Gynecologists (ACOG) has not included the White classification system in its *Technical Bulletins* since 1986 because it is considered less helpful since fetal assessment, neonatal care, and the overall management of pregnancy have improved.[46] However, two recent studies have found White's classification system still useful for pregnancies with preexisting diabetes in the presence of hypertension or in estimating the risk of preeclampsia.[47,48] Sacks and Metzger proposed a classification using the American Diabetes Association's (ADA) definitions of diabetes tailored specifically to pregnancy (Box 1.5).[49] The proposal has not yet been accepted by ACOG or ADA.[49]

Medical Nutrition Therapy and Diabetes in Pregnancy

The ADA 2008 guidelines for medical nutrition therapy (MNT) specify:

> *It is recommended that a registered dietitian, knowledgeable and skilled in MNT, be the team member who plays the leading role in providing nutrition care. However, it is important that all team members, including physicians and nurses, be knowledgeable about MNT and support its implementation.*[50]

The Academy of Nutrition and Dietetics defines MNT as a specific application of the Nutrition Care Process in clinical settings that is focused on the management of diseases. MNT involves in-depth individualized nutrition assessment and a duration and frequency of care using the Nutrition Care Process to manage disease.[51] Medical

TABLE 1.1 Medical Nutrition Therapy for Diabetes in Pregnancy, 1898 to 1952

Year	Author	Energy	Carbohydrate	Protein	Fat	Other components of treatment plan
1898 through 1914	Naunyn (reported by Ney and Hollingsworth, 1981[54])	Unknown	≤15%	85% (with fat)	Unknown	Weekly antepartum visits
1937	White, 1937[42]	30 kcal/kg BW[a]	≥150 g	1 g/kg ABW[b]	Remainder of calories	
1943	Lavietes et al, 1943[55]		150-250 g	80 g	Remainder of calories	
1945	Bigby and Jones, 1945[56]	2,200-2,500 kcal	220-300 g	Unknown	Unknown	
1951	Duncan, 1951[57]	[IBW[c] (lb) × 10] + 100 kcal	180-250 g	IBW × ⅞	Remainder of calories	If edema: salt intake moderately restricted (3 g/d max), further reduced if water retention increased, plus 4 to 8 g ammonium chloride daily × 3 days as diuretic with rest for 2 to 3 days. 1 qt milk for adequate calcium
1951	Moss and Mulholland, 1951[58]	30 kcal/kg optimal BW	Added to supply 50 g to fetus	2 g/kg BW	Remainder of calories	Sodium restriction Weight gain limited to 20 lb
1952	Reis et al, 1952[35]	25 kcal/kg BW (light work); 30 kcal/kg BW (moderate work)	Unknown	Unknown	Remainder of calories	

[a] BW = body weight | [b] ABW = actual body weight | [c] IBW = ideal body weight

nutrition therapy always has been an important adjunct to treatment for diabetes in pregnancy. Throughout the years, diets have varied—from those that included periods of starvation[52,53] to high fat[54] whereas others advocated low- or high-carbohydrate intake.[54] Table 1.1 provides a summary of nutrition management strategies used by researchers in the early 19th and mid-20th centuries. Chapters 4 through 6 discuss medical nutrition therapy used today.

Summary

The management of diabetes in pregnancy has dramatically changed in the last 100 years. Medical nutrition therapy has also changed from starvation diets and beer to an emphasis on healthy eating to improve pregnancy outcomes. Although the complications associated with diabetes have improved with the discovery of insulin, the risk of complications in pregnancy is higher than a pregnancy without diabetes. These complications include fetal macrosomia in those with GDM, fetal congenital anomalies in pregnancies with preexisting type 1 and type 2 diabetes, and an increased risk of obesity, hypertension, and type 2 diabetes mellitus in their offspring later in life.[6] However, care of the persons with diabetes, which begins prior to and continues throughout their pregnancy, will help to improve both perinatal morbidity and mortality.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Centers for Disease Control and Prevention, U.S. Dept. of Health and Human Services; 2020. Accessed September 3, 2020. www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
2. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. Diabetes in the US population. *JAMA.* 2015;314:1021-1029. doi:10.1001/jama.2015.10029
3. Bansal N. Prediabetes diagnosis and treatment: a review. *World J Diabetes.* 2015;6(2):296-303. doi:10.4239/wjd.v6.i2.296
4. National Center for Health Statistics. *Health, United States, 2016: With Chartbook on Long-term Trends in Health*. US Department of Health and Human Services. 2017. Accessed November 13, 2017. www.cdc.gov/nchs/data/hus/hus16.pdf
5. Stokes A, Preston SH. Deaths attributable to diabetes in the United States: comparison of data sources and estimation approaches. *PLoS One.* 2017;12(1):e0170219. doi:10.1371/journal.pone.0170219
6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2014;37(suppl 1):S81-S90. doi:10.2337/dc10-S062
7. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care.* 2020;43(suppl 1):S14-S31. doi:10.2337/dc2-S002
8. Deputy NP, Kim SY, Coney EJ, McKeever Bullard K. Prevalence and changes in preexisting diabetes and gestational amoung women who had a live birth—United States, 2012–2016. *MMWR Morb Mortal Wkly Rep*. 2018:67:1201-1207. doi:10.15585/mmwr.mm6743a2
9. Fujimoto W, Samoa R, Wotring A. Gestational diabetes in high-risk populations. *Clinical Diabetes.* 2013;31:90-94. doi:10.2337/diaclin.31.2.90
10. Steel JM, Johnstone FD, Hepburn DA, Smith AF. Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *BMJ.* 1990;301:1070-1074. doi:10.1136/bmj.301.6760.1070
11. Langer O, Conway DL. Level of glycemia and perinatal outcome in pregestational diabetes. *J Matern Fetal Med.* 2000;9:35-41. doi:10.1002/(SICI)1520-6661(200001/02)9:1<35::AID-MFM8>3.0.CO;2-6

12. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Preconception care of diabetes. Glycemic control prevents congenital anomalies. *JAMA.* 1991;265:731-736.
13. Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA. Pre-conception management of insulin-dependent diabetes: improvement of pregnancy outcome. *Obstet Gynecol.* 1991;77:846-849.
14. White P. *Diabetes in Childhood and Adolescence.* Lea and Febiger; 1932.
15. Tew WP. The diabetic maternity patient and her baby. *Can Med Assoc J.* 1947;57(5):441-445.
16. Gilbert JAL, Dunlop DM. Diabetic fertility, maternal mortality, and foetal loss rate. *Br Med J.* 1949;1(4607):48-54. doi:10.1136/bmj.1.4592.48
17. Beattie WA. Diabetes in pregnancy, with report of cases. *CA State J Med.* 1917;15:11-13.
18. Bennewitz HG. *De Diabete Mellito, gravidatatis symptomate* [doctorate thesis]. University of Berlin; 1824.
19. Hadden DR, Hillebrand B. The first recorded case of diabetic pregnancy. *Diabetologia.* 1989;32:625. doi:10.1007/bf00285339
20. Gabbe SG. A story of two miracles: the impact of the discovery of insulin on pregnancy in women with diabetes mellitus. *Obstet Gynecol.* 1992;79:295-299.
21. Duncan JM. On puerperal diabetes. *Trans London Obstet Soc.* 1882;24:256-285.
22. Hadden DR. A historical perspective on gestational diabetes. *Diabetes Care.* 1998;21(suppl 2):B3-B4.
23. Joslin EP. Pregnancy and diabetes. *Boston Med Surg J.* 1915;173:841-849.
24. White JR. A brief history of the development of diabetes medications. *Diabetes Spectrum.* 2014;27(2): 82-86. http://spectrum.diabetesjournals.org/content/27/2/82
25. Mestman JH. Historical notwson diabetes and pregnancy. *The Endocrinologist*. 2002;12:224-242. doi:10.1097/00019616-200205000-0010
26. Oakley W. Prognosis in diabetic pregnancy. *Br Med J.* 1953;1(4825):1413–1415. doi:10.1136/bmj.1.4825.1413
27. Peel J. A historical review of diabetes and pregnancy. *J Obstet Gynaecol Br Commonw.* 1972;79:385-395. doi:10.1111/j.1471-0528.1972.tb14176.x
28. Feudtner C, Gabbe SG. Diabetes and pregnancy: four motifs of modern medical history. *Clin Obstet Gynecol.* 2000;43:4-16. doi:10.1097/00003081-200003000-00002.1097/1
29. McIlroy L, Hill G, Pillman-Williams EC. Diabetes and pregnancy, with the record of seven cases. *Postgrad Med J*. 1931;70:159-170. doi:10.1136/pgmj.6.70.159
30. Barns HF, Morgans ME. The conduct of pregnancy complicated by diabetes mellitus. *Br Med J.* 1952;1(4767):1058-1060. doi:10.1136/bmj.1.4767.1058
31. Rowe AW, Gallivan DE, Matthews H. The metabolism of pregnancy: the carbohydrate metabolism. *Am J Physiol.* 1931;96:94-100.
32. Richardson R, Bitter RS. Glycosuria in pregnancy. *Am J Obstet Gynecol.* 1932;24:362-369. doi:10.1016/S0002-9378(32)90713-3
33. Eastman NJ. Diabetes mellitus and pregnancy: a review. *Obstet Gynecol Surv.* 1946;1:3-31.
34. Hoet JP, Lukens FD. Carbohydrate metabolism during pregnancy. *Diabetes.* 1954;3:1-12. doi:10.2337/diab.3.1.1
35. Reis RA, DeCosta EJ, Allweiss MD. *Diabetes and Pregnancy.* Charles C. Thomas; 1952.
36. Hagbard L, Svanborg A. Prognosis of diabetes mellitus with onset during pregnancy: a clinical study of seventy-one cases. *Diabetes.* 1960;9:296-302. doi:10.2337/diab.9.4.296
37. Jackson WP. Present status of prediabetes. *Diabetes.* 1960;9:373-378. doi:10.2337/diab.9.5.373
38. Miller HC. The effect of diabetic and prediabetic pregnancies on the fetus and newborn infant. *J Pediatr.* 1946;29(4):455-461. doi:10.1016/s0022-3476(46)80164-1
39. Wilkerson HL. Pregnancy and the prediabetic state. *Ann N Y Acad Sci.* 1959;82:219-228. doi:10.1111/j.1749-6632.1959.tb44902.x
40. O'Sullivan JB. Gestational diabetes: unsuspected, asymptomatic diabetes in pregnancy. *N Engl J Med.* 1961;264:1082-1085. doi:10.1056/NEJM196105252642104
41. White P. Pregnancy complicating diabetes. *Am J Med.* 1949;7(5):609-616. doi:10.1016/0002-9343(49)90382-4
42. White P. Diabetes complicating pregnancy. *Am J Obstet Gynecol.* 1937;33:380-385.
43. White P. Pregnancy and diabetes, medical aspects. *Med Clin North Am.* 1965;49:1015-1024. doi:10.1016/s0025-7125(16)33292-8
44. White P. Classification of obstetric diabetes. *Am J Obstet Gynecol.* 1978;130(2):228-230. doi:10.1016/0002-9378(78)90373-3
45. Hare JW, White P. Gestational diabetes and the White classification. *Diabetes Care.* 1980;3:394. doi:10.2337/diacare.3.2.394
46. American College of Obstetricians and Gynecologists. Management of diabetes mellitus in pregnancy. *ACOG Technical Bulletin* 92. American College of Obstetricians and Gynecologists; 1986.

47. Bennet SN, Tita A, Owen J, et al. Assessing White's classification of pregestational diabetes in a contemporary diabetic population. *Obstet Gynecol.* 2015;125:1217-1223. doi:10.1097/AOG.0000000000000820
48. Klemetti MM, Laivuori H, Tikkanen M, Nuutila M, Hiilesmaa V, Teramo K. White's classification and pregnancy outcome in women with type 1 diabetes: a population-based cohort study. *Diabetologia*. 2016;59:92-100. doi:10.1007/s00125-015-3787-1
49. Sacks DA, Metzger BE. Classification of diabetes in pregnancy. Time to reassess the alphabet. *Obstet Gynecol.* 2013;121:345-348. doi:10.1097/AOG.0b013e31827f09b5
50. American Diabetes Association, Bantle JP, Wylie-Rosett J, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care.* 2008;31(suppl 1):S61-S78. doi:10.2337/dc08-S061
51. Academy of Nutrition and Dietetics. MNT versus nutrition education. Accessed February 20, 2019. www.eatrightpro.org/payment/coding-and-billing/mnt-vs-nutrition-education
52. Joslin EP. *The Treatment of Diabetes Mellitus*. 2nd ed. Lea & Febiger; 1917:364-367.
53. Mazur A. Why were "starvation diets" promoted for diabetes in the pre-insulin period? *Nutr J.* 2011;10:23. doi:10.1186/1475-2891-10-23
54. Ney D, Hollingsworth DR. Nutritional management of pregnancy complicated by diabetes: historical perspective. *Diabetes Care.* 1981;4:647-655. doi:10.2337/diacare.4.6.647
55. Lavietes PHJ, Leary DC, Winkler AW, Peters JP. Diabetes mellitus and pregnancy. *Yale J Biol Med.* 1943;16:151-166.
56. Bigby MA, Jones FA. Pregnancy and diabetes. *Br Med J.* 1945;1:360-363. doi:10.1136/bmj.1.4393.360
57. Duncan GG. *Diabetes Mellitus: Principles & Treatment.* WB Saunders: 1951.
58. Moss JM, Mulholland HB. Diabetes and pregnancy: with special reference to the prediabetic state. *Ann Intern Med.* 1951;34:678-699. doi:10.7326/0003-4819-34-3-678

CHAPTER

2

Physiology of Pregnancy and the Effects of Diabetes

Celeste Durnwald, MD

CHAPTER OBJECTIVES

- Describe the major physiological changes in glucose, protein, and lipid metabolism in normal pregnancy.
- Explain the role of insulin resistance and placental hormones in glucose homeostasis.
- Describe the effect of glucose metabolism in pregnancies with diabetes.
- Discuss the effect of gestational hyperglycemia on fetal growth and development.

Normal Metabolism in Pregnancy

Throughout pregnancy, the body's metabolism adapts to the needs of the growing fetus. These physiologic changes are designed specifically to increase placental glucose transfer, thereby providing a continuous supply of glucose to meet the increasing metabolic requirements of the fetus.[1] Circulating placental hormones, such as human placental lactogen (hPL) and cortisol, also increase gestational glucose concentrations to support the fetus. Postprandial insulin concentrations enhance glucose uptake into skeletal muscle and adipose tissue and suppress hepatic glucose production. Adaptations in metabolism include 1) transient postprandial gestational hyperglycemia (due to increasing insulin resistance) and 2) transient hypoglycemia between meals (due to a constant need for glucose by the developing fetus).[2] In the fasting state, plasma glucose and amino acids decrease in conjunction with an increase in free fatty acids (a concept known as *accelerated starvation*[3]). As pregnancy progresses, postprandial glucose gradually increases and insulin sensitivity decreases to foster fetal growth.[4] Consequently, "normal" pregnancy is characterized as a diabetogenic state (producing or causing diabetes)[5]; to maintain

normoglycemia during pregnancy, insulin production is increased two- to threefold.

Glucose Metabolism

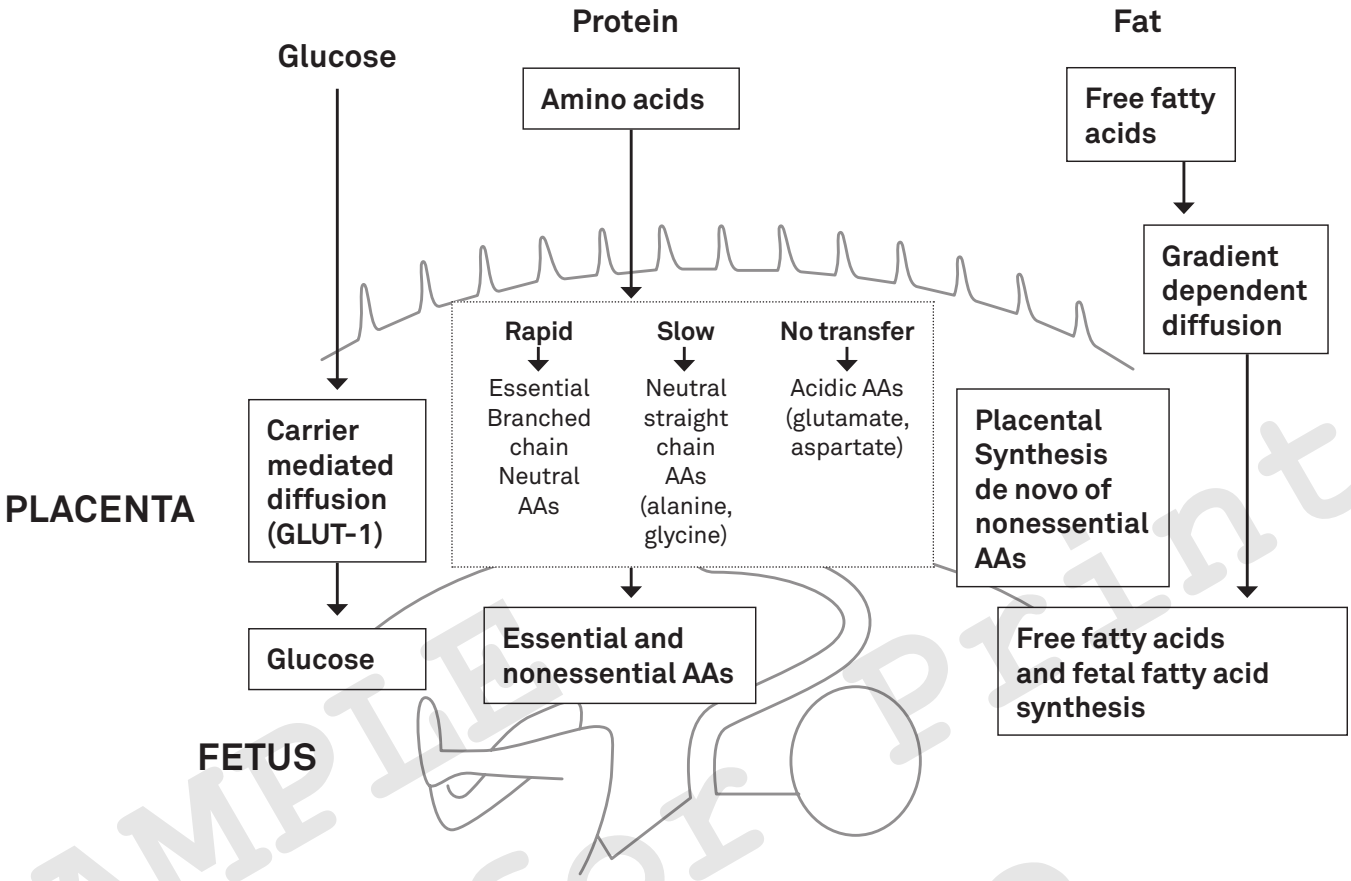
During the first trimester, elevations of hPL and cortisol decrease gestational glucose levels.[6] Serum estrogen and progesterone levels also increase, which stimulate production and secretion of additional insulin while increasing insulin sensitivity. The result is decreased fasting and postprandial glucose levels during the first 12 weeks of gestation.[6] Fasting glucose levels in a normal pregnancy is 10% to 20% lower than those in a nonpregnant state.[7] The lower glucose levels protect the fetus from receiving excessive glucose during the critical period of organogenesis.

As glucose levels increase after eating, the pancreas secretes additional insulin to normalize glucose levels relatively quickly and ensure adequate energy supply to the fetus. The constant need for glucose by the fetus tends to cause gestational hypoglycemia between meals and during the night.[6] The body is able to compensate for this drain on glycemic levels by an enhanced capacity for nutrient storage during feeding. Early pregnancy is viewed as an anabolic state in which there is both an increase in gestational fat storage to compensate for the increasing energy demands of later pregnancy and a decrease in free fatty acid concentrations.[1] Insulin is responsible for storing the excess calories at lipid and tissue sites for later use during pregnancy.

The placenta regulates transfer of nutrients to the fetus (see Figure 2.1).[8,9] Glucose is transported to the fetus through the placenta via facilitated diffusion.[8] Fetal glucose concentrations are 10 to 20 mg/dL lower than maternal concentrations.[7] The placenta contains high concentrations of insulin-dependent glucose transport molecules (GLUT) that assist in the passage of glucose across the placenta.[10] Alterations in the rate of GLUT transporters produce a change in circulating glucose concentration, and higher glucose levels lead to increased glucose transport to the fetus.

During the second trimester, estrogen, progesterone, and placental hormones (hPL, prolactin, and cortisol) levels increase and work synergistically to increase insulin resistance and decrease insulin sensitivity, resulting in higher fasting and postprandial blood glucose levels.[12] hPL is a main contributor to reduced insulin sensitivity and impaired glucose tolerance. Increased secretion of hPL also inhibits the uptake of glucose in peripheral tissues and stimulates fetal pancreatic insulin secretion. Elevated prolactin concentrations

FIGURE 2.1 Placental permeability and the relationship between gestational fuels



GLUT = glucose transporter | AA = amino acid

Adapted from Shshidhar A, Chandrasekaran A. In utero fuel homeostasis: lessons for a clinician. *Indian J Endocrinol Metab*. 2013;17(1):60-68. doi:10.4103/2230-8210.107851. See reference 11.

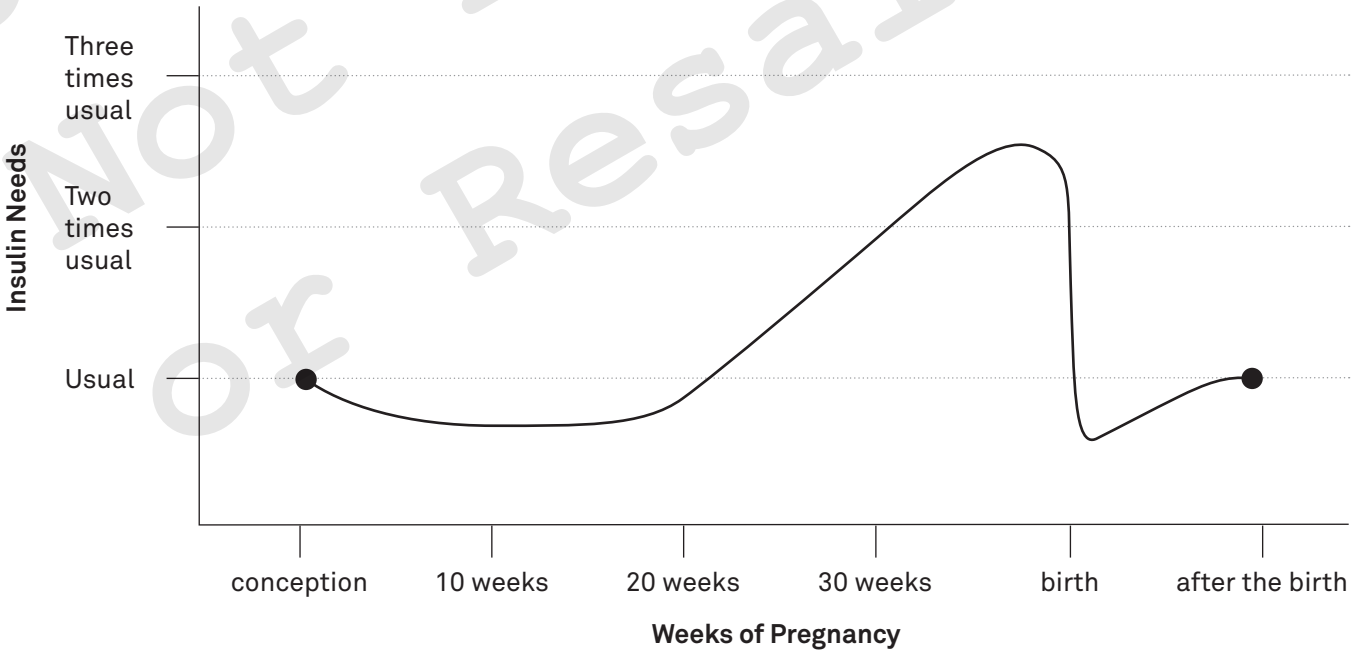
contribute to blunting the action of insulin, whereas elevations in cortisol increase the hepatic production of glucose.[13] As fetal nutrient demands increase, the liver is stimulated to mobilize gestational glucose stores and increase the concentration of circulating glucose. In a healthy person with a normal body mass index, basal hepatic glucose production increases 30% by the third trimester, matched by an increase in basal insulin production.[14] Increasing insulin resistance places a greater demand on β cells of the pancreas to secrete additional insulin.[7] Gestational insulin resistance continues into the third trimester, culminating in a threefold increase in insulin production above nonpregnant levels to maintain normoglycemia.[6]

Protein and Lipid Metabolism

Protein is essential for fetal growth and development. In pregnancy, progesterone increases the hepatic utilization of amino acids, thereby decreasing plasma amino acid levels, compared with the nonpregnant state. Cortisol, prolactin, and hPL also act to ensure the fetus receives a continuous supply of amino acids.[7] As a result of the active transport of amino acids across the placenta, fetal amino acid levels are higher than gestational levels.[1]

Pregnancy is associated with increased levels of triglycerides, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and total cholesterol.[1] Fat deposited in adipose tissue during the first half of pregnancy is later mobilized, increasing the production of plasma free fatty acids and ketones.[7] In a normal pregnancy, increasing free fatty acids causes insulin resistance.[15] Free fatty acids may also influence the hepatic production of glucose, resulting in increased insulin resistance and decreased insulin sensitivity. In pregnancy, these lipids are used for energy metabolism, whereas the fetus depends on glucose as its primary fuel source. This mechanism protects the fetus during any period of starvation in pregnancy. Conversely, in instances of starvation, the fetus uses ketones transported across the placenta as an energy source.[16]

FIGURE 2.2 Normal insulin production in pregnancy



Adapted with permission from 2016 International Diabetes Center at Park Nicollet, Minneapolis, MN.

Development of Progressive Insulin Resistance

As pregnancy continues, insulin resistance develops progressively: physiologic insulin concentrations stimulate a decreased biologic response in target tissues, and the body compensates by producing more insulin. By the third trimester, insulin sensitivity decreases 50% to 60%,[17] and glucose uptake by skeletal muscle and adipose tissue decreases. This insulin resistance is more exaggerated in those who had decreased insulin sensitivity before pregnancy, such as those with obesity. Two main physiologic mechanisms underlie insulin resistance during pregnancy.

Decreased Insulin Receptor Signal Transduction

To initiate a physiologic response in target tissues, the insulin receptor (a member of the ligand-activated receptor and tyrosine kinase family of transmembrane signaling proteins) auto-phosphorylates and activates downstream molecules, such as insulin receptor substrate-1. In pregnancy, this insulin receptor signal transduction is decreased. Levels of insulin receptor substrate-1 are observed to be lower in the skeletal muscle during late pregnancy than in a nonpregnant state.[18]

Placental Factors

The placenta produces hPL, progesterone, estrogen, and tumor necrosis factor, all of which contribute to insulin resistance. After delivery insulin resistance reverses and insulin requirements decrease.[19]

Diabetes During Pregnancy

Type 1 Diabetes Mellitus

Data are limited on the specific changes in glucose metabolism during pregnancy with type 1 diabetes mellitus (T1DM). One study demonstrated a 50% decrease in insulin sensitivity during late gestation in participants‡ with T1DM.[20] No difference in insulin sensitivity was observed during early gestation and the postpartum period (1 week after delivery) compared with nonpregnant subjects who had T1DM.

C-peptide is elevated during pregnancy, compared to the nonpregnant state. However, C-peptide levels in those with T1DM are low to undetectable during pregnancy, compared to a pregnancy with type 2 diabetes mellitus (T2DM).[21] Therefore, there is little residual β cell function in T1DM.[22] Plasma triglyceride levels and free fatty acids in those with T1DM are higher during the third trimester than in the nonpregnant state.[23]

In persons with well-controlled T1DM, insulin requirements are decreased in the first trimester to early second trimester (9 to 18 weeks). Hypoglycemia is common during the first trimester in persons with T1DM. This is coupled with decreased hypoglycemia awareness, which is thought to be a result of a diminished sympathetic reaction in pregnancy. Clinicians need to be aware of these two important physiologic changes and the potential need for decreased insulin doses at this point in pregnancy. Conversely, insulin requirements increase in the late second trimester through the third trimester (18 to 37 weeks). This is followed by a plateau or slight decline in insulin needs after 37 weeks' gestation. The overall insulin requirement during pregnancy with T1DM increases by 40%, compared with an nearly 100% increase in those with T2DM.[24]

Type 2 Diabetes Mellitus

T2DM is characterized by a β cell deficiency leading to secretory defects, most commonly in the setting of inflammation and metabolic stress. The physiologic changes that occur in normal pregnancy are the primary drivers for the profound increased insulin resistance and decreased insulin sensitivity in those with T2DM. Similar to T1DM, the increasing insulin resistance and decreased insulin sensitivity as the pregnancy progresses result in an excessive amount of glucose to the fetus. There has been limited research that has exclusively evaluated pregnancy and T2DM.

Gestational Diabetes Mellitus

Gestational diabetes (GDM) is one of the most common medical complications of pregnancy, affecting up to 7% of pregnancies.[25,26] Approximately 200,000 deliveries in the United States every year occur in persons who develop GDM.[27] With the increased incidences of obesity, delayed childbearing, and multiple gestations, the diagnosis of GDM is expected to increase.

Most cases of GDM share the underlying pathophysiology of T2DM, which unmasks the β cell defect related to obesity and chronic insulin resistance. In the majority of GDM cases, an underlying pancreatic β cell dysfunction leads to an insufficient amount of insulin to counteract the increasing insulin resistance in late pregnancy. Although this is the most common underlying mechanism for the pathophysiology of GDM, other less common causes are possible. In a small percentage (<10%) of GDM cases, circulating immune complexes (anti-islet cell antibodies or antibodies to glutamate decarboxylase 65) are diagnostic of evolving T1DM.[28]

Effects of Diabetes on Gestational and Fetal Health

Organogenesis

The increased risk for diabetic embryopathy is directly proportional to elevations in the gestational hemoglobin A1c (HbA1c) during the first 10 weeks of pregnancy.[29]

Organogenesis, the critical period of development, occurs in humans from about gestation day 20 to day 55. Malformation rates are directly linked to poor glycemic control during this period. An embryo exposed to excess hyperglycemia during organogenesis is at high risk of developing congenital anomalies. The most common organ systems affected include the brain and spinal cord, kidneys, heart and major vessels, gastrointestinal system, genitourinary system,[30] and skeletal structures.[31] The fetal malformation rate in preexisting diabetes (T1DM and T2DM) is estimated to be 1.9 to 10 times higher than in the general population. Although GDM is not associated with fetal malformation rates as high as in preexisting diabetes, the rate is 1.5 times higher than in pregnancies without diabetes and 3.4-fold higher in GDM with higher than normal fasting blood glucose levels.[32] One study demonstrated a 3.4% risk of anomalies when HbA1c levels were below 8.5% compared with a 22.4% risk of anomalies in those with a level higher than 8%.[32]

Glycemic control optimized before conception (HbA1c lower than 6.5%) is associated with the lowest risk of congenital anomalies.[33] According to the American Diabetes Association, those of childbearing age who have diabetes should receive education about:

- risks of malformation associated with unplanned pregnancy and poor metabolic control, and
- continual use of an effective form of contraception to prevent unplanned pregnancies.[33]

Fetal Development

Glucose, the primary fuel source used by the fetus, crosses the placenta by facilitated diffusion.[8] Amino acids, as described previously, are used in much smaller amounts.[7] Elevations in gestational blood glucose precipitate increased glucose diffusion across the placenta and higher glucose levels in the fetus. Fetuses consistently exposed to higher levels of circulating glucose experience increased fetal insulin production known as *fetal hyperinsulinemia*.[34] Transplacental diffusion of insulin bound to immunoglobulin G (IgG) antibodies is limited. Insulin acts as a fetal growth hormone and is a major contributor to fetal overgrowth in pregnancies complicated by diabetes. In

response to continual excessive glucose, fetal hyperinsulinemia also can lead to β cell hyperplasia of the fetal pancreas.

Production of insulin in the fetal pancreas begins at approximately 11 or 12 weeks' gestation.[7] Insulin is excreted in fetal urine and found in amniotic fluid by the 12th week of gestation.[7] With advancing gestation, insulin levels increase in the amniotic fluid in response to fetal secretion. Fetal morbidities, such as macrosomia, intrauterine growth restriction, preeclampsia, and intrauterine fetal demise have been associated with both excessive insulin levels and low insulin levels in amniotic fluid.[7,35]

Congenital Malformations

The incidence of fetal complications in GDM is lower than in those with preexisting diabetes but higher than in normal pregnancies.[36] Infants born to persons with T1DM and T2DM have an approximately twofold to sixfold increase in major congenital malformations.[37,38] The most common fetal anomalies include cardiac defects and neural tube defects, leading to central nervous system anomalies, especially spina bifida and anencephaly.[39] Although GDM was defined as "diabetes first recognized in the current pregnancy,"[40] it is reasonable to assume that GDM diagnosed before 20 weeks' gestation actually might have overt T2DM. In these cases, the underlying impaired glucose tolerance might predate the pregnancy, and the risks of fetal morbidities are likely closer to those with preexisting diabetes.

The risk for cardiac defects has an increased odds ratio of roughly 2.5 compared with those who do not have diabetes.[41] Billionnet and colleagues[42] reported an increased rate of cardiac malformations (odds ratio [OR] 1.3 [95% confidence interval [CI] 1.1 to 1.4]) in participants‡ with GDM, compared with those without diabetes. Higher risks were observed in those with insulin-treated GDM than in those with diet-treated GDM. The study excluded those suspected to have undiagnosed preexisting diabetes.‡ Hypertrophic cardiomyopathy, a cardiac malformation characterized by thickening of the heart muscle, is thought to be caused by fetal hyperinsulinemia, leading to accelerated growth of cardiac cells.[43]

Growth Disturbances

Diabetes in pregnancy carries an increased risk for intrauterine growth restriction and fetal macrosomia. Asymmetric intrauterine growth restriction can develop in persons with diabetes who have vascular

‡ Study participants were described as women. Gender was not further specified. Please see pages xix to xx and Appendix A for more on gender-inclusive terminology. This note applies to all appearances of the ‡ symbol in this chapter.

disease (such as nephropathy and retinopathy), recurrent hypoglycemia and ketosis, or preeclampsia. More commonly, neonates of those with diabetes are known to have increased body fat in addition to higher rates of macrosomia. Several studies have demonstrated a strong correlation between gestational blood glucose concentrations and neonatal birth weight as well as neonatal adiposity.[44]

Macrosomia

Macrosomia, or fetal overgrowth, is the most common fetal complication associated with gestational diabetes.[36] The incidence of macrosomia has increased in the United States and other developed countries.[45,46] Although more than 75% of macrosomic infants are born to those with normal glucose tolerance, the incidence of macrosomia in GDM is 20% to 50%.[1] This parallels the increasing rates of GDM. Fetal overgrowth often is defined as either macrosomia or large for gestational age,[47] but there is no standard definition for macrosomia, regardless of gestational age (reports range from 4,000 to 4,500 g).[48] A more precise measure of fetal overgrowth for infants not born at term is large for gestational age or above the 90th percentile, based on population- and sex-specific curves.

Fetal overgrowth is a direct result of gestational hyperglycemia. Glucose freely crosses the placenta and is a growth factor for the developing fetus. Exposure to elevated glucose levels results in fetal hyperglycemia and a resultant increase in fetal β-cell mass and hyperinsulinemia. This phenomenon, referred to as the *Pedersen hypothesis*, also accounts for higher rates of neonatal hypoglycemia after birth in infants born to those with any form of diabetes.[49] Postprandial glucose, as opposed to fasting glucose, has been shown to be more predictive of fetal overgrowth and macrosomia.[50,51] Similarly, medication adjustment based on postprandial glucose levels decreased rates of macrosomia and neonatal hypoglycemia.[52] Studies also have identified elevated lipid and amino acid levels as contributors to excessive fetal growth.[16]

Although fetal overgrowth is defined by birth weight, it is more accurately characterized by estimating body composition, both lean body mass and fat mass. Lean body mass is metabolically active and relatively stable in utero.[53] Fat mass is more variable and sensitive to factors, such as elevated gestational glucose.[54] Infants with average-for-gestational-age birth weights born to those with any form of preexisting diabetes have been shown to have increased body fat, compared with infants from a pregnancy with normal glucose tolerance.[55] This same phenomenon holds true for large-for-gestational-age

infants born to those with GDM.[56] In addition to an overall increase in fat mass, there is disproportionate growth with excessive adipose tissue deposits in the chest and abdominal area.[57] This disproportion is a leading contributor to the higher rate of shoulder dystocia in infants born to those with diabetes, even at birth weights below the macrosomia threshold. In persons with diabetes, the risk for shoulder dystocia with a fetal weight greater than 4,000 g is approximately 30%.[58] Shoulder dystocia can lead to both perinatal and neonatal morbidity.[59] Perinatal morbidities include an increased risk for postpartum hemorrhage and a higher degree of perineal lacerations. Neonatal morbidities include brachial plexus injuries, clavicular and humeral fractures, perinatal asphyxia, neonatal encephalopathy, and death.[60]

Additional investigation of the relationship between the prevalence of risk factors (such as obesity), preexisting diabetes mellitus, and changes in the incidence of macrosomia is warranted. More research is needed to determine whether clinical interventions to treat patients with specific risk factors are effective in preventing macrosomia.

Given the difficulty in preventing birth injury due to macrosomia, it is best to prevent fetal overgrowth with tight glycemic control. Prophylactic cesarean delivery should be considered for pregnancies with diabetes and an estimated fetal weight of 4,500 g or more.[44] The presence of both T2DM and obesity before pregnancy has been associated with an increased risk for cesarean delivery.[61]

Polyhydramnios

Polyhydramnios (excessive amniotic fluid) occurs in approximately 1% of pregnancies. Its prevalence is higher in pregnancies with diabetes, ranging between 1% to 20%.[62] Although several mechanisms have been proposed, the most likely etiology is related to fetal polyuria as a result of fetal hyperglycemia. Polyhydramnios is more common in those with suboptimal glycemic control (mainly in preexisting T1DM or T2DM).[62,63] In one GDM study‡, polyhydramnios was not associated with increased perinatal morbidity or mortality, compared with those who had normal amniotic fluid volumes.[64] A diagnosis of polyhydramnios often coexists with fetal overgrowth and should prompt close surveillance of blood glucose levels.

Neonatal Hypoglycemia

Neonatal hypoglycemia occurs shortly after birth when the infant is no longer receiving a continuous supply of glucose but still has high circulating insulin levels. It is most often defined as a blood glucose level below 35 to 40 mg/dL during the first 12 hours of life.[1] Infants with macrosomia are at increased risk for neonatal hypoglycemia.[65] Poor glucose control during pregnancy, both in the antepartum and intrapartum periods, is also associated with higher rates of neonatal hypoglycemia.[66] The condition is often adequately treated with early initiation of neonatal oral feeding and frequent blood glucose monitoring. In rare cases, intravenous glucose is needed. Unrecognized and inadequately treated neonatal hypoglycemia can lead to seizures, cerebral damage, and death.

Respiratory Distress Syndrome

Respiratory distress syndrome is characterized by the lack of surfactant production in the fetal lungs, resulting in the collapse of terminal air spaces. Diabetes and preterm delivery are risk factors for respiratory distress syndrome.[67] Fetal hyperglycemia with resultant hyperinsulinemia inhibits expression of surfactant proteins.[1,68] A delay in the appearance of phosphatidylglycerol, a major lipid component of surfactant, is also seen.[68] Fetal lung maturity is correlated with glycemic control. Poor glycemic control during pregnancy is associated with the delayed appearance of phosphatidylglycerol and higher rates of respiratory distress syndrome.[69] Adequate glycemic control does not appear to delay fetal lung function.

Neonatal Hypocalcemia

Neonatal hypocalcemia (serum calcium level <7 mg/dL) occurs in less than 5% of pregnancies with diabetes.[70] During pregnancy, calcium, magnesium, and other minerals are transported to the fetus. In the healthy neonate, parathyroid hormone and vitamin D are stimulated into action when the serum calcium level decreases. However, individuals with T1DM also have reduced levels of magnesium and parathyroid hormone.[71] Fetal hypomagnesemia can lead to lower levels of fetal parathyroid hormone and eventually to neonatal hypocalcemia.[67,71] Infants born with hypocalcemia may exhibit jitteriness, cyanosis, feeding difficulties, or seizures. The treatment for hypocalcemia is an infusion of 10% calcium gluconate. If hypomagnesemia is also present, treatment focuses on correcting magnesium levels before calcium levels.[71]

Neonatal Hyperbilirubinemia and Polycythemia

Hyperbilirubinemia in the neonate (serum bilirubin >13 mg/dL[72]) affects 20% to 35% of all pregnancies with diabetes, compared with only 10% in pregnancies with normal glucose levels.[1,67] The pathogenesis of hyperbilirubinemia is not well understood, although a common pathway is related to an increase in red blood cell production, resulting in polycythemia[6] (hematocrit >65%). The exact mechanism is unknown, but polycythemia may result from increased red cell production in response to a decrease in available oxygen to the fetus.[67] Fetal hypoxia occurring in the presence of fetal hyperinsulinemia can increase oxygen consumption and cardiac load as a result of poor gestational glycemic control.[6] A higher incidence of polycythemia is found in infants who were born to those with diabetes.

The primary treatment for hyperbilirubinemia is phototherapy. Phototherapy converts bilirubin into a water-soluble compound, which is excreted in the urine and bile without requiring conjugation in the liver. In rare cases, exchange transfusion may be necessary.[1]

Miscarriage and Stillbirth

Throughout the last 40 years, the frequency of intrauterine fetal demise has declined significantly. Despite these improvements, stillbirth and neonatal death still occur in those who have diabetes before pregnancy—and particularly with suboptimal glycemic control, no preconception care, or vascular compromise—at rates significantly higher than in pregnancies without diabetes.[73,74] Stillbirth rates remain four to six times higher in diabetes-related pregnancies than in pregnancies without diabetes.

Perinatal Health

Hypertension in Pregnancy

In 2013, the American College of Obstetricians and Gynecologists convened a task force to provide evidence-based recommendations for the management of hypertension in pregnancy.[75] A diagnosis of gestational hypertension of preeclampsia is made when two or more blood pressure readings, measured at least 6 hours apart, reveal a systolic pressure of 140 mm Hg or higher, or a diastolic pressure of 90 mm Hg or higher.

The four categories of classification for hypertension in pregnancy are as follows[75]:

1. Preeclampsia-eclampsia
2. Chronic hypertension (of any cause): hypertension that

predates conception or detected before 20 weeks of gestation
3. Chronic hypertension with superimposed preeclampsia: chronic hypertension in association with preeclampsia
4. Gestational hypertension: blood pressure elevations occurring after 20 weeks in the absence of proteinuria or systemic findings

In this classification system, both proteinuria and intrauterine growth restriction were removed from the diagnosis and severity assessment. Glycemic control has been correlated with the development of hypertensive disorders of pregnancy.[76,77] Insulin resistance has been associated with the development of preeclampsia.[78] Both the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial and National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) mild GDM trial showed a reduction in rates of hypertensive disorders in pregnancy with the treatment of GDM compared with no-treatment groups.[79,80] Before these two studies were published, no confirmatory data showed that treating patients with GDM led to a reduction in gestational hypertension or preeclampsia.

Preeclampsia and Eclampsia

The diagnosis of preeclampsia includes hypertension in association with thrombocytopenia (platelet count <100,000), impaired liver function (elevated liver transaminases double the normal values), severe persistent right upper-quadrant or epigastric pain, renal insufficiency (serum creatinine level >1.1 mg/dL or a doubling of the level in absence of other renal disease), pulmonary edema, and new onset of cerebral or visual disturbances. Eclampsia is the convulsive phase of preeclampsia and often is preceded by severe headaches and hyperreflexia but can occur in the absence of warning signs and symptoms. Eclampsia can occur before, during, or after labor.

Preeclampsia is among the most common pregnancy-related complications for those with preexisting diabetes, and it occurs in 2% to 8% of pregnancies. Risk factors include longer duration of diabetes prior to pregnancy, preexisting nephropathy, chronic hypertension, and poor glycemic control.[81] Low-dose aspirin confers an approximately 24% reduction in the development of preeclampsia. In those who have T1DM or T2DM, practitioners should recommend low-dose aspirin from the end of the first trimester until birth[32] in order to reduce the risk for developing preeclampsia or any other high-risk factor for preeclampsia, such as a history of preeclampsia, multifetal gestation, chronic hypertension, renal disease, or autoimmune disease.[82] Research by Sato and colleagues showed that in

persons with preexisting T1DM and T2DM, elevated prepregnancy body mass index, gestational weight gain, a history of chronic hypertension, and diabetic nephropathy and diabetic retinopathy were individually associated with an increased risk for pregnancy-induced hypertension.[61]

Endothelial dysfunction plays a role in both the pathophysiology of gestational diabetes and preeclampsia. GDM increases the risk for hypertensive disorders of pregnancy. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed a continuous positive association between gestational glucose levels and preeclampsia, even at thresholds below the diagnosis of GDM.[83]

Labor Induction and Cesarean Delivery

The higher rates of cesarean delivery seen in persons with diabetes are, in part, attributed both to fetal overgrowth and the potential need to induce labor.[84,85] In cases of a large-for-gestational-age fetus or suspected macrosomia, clinicians might recommend cesarean delivery to prevent shoulder dystocia. Regardless of delivery recommendations, the HAPO study showed a positive continuous association between gestational glucose levels and rate of primary cesarean delivery.[83] However, a meta-analysis of 10 studies evaluating the effect of treatment on adverse pregnancy outcomes in GDM failed to show a reduction in either labor induction or cesarean delivery rates.[86] Conversely, the ACHOIS study revealed higher rates of labor induction in the treatment group compared with those receiving routine care.[79] (This may be related to the label of gestational diabetes, which may have influenced the providers' decision-making.) Despite higher rates of labor induction, cesarean delivery rates were similar between groups. In the MFMU GDM trial, labor induction rates were similar between treated and nontreated GDM; however, a significant decrease in the rate of cesarean delivery was observed in the treatment group.[79]

Summary

Normal physiologic changes in pregnancy affect nutrient metabolism and insulin resistance. Glucose is the primary nutrient affecting glycemic levels, but amino acids and lipids also play a role. Gestational hyperglycemia can result from increased insulin resistance or an inability to increase insulin production to meet the demands of pregnancy. The numerous risks to fetal development and birth outcomes resulting from prolonged hyperglycemia are well documented,

although the exact mechanisms by which diabetes can adversely affect fetal growth and development are not entirely understood. These risks are decreased with optimal glycemic control during pregnancy. The goal is to achieve and maintain blood glucose control to near-normal limits before and throughout pregnancy.

References

1. Gabbe S, Niebyl J, Simpson J, et al. *Obstetrics: Normal and Abnormal Pregnancies.* 7th edition. Elsevier; 2016.
2. Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. *Diabetologia.* 2016;59:1089-1094. doi:10.1007/s00125-016-3931-6
3. McCance DR. Diabetes in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2015;29(5):685-699. doi:10.1016/j.bpobgyn.2015.04.009
4. Mukherjee MS, Coppenrath VA, Dallinga BA. Pharmacologic management of types 1 and 2 diabetes mellitus and their complications in women of childbearing age. *Pharmacotherapy.* 2015;35(2):158-174. doi:10.1002/phar.1535
5. *Dorland's Medical Dictionary for Health Consumers.* WB Saunders; 2007.
6. Resnik R, Lockwood CJ, Moore T, Greene M, Copel J, Silver RM. *Creasy and Resnick's Maternal Fetal Medicine.* 8th ed. Elsevier; 2019.
7. Dickinson JE, Palmer SM. Gestational diabetes: pathophysiology and diagnosis. *Semin Perinatol.* 1990;14:2-11.
8. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes.* 1980;29:1023-1035. doi:10.2337/diab.29.12.1023
9. Blackburn ST, Loper DL. *Maternal, Fetal, and Neonatal Physiology.* WB Saunders; 1992:599.
10. Buchanan T. *Diabetes Mellitus: A Fundamental and Clinical Text.* Lippincott Williams & Wilkins; 1996.
11. Shshidhar A, Chandrasekaran A. In utero fuel homeostasis: lessons for a clinician. *Indian J Endocrinol Metab*. 2013;17(1):60-68. doi:10.4103/2230-8210.107851
12. Yamashita H, Shao J, Friedman JE. Physiologic and molecular alterations in carbohydrate metabolism during pregnancy and gestational diabetes mellitus. *Clin Obstet Gynecol.* 2000;43(1):87-98. doi:10.1097/00003081-200003000-00009
13. Kuhl C. Etiology and pathogenesis of gestational diabetes. *Diabetes Care.* 1998;21(suppl 2):B19-B26.
14. Catalano PM, Tyzbir ED, Wolfe RR, Roman NM, Amini SB, Sims EA. Longitudinal changes in basal hepatic glucose production and suppression during insulin infusion in normal pregnant women. *Am J Obstet Gynecol.* 1992;167(4 Pt 1):913-919. doi:10.1016/s0002-9378(12)80011-1
15. Sivan E, Boden G. Free fatty acids, insulin resistance, and pregnancy. *Curr Diab Rep.* 2003;3:319-322. doi:10.1007/s11892-003-0024-y
16. Knopp RH, Bergelin RO, Wahl PW, Walden CE. Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries, and body weight at 36 weeks' gestation. *Diabetes.* 1985;34(suppl 2):71-77. doi:10.2337/diab.34.2.s71
17. Catalano PM, Tyzbir ED, Roman NM, Amin SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. *Am J Obstet Gynecol.* 1991;165(6 Pt 1):1667-1672. doi:10.1016/0002-9378(91)90012-g

18. Friedman JE, Ishizuka T, Shao J, Huston L, Highman T, Catalano P. Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes. *Diabetes.* 1999;48(9):1807-1814. doi:10.2337/diabetes.48.9.1807
19. Ryan EA, O'Sullivan MJ, Skyler JS. Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes.* 1985;34(4):380-389. doi:10.2337/diab.34.4.380
20. Schmitz O, Klebe J, Moller J, et al. In vivo insulin action in type 1 (insulin-dependent) diabetic pregnant women as assessed by the insulin clamp technique. *J Clin Endocrinol Metab.* 1985;61(5):877-881. doi:10.1210/jcem-61-5-877
21. Lewis SB, Wallin JD, Kuzuya H, et al. Circadian variation of serum glucose, C-peptide immunoreactivity and free insulin normal and insulin-treated diabetic pregnant subjects. *Diabetologia.* 1976;12(4):343-350. doi:10.1007/bf00420978
22. Magon N, Chauhan M. Pregnancy in type 1 diabetes mellitus: how special are special issues? *N Am J Med Sci.* 2012;4(6):250-256. doi:10.4103/1947-2714.97202
23. Ghafoor S, Saleem A, Shaheena, Shaikh AW. Impact of pregnancy on C-peptide levels of type-II diabetic women. *Pak J Med Health Sci*. 2012;6(2):358-361.
24. Knopp RH, Montes A, Childs M, Li JR, Mabuchi H. Metabolic adjustments in normal and diabetic pregnancy. *Clin Obstet Gynecol.* 1981;24(1):21-49. doi:10.1097/00003081-198103000-00006
25. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstet Gynecol.* 2013;122:406-416. doi:10.1097/01.AOG.0000433006.09219.f1
26. Landon MB, Gabbe SG. Gestational diabetes mellitus. *Obstet Gynecol.* 2011;118:1379-1393. doi:10.1097/AOG.0b013e31823974e2
27. Gabbe SG, Landon MB, Warren-Boulton E, Fradkin J. Promoting health after gestational diabetes: a National Diabetes Education Program call to action. *Obstet Gynecol.* 2012;119(1):171-176. doi:10.1097/AOG.0b013e3182393208
28. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. *Nat Rev Endocrinol.* 2012;8(11):639-649. doi:10.1038/nrendo.2012.96
29. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *J Am Coll Cardiol.* 2008;52(3):171-180. doi:10.1016/j.jacc.2008.03.049
30. Allen VM, Armson BA. Teratogenicity associated with pre-existing and gestational diabetes. *J Obstet Gynaecol Can.* 2007;29(11):927-934. doi:10.1016/S1701-2163(16)32653-6
31. Loeken MR. Challenges in understanding diabetic embryopathy. *Diabetes.* 2008;57(12):3187-3188. doi:10.2337/db08-1201
32. 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;304(22):1331-1334. doi:10.1056/NEJM198105283042204
33. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in diabetes—2020. *Diabetes Care.* 2020;43(suppl 1):S183-S192. doi:10.2337/dc20-S014
34. Kalkhoff RK. Impact of maternal fuels and nutritional state on fetal growth. *Diabetes.* 1991;40(suppl 2):61-65. doi:10.2337/diab.40.2.s61
35. Buchanan TA, Coustan DR. Diabetes Mellitus. In: Burrow GN, Ferris FT, eds. *Medical Complications During Pregnancy.* 4th ed. WB Saunders; 1995:29-61.
36. Anoon SS, Rizk DE, Ezimokhai M. Obstetric outcome of excessively overgrown fetuses (>or = 5000 g): a case-control study. *J Perinat Med.* 2003;31(4):295-301. doi:10.1515/JPM.2003.041
37. Jensen DM, Korsholm L, Ovesen P, et al. Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care.* 2009;32(6):1046-1048. doi:10.2337/dc08-2061
38. 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(11):671-676. doi:10.1056/NEJM198803173181104
39. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics.* 1990;85(1):1-9.
40. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes Care.* 2020;43(suppl 1):S14-S21. doi:10.2337/dc20-S002
41. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in diabetic pregnancies: a large population based study. *Diabetes Care.* 2009;32(11):2005-2009. doi:10.2337/dc09-0656
42. Billionnet C, Mitanchez D, Weill A, et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia.* 2017;60(4):636-644. doi:10.1007/s00125-017-4206-6
43. Russell NE, Foley M, Kinsley BT, Firth RG, Coffey M, McAuliffe FM. Effect of pregestational diabetes mellitus on fetal cardiac function and structure. *Am J Obstet Gynecol.* 2008;199(3):e311-e317. doi:10.1016/j.ajog.2008.07.016

44. Uvena-Celebrezze J, Fung C, Thomas AJ. Relationship of neonatal body composition to maternal glucose control in women with gestational diabetes mellitus. *J Matern Fetal Neonatal Med.* 2002;12(6):396-401. doi:10.1080/jmf.12.6.396.401
45. Johar R, Rayburn W, Weir D, Eggert L. Birth weights in term infants. A 50-year perspective. *J Reprod Med.* 1988;33:813-816.
46. Sacks DA, Chen W. Estimating fetal weight in the management of macrosomia. *Obstet Gynecol Surv.* 2000;55:229-239. doi:10.1097/00006254-200004000-00022
47. Mitanchez D, Yzydorczyk C, Siddeek B, Boubred F, Benahmed M, Simeoni U. The offspring of the diabetic mother—short- and long-term implications. *Best Pract Res Clin Obstet Gynaecol.* 2015;29:256-269. doi:10.1016/j.bpobgyn.2014.08.004
48. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 173: Fetal macrosomia. *Obstet Gynecol.* 2016;128(5):e195-e209. doi:10.1097/AOG.0000000000001767
49. Pedersen J. Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol (Copenh).* 1954;16(4):330-342. doi:10.1530/acta.0.0160330
50. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol.* 1991;164(1 Pt 1):103-111. doi:10.1016/0002-9378(91)90637-7
51. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care.* 1992;15(10):1251-1257. doi:10.2337/diacare.15.10.1251
52. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med.* 1995;333(19):1237-1241. doi:10.1056/NEJM199511093331901
53. Miller AT Jr, Blyth CS. Lean body mass as a metabolic reference standard. *J Appl Physiol.* 1953;5(7):311-316. doi:10.1152/jappl.1953.5.7.311
54. Sparks JW. Human intrauterine growth and nutrient accretion. *Semin Perinatol.* 1984;8(2):74-93.
55. Catalano PM, Thomas A, Huston-Presley L, Amini SB. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *Am J Obstet Gynecol.* 2003;189(6):1698-1704. doi:10.1016/s0002-9378(03)00828-7
56. Durnwald C, Huston-Presley L, Amini S, Catalano P. Evaluation of body composition of large-for-gestational-age infants of women with gestational diabetes mellitus compared with women with normal glucose tolerance levels. *Am J Obstet Gynecol.* 2004;191(3):804-808. doi:10.1016/j.ajog.2003.11.033
57. Persson B, Hanson U. Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care.* 1998;21(suppl 2):B79-B84.
58. Acker DB, Sachs BP, Friedman EA. Risk factors for shoulder dystocia. *Obstet Gynecol.* 1985;66(6):762-768.
59. Berkus MD, Conway D, Langer O. The large fetus. *Clin Obstet Gynecol.* 1999;42(4):766-784. doi:10.1097/00003081-199912000-00006
60. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 178: Shoulder dystocia. *Obstet Gynecol.* 2017;129(5):e123-e33. doi:10.1097/AOG.0000000000002043
61. Sato TS, Sugiyama T, Kurakata M, et al. Pregnancy outcomes in women with type 1 and type 2 diabetes mellitus in a retrospective multi-instutional study in Japan. *Endocr J.* 2014;61(8):759-764. doi:10.1507/endocrj.ej14-0140
62. Idris N, Wong SF, Thomae M, Gardener G, McIntyre DH. Influence of polyhydramnios on perinatal outcome in pregestational diabetic pregnancies. *Ultrasound Obstet Gynecol.* 2010;36(3):338-343. doi:10.1002/uog.7676
63. Biggio JR Jr, Wenstrom KD, Dubard MB, Cliver SP. Hydramnios prediction of adverse perinatal outcome. *Obstet Gynecol.* 1999;94(5 Pt 1):773-777. doi:10.1016/s0029-7844(99)00370-1
64. Shoham I, Wiznitzer A, Silberstein T, et al. Gestational diabetes complicated by hydramnios was not associated with increased risk of perinatal morbidity and mortality. *Eur J Obstet Gynecol Reprod Biol.* 2001;100(1):46-49. doi:10.1016/s0301-2115(01)00426-2
65. 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(5):1089-1095. doi:10.1016/0002-9378(87)90116-5
66. Taylor R, Lee C, Kyne-Grzebalski D, Marshall SM, Davison JM. Clinical outcomes of pregnancy in women with type 1 diabetes. *Obstet Gynecol.* 2002;99(4):537-541. doi:10.1016/s0029-7844(01)01790-2
67. Uvena-Celebrezze J, Catalano PM. The infant of the woman with gestational diabetes mellitus. *Clin Obstet Gynecol.* 2000;43(1):127-139. doi:10.1097/00003081-200003000-00013

68. Azad MB, Moyce BL, Guillemette L, et al. Diabetes in pregnancy and lung health in offspring: developmental origins of respiratory disease. *Paediatr Respir Rev.* 2017;21:19-26. doi:10.1016/j.prrv.2016.08.007
69. Piper JM. Lung maturation in diabetes in pregnancy: if and when to test. *Semin Perinatol.* 2002;26(3):206-209. doi:10.1053/sper.2002.33969
70. Landon MB, Gabbe SG. Diabetes Mellitus. In: Barron WM, Lindheimer MD, eds *Medical Disorders During Pregnancy.* 3rd ed. Mosby. 2000:71-100.
71. Cruikshank DP, Pitkin RM, Reynolds WA, Williams GA, Hargis GK. Altered maternal calcium homeostasis in diabetic pregnancy. *J Clin Endocrinol Metab.* 1980;50(2):264-267. doi:10.1210/jcem-50-2-264
72. Widness JA, Cowett RM, Coustan DR, Carpenter MW, Oh W. Neonatal morbidities in infants of mothers with glucose intolerance in pregnancy. *Diabetes.* 1985;34(suppl 2):61-65. doi:10.2337/diab.34.2.s61
73. Temple RC, Aldridge VJ, Murphy HR. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. *Diabetes Care.* 2006;29:1744-1749. doi:10.2337/dc05-2265
74. Mathiesen ER, Ringholm L, Damm P. Stillbirth in diabetic pregnancies. *Best Pract Res Clin Obstet Gynaecol*. 2011;25(1):105-111. doi:10.1016/j.bpobgyn.2010.11.001
75. American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. *Obstet Gynecol.* 2013;122(5):1122-1131. doi:10.1097/01.AOG.0000437382.03963.88
76. Pettitt DJ, Knowler WC, Baird HR, Bennett PH. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. *Diabetes Care.* 1980;3(3):458-464. doi:10.2337/diacare.3.3.458
77. Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M, Fontaine P. Pregnancy induced hypertension in women with gestational carbohydrate intolerance: the Diagest Study. *Eur J Obstet Gynecol Reprod Biol.* 2002;102(1):31-35. doi:10.1016/s0301-2115(01)00556-5
78. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339-1348. doi:10.1056/NEJMoa0902430
79. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352(24):2477-2486. doi:10.1056/NEJMoa042973
80. Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL, Thadhani R. First trimester insulin resistance and subsequent preeclampsia: a prospective study. *J Clin Endocrinol Metab.* 2002;87(4):1563-1568. doi:10.1210/jcem.87.4.8405
81. Landon MB, Mele L, Spong CY, et al.The relationship between maternal glycemia and perinatal outcome. *Obstet Gynecol.* 2011;117(2 Pt 1):218-224. doi:10.1097/aog.0b013e318203ebe0
82. Bibbins-Domingo K, US Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2016;164(12):836-845. doi:10.7326/M16-0577
83. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991-2002. doi:10.1056/NEJMoa0707943
84. Xiong X, Saunders LD, Wang FL, Demianczuk NN. Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes. *Int J Gynaecol Obstet.* 2001;75(3):221-228. doi:10.1016/s0020-7292(01)00496-9
85. Conway DL. Delivery of the macrosomic infant: cesarean section versus vaginal delivery. *Semin Perinatol.* 2002;26(3):225-231. doi:10.1053/sper.2002.33975
86. Poolsup N, Suksomboon N, Amin M. Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. *PLoS One.* 2014;9(3):e92485. doi:10.1371/journal.pone.0092485

Index

Letters *b*, *f*, and *t* after page number indicate box, figure, and table, respectively.

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

U

V

W