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Diabetes and Pregnancy:
An Endocrine Society Clinical Practice Guideline

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Co-Sponsoring Associations: American Diabetes Association, European Association of Perinatal Medicine, and European Society of Endocrinology.

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Table of Contents

Continuing Medical Education Information	3
Abstract	6
Summary of Recommendations	7
Method of Development of Evidence-Based Clinical Practice Guidelines	13
Introduction and Background.	13
Preconception Care of Women with Diabetes.	14
Gestational Diabetes.	18
Glucose Monitoring and Glycemic Targets	20
Nutrition Therapy and Weight Gain Targets for Women with Overt or Gestational Diabetes	22
Blood Glucose-Lowering Pharmacological Therapy During Pregnancy	23
Labor, Delivery, Lactation, and Postpartum Care	26
References	28
CME Learning Objectives and Post-Test Questions	38
CME Answers and Explanations	40
Order Form	43
Reprint Information, Questions & Correspondences	Inside Back Cover

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Learning Objectives

Upon completion of this educational activity, learners will be able to:

- Recognize the appropriate target level of glycemic control (as reflected by the HbA1C) for a woman with established diabetes before attempting to conceive.
- Evaluate self-monitored blood glucose target levels for a woman with gestational diabetes and the appropriate therapeutic intervention if these targets are being exceeded.
- Determine the appropriate frequency for ocular assessment for a pregnant woman with diabetes and known retinopathy.
- Select appropriate antihyperglycemic medication for a breastfeeding woman with type 2 diabetes.

Target Audience

This continuing medical education activity should be of substantial interest to endocrinologists and other health care professionals that treat patients with diabetic patients during pregnancy and postpartum.

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David R. Hadden, MD is a member of the data monitoring committee for Novo Nordisk and a technical editor for Wiley-Blackwell Publishing.

The following committee members who planned and/or reviewed content for this activity reported no relevant financial relationships: M. Hassan Murad, MD; Lois Jovanovic, MD; Jorge H. Mestman, MD; Eran Hadar, MD; Yariv Yogev, MD.

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Last Review Date: October 2013

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Activity Expiration Date: November 2016

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Abstract

Objective: Our objective was to formulate a clinical practice guideline for the management of the pregnant woman with diabetes.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of the Endocrine Society, 5 additional experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and innumerable e-mail communications enabled consensus for all recommendations save one with a majority decision being employed for this single exception.

Conclusions: Using an evidence-based approach, this Diabetes and Pregnancy Clinical Practice Guideline addresses important clinical issues in the contemporary management of women with type 1 or type 2 diabetes preconceptionally, during pregnancy, and in the postpartum setting and in the diagnosis and management of women with gestational diabetes during and after pregnancy.

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Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; GFR, glomerular filtration rate; HbA1C, hemoglobin A1C; IADPSG, International Association of Diabetes and Pregnancy Study Groups; NPH, neutral protamine Hagedorn; OGTT, oral glucose tolerance test.

SUMMARY OF RECOMMENDATIONS

1.0. Preconception care of women with diabetes

Preconception counseling

1.1. We recommend that preconception counseling be provided to all women with diabetes who are considering pregnancy. (1 | ⊕⊕○○)

Preconception glycemic control

1.2. We suggest that women with diabetes seeking to conceive strive to achieve blood glucose and hemoglobin A1C (HbA1C) levels as close to normal as possible when they can be safely achieved without undue hypoglycemia. (2 | ⊕⊕○○) (See Recommendations 3.2a–d.)

Insulin therapy

1.3a. We recommend that insulin-treated women with diabetes seeking to conceive be treated with multiple daily doses of insulin or continuous sc insulin infusion in preference to split-dose, premixed insulin therapy, because the former are more likely to allow for the achievement and maintenance of target blood glucose levels preconceptionally and, in the event of pregnancy, are more likely to allow for sufficient flexibility or precise adjustment of insulin therapy. (1 | ⊕⊕○○)

1.3b. We suggest that a change to a woman's insulin regimen, particularly when she starts continuous sc insulin infusion, be undertaken well in advance of withdrawing contraceptive measures or otherwise trying to conceive to allow the patient to acquire expertise in, and the optimization of, the chosen insulin regimen. (Ungraded recommendation)

1.3c. We suggest that insulin-treated women with diabetes seeking to conceive be treated with rapid-acting insulin analog therapy (with insulin aspart or insulin lispro) in preference to regular (soluble) insulin. (2 | ⊕⊕○○)

1.3d. We suggest that women with diabetes successfully using the long-acting insulin analogs insulin detemir or insulin glargine preconceptionally may continue with this therapy before and then during pregnancy. (2 | ⊕⊕○○)

Folic acid supplementation

1.4. We recommend that beginning 3 months before withdrawing contraceptive measures or otherwise trying to conceive, a woman with diabetes take a daily folic acid supplement to reduce the risk of neural tube defects. (1 | ⊕⊕○○) We suggest a daily dose of 5 mg based on this dose's theoretical benefits. (2 | ⊕⊕○○)

Ocular care (preconception, during pregnancy, and postpartum)

1.5a. We recommend that all women with diabetes who are seeking pregnancy have a detailed ocular assessment by a suitably trained and qualified eye care professional in advance of withdrawing contraceptive measures or otherwise trying to conceive (1 | ⊕⊕⊕⊕), and if retinopathy is documented, the patient should be apprised of the specific risks to her of this worsening during pregnancy. If the degree of retinopathy warrants therapy, we recommend deferring conception until the retinopathy has been treated and found to have stabilized. (1 | ⊕⊕⊕⊕)

1.5b. We recommend that women with established retinopathy be seen by their eye specialist every trimester, then within 3 months of delivering, and then as needed. (1 | ⊕○○○)

1.5c. We suggest that pregnant women with diabetes not known to have retinopathy have ocular assessment performed soon after conception and then periodically as indicated during pregnancy. (2 | ⊕⊕○○)

Renal function (preconception and during pregnancy)

1.6a. We suggest that all women with diabetes considering pregnancy have their renal function assessed (by measuring their urine albumin to creatinine ratio, serum creatinine, and estimated glomerular filtration rate [GFR]) in advance of withdrawing contraceptive measures or otherwise trying to

conceive. (Ungraded recommendation) We suggest that a woman with diabetes who has a significantly reduced GFR be assessed by a nephrologist before pregnancy, both for baseline renal assessment and to review the woman's specific risk of worsening renal function in the event of pregnancy. (Ungraded recommendation)

1.6b. We suggest that all women with diabetes and preconceptional renal dysfunction have their renal function monitored regularly during pregnancy. (Ungraded recommendation)

Management of hypertension

1.7a. We recommend that satisfactory blood pressure (BP) control (<130/80 mm Hg) be achieved and maintained before withdrawing contraception or otherwise trying to conceive. (1 | ⊕⊕○○)

1.7b. We recommend that a woman with diabetes who is seeking conception while taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker in almost all cases should discontinue the medication before withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕⊕○○)

1.7c. We suggest that in the exceptional case where the degree of renal dysfunction is severe and there is uncertainty about when conception will occur, physicians and patients be engaged in shared decision-making about whether to continue ACE inhibitors or angiotensin-receptor blockers. The patients should be informed about the possible loss of the renal protective properties if the medication is discontinued and the risk of teratogenesis if it is continued. (Ungraded recommendation)

1.7d. We recommend when ACE inhibitors or angiotensin-receptor blockers have been continued up to the time of conception that the medication should be withdrawn immediately upon the confirmation of pregnancy. (1 | ⊕⊕○○)

Elevated vascular risk

1.8a. We recommend that if a woman with diabetes has sufficient numbers of vascular risk factors

(particularly the duration of the woman's diabetes and her age), screening studies for coronary artery disease (CAD) be undertaken in advance of withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕○○○)

1.8b. We recommend that if a woman with diabetes is seeking pregnancy and has CAD, its severity should be ascertained, treatment instituted, and counseling provided as to the potential risks of pregnancy to the woman and fetus before the woman withdraws contraception or otherwise tries to conceive. (1 | ⊕⊕⊕⊕)

Management of dyslipidemia

1.9a. We recommend against the use of statins in women with diabetes who are attempting to conceive. (1 | ⊕⊕○○)

1.9b. In view of their unproven safety during pregnancy, we suggest against the routine use of fibrates and/or niacin for women with diabetes and hypertriglyceridemia attempting to conceive. (2 | ⊕⊕○○)

1.9c. We suggest that bile acid-binding resins may be used in women with diabetes to treat hypercholesterolemia; however, this is seldom warranted. (2 | ⊕⊕○○)

Thyroid function

1.10. For women with type 1 diabetes seeking conception, we recommend measurement of serum TSH and, if their thyroid peroxidase status is unknown, measurement of thyroid peroxidase antibodies before withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕○○○)

Overweight and obesity

1.11. We recommend weight reduction before pregnancy for overweight and obese women with diabetes. (1 | ⊕⊕⊕○)

2.0. Gestational diabetes

Testing for overt diabetes in early pregnancy

2.1. We recommend universal testing for diabetes (see Table 1) with a fasting plasma glucose, HbA1C, or an untimed random plasma glucose at the first prenatal visit (before 13 weeks gestation or as soon as possible thereafter) for those women not known to already have diabetes. (1 | ⊕⊕⊕⊕) In the case of overt diabetes, but not gestational diabetes, a second test (either a fasting plasma glucose, untimed random plasma glucose, HbA1C, or OGTT) must be performed in the absence of symptoms of hyperglycemia and found to be abnormal on another day to confirm the diagnosis.

Testing for gestational diabetes at 24 to 28 weeks gestation

2.2. We recommend that pregnant women not previously identified (either during testing performed as per recommendation 2.1 or at some other time before 24 weeks gestation) with overt diabetes or gestational diabetes be tested for gestational diabetes (see Table 2) by having a 2-hour, 75-g OGTT performed at 24 to 28 weeks gestation. (1 | ⊕⊕⊕⊕) We recommend that gestational diabetes be diagnosed on this test using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (majority opinion of this committee). (1 | ⊕⊕⊕⊕)

The 75-g OGTT should be performed after an overnight fast of at least 8 hours (but not more than 14 hours) and without having reduced usual carbohydrate intake for the preceding several days. The test should be performed with the patient seated, and the

TABLE 1. Diagnostic Criteria for Overt Diabetes and Gestational Diabetes at the First Prenatal Visit (Before 13 Weeks Gestation or as Soon as Possible Thereafter) for Those Women Not Known to Already Have Diabetes^a

Diagnosis	Fasting Plasma Glucose, ^b mg/dL (mmol/L)	Untimed (Random) Plasma Glucose, ^b mg/dL (mmol/L)	HbA1C, ^c %
Overt diabetes (type 1, type 2, or other)	≥126 (≥7.0)	≥200 (≥11.1)	≥6.5%
Gestational diabetes	92–125 (5.1–6.9)	NA	NA

Abbreviation: NA, not applicable.

- a These criteria for the diagnosis of overt diabetes in early pregnancy are congruent with those of the American Diabetes Association (57) and differ somewhat from those of the IADPSG (70).
- b Testing should use plasma glucose analyzed at a laboratory, not capillary blood glucose analyzed with a blood glucose meter.
- c Performed using a method that is certified by the NGSP (National Glycohemoglobin Standardization Program) and standardized to the Diabetes Control and Complications Trial (DCCT) (39) reference assay.

TABLE 2. Diagnostic Criteria for Overt Diabetes and Gestational Diabetes Using a 2-Hour 75-g OGTT at 24 to 28 Weeks Gestation^a

Diagnosis	Fasting Plasma Glucose, ^b mg/dL (mmol/L)	1-h Value, mg/dL (mmol/L)	2-h Value, mg/dL (mmol/L)
Overt diabetes (type 1, type 2, or other)	≥126 (≥7.0)	NA	≥200 (≥11.1)
Gestational diabetes	92–125 (5.1–6.9)	≥180 (≥10.0)	153–199 (8.5–11.0)

Abbreviation: NA, not applicable.

- a These criteria for diagnosing overt diabetes based on the results of the 24- to 28-week glucose tolerance test differ somewhat from those of the American Diabetes Association (57) and the IADPSG (70).
- b Testing should use plasma glucose analyzed at a laboratory, not capillary blood glucose analyzed with a blood glucose meter.

patient should not smoke during the test. One or more abnormal values establishes the diagnosis, with the exception that in the case of overt diabetes, but not gestational diabetes, a second test (either a fasting plasma glucose, untimed random plasma glucose, HbA1C, or OGTT), in the absence of symptoms of hyperglycemia, must be performed and found to be abnormal on another day to confirm the diagnosis of overt diabetes.

Management of elevated blood glucose

2.3a. We recommend that women with gestational diabetes target blood glucose levels as close to normal as possible. (1 | ⊕⊕○○)

2.3b. We recommend that the initial treatment of gestational diabetes should consist of medical nutrition therapy (see Section 4.0) and daily moderate exercise for 30 minutes or more. (1 | ⊕⊕⊕○)

2.3c. We recommend using blood glucose-lowering pharmacological therapy if lifestyle therapy is insufficient to maintain normoglycemia in women with gestational diabetes. (1 | ⊕⊕⊕⊕)

Postpartum care

2.4a. We recommend that postpartum care for women who have had gestational diabetes should include measurement of fasting plasma glucose or fasting self-monitored blood glucose for 24 to 72 hours after delivery to rule out ongoing hyperglycemia. (1 | ⊕○○○)

2.4b. We recommend that a 2-hour, 75-g OGTT should be undertaken 6 to 12 weeks after delivery in women with gestational diabetes to rule out prediabetes or diabetes. (1 | ⊕⊕⊕○) If results are normal, we recommend this or other diagnostic tests for diabetes should be repeated periodically as well as before future pregnancies. (1 | ⊕⊕○○)

2.4c. We suggest the child's birth weight and whether or not the child was born to a mother with gestational diabetes become part of the child's permanent medical record. (Ungraded recommendation)

2.4d. We recommend that all women who have had gestational diabetes receive counseling on lifestyle measures to reduce the risk of type 2 diabetes, the need for future pregnancies to be planned, and the need for regular diabetes screening, especially before any future pregnancies. (1 | ⊕○○○)

2.4e. We suggest blood glucose-lowering medication should be discontinued immediately after delivery for women with gestational diabetes unless overt diabetes is suspected, in which case the decision to continue such medication should be made on a case-by-case basis. (2 | ⊕⊕○○)

3.0. Glucose monitoring and glycemic targets

Self-monitoring of blood glucose

3.1. We recommend self-monitoring of blood glucose in all pregnant women with gestational or overt diabetes (1 | ⊕⊕⊕⊕) and suggest testing before and either 1 or 2 hours after the start of each meal (choosing the postmeal time when it is estimated that peak postprandial blood glucose is most likely to occur) and, as indicated, at bedtime and during the night. (2 | ⊕⊕○○)

Glycemic targets (Table 3)

3.2a. We recommend pregnant women with overt or gestational diabetes strive to achieve a target preprandial blood glucose <95 mg/dL (5.3 mmol/L).

Table 3. Glycemic Targets Preconceptionally for Women with Overt Diabetes and During Pregnancy for Women With Either Overt Diabetes or Gestational Diabetes^a

	Target Value, mg/dL (mmol/L)
Preprandial blood glucose	≤95 (5.3) ^b
1 h after the start of a meal	≤140 (7.8)
2 h after the start of a meal	≤120 (6.7)

^a Note that blood glucose meters use capillary blood but display corrected results equivalent to plasma glucose levels.

^b Target fasting blood glucose is ≤90 (5.0 mmol/L) if this can be safely achieved without undue hypoglycemia.

(1 | ⊕⊕○○) for fasting target, 1 | ⊕○○○) for other meals).

3.2b. We suggest that an even lower fasting blood glucose target of <90 mg/dL (5.0 mmol/L) be strived for (2 | ⊕○○○) if this can be safely achieved without undue hypoglycemia.

3.2c. We suggest pregnant women with overt or gestational diabetes strive to achieve target blood glucose levels 1 hour after the start of a meal <140 mg/dL (7.8 mmol/L) and 2 hours after the start of a meal <120 mg/dL (6.7 mmol/L) (2 | ⊕○○○) when these targets can be safely achieved without undue hypoglycemia.

3.2d. We suggest pregnant women with overt diabetes strive to achieve a HbA1C <7% (ideally <6.5%). (2 | ⊕○○○)

Continuous glucose monitoring

3.3. We suggest that continuous glucose monitoring be used during pregnancy in women with overt or gestational diabetes when self-monitored blood glucose levels (or, in the case of the woman with overt diabetes, HbA1C values) are not sufficient to assess glycemic control (including both hyperglycemia and hypoglycemia). (2 | ⊕⊕○○)

4.0. Nutrition therapy and weight gain targets for women with overt or gestational diabetes

Nutrition therapy

4.1. We recommend medical nutrition therapy for all pregnant women with overt or gestational diabetes to help achieve and maintain desired glycemic control while providing essential nutrient requirements. (1 | ⊕⊕○○)

Weight management

4.2a. We suggest that women with overt or gestational diabetes follow the Institute of Medicine revised guidelines for weight gain during pregnancy (1) (Table 4). (Ungraded recommendation)

4.2b. We suggest obese women with overt or gestational diabetes reduce their calorie intake by approximately one-third (compared with their usual intake before pregnancy) while maintaining a minimum intake of 1600 to 1800 kcal/d. (2 | ⊕⊕○○)

Carbohydrate intake

4.3. We suggest women with overt or gestational diabetes limit carbohydrate intake to 35% to 45% of total calories, distributed in 3 small- to moderate-sized meals and 2 to 4 snacks including an evening snack. (2 | ⊕⊕○○)

TABLE 4. 2009 Institute of Medicine Recommendations for Total Weight Gain and Rate of Weight Gain During Pregnancy, by Prepregnancy BMI (130)

Pregpregnancy BMI	Total Weight Gain		Rates of Weight Gain in Second and Third Trimester ^a	
	Range, kg	Range, lb	Mean (Range), kg/wk	Mean (Range), lb/wk
Underweight (<18.5 kg/m ²)	12.5–18	28–40	0.51 (0.44–0.58)	1 (1–1.3)
Normal weight (18.5–24.9 kg/m ²)	11.5–16	25–35	0.42 (0.35–0.50)	1 (0.8–1)
Overweight (25.0–29.9 kg/m ²)	7–11.5	15–25	0.28 (0.23–0.33)	0.6 (0.5–0.7)
Obese (≥30.0 kg/m ²)	5–9	11–20	0.22 (0.17–0.27)	0.5 (0.4–0.6)

^a Calculations assume a 0.5- to 2-kg (1.1–4.4 lb) weight gain in the first trimester.

Nutritional supplements

4.4. We recommend pregnant women with overt or gestational diabetes should follow the same guidelines for the intake of minerals and vitamins as for women without diabetes (1 | ⊕⊕○○), with the exception of taking folic acid 5 mg daily beginning 3 months before withdrawing contraceptive measures or otherwise trying to conceive (see Recommendation 1.4). We suggest that at 12 weeks gestation, the dose of folic acid be reduced to 0.4 to 1.0 mg/d, which should be continued until the completion of breastfeeding. (2 | ⊕⊕○○)

5.0. Blood glucose-lowering pharmacological therapy during pregnancy

Insulin therapy

5.1a. We suggest that the long-acting insulin analog detemir may be initiated during pregnancy for those women who require basal insulin and for whom neutral protamine Hagedorn (NPH) insulin, in appropriate doses, has previously resulted in, or for whom it is thought NPH insulin may result in, problematic hypoglycemia; insulin detemir may be continued in those women with diabetes already successfully taking insulin detemir before pregnancy. (2 | ⊕⊕⊕⊕)

5.1b. We suggest that those pregnant women successfully using insulin glargine before pregnancy may continue it during pregnancy. (2 | ⊕⊕○○)

5.1c. We suggest that the rapid-acting insulin analogs lispro and aspart be used in preference to regular (soluble) insulin in pregnant women with diabetes. (2 | ⊕⊕⊕⊕)

5.1d. We recommend the ongoing use of continuous sc insulin infusion during pregnancy in women with diabetes when this has been initiated before pregnancy (1 | ⊕⊕⊕⊕), but suggest that continuous sc insulin infusion not be initiated during pregnancy unless other insulin strategies including multiple daily doses of insulin have first been tried and proven unsuccessful. (2 | ⊕⊕○○)

Noninsulin antihyperglycemic agent therapy

5.2a. We suggest that glyburide (glibenclamide) is a suitable alternative to insulin therapy for glycemic control in women with gestational diabetes who fail to achieve sufficient glycemic control after a 1-week trial of medical nutrition therapy and exercise except for those women with a diagnosis of gestational diabetes before 25 weeks gestation and for those women with fasting plasma glucose levels >110 mg/dL (6.1 mmol/L), in which case insulin therapy is preferred. (2 | ⊕⊕○○)

5.2b. We suggest that metformin therapy be used for glycemic control only for those women with gestational diabetes who do not have satisfactory glycemic control despite medical nutrition therapy and who refuse or cannot use insulin or glyburide and are not in the first trimester. (2 | ⊕⊕○○)

6.0. Labor, delivery, lactation, and postpartum care

Blood glucose targets during labor and delivery

6.1. We suggest target blood glucose levels of 72 to 126 mg/dL (4.0 to 7.0 mmol/L) during labor and delivery for pregnant women with overt or gestational diabetes. (2 | ⊕⊕○○)

Lactation

6.2a. We recommend whenever possible women with overt or gestational diabetes should breastfeed their infant. (1 | ⊕⊕⊕⊕)

6.2b. We recommend that breastfeeding women with overt diabetes successfully using metformin or glyburide therapy during pregnancy should continue to use these medications, when necessary, during breastfeeding. (1 | ⊕⊕⊕⊕)

Postpartum contraception

6.3. We recommend that the choice of a contraceptive method for a woman with overt diabetes or a history of gestational diabetes should not be influenced by virtue of having overt diabetes or a history of gestational diabetes. (1 | ⊕⊕⊕⊕)

Screening for postpartum thyroiditis

6.4. We suggest that women with type 1 diabetes be screened for postpartum thyroiditis with a TSH at 3 and 6 months postpartum. (2 | ⊕⊕○○)

METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

The Clinical Guidelines Subcommittee of the Endocrine Society deemed the diagnosis and treatment of diabetes and pregnancy a priority area in need of a clinical practice guideline and appointed a Task Force to formulate evidence-based recommendations. The Task Force commissioned two systematic reviews and used the best available research evidence to develop the recommendations.

The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (2). A detailed description of the grading scheme has been published elsewhere (3). The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and less strong recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Less strong recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence that panelists considered in making the recommendation.

For some recommendations, remarks are present that provide additional background information, commentary, or technical suggestions.

The panelists on a few occasions left some recommendations ungraded (4). These are recommendations that were supported only by indirect evidence or by the unsystematic observations of the committee members and resulted from their consensus and discussion and have been included owing to their clinical relevance and practicality. These recommendations should be considered suggestions (*i.e.*, deviation from these recommendations is not unreasonable) and are explicitly left ungraded due to the lack of direct evidence.

INTRODUCTION AND BACKGROUND

In recent years, important new research has emerged in the field of diabetes and pregnancy. This guideline has been developed to address and distill this burgeoning literature with the goal of assisting health-care providers to best manage their pregnant patients living with overt or gestational diabetes using contemporary, evidence-based strategies.

In this guideline, all references to diabetes specifically and exclusively refer to diabetes mellitus. Also, unless stated otherwise, the terms diabetes, overt diabetes, and pregestational diabetes refer to either type 1 or type 2 diabetes.

We use the traditional term gestational diabetes to describe what has customarily been defined as “any degree of glucose intolerance with onset or first definition during pregnancy” (5) while acknowledging that the more contemporary term hyperglycemia in pregnancy has strong merit as a more appropriate term (6). We have retained the longstanding term (gestational diabetes) owing to its widespread familiarity and traditional usage.

Select thyroid recommendations in this Diabetes and Pregnancy Guideline are included as they relate

specifically to thyroid disease in pregnant women with diabetes. See the 2012 Endocrine Society Clinical Practice Guideline on pregnancy and thyroid disease for a detailed discussion on this topic (7).

This guideline advocates for use of best practices based on an analysis of the contemporary (and older) medical literature. It is, however, recognized that cost considerations and other practical realities may not necessarily allow for implementation of certain of our recommendations in some locales.

1.0. PRECONCEPTION CARE OF WOMEN WITH DIABETES

Preconception counseling

1.1. We recommend that preconception counseling be provided to all women with diabetes who are considering pregnancy. (1 | ⊕⊕○○)

1.1. Evidence

Women with diabetes who receive preconception counseling have better preconception glycemic control (8–9) and are more likely to have favorable pregnancy outcomes, including lower rates of congenital anomalies (9–10) and spontaneous abortions (11–12). By the time that a woman knows she is pregnant, much fetal organogenesis has typically been completed (13).

1.1. Remarks

Preconception counseling can optimally be provided by a multidisciplinary team that includes the diabetes specialist, diabetes educator, dietitian, obstetrician, and other healthcare providers, as indicated. If possible, and with the patient's consent, the woman's partner can be included as part of a supportive and mentoring therapeutic relationship. Preconception counseling should include a discussion regarding 1) the need for pregnancy to be planned and to occur only when the woman has sufficient glycemic control,

has had appropriate assessment and management of comorbidities including hypertension and retinopathy, has discontinued potentially unsafe (during pregnancy) medications, and has been taking appropriate folate supplementation beforehand (see the recommendations and evidence that follow in this section); 2) the importance of smoking cessation; 3) the major time commitment and effort required by the patient in both self-management and engagement with the healthcare team, both preconceptionally and during pregnancy; and 4) the importance of notifying the healthcare team without delay in the event of conception.

Preconception glycemic control

1.2. We suggest that women with diabetes seeking to conceive strive to achieve blood glucose and HbA1C levels as close to normal as possible when they can be safely achieved without undue hypoglycemia. (2 | ⊕⊕○○) (See Recommendations 3.2a–d.)

1.2. Evidence

Maternal hyperglycemia in the first few weeks of pregnancy increases the risk of fetal malformations, spontaneous abortions, and perinatal mortality (14–18). Ideal preconception blood glucose levels have not been definitively established (19), and the exact degree of risk of a congenital anomaly for a given HbA1C is not precisely known. It has been reported (16, 18) that the risk progressively rises in concert with the degree of periconceptual HbA1C elevation, although an increased risk compared with the general childbearing population has been observed with an HbA1C as low as 6.4% (18). It has, however, also been reported (20) that there is a stable degree of anomaly risk of 3.9% to 5.0% with a periconceptual HbA1C of up to 10.4%, with this risk then climbing to 10.9% if the HbA1C is 10.4% or higher.

Insulin therapy

1.3a. We recommend that insulin-treated women with diabetes seeking to conceive be treated with multiple daily doses of insulin or continuous sc insulin infusion in preference to split-dose, premixed insulin therapy, because the former are more likely to allow

for the achievement and maintenance of target blood glucose levels preconceptionally and, in the event of pregnancy, are more likely to allow for sufficient flexibility or precise adjustment of insulin therapy. (1 | ⊕⊕○○)

1.3b. We suggest that a change to a woman's insulin regimen, particularly when she starts continuous sc insulin infusion, be undertaken well in advance of withdrawing contraceptive measures or otherwise trying to conceive to allow the patient to acquire expertise in, and the optimization of, the chosen insulin regimen. (Ungraded recommendation)

1.3c. We suggest that insulin-treated women with diabetes seeking to conceive be treated with rapid-acting insulin analog therapy (with insulin aspart or insulin lispro) in preference to regular (soluble) insulin. (2 | ⊕⊕○○)

1.3d. We suggest that women with diabetes successfully using the long-acting insulin analogs insulin detemir or insulin glargine preconceptionally may continue with this therapy before and then during pregnancy. (2 | ⊕⊕○○)

1.3a–d. Evidence

Rapid-acting insulin analogs are likely more able than regular human insulin to help a woman achieve postprandial blood glucose targets and are less likely to cause hypoglycemia; fetal outcomes, however, seem comparable (28–30). Compared with NPH insulin, use of the long-acting insulin analogs insulin detemir or insulin glargine is associated with lower rates of nocturnal hypoglycemia (31–32). Insulin detemir, but not insulin glargine, is approved for use by the U.S. Food and Drug Administration (FDA) during pregnancy. Both of these long-acting insulin analogs, however, are widely used in pregnancy, with evidence of safety in this setting (33–37). Long-acting insulin analogs are, however, more expensive than NPH insulin.

1.3a–d. Remarks

The issues of insulin glargine not being FDA-approved for use during pregnancy and glargine's theoretical

mitogenicity should be discussed preconceptionally with women with diabetes who are using insulin glargine. When appropriate, insulin glargine may be replaced by insulin detemir or NPH insulin. Glulisine is not yet proven safe for use during pregnancy (studies are ongoing) and is not currently FDA-approved for this indication; as such, insulin aspart and lispro (both of which have been found to be safe in pregnancy and are FDA-approved) are preferred. For additional remarks, please refer to Remarks 5.1a–b.

Folic acid supplementation

1.4. We recommend that beginning 3 months before withdrawing contraceptive measures or otherwise trying to conceive, a woman with diabetes take a daily folic acid supplement to reduce the risk of neural tube defects. (1 | ⊕⊕○○) We suggest a daily dose of 5 mg based on this dose's theoretical benefits. (2 | ⊕⊕○○)

1.4. Evidence

Taking a daily folic acid supplement preconceptionally reduces the risk of neural tube defects (38). The optimal amount of folate that should be taken is uncertain, but 5 mg/d has a good rationale (38).

Ocular care (preconception, during pregnancy, and postpartum)

1.5a. We recommend that all women with diabetes who are seeking pregnancy have a detailed ocular assessment by a suitably trained and qualified eye care professional in advance of withdrawing contraceptive measures or otherwise trying to conceive (1 | ⊕⊕⊕⊕), and if retinopathy is documented, the patient should be apprised of the specific risks to her of this worsening during pregnancy. If the degree of retinopathy warrants therapy, we recommend deferring conception until the retinopathy has been treated and found to have stabilized. (1 | ⊕⊕⊕⊕)

1.5b. We recommend that women with established retinopathy be seen by their eye specialist every trimester, then within 3 months of delivering, and then as needed. (1 | ⊕⊕○○)

1.5c. We suggest that pregnant women with diabetes not known to have retinopathy have ocular assessment performed soon after conception and then periodically as indicated during pregnancy. (2 | ⊕⊕○○)

1.5a–c. Evidence

Established retinopathy can rapidly progress during, and up to 1 year after, pregnancy and can lead to sight-threatening deterioration (38–42). The greater the degree of preconceptional retinopathy, the greater is the risk of retinopathy progressing during pregnancy (40). The absence of retinopathy before conception confers very small risk of development of significant retinopathy during pregnancy; nonetheless, significant retinopathy can develop and progress during pregnancy, even if not identified preconceptionally (40). Additional risk factors for progression of retinopathy during pregnancy include preexisting hypertension (43), poorly controlled hypertension during pregnancy (44), preeclampsia (45), and poor glycemic control at the onset of and during pregnancy (41).

Renal function (preconception and during pregnancy)

1.6a. We suggest that all women with diabetes considering pregnancy have their renal function assessed (by measuring their urine albumin to creatinine ratio, serum creatinine, and estimated GFR) in advance of withdrawing contraceptive measures or otherwise trying to conceive. (Ungraded recommendation) We suggest that a woman with diabetes who has a significantly reduced GFR be assessed by a nephrologist before pregnancy, both for baseline renal assessment and to review the woman's specific risk of worsening renal function in the event of pregnancy. (Ungraded recommendation)

1.6b. We suggest that all women with diabetes and preconceptional renal dysfunction have their renal function monitored regularly during pregnancy. (Ungraded recommendation)

1.6a–b. Evidence

Renal dysfunction in a pregnant woman with type 1 diabetes is associated with an increased risk of adverse

maternal and fetal outcomes, including an increased risk of preeclampsia (46–48). Mild preconceptional renal dysfunction manifesting only as microalbuminuria may worsen during pregnancy with greater amounts of proteinuria (47); however, the degree of worsening is typically both modest and reversible once pregnancy is completed so long as BP and blood glucose remain well controlled during the pregnancy (48). More severe preconceptional renal dysfunction, as evidenced by a reduced GFR and elevated serum creatinine, can significantly deteriorate during pregnancy and may not be reversible (42, 50–51).

Management of hypertension

1.7a. We recommend that satisfactory BP control (<130/80 mm Hg) be achieved and maintained before withdrawing contraception or otherwise trying to conceive. (1 | ⊕⊕○○)

1.7b. We recommend that a woman with diabetes who is seeking conception while taking an ACE inhibitor or angiotensin-receptor blocker in almost all cases should discontinue the medication before withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕⊕○○)

1.7c. We suggest that in the exceptional case where the degree of renal dysfunction is severe and there is uncertainty about when conception will occur, physicians and patients be engaged in shared decision-making about whether to continue ACE inhibitors or angiotensin-receptor blockers. The patients should be informed about the possible loss of the renal protective properties if the medication is discontinued and the risk of teratogenesis if it is continued. (Ungraded recommendation)

1.7d. We recommend that when ACE inhibitors or angiotensin-receptor blockers have been continued up to the time of conception that the medication should be withdrawn immediately upon the confirmation of pregnancy. (1 | ⊕⊕○○)

1.7a–d. Evidence

ACE inhibitors (52–53) and angiotensin-receptor blockers (53–54) are teratogenic (55). This is most

proven for use of these drugs during the second and third trimesters (55). Hypertension in a preconceptual woman increases the risk of adverse outcomes during pregnancy, especially her risk of developing preeclampsia (56).

1.7a–d. Remarks

Safe and effective alternatives to ACE inhibitors and angiotensin-receptor blockers for treating hypertension during pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin (57).

Elevated vascular risk

1.8a. We recommend that if a woman with diabetes has sufficient numbers of vascular risk factors (particularly the duration of the woman's diabetes and her age), screening studies for CAD be undertaken in advance of withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕○○○)

1.8b. We recommend that if a woman with diabetes is seeking pregnancy and has CAD, its severity should be ascertained, treatment instituted, and counseling provided as to the potential risks of pregnancy to the woman and fetus before the woman withdraws contraception or otherwise tries to conceive. (1 | ⊕⊕⊕⊕)

1.8a–b. Evidence

Myocardial infarction during pregnancy is associated with adverse maternal and fetal outcomes including maternal and fetal demise (58–59). More recent evidence indicates that the prognosis has improved compared with older studies; however, high maternal (11%) and fetal (9%) mortality rates continue to be observed (60).

Management of dyslipidemia

1.9a. We recommend against the use of statins in women with diabetes who are attempting to conceive. (1 | ⊕⊕○○)

1.9b. In view of their unproven safety during pregnancy, we suggest against the routine use of fibrates and/or niacin for women with diabetes and

hypertriglyceridemia attempting to conceive. (2 | ⊕⊕○○)

1.9c. We suggest that bile acid-binding resins may be used in women with diabetes to treat hypercholesterolemia; however, this is seldom warranted. (2 | ⊕⊕○○)

1.9a–c. Evidence

Dyslipidemia, if not treated pharmacologically, seldom poses a threat to the health of a woman with diabetes during the comparatively short duration of pregnancy and, typically, the relatively few months leading up to conception. Also, there is uncertain safety of statins during pregnancy (61–62).

Thyroid function

1.10. For women with type 1 diabetes seeking conception, we recommend measurement of serum TSH and, if their thyroid peroxidase status is unknown, measurement of thyroid peroxidase antibodies before withdrawing contraceptive measures or otherwise trying to conceive. (1 | ⊕○○○)

1.10. Evidence

Autoimmune thyroid disease is common among women of childbearing age with type 1 diabetes with prevalence rates as high as 44% (63). Hypothyroidism is common among individuals with type 1 diabetes (64). Untreated or insufficiently treated hypothyroidism reduces fertility and, in the event of pregnancy, increases the risk of miscarriage and impaired fetal brain development (65–69).

Overweight and obesity

1.11. We recommend weight reduction before pregnancy for overweight and obese women with diabetes. (1 | ⊕⊕⊕○)

1.11. Evidence

Women who are overweight or obese before pregnancy are at an increased risk for complications during pregnancy (see Evidence 4.2a–b).

2.0. GESTATIONAL DIABETES

Testing for overt diabetes in early pregnancy

2.1. We recommend universal testing for diabetes (see Table 1) with a fasting plasma glucose, HbA1C, or an untimed random plasma glucose at the first prenatal visit (before 13 weeks gestation, or as soon as possible thereafter) for those women not known to already have diabetes. (1 | ⊕⊕○○) In the case of overt diabetes, but not gestational diabetes, a second test (either a fasting plasma glucose, untimed random plasma glucose, HbA1C, or OGTT) must be performed in the absence of symptoms of hyperglycemia and found to be abnormal on another day to confirm the diagnosis.

2.1. Evidence

As discussed in Section 1.0, pregnant women with overt diabetes and insufficient blood glucose control in early pregnancy are at increased risk of having a fetus with congenital anomalies and are at increased personal risk of worsening of diabetic retinopathy and nephropathy. Early diagnosis of previously undiscovered overt diabetes in a pregnant woman may allow for the rapid institution of therapy to mitigate these risks. A systematic review and meta-analysis (71) demonstrated that abnormal screening test results were associated with worse maternal and fetal outcomes. The quality of supporting evidence for screening, however, remains low because there are no randomized trials that compare a screening *vs.* no-screening strategy and measure patient-important outcomes.

2.1. Remarks

We acknowledge that with universal testing for diabetes in early pregnancy, there will be a high rate of false-positive results (71) and that women with positive testing may have anxiety and will suffer the burden of additional testing. Nevertheless, we recommended universal testing because we place the highest value on preventing fetal complications. The Task

Force assumed that these values and preferences would be consistent with those of most pregnant women.

Testing for gestational diabetes at 24 to 28 weeks gestation

2.2. We recommend that pregnant women not previously identified (either during testing performed as per recommendation 2.1 or at some other time before 24 weeks gestation) with overt diabetes or gestational diabetes be tested for gestational diabetes (see Table 2) by having a 2-hour, 75-g OGTT performed at 24 to 28 weeks gestation. (1 | ⊕⊕⊕○) We recommend that gestational diabetes be diagnosed on this test using the IADPSG criteria (majority opinion of this committee [see 2.2. Remarks below]). (1 | ⊕⊕⊕○)

The 75-g OGTT should be performed after an overnight fast of at least 8 hours (but not more than 14 hours) and without having reduced usual carbohydrate intake for the preceding several days. The test should be performed with the patient seated, and the patient should not smoke during the test. One or more abnormal values establishes the diagnosis, with the exception that in the case of overt diabetes, but not gestational diabetes, a second test (either a fasting plasma glucose, untimed random plasma glucose, HbA1C, or OGTT), in the absence of symptoms of hyperglycemia, must be performed and found to be abnormal on another day to confirm the diagnosis of overt diabetes.

2.2. Evidence

Pregnant women who develop gestational diabetes are at risk of adverse pregnancy outcomes, which may be prevented by adequate treatment (6, 72). The Hyperglycemia and Adverse Pregnancy Outcome study (6) and other studies (73–77) have confirmed continuous graded relationships between higher maternal glucose and increasing frequency of birth weight above the 90th percentile, primary cesarean section, neonatal hypoglycemia, and elevated cord C-peptide level (a surrogate marker for fetal hyperinsulinemia) as well as an increased risk for preeclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia, and neonatal intensive care admission.

The Task Force commissioned a systematic review (71) to assess the yield, utility, and benefits of previously employed screening tests for gestational diabetes. The review identified 39 original studies enrolling 87,830 women. None of the studies directly compared the maternal and fetal outcomes of women who received screening *vs.* women who did not receive screening. The studies, however, described a statistically significant correlation between a positive screening test and the development of macrosomia and gestational hypertension. The yield and diagnostic accuracy of screening tests were, overall, modest in predicting future development of gestational diabetes and clearly correlated with established risk factors. The overall quality of this evidence was considered low. Nevertheless, the Task Force made several assumptions about patients' values and preferences, including that patients will be more interested in preventing pregnancy complications and would likely place lower values on the burdens and costs of screening.

2.2. Remarks

The current definition of gestational diabetes (“any degree of glucose intolerance with onset or first definition during pregnancy”) includes pregnant patients who have a marked degree of hyperglycemia consistent with previously undiagnosed overt diabetes. To exclude from the definition of gestational diabetes those women with overt diabetes, most of our committee supports redefining gestational diabetes as defined in the Hyperglycemia and Adverse Pregnancy Outcome study; that is, gestational diabetes is “the condition associated with degrees of maternal hyperglycemia less severe than those found in overt diabetes but associated with an increased risk of adverse pregnancy outcomes” (6).

Based on the preceding evidence (Evidence 2.2) and the analysis thereof, this committee reached a majority opinion recommending screening using the protocol and threshold values as established by the consensus panel of the IADPSG (70). The reader is referred to the IADPSG recommendations on the diagnosis and classification of hyperglycemia in pregnancy for further reading on this subject (70).

Our recommendation, although in agreement with the recommendations of the IADPSG and American Diabetes Association (57, 70), differs materially from the recommendation of other organizations including the American College of Obstetricians and Gynecologists (78) and the National Institutes of Health (79). It is acknowledged that this is an arguable and controversial recommendation; indeed, our committee failed to establish unanimity on advocating for this recommendation. It is recognized that implementation of the IADPSG criteria will lead to a substantial increase in the numbers of pregnant women being diagnosed with gestational diabetes with the attendant medicalization of pregnancies and with a concomitant increase in healthcare costs both to individuals and to society. Nonetheless, for those reasons as outlined above, most of this committee has concluded that, pending further evidence, adopting the IADPSG criteria is warranted.

Management of elevated blood glucose

2.3a. We recommend that women with gestational diabetes target blood glucose levels as close to normal as possible. (1 | ⊕⊕○○)

2.3b. We recommend that the initial treatment of gestational diabetes should consist of medical nutrition therapy (see Section 4.0) and daily moderate exercise for 30 minutes or more. (1 | ⊕⊕⊕○)

2.3c. We recommend using blood glucose-lowering pharmacological therapy if lifestyle therapy is insufficient to maintain normoglycemia in women with gestational diabetes. (1 | ⊕⊕⊕⊕)

2.3a–c. Evidence

Plasma glucose acts as a continuous variable in exerting its effects on the fetus (6, 80). Even mild hyperglycemia alters the normal metabolic adaptation to pregnancy (81–82), and correction of maternal hyperglycemia reduces or prevents adverse outcomes (83).

Lifestyle therapy for gestational diabetes results in a lower incidence of reduced birth weight, large-for-gestational-age births, and preeclampsia (72, 83).

Both aerobic exercise (84–87) and non-weight-bearing exercise (88) have been shown to lower blood glucose levels in women with gestational diabetes.

Blood glucose-lowering pharmacological therapy is effective at improving outcomes in women with gestational diabetes whose hyperglycemia does not respond sufficiently to lifestyle therapy (72, 83, 89–91). See Section 5.0 for a discussion on blood glucose-lowering pharmacological therapy during pregnancy.

Postpartum care

2.4a. We recommend that postpartum care for women who have had gestational diabetes should include measurement of fasting plasma glucose or fasting self-monitored blood glucose for 24 to 72 hours after delivery to rule out ongoing hyperglycemia. (1 | ⊕○○○)

2.4b. We recommend that a 2-hour, 75-g OGTT should be undertaken 6 to 12 weeks after delivery in women with gestational diabetes to rule out prediabetes or diabetes. (1 | ⊕⊕⊕○) If results are normal, we recommend this or other diagnostic tests for diabetes should be repeated periodically as well as before future pregnancies. (1 | ⊕⊕○○)

2.4c. We suggest the child's birth weight and whether or not the child was born to a mother with gestational diabetes become part of the child's permanent medical record. (Ungraded recommendation)

2.4d. We recommend that all women who have had gestational diabetes receive counseling on lifestyle measures to reduce the risk of type 2 diabetes, the need for future pregnancies to be planned, and the need for regular diabetes screening, especially before any future pregnancies. (1 | ⊕○○○)

2.4e. We suggest blood glucose-lowering medication should be discontinued immediately after delivery for women with gestational diabetes unless overt diabetes is suspected in which case the decision to continue such medication should be made on a case-by-case basis. (2 | ⊕⊕○○)

2.4a–e. Evidence

Women who have had gestational diabetes are at high risk for the later development of impaired fasting glucose, impaired glucose tolerance, overt diabetes (92–94), and the metabolic syndrome (92, 95–107). Infants born to mothers with gestational diabetes are at increased risk of the later development of obesity or type 2 diabetes (108).

2.4a–e. Remarks

Blood glucose-lowering medication is not indicated for women with gestational diabetes after delivery and should be discontinued unless overt diabetes is suspected with accompanying hyperglycemia of a degree unlikely to respond sufficiently to lifestyle therapy alone.

3.0. GLUCOSE MONITORING AND GLYCEMIC TARGETS

Self-monitoring of blood glucose

3.1. We recommend self-monitoring of blood glucose in all pregnant women with gestational or overt diabetes (1 | ⊕⊕⊕⊕) and suggest testing before and either 1 or 2 hours after the start of each meal (choosing the postmeal time when it is estimated that peak postprandial blood glucose is most likely to occur) and, as indicated, at bedtime and during the night. (2 | ⊕⊕○○)

Glycemic targets

3.2a. We recommend pregnant women with overt or gestational diabetes strive to achieve a target preprandial blood glucose ≤ 95 mg/dL (5.3 mmol/L) (Table 3). (1 | ⊕⊕○○) for fasting target, 1 | ⊕○○○) for other meals)

3.2b. We suggest that an even lower fasting blood glucose target of ≤ 90 mg/dL (5.0 mmol/L) be strived for (2 | ⊕○○○) if this can be safely achieved without undue hypoglycemia.

3.2c. We suggest pregnant women with overt or gestational diabetes strive to achieve target blood glucose levels 1 hour after the start of a meal ≤ 140 mg/dL (7.8 mmol/L) and 2 hours after the start of a meal ≤ 120 mg/dL (6.7 mmol/L) (2 | $\oplus\oplus\oplus\oplus$) when these targets can be safely achieved without undue hypoglycemia.

3.2d. We suggest pregnant women with overt diabetes strive to achieve an HbA1C $\leq 7\%$ (ideally $\leq 6.5\%$). (2 | $\oplus\oplus\oplus\oplus$)

Continuous glucose monitoring

3.3. We suggest that continuous glucose monitoring be used during pregnancy in women with overt or gestational diabetes when self-monitored blood glucose levels (or, in the case of the woman with overt diabetes, HbA1C values) are not sufficient to assess glycemic control (including both hyperglycemia and hypoglycemia). (2 | $\oplus\oplus\oplus\oplus$)

3.1.–3.3. Evidence

The Task Force commissioned a systematic review (109) to evaluate the association between different blood glucose targets achieved during pregnancy and maternal and fetal outcomes of women with gestational or overt diabetes. The review identified 34 original studies enrolling 9,433 women (15 randomized controlled trials, 18 cohort studies, and 1 case-control study). Meta-regression results demonstrated that a cutoff point of 90 mg/dL (5.0 mmol/L) for fasting plasma glucose was associated with the most reduction in the risk of macrosomia (odds ratio = 0.53, 95% confidence interval = 0.31–0.90, $P = .02$). This effect was mainly demonstrated in women with gestational diabetes during the third trimester. A cutoff point of <90 mg/dL (5.0 mmol/L) for preprandial value with other meals was associated with a similar reduction in risk but it did not reach statistical significance, likely due to the smaller sample size of that subgroup (odds ratio = 0.69, 95% confidence interval = 0.17–2.94, $P = .58$). Data in women with type 1 and type 2 diabetes and for postprandial targets were sparse. The analysis controlled for study intervention, diabetes type, and trimester but was unable to control for maternal body mass index (BMI). The

analysis was associated with significant heterogeneity. The overall quality of this evidence was low. The Task Force considered the putative benefits of tight blood glucose control and possible risk of hypoglycemia, as well as patients' values and preferences in that they would likely be most averse to possible pregnancy complications. Therefore, the Task Force recommended a target preprandial glucose of ≤ 95 mg/dL (5.3 mmol/L) and suggested a lower preprandial glucose of ≤ 90 mg/dL (5.0 mmol/L) when this can be achieved without undue hypoglycemia. The Task Force also suggested (rather than recommended) postprandial targets, considering that postprandial targets, compared with preprandial targets, are supported by relatively lower quality evidence.

Pregnant women with type 1 diabetes are at increased risk of hypoglycemia including severe hypoglycemia, especially during the first trimester (21–25). There is also an increased risk of hypoglycemia in pregnant women with type 2 diabetes (26). Maternal hypoglycemia has not been proven to be deleterious to the fetus and in particular has not been found to be associated with an increased risk of congenital anomalies (27).

Although there is a paucity of literature on continuous glucose monitoring use during pregnancy, there is evidence that in gestational diabetes, it will detect clinically meaningful hypoglycemia and postprandial hyperglycemia that may go unrecognized by self-monitoring of blood glucose (110–111). There is also some evidence of improved HbA1C in women with overt diabetes using continuous glucose monitoring during pregnancy (112). The cost-effectiveness of continuous glucose monitoring is not yet established.

3.1.–3.3. Remarks

The recommendation regarding measuring blood glucose at certain specific times after the start of a meal allows for consistency in testing across different cultural and personal eating preferences and also takes into consideration the first phase of insulin secretion. Routine testing for the presence of urine (or blood) ketones is not warranted during pregnancy except for those pregnant women with overt diabetes

(particularly those women with type 1 diabetes) in the setting of suspected incipient or overt diabetic ketoacidosis.

There are some data to suggest that increased fetal abdominal circumference, as detected on ultrasound, may be used to help determine whether insulin should be introduced in women with gestational diabetes (113–114). We feel that at present, these data are insufficient to warrant routine use of this parameter in determining the optimal timing for, or need for, introducing insulin or other antihyperglycemic medication in women with gestational diabetes.

4.0. NUTRITION THERAPY AND WEIGHT GAIN TARGETS FOR WOMEN WITH OVERT OR GESTATIONAL DIABETES

Nutrition therapy

4.1. We recommend medical nutrition therapy for all pregnant women with overt or gestational diabetes to help achieve and maintain desired glycemic control while providing essential nutrient requirements. (1 | ⊕⊕○○)

4.1. Evidence

Although nutrition intervention for overt diabetes and gestational diabetes is a fundamental treatment modality (115–119), there is a paucity of evidence-based data on this topic. Nevertheless, nutrition therapy has been shown to improve glycemic control for people living with overt diabetes (120–121) and for women with gestational diabetes (122).

4.1. Remarks

Medical nutrition therapy, defined as “a carbohydrate-controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycemia and the absence of ketosis” (123), is an individualized

nutrition program, adjusted as needed as pregnancy progresses. It emphasizes healthy food choices, portion control, and good cooking practices while taking into account personal and cultural eating preferences, prepregnancy BMI, desired body weight, physical activity, and blood glucose levels and targets.

Weight management

4.2a. We suggest that women with overt or gestational diabetes follow the Institute of Medicine revised guidelines for weight gain during pregnancy (1) (Table 4). (Ungraded recommendation)

4.2b. We suggest obese women with overt or gestational diabetes reduce their calorie intake by approximately one-third (compared with their usual intake before pregnancy) while maintaining a minimum intake of 1600 to 1800 kcal/d. (2 | ⊕⊕○○)

4.2a–b. Evidence

In the absence of definitive evidence regarding optimal weight gain for women with gestational or overt diabetes—and with evidence both that women who gain excess weight during pregnancy may retain it after childbirth (124) and that women who are overweight or obese before pregnancy are at an increased risk for complications during pregnancy (including hypertensive complications, stillbirth, and increased risk for cesarean section) (125–128)—and with the reassurance that limiting maternal weight gain is not associated with a decrease in fetal birth weight (129), we conclude that following the Institute of Medicine recommendations for weight gain during pregnancy, although not written specifically for women with overt or gestational diabetes, is nonetheless appropriate for women with these conditions (Table 4) (130).

Moderate energy restriction (1600–1800 kcal/d) in pregnant women with overt diabetes improves mean glycemia and fasting insulinemia without inhibiting fetal growth or birth weight or inducing ketosis (129). Energy intake of approximately 2050 kcal in all BMI categories in women with gestational diabetes has been reported to limit maternal weight gain, maintain euglycemia, avoid ketonuria, and maintain an average birth weight of 3542 g (131).

4.2a–b. Remarks

Successful pregnancy outcomes have been reported within a wide range of calorie intakes ranging from 1500 to 2800 kcal/d (129, 131–135); however, most studies have been small and uncontrolled and relied on self-reported dietary intake. Severe calorie restriction (<1500 kcal/d, or 50% reduction from prepregnancy), however, is to be avoided because there is evidence, at least in pregnant women with type 1 diabetes, that this degree of calorie restriction increases ketosis, which has been linked to impaired fetal brain development (134). Moderate calorie restriction (1600–1800 kcal/d, 33% reduction) does not lead to significant ketosis (136–137) and is appropriate for overweight or obese women with overt or gestational diabetes. Calorie restriction is not warranted for underweight or normal-weight women with these conditions so long as fetal growth and weight gain targets are being met.

Carbohydrate intake

4.3. We suggest women with overt or gestational diabetes limit carbohydrate intake to 35% to 45% of total calories, distributed in 3 small- to moderate-sized meals and 2 to 4 snacks including an evening snack. (2 | ⊕⊕○○)

4.3. Evidence

There is no definitive evidence for the optimal proportion of carbohydrate in the diet of women with overt or gestational diabetes; values from 40% to 45% of energy intake (138) to 60% (if the carbohydrate is from complex sources) (139) have been recommended. Some authorities suggest that a minimum of 175 g/d carbohydrate should be provided, which is higher than the 130 g/d recommended for nonpregnant women (1). Nonetheless, restricting the total amount of carbohydrate ingested may assist with glycemic control as may distributing carbohydrates over several meals and snacks, manipulating the types of carbohydrate consumed, and choosing low-glycemic-index foods (140–141). No interventional studies, however, have been conducted using the glycemic index in pregnant women with diabetes.

Nutritional supplements

4.4. We recommend pregnant women with overt or gestational diabetes should follow the same guidelines for the intake of minerals and vitamins as for women without diabetes (1 | ⊕⊕○○), with the exception of taking folic acid 5 mg daily beginning 3 months before withdrawing contraceptive measures or otherwise trying to conceive (see Recommendation 1.4). We suggest that at 12 weeks gestation, the dose of folic acid be reduced to 0.4 to 1.0 mg/d, which should be continued until the completion of breastfeeding (2 | ⊕⊕○○).

4.4. Evidence

There is no indication that pregnant women with overt or gestational diabetes should not follow the same guidelines for nutrient intakes that are indicated for all pregnant women, with the exception of folic acid supplementation for which there is theoretical benefit to be achieved by taking higher than usual doses (see Evidence 1.4).

5.0. BLOOD GLUCOSE- LOWERING PHARMACO- LOGICAL THERAPY DURING PREGNANCY

Insulin therapy

5.1a. We suggest that the long-acting insulin analog detemir may be initiated during pregnancy for those women who require basal insulin and for whom NPH insulin, in appropriate doses, has previously resulted in, or for whom it is thought NPH insulin may result in, problematic hypoglycemia; insulin detemir may be continued in those women with diabetes already successfully taking insulin detemir before pregnancy. (2 | ⊕⊕⊕⊕)

5.1b. We suggest that those pregnant women successfully using insulin glargine before pregnancy may continue it during pregnancy. (2 | ⊕⊕○○)

5.1c. We suggest that the rapid-acting insulin analogs lispro and aspart be used in preference to regular (soluble) insulin in pregnant women with diabetes. (2 | ⊕⊕⊕○)

5.1d. We recommend the ongoing use of continuous sc insulin infusion during pregnancy in women with diabetes when this has been initiated before pregnancy (1 | ⊕⊕⊕○) but suggest that continuous sc insulin infusion not be initiated during pregnancy unless other insulin strategies including multiple daily doses of insulin have first been tried and proven unsuccessful. (2 | ⊕⊕⊕○)

5.1a–b. Evidence

In nonpregnant women, insulin detemir is associated with less hypoglycemia than NPH insulin (142–144). Insulin detemir has not shown adverse maternal or neonatal effects (34, 145). Glargine use during pregnancy was not associated with unexpected adverse maternal or fetal outcomes in a large cohort study; however, the lack of a control group and the retrospective nature of this study limit the interpretation of the findings (33). Several retrospective cohort and case-control studies of pregnant women found that overall, the outcome with insulin glargine treatment was no different from, or was superior to, NPH insulin (35, 146–150).

5.1a–b. Remarks

Of the two available long-acting insulin analogs, detemir has a theoretical advantage over glargine during pregnancy because glargine's much higher affinity for the IGF-1 receptor (151) raises concerns about increased mitogenic activity (151–153). Nonetheless, glargine is unlikely to cross the placenta (36), animal studies have not shown glargine to be embryotoxic (154), and women treated with insulin glargine during the first trimester have a similar rate of congenital malformations as women treated with insulin NPH (33, 155–156). Insulin detemir is now approved (Category B) by the FDA for use during pregnancy, whereas insulin glargine does not currently have such approval.

Before instituting insulin glargine or detemir in a pregnant woman, the clinician should fully and frankly discuss their advantages and possible disadvantages compared with NPH therapy and, in the case of insulin glargine, its lack of FDA approval for use in pregnancy.

5.1c. Evidence

Compared with human regular (soluble) insulin, rapid-acting insulin used during pregnancy allows greater lifestyle flexibility, greater patient satisfaction, and improved quality of life (157) and may also provide better postprandial blood glucose control (158) and HbA1C reduction (159). Rapid-acting insulin is, however, more expensive than regular insulin. In most other respects, rapid-acting insulin and regular insulin are comparable during pregnancy (30, 159–163). Moreover, both are associated with similar rates of prematurity, cesarean delivery, worsening of retinopathy, hypertensive complications, rates of shoulder dystocia, admission to a neonatal intensive care unit, and neonatal hypoglycemia. Rapid-acting insulin does not increase the risk of teratogenicity (30, 158–159, 164–166).

5.1c. Remarks

We suggest glulisine not be used during pregnancy because it is not FDA-approved for use in pregnancy and does not offer a proven advantage over lispro or aspart.

5.1d. Evidence

Compared with multiple daily doses of insulin, continuous sc insulin infusion used during pregnancy in women with overt diabetes provides comparable or better (167–168) glycemic control and pregnancy outcomes (169–170) with no greater risk or possibly lower risk (171) of maternal hypoglycemia (172). Additionally, compared with multiple daily doses of insulin, continuous sc insulin infusion provides greater lifestyle flexibility, easier blood glucose management in women experiencing morning nausea, less blood glucose variability, and facilitates managing glucose control in the peridelivery setting (171). An increased

risk of maternal ketoacidosis and neonatal hypoglycemia has, however, been reported (173).

5.1d. Remarks

Owing to the potential risk of temporarily worsened blood glucose control, ketoacidosis, and hypoglycemia when continuous sc insulin infusion is initiated, its use during pregnancy should be limited to those patients already successfully using this method of insulin administration before pregnancy and to those women who, during pregnancy, have not succeeded with other insulin strategies including multiple daily doses of insulin.

Noninsulin antihyperglycemic agent therapy

5.2a. We suggest that glyburide (glibenclamide) is a suitable alternative to insulin therapy for glycemic control in women with gestational diabetes who fail to achieve sufficient glycemic control after a 1-week trial of medical nutrition therapy and exercise except for those women with a diagnosis of gestational diabetes before 25 weeks gestation and for those women with fasting plasma glucose levels >110 mg/dL (6.1 mmol/L), in which case insulin therapy is preferred. (2 | ⊕⊕○○)

5.2b. We suggest that metformin therapy be used for glycemic control only for those women with gestational diabetes who do not have satisfactory glycemic control despite medical nutrition therapy and who refuse or cannot use insulin or glyburide and are not in the first trimester. (2 | ⊕⊕○○)

5.2a. Evidence

In pregnant women taking glyburide, the umbilical cord glyburide concentration is undetectable (91, 174–177) or, at most, very low (178). Glyburide is effective in controlling blood glucose in women with gestational diabetes and has been associated with favorable neonatal outcomes including the rate of large-for-gestational-age infants, macrosomia, neonatal intensive care unit admission, and neonatal hypoglycemia (91). Although some evidence does exist of higher rates of macrosomia and large-for-gestational-age infants (177) in pregnant women

taking glyburide compared with women taking insulin, neonates had similar body composition, measures of glycemic control, and cord metabolic biomarkers. The safety of glyburide in pregnancy is also supported by a meta-analysis (179) of 6 randomized trials with overall good methodological quality, which found no significant differences in glycemic control, neonatal hypoglycemia, birth weight, or rate of large-for-gestational-age infants born to mothers taking oral agents (metformin or glyburide) vs. mothers taking insulin. Glyburide, however, has been found to be less likely to maintain satisfactory blood glucose control in women with gestational diabetes who have a fasting blood glucose >110 mg/dL (6.1 mmol/L) on a 100-g OGTT (180) or 50-g glucose challenge (181, 182), have had their gestational diabetes detected before 25 weeks gestation (183), have glyburide initiated after 30 weeks, have fasting plasma glucose ≥110 mg/dL (6.1 mmol/L) or 1-hour postprandial glucose ≥140 mg/dL (7.8 mmol/L) (184), or have pregnancy weight gain >12 kg (182).

5.2a. Remarks

Glyburide appears to be a safe and effective alternative to insulin in most women with gestational diabetes. Compared with insulin, glyburide may be more convenient, is less expensive (185), does not require intensive educational instruction at initiation of therapy, and is preferred by most patients (180, 184). Before instituting glyburide to treat gestational diabetes, the clinician should have a full and frank discussion with the pregnant woman regarding glyburide's possible advantages and disadvantages compared with insulin therapy and its lack of FDA approval for this indication. Unlike the case with glyburide use during pregnancy complicated by gestational diabetes, there are no randomized clinical trials regarding the use of noninsulin antihyperglycemic medications in pregnant women with type 2 diabetes. Most women with type 2 diabetes requiring blood glucose-lowering medications are treated with insulin in anticipation of, and then during, pregnancy.

5.2b. Evidence

Pregnancy outcomes in women exposed to metformin at the time of conception and during early pregnancy have been favorable (186–193). Compared with women with gestational diabetes taking insulin, those taking metformin have no difference in maternal glycemic control, significantly lower rates of neonatal hypoglycemia, and no increased risk of congenital anomalies or other serious maternal or neonatal adverse events. Although not shown to be deleterious to the fetus, metformin does cross freely through the placenta, with similar metformin concentrations in the fetal and maternal circulation (194–195), and long-term follow-up studies establishing safety are not yet available. Also, nearly half of women with gestational diabetes treated with metformin monotherapy have glycemic control failure rates requiring conversion to insulin therapy. Additionally, metformin-treated women with gestational diabetes have increased rates of preterm birth (90).

5.2b. Remarks

Compared with insulin therapy, metformin is typically more convenient and less expensive and is not associated with the risk of hypoglycemia. Nonetheless, certain concerns, as described, still preclude its routine use in the treatment of gestational diabetes.

Because data on the safety and efficacy of the use of other noninsulin antihyperglycemic medications (apart from those discussed above) during pregnancy, including the use of incretin-based therapies during pregnancy, are not yet available, we do not recommend their use in this setting.

6.0. LABOR, DELIVERY, LACTATION, AND POSTPARTUM CARE

Blood glucose targets during labor and delivery

6.1. We suggest target blood glucose levels of 72 to 126 mg/dL (4.0–7.0 mmol/L) during labor and delivery for pregnant women with overt or gestational diabetes. (2 | ⊕⊕○○)

6.1. Evidence

Elevated maternal blood glucose during labor and delivery increases the risk of neonatal hypoglycemia and fetal distress (196–201) as well as birth asphyxia and abnormal fetal heart rate (201–202), albeit with these associations having been mainly demonstrated in observational studies of women with type 1 diabetes.

6.1. Remarks

Because we did not determine there to be a single best way of maintaining target blood glucose levels during labor and delivery, we have not provided a recommendation regarding how this is to be achieved, instead leaving it to the discretion of the individual practitioner to implement their preferred management strategy.

Lactation

6.2a. We recommend whenever possible women with overt or gestational diabetes should breastfeed their infant. (1 | ⊕⊕⊕⊕)

6.2b. We recommend that breastfeeding women with overt diabetes successfully using metformin or glyburide therapy during pregnancy should continue to use these medications, when necessary, during breastfeeding. (1 | ⊕⊕⊕⊕)

6.2a–b. Evidence

The increased risk of infants born to women with diabetes for childhood obesity and the later development of impaired glucose intolerance and diabetes (82) is reduced by breastfeeding (203–212). Breastfeeding may also facilitate postpartum weight loss and reduce maternal and neonatal risk for the later development of type 2 diabetes (213–214).

The concentrations of metformin in breast milk are generally low, and the mean infant exposure to metformin has been reported in the range 0.28% to 1.08% of the weight-normalized maternal dose, well below the level of concern for breastfeeding (215). Metformin use by the breastfeeding woman *vs.* formula feeding appears to have no adverse effects on infant growth, motor-social development, and intercurrent illness during the first 6 months of life (216). Glyburide was not detected in breast milk, and hypoglycemia was not observed in nursing infants of women using glyburide (217). The exposure of infants to second-generation sulfonylureas (such as glipizide and glyburide) through breast milk is expected to be minimal, based on the limited data available. The benefits of breastfeeding greatly outweigh the risks of these medications, if any (218).

Postpartum contraception

6.3. We recommend that the choice of a contraceptive method for a woman with overt diabetes or a history of gestational diabetes should not be influenced by virtue of having overt diabetes or a history of gestational diabetes. (1 | ⊕⊕⊕○)

6.3. Evidence

Combined oral contraceptive use by women with type 1 diabetes does not affect their glycemic control or increase their risk of end-organ injury (219–221). Combined oral contraceptive use by women with a history of gestational diabetes does not increase the risk of later developing type 2 diabetes (222–225). Use of a contraceptive patch (226) or vaginal ring (227) exerts a similar metabolic effect to that of oral contraceptives. Compared with women without diabetes, women with diabetes using an intrauterine

device (copper or levonorgestrel-releasing) are not at increased risk of untoward effects (228–232). Progestin-only oral contraceptives do not affect blood glucose values or BP in women with type 1 diabetes (233–234); however, there is some limited evidence that these medications increase the risk for later developing type 2 diabetes in women who have had gestational diabetes (224, 235).

Screening for postpartum thyroiditis

6.4. We suggest women with type 1 diabetes be screened for postpartum thyroiditis with a TSH at 3 and 6 months postpartum. (2 | ⊕⊕○○)

6.4. Evidence

Postpartum thyroiditis is common in women who have type 1 diabetes (63, 236).

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Diabetes and Pregnancy:

An Endocrine Society Clinical Practice Guideline

CME Learning Objectives and Post-Test Questions

LEARNING OBJECTIVES

Upon completion of this educational activity, learners will be able to:

- Recognize the appropriate target level of glycemic control (as reflected by the HbA1C) for a woman with established diabetes before attempting to conceive.
- Evaluate self-monitored blood glucose target levels for a woman with gestational diabetes and the appropriate therapeutic intervention if these targets are being exceeded.
- Determine the appropriate frequency for ocular assessment for a pregnant woman with diabetes and known retinopathy.
- Select appropriate antihyperglycemic medication for a breastfeeding woman with type 2 diabetes.

CME Question #1

A 25-year-old woman with a 5-year history of type 1 diabetes advises you she would like to try to conceive as soon as possible. Her current haemoglobin A1C (HbA1C) is 8.5 percent.

What advice should you give her?

- A) She can safely proceed with trying to conceive.
- B) She should defer trying to conceive until her HbA1C is <6 percent.
- C) She should defer trying to conceive until her HbA1C is as close to normal as possible when this can be safely achieved.
- D) She should begin using continuous glucose monitoring.

CME Question #2

A 30-year-old woman is 24 weeks pregnant and is diagnosed with gestational diabetes. After 1 week of medical nutrition therapy and exercise her self-monitored blood glucose (SMBG) levels are averaging 100 mg/dl (5.6 mmol/L) before meals and 130 mg/dl (7.2 mmol/L) 2 hours after meals.

What is the preferred next step in managing this patient?

- A) Make no change to her current therapy as her SMBG values are within target.
- B) Recommend she start glyburide.
- C) Recommend she start metformin.
- D) Recommend she start insulin therapy.

CME Question #3

A 29-year-old woman with type 1 diabetes and hypertension is newly pregnant. She has known, stable retinopathy. Her HbA1C is 6.5 percent. Her blood pressure is 125/85.

What advice should you give her regarding her retinopathy?

- A) Tell her that her retinopathy can worsen during pregnancy and arrange for regular eye exams during the pregnancy.
- B) Tell her that as her retinopathy is stable it is unlikely to progress during the pregnancy.
- C) Advise her of the great dangers to her vision if she continues the pregnancy and recommend she terminate the pregnancy.
- D) Recommend she see an eye care professional in the near future then again after she has delivered.

CME Question #4

A 32-year-old woman with type 2 diabetes being treated with glyburide has just delivered a healthy infant at term. She will be breastfeeding the baby.

What should you recommend for this woman?

- A) She should discontinue the glyburide and take insulin instead.
- B) She should continue the glyburide.
- C) She should not breastfeed the infant.
- D) She should discontinue the glyburide and take metformin instead.

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Diabetes and Pregnancy:

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CME Answers and Explanations

CME Question #1

Correct answer: C, A woman with overt diabetes should defer trying to conceive until her HbA1C is as close to normal as possible when this can be safely achieved.

Discussion: Maternal hyperglycemia in the first few weeks of pregnancy increases the risk of fetal mal-formations, spontaneous abortions, and perinatal mortality. Although the exact degree of risk of a congenital anomaly for a given HbA1C is not precisely known, it has been reported that the risk progressively rises in concert with the degree of periconceptual HbA1C elevation. A limiting factor, however, in striving to achieve an optimal HbA1C is the occurrence of hypoglycemia.

CME Question #2

Correct answer: D, Recommend she start insulin therapy.

Discussion: Target SMBG values for a woman with gestational (or overt) diabetes are equal to or less than 95 mg/dl (5.3 mmol/L) before meals (equal to or less than 90 mg/dl (5.0 mmol/L) fasting *if this can be safely achieved*); equal to or less than 140 mg/dl (7.8 mmol/L) one hour after the start of a meal; equal to or less than 120 mg/dl (6.7 mmol/L) two hours after the start of a meal. Elevated blood glucose in a pregnant woman is associated with an increased risk of harm to the fetus. Insulin therapy is the preferred blood glucose-lowering medication in women diagnosed with gestational diabetes prior to 25 weeks' gestation.

CME Question #3

Correct answer: A, Tell her that her retinopathy can worsen during the pregnancy and arrange for regular eye exams during the pregnancy.

Discussion: Established retinopathy can rapidly progress during—and up to one year after—pregnancy and can lead to sight-threatening deterioration. The greater the degree of preconceptual retinopathy, the greater is the risk of retinopathy progressing during pregnancy. Additional risk factors for progression of retinopathy during pregnancy include pre-existing hypertension, poorly controlled hypertension during pregnancy, preeclampsia, and poor glycemic control at the onset of and during pregnancy. Pregnant women with established retinopathy should be seen by their eye specialist every trimester, then within three months of delivering, then as needed.

CME Question #4

Correct answer: B, She should continue the glyburide.

Discussion: Glyburide is not found in significant quantities in breast milk and is not associated with hypoglycemia in nursing infants. Metformin can also be safely taken by breast feeding women.

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