Managing Preexisting Diabetes for Pregnancy

Summary of evidence and consensus recommendations for care

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This document presents consensus panel recommendations for the medical care of pregnant women with preexisting diabetes, including type 1 and type 2 diabetes. The intent is to help clinicians deal with the broad spectrum of problems that arise in management of diabetes before and during pregnancy, and to prepare diabetic women for treatment that may reduce complications in the years after pregnancy. A thorough discussion of the evidence supporting the recommendations is presented in the book, *Management of Preexisting Diabetes and Pregnancy*, authored by the consensus panel and published by the American Diabetes Association (ADA) in 2008 (1). A consensus statement on obstetrical and postpartum management will appear separately.

The recommendations are diagnostic and therapeutic actions that are known or believed to favorably affect maternal and perinatal outcomes in pregnancies complicated by diabetes. The grading system adapted by the ADA was used to clarify and codify the evidence that forms the basis for the recommendations (2). Unfortunately there is a paucity of randomized controlled trials (RCTs) of the different aspects of management of diabetes and pregnancy. Therefore our recommendations are often based on trials conducted in nonpregnant diabetic women or nondiabetic pregnant women, as well as on peer-reviewed experience before and during pregnancy in women with preexisting diabetes (3–4). We also reviewed and adapted existing diabetes and pregnancy guidelines (5–10) and guidelines on diabetes complications and comorbidities (2,3,11–14).

I. MANAGING PREEXISTING DIABETES FOR PREGNANCY

A. Organization of preconception and pregnancy care

Recommendations

- Women with diabetes and childbearing potential should be educated about the need for good glucose control before pregnancy and should participate in effective family planning. (E)
- Whenever possible, organize multidiscipline patient-centered team care for women with preexisting diabetes in preparation for pregnancy. (B)
- Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic nephropathy, neuropathy, and retinopathy, as well as cardiovascular disease (CVD), hypertension, dyslipidemia, depression, and thyroid disease. (E)
- Medication use should be evaluated before conception, since drugs commonly used to treat diabetes and its complications may be contraindicated or not recommended in pregnancy, including statins, ACE inhibitors, angiotensin II receptor blockers (ARBs), and most noninsulin therapies. (E)
- Continue multidiscipline patient-centered team care throughout pregnancy and postpartum. (E)
- Regular follow-up visits are important

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A complete list of relationships disclosed by the authors that could be construed as representing potential conflicts of interest is provided in Table 3.

Abbreviations: ACR, albumin-to-creatinine ratio; ADA, American Diabetes Association; ARB, angiotensin II receptor blocker; CAN, cardiac autonomic neuropathy; CHD, coronary heart disease; CrCl, creatinine clearance; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; DPN, distal polyneuropathy; ECG, electrocardiogram; GFR, glomeruler filtration rate; IOM, Institute of Medicine; MNT, medical nutrition therapy; NPDR, nonproliferative diabetic retinopathy; PAD, peripheral arterial disease; PDR, proliferative diabetic retinopathy; RCT, randomized controlled trial; SMBP, self-monitoring of blood glucose; UAE, urinary albumin excretion.

DOI: 10.2337/dc08-9020

for adjustments in the treatment plan related to stage of pregnancy, glycemic and blood pressure control, weight gain, and individual patient needs. (E)
- Educate pregnant diabetic women about the strong benefits of *1*) long-term CVD risk factor reduction, *2*) breastfeeding, and *3*) effective family planning with good glycemic control before the next pregnancy. (E)

Pregnancy profoundly affects the management of diabetes (15–18). Placental hormones, growth factors, and cytokines cause a progressive increase in insulin resistance, necessitating intensive medical nutrition therapy and frequently adjusted insulin administration to prevent hyperglycemia dangerous to the fetus. Insulin resistance enhances the risk of ketoacidosis in response to the stress of concurrent illnesses or drugs used in the management of obstetrical complications. Insulin-induced hypoglycemia is more rapid in onset during pregnancy and a danger to the gravida, especially in patients with type 1 diabetes. Women with type 2 diabetes often start pregnancy with marked insulin resistance and obesity, adding to the difficulty of securing optimal glycemic control.

These challenges led to the development of multidisciplinary programs at centers of excellence that greatly reduced maternal, fetal, and neonatal complications. However, population-based data continue to show excess rates of congenital malformations and perinatal morbidity and mortality (1). Extended efforts are necessary for better access to quality prenatal care and improved glycemic control throughout pregnancy in patients with diabetes (4,19–27). Models of care with a responsible patient at the center of the management team (2,28–31) have had the best success. The book, *Management of Preexisting Diabetes and Pregnancy* (1), contains a full discussion of the roles of the different clinicians in multidisciplinary diabetes and pregnancy programs.

It is important to incorporate components of care designed to benefit long-term maternal health with special reference to CVD and diabetic microvascular and neurologic complications. Fortunately there is evidence that pregnancy is not an independent risk factor for long-term progression of microvascular complications (32–35). However, we need more data on the influence of glucose, blood pressure, lipids, albuminuria, oxidative stress, and inflammation during pregnancy on the long-term risk of CVD. Clinicians can take advantage of the heightened motivation of pregnant diabetic women to teach behaviors and self-management skills that are expected to control CVD risk factors. For optimal long-term outcomes, we need to find ways to foster seamless continuation of intensified management in the years after pregnancy and in preparation for the next desired conception.

Initial evaluation

Recommendations for review of patient history and physical examination.

At the onset of preconception care, or in its absence, early in pregnancy, a complete medical evaluation should be performed to:
- classify the patient and detect the presence of diabetic, cardiovascular, thyroid, or obstetrical complications
- review history of eating patterns, physical activity/exercise, and psychosocial problems
- counsel the patient on prognosis
- set expectations for patient participation
- assist in formulating a management plan with team care members
- provide a basis for continuing care and laboratory tests

The evaluation should review the history of prior pregnancies and comorbidities such as dyslipidemias and other cardiac risk factors, hypertension, albuminuria, variant symptoms of cardiac ischemia or failure, and peripheral vascular disease, symptoms of neuropathies, hypoglycemia awareness and severe hypoglycemic episodes, bowel symptoms, celiac disease, thyroid disorders, and infectious diseases, as well as previous diabetes education, treatment, and past and present degrees of glycemic control.

In addition to appropriate obstetrical examination, physical examination should include sitting blood pressure determination (11), orthostatic heart rate and blood pressure responses when indicated (36); thyroid palpation; auscultation for carotid and femoral bruits, palpation of dorsalis pedis and posterior tibial pulses; presence/absence of Achilles reflexes and determination of vibration and monofilament sensation in the feet (37); and visual inspection of both feet.

Recommendations for laboratory tests appropriate to the evaluation of the patient's condition are listed in Table 1. Although some complications cannot be treated with optimal drugs during pregnancy, their identification allows for intensified management postpartum. All preconception or pregnant patients should be tested for A1C, lipid profile, iron status, thyroid status, steatosis, albuminuria, and diabetic retinopathy. Selected patients may need electrocardiogram (ECG) or echocardiography due to the risk of coronary heart disease (CHD) associated with age and duration of diabetes or symptomatology. Patients with type 1 diabetes without recent testing should be screened for vitamin B12 status and celiac disease due to the association with disease-producing autoimmunity. Patients with random urine albumin-to-creatinine ratio (ACR) at the upper end of normal for women (25–29 μg/mg) may benefit from a 24-h urine collection for microalbuminuria. Patients with proteinuria on dipstick should have a 24-h urine for total urinary protein and creatinine clearance (CrCl).

A focus on the components of comprehensive diabetes evaluation (Table 7 in Standards of Medical Care in Diabetes—2008 [2]) will assist the health care team to provide optimal management of the woman with preexisting diabetes in the preconception period and during pregnancy.

B. Glycemic control

1. Perinatal outcome and glycemic goals

Recommendations
- Before pregnancy, in order to prevent excess spontaneous abortions and major congenital malformations, target A1C is as close to normal as possible without significant hypoglycemia. (B)
- Ensure effective contraception until stable and acceptable glycemia is achieved. (E)
- Excellent glycemic control in the first trimester continued throughout pregnancy is associated with the lowest frequency of maternal, fetal, and neonatal complications. Develop or adjust the management plan to achieve near-normal glycemia, while minimizing significant hypoglycemia. (B)
- Throughout pregnancy, optimal glycemic goals are premeal, bedtime, and overnight glucose 60–99 mg/dl, peak postprandial glucose 100–129 mg/dl, mean daily glucose <110 mg/dl, and A1C <6.0. (B)
- Higher glucose targets may be used in patients with hypoglycemia unawareness or the inability to cope with intensified management. (E)

Table 1—*Laboratory and special exam components of the initial and subsequent evaluation of pregnant women with preexisting type 1 or type 2 diabetes (in addition to usual prenatal lab tests)*

Initial evaluation	Subsequent testing
A1C	Every 1–3 months
Fasting lipid profile,* including triglycerides, total, HDL, and LDL cholesterol	As indicated
TSHU and thyroid peroxidase antibodies; consider TSH-receptor antibodies if TSH is suppressed <0.03 μU/ml	To monitor treatment
Hemoglobin, serum ferritin; consider vitamin B12 in type 1 diabetes	To monitor treatment
Consider anti-tTG or anti-EMA plus IgA level in type 1 diabetes to diagnose celiac disease*	Repeat to confirm abnormal result or monitor effect of gluten-free diet
ALT/AST; possible liver ultrasound	As indicated
Random urine for ACR *or* 24-h urine collection for microalbuminuria and creatinine clearance (measure 24-h total protein excretion if urine is dipstick positive for albumin or protein). Serum creatinine for estimated GFR if preconception; creatinine clearance if pregnant	Every 1–3 months if abnormal
Dilated retinal exam*	Every 1–6 months according to risk of progression
Assess risk factors for CHD. Resting ECG* in asymptomatic patients age 35 years or older (note changes of prior silent ischemia, LVH, and QTc). Women with suspect angina, atypical chest pain, significant dyspnea, abnormal ECG, or other reasons to suspect CHD should have cardiology consultation with stress ECG, stress echocardiogram, or another appropriate imaging technique*	As indicated
Consider testing* for cardiac autonomic neuropathy (heart rate variability with deep breathing, blood pressure response to standing)	As indicated
Consider 2-D or Doppler echocardiogram or tissue Doppler imaging* with indication of diabetic cardiomyopathy or systolic or diastolic heart failure	As indicated
Consider testing* for peripheral arteriosclerotic vascular disease if high risk (carotid ultrasound, ankle/brachial blood pressure)	As indicated

*May be delayed or omitted if performed before pregnancy. EMA, endomyosial antibody; LVH, left ventricular hypertrophy; QTc, Q-T interval controlled for heart rate; tTG, tissue transglutaminase.

Maternal hyperglycemia during the first few weeks of pregnancy is strongly associated with excess spontaneous abortions and major congenital malformations (23,24). Glycemic thresholds for the increased risk include A1C values ≥3 SDs above the nondiabetic mean for pregnancy (≥6.3%). The risk rises as glucose levels worsen (1,38–41). The relation of maternal glucose to pregnancy outcome is a continuum, and ideal results are achieved when maternal glucose concentrations are within normal limits (42–46), but not excessively low (47).

After 12 weeks' gestation, hyperglycemia induces fetal hyperinsulinemia, accelerated growth, and excess adiposity in animal models and diabetic women. Macrosomia (birth weight >4,000–4,500 g) (16) occurs in 27–62% of infants of diabetic mothers compared with ~10% of nondiabetic control subjects. Macrosomia is associated with increased rates of operative delivery and birth trauma, fetal death, and neonatal complications including hypoglycemia, hypertrophic cardiomyopathy, polycythemia, and hyperbilirubinemia (1).

Several studies indicate that midtrimester glycemia is the best predictor of excess fetal size, and that macrosomia and other neonatal complications are minimized with intensified glycemic control (1,48). Postprandial glucose values were most strongly associated with excess birth weight in the studies in which both pre- and postmeal glucose were measured (49–52). Control that is too tight (mean plasma glucose <80–90 mg/dl) has been associated with fetal growth restriction, which carries its own set of neonatal and child development problems (1).

Fetal hyperglycemia causes fetal hypoxia and acidosis, which may explain the excess stillbirth rates still observed in poorly controlled diabetic women (1). Infants with macrosomia due to poor maternal glycemic control and fetal hyperinsulinemia are more likely to develop obesity and glucose intolerance later (1,53), and long-term (5–15 years) follow-up studies of infants of diabetic mothers suggest that poor glycemic control during pregnancy has a negative influence on intellectual and psychomotor development (1). Both findings highlight the prolonged offspring effects of intrauterine exposure to diabetes (1,53). Decades of work indicate that good glycemic control reduces perinatal morbidity and mortality. Tight glycemic control may also directly benefit the mother, in that elevated glucose during pregnancy is related to progression of retinopathy and nephropathy and the frequency of preeclampsia and premature labor (1).

2. Assessment of metabolic control
Recommendations

- Self-monitoring of blood glucose (SMBG) is a key component of diabetes therapy during pregnancy and should be included in the management plan. Daily SMBG both before and after meals, at bedtime, and occasionally at 2:00 A.M.–4:00 A.M. will provide optimal results in pregnancy. (E)
- Fingerstick SMBG is best in pregnancy, since alternate site testing may not identify rapid changes in glucose concentrations characteristic of pregnant women with diabetes. (E)
- Postprandial capillary glucose measured 1-h after beginning the meal on average best approximates postmeal peak glucose measured continuously (C), but due to individual differences it may be useful for each patient to determine her own peak postprandial testing time. (E)
- Continuous glucose monitoring may be a supplemental tool to SMBG for selected patients with type 1 diabetes, especially those with hypoglycemia unawareness. (E)
- Teach the pregnant patient to perform urine ketone measurements at times of illness or when the blood glucose reaches 200 mg/dl. Positive values should be reported promptly to the health care professional. (E)
- Perform the A1C test, using a Diabetes Control and Complications Trial (DCCT)-aligned assay, at the initial visit during pregnancy, monthly until target levels <6.0 are achieved, and then every 2–3 months thereafter. (E)

SMBG allows the patient to evaluate her individual response to therapy and assess whether glycemic targets are being achieved. Frequent sampling is optimal in pregnancy due to the increased potential for rapid-onset hypoglycemia in the absence of food or presence of exercise, and the exacerbated hyperglycemic responses to food ingestion, psychological stress, and intercurrent illness. SMBG before and after meals and occasionally at nighttime is recommended (1). The value of postprandial testing in pregnancy is supported by controlled trials (54,55). Use of alternate site testing in the dynamic state of pregnancy with rapid changes in blood glucose may give different results than fingerstick testing (1). The accuracy of SMBG is instrument- and user-dependent (56), and health care providers should evaluate each patient's monitoring technique initially and at regular intervals thereafter. Optimal use of SMBG requires proper interpretation of the data to adjust food intake, exercise, or insulin therapy in order to achieve specific glycemic goals. Health professionals should regularly evaluate the patient's ability to use data to guide therapy. Patients should use meters calibrated to plasma glucose and with memory capacity, but additionally should record data in a logbook. Patients should have ready access to the health care team by telephone or other means for regular inter-visit review of data and to discuss problems in management.

Ketone testing is important during pregnancy, since the presence of ketones can indicate impending diabetic ketoacidosis (DKA), which may develop quickly in pregnancy when persistent blood glucose values exceed 200 mg/dl (57). DKA is associated with a high fetal mortality rate. Urine ketones should be measured when the pregnant diabetic woman is ill or has persistent hyperglycemia. Fasting ketonemia in poorly controlled pregnant diabetic women has been associated with decreased intelligence and fine motor skills in offspring (58). Home tests for β-hydroxybutyric acid are available for use on sick days, but they have not been evaluated systematically in pregnancy (1).

C. Medical nutrition therapy
Recommendations

- Pregnant women with diabetes should receive individualized medical nutrition therapy (MNT) as needed to achieve treatment goals, preferably by a registered dietitian familiar with the components of MNT for diabetes and pregnancy, in concert with the other clinical team members, who should also understand and support the individualized food plan. (B)
- Assess pregravid BMI and target individual gestational weight gain at lower range of Institute of Medicine (IOM) recommendations according to BMI group; base energy intake on BMI group, physical activity level, fetal growth pattern, and desire to prevent excess maternal weight gain and postpartum weight retention. (E)
- Develop the food plan (daily meal and snack pattern) based on individual preferences to include *1*) appropriate calorie level, *2*) adequate consumption of protein (1.1 $g \cdot kg^{-1} \cdot day^{-1}$), fats, and micronutrients, *3*) consumption of 175 g/day digestible carbohydrate, and *4*) a distribution of carbohydrate intake that will promote optimal glycemic control and avoidance of hypoglycemia and ketonemia. (E)
- Promote consumption of a wholesome, balanced diet consistent with ethnic, cultural, and financial considerations. Maintain the pleasure of eating by selecting food choices according to scientific evidence, weight gain, and postprandial glucose responses. (E)
- Instruct the woman with diabetes to estimate the quantity of carbohydrate per serving and meal/snack and to select the type of carbohydrates that will contribute to postprandial glucose control; encourage fiber intake (28 g/day) by use of whole grains, fruits, and vegetables. (E)
- Emphasize consistent timing of meals and snacks on a daily basis to minimize hypoglycemia and in proper relation to insulin doses to prevent hyperglycemia. (E)
- Encourage patients to record all food and beverage intake continuously or for at least 1 week before each visit for assessment of adequacy of nutrient intake and comparison of carbohydrate intake with SMBG records. (E)
- Teach patients to control fat intake in the interest of long-term maternal health; encourage consumption of unsaturated fatty acids including the n-6 and n-3 fatty acids; limit saturated fat to <10% of energy intake and *trans* fats to the minimal amount possible. (A)
- Consume folate at 600 μg/day in the periconception and prenatal periods through supplementation or fortified food sources. (A)
- Supplement mineral, trace element, and vitamin intake to achieve adequate intake or recommended dietary allowance levels recommended by the IOM during all trimesters of pregnancy. (E)

Goals for MNT in pregnancy include: *a*) adequate nutrient intake to support a healthy pregnancy, *b*) excellent glucose control by balancing food/carbohydrate intake with physical activity and insulin treatment, *c*) adequate but not excessive weight gain, and *d*) learning appropriate food and exercise behaviors that can contribute to long-term maternal health. Clinical trials in nonpregnant diabetic women and clinical experience in pregnancy support the effectiveness of MNT provided by registered dietitians in concert with other health care team personnel (1). *Management of Preexisting Diabetes and Pregnancy* (1) provides a thorough

discussion of energy requirements and adequate intake of water, electrolytes, macronutrients, and micronutrients (minerals and vitamins) for pregnancy complicated by diabetes, based on the IOM nutrition documents (1,59,60).

Due to the risk of neural tube defects, it is recommended that women capable of becoming pregnant consume 400 μg folic acid daily from supplements, fortified foods, or both, in addition to a varied diet. During periconception and prenatal periods, intake of 600 μg/day through supplementation or fortified food sources is recommended. Folate supplementation may mask signs of B12 deficiency in women with type 1 diabetes who can have autoimmune gastritis. Therefore, consider obtaining baseline vitamin B12 levels in these patients (1).

Four studies of nutritional intake by diabetic pregnant women in the U.S. and the U.K. suggest that consumption of calcium, copper, magnesium, zinc, vitamin C, and vitamin E may be suboptimal (1). Women are encouraged to acquire micronutrients from natural food sources, but a prenatal supplement of vitamins and minerals should be considered in women with preexisting diabetes. Iron need not be supplemented unless hemoglobin is <11.0 g/dl in the first and third trimesters or <10.5 g/dl in the second trimester and there is laboratory evidence of iron deficiency (61). Vegetarian pregnant women may need supplements of vitamin D and vitamin B12. Evidence is insufficient to recommend general supplements of n-3 fatty acids in diabetic pregnancy (1).

Weight should be monitored at each visit and adjustments made in nutrient intake or physical activity to achieve desired outcomes. Gestational weight gain targets are based on pregravid BMI: lower gains for overweight women and higher gains for underweight women (59). Maternal weight gain impacts perinatal outcome (1). Excessive weight gain is associated with increased fetal macrosomia, potential birth trauma, cesarean section, and postpregnancy fat and weight retention.

Among medical conditions linked to diabetes, celiac disease, autoimmune atrophic gastritis, and nonalcoholic hepatic steatosis require special dietary approaches during pregnancy, as do women treated after gastric bypass surgery for extreme obesity. Prevalence, pathophysiology, and treatment of these conditions are discussed in the book (1). Eating disorders are considered in the section on behavioral therapy (II. G.). Due to the risks of CVD or hypertriglyceridemia, diabetic women are encouraged to eat at least two meals of oily ocean fish per week to increase n-3 fatty acids (eicosapentenoic and docosahexanoic acids), but pregnant women should avoid eating fish potentially high in methylmercury (e.g., swordfish, king mackerel, shark, or tilefish) (1).

D. Insulin therapy

Recommendations

- For optimal glycemic control in pregnancy in women with preexisting diabetes, provision of basal and prandial insulin needs with intensified insulin regimens (multiple dose regimens of subcutaneous long- and short-acting insulins or continuous subcutaneous insulin infusion [CSII]) usually gives the best results. (E)
- Patients who are taking insulins detemir or glargine should be transitioned to NPH insulin twice or three times daily, preferably before pregnancy or at the first prenatal visit, pending clinical trials proving efficacy and safety with these analogs. (E)
- Match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated activity. (E)
- Rapid-acting insulin analogs such as lispro or aspart may produce better postprandial control with less hypoglycemia compared with the use of premeal regular insulin. (E)
- Injections should be given in the abdomen or hips for consistency of absorption. (E)
- Because of the heightened risks of ketosis in pregnancy, patients using CSII should be well trained in the detection and treatment of unexplained hyperglycemia due to insulin under-delivery (pump or infusion site problems). (E)

Subcutaneous insulin administration is the mainstay of intensified therapy for preexisting diabetes in pregnancy. Basal-prandial insulin delivery through a multiple-injection regimen or CSII is most effective. In patients with type 1 diabetes, there may be an initial period of increased insulin sensitivity at 10–14 weeks' gestation. After that, insulin dosage usually rises sequentially, with rather wide individual variation, often leveling off or declining after 35 weeks. An algorithm for adjusting premeal insulin doses to correct for glucose values outside the target range is appropriate for most patients. For converting women with type 2 diabetes to insulin therapy, an initial total daily dose of 0.7–1.0 units/kg actual body weight is often effective, adjusted according to subsequent blood glucose concentrations. Obese women may require higher insulin dosage, and insulin requirements may double or triple during the course of pregnancy. Protocols for the initiation and management of insulin therapy are presented in the book (1) and elsewhere (62,63). Of the insulin analogs, only aspart and lispro have been shown to be safe and effective in clinical trials in pregnancy (1).

RCTs of multiple daily injections versus CSII in pregnancy generally showed equivalent glycemic control and perinatal outcome. The multiple adjustable basal rates offered by CSII can be especially useful for patients with daytime or nocturnal hypoglycemia or a prominent dawn phenomenon (increased insulin requirement between 4:00 A.M. and 8:00 A.M.). The disadvantages of CSII are cost and the potential for marked hyperglycemia and risk of DKA as a consequence of insulin delivery failure (usually due to kinking of the catheter or other infusion site issues), so patient training is very important (1).

E. Oral antihyperglycemic agents for type 2 diabetes

Recommendations

- Oral medications for treatment of type 2 diabetes should be stopped and insulin started and titrated to achieve acceptable glucose control before conception. (E)
- Women who become pregnant while taking oral medications should start insulin as soon as possible. It may be inferred from limited first trimester data that metformin and glyburide can be continued until insulin is started, in order to avoid severe hyperglycemia, a known teratogen. (E)
- Controlled trials are needed to determine whether glyburide treatment of women with type 2 diabetes (alone or in combination with insulin) is safe in early pregnancy or effective later in gestation. (E)
- Metformin should be used only in the setting of properly controlled trials during pregnancy until there is ample evidence of efficacy and safety. Such trials should include a focus on long-term development and metabolic function of the infants. (E)
- Thiazolidinediones, metglitinide inhibitors, and incretins should be used during pregnancy only in the setting of approved clinical trials. (E)

Use of oral agents in pregnant women with type 2 diabetes is controversial due to *a*) concern for transplacental passage of the drugs during organogenesis and later fetal development and *b*) the increased insulin resistance of pregnancy, making it problematic whether optimal glycemic targets would be met. Of the sulfonylurea agents, glyburide/glibenclamide may have the least net placental transfer (1). A landmark RCT in women with gestational diabetes treated with glyburide after the first trimester demonstrated no apparent fetal/neonatal harm and produced glycemic control equivalent to insulin treatment in patients with mild hyperglycemia. The study was underpowered to prove equivalent perinatal outcome in gestational diabetic patients with marked hyperglycemia (64,65). There are no reported trials of glyburide in pregnant women with type 2 diabetes. Metformin readily crosses the placenta, but this biguanide has been used during pregnancy in observational studies of women with polycystic ovarian syndrome. Results of clinical trials are awaited to determine whether metformin is effective and safe in pregnant women with type 2 diabetes. Limited human placental transfer of rosiglitazone has been demonstrated with ex vivo perfusion experiments in the first trimester and at-term pregnancy, and the glitazone-targeted peroxisome proliferator–activated receptor-γ receptors are expressed in trophoblast cells. It is unknown whether thiazolidinediones (glitazones) would cause harm or benefit to the fetus. Meglitinide analogs, α-glucosidase inhibitors, and incretins have not been well studied in pregnancy, and thus their safety and efficacy in pregnancy is not confirmed (1).

F. Physical activity/exercise

Recommendations

- Educate women with diabetes as to the benefits of appropriate daily physical activity. (A)
- Evaluate specific types of physical activity practiced before conception. Evaluate all pregnant women with preexisting diabetes for medical complications such as CVD, retinopathy, nephropathy, and neuropathy. If present, modifications in physical activity may need to be made. (E)
- Encourage pregnant women without contraindications to use physical activity as part of their overall diabetes management, at least 30 min/day. (E)
- Monitor capillary glucose closely around times of exercise, consider adjustments in carbohydrate and insulin requirements, and maintain good hydration before, during, and after exercise. (E)
- Instruct women to monitor the intensity of physical activity and to choose activities that will avoid the supine position and minimize the risk of loss of balance and fetal trauma. (E)
- Teach patients the warning signs to terminate exercise and seek medical attention. (E)

The benefits of exercise for pregnant women include a sense of wellbeing, decreased weight gain, reduction of fetal adiposity, improved glucose control, and better tolerance of labor (66). Normal physiologic adaptations of pregnancy need to be taken into consideration when planning for exercise, which should be modified if there is poor weight gain or evidence of fetal growth restriction. For pregnant women without complications of diabetes, 30 min or more of moderate intensity physical activity that does not have a high risk of falling or abdominal trauma, such as walking, is recommended most days (67–69). The minimal target of 30 min can be divided into three 10-min sessions preferably after meals. Adjustments to the diabetes regimen are essential to decrease the risk of exercise-induced hypoglycemia that may be exacerbated in pregnancy. Carbohydrate consumed before, during, and after physical activity will help avoid hypoglycemia, especially if glucose is <100 mg/dl.

Contraindications to aerobic exercise during pregnancy outlined by both the American College of Obstetrics and Gynecology (66) and the Society of Obstetricians and Gynecologists of Canada (70) are tabulated in the book (1). Both organizations recommend that women who experience dyspnea, shortness of breath, chest pain, dizziness, headache, calf pain or swelling, vaginal bleeding, leakage of amniotic fluid, or painful uterine contractions should stop exercising and seek medical attention.

G. Behavioral therapy

Recommendations

- Incorporate psychological assessment and treatment into routine care rather than waiting for identification of a specific problem or deterioration in psychological status. (E)
- Psychosocial screening and follow-up should include, but is not limited to, attitudes about diabetes, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history. (E)
- Screen diabetic pregnant women for depression, anxiety/stress, and disordered eating and adjust the team management plan as indicated. (E)
- Use structured psychotherapy for first-line treatment of mild depression. (A)
- Continue or initiate psychopharmacologic treatment for major depressive disorder during pregnancy after appropriate consultation, risk-benefit analysis, and informed consent. (E)
- Provide intensified interventions for women with anorexia nervosa to ensure adequate prenatal nutrition and fetal development. (E)
- Offer specifically adapted cognitive behavior therapy to women with bulimia nervosa or binge-eating disorder. (A)

Emotional well-being is part of diabetes management (2). Psychological disorders, which can affect glycemic control, are detectable in up to one-third of diabetic patients (1,71), including women who are pregnant. Psychosocial therapies are of proven benefit in the management of diabetes (72). Thorough assessment of psychosocial issues that may influence a patient's ability to respond to treatment and to collaborate with the diabetes and pregnancy care team is indicated (73). A simple assessment tool promulgated by the American College of Obstetricians and Gynecologists (72) is available in the book (1).

Depression in diabetic women is strongly associated with poor self-care and glycemic control, micro- and macrovascular complications, and increased health care expenditures (74). The hormonal changes and other stresses of pregnancy are thought to increase vulnerability to the onset or return of depression (75), which is associated with poor perinatal outcome (76). Structured psychotherapy can be a useful first-line therapy for mild depression, but pharmacotherapy is needed for severe depression. The risk of fetal exposure to untreated major depressive disorder is considered a greater cause for concern than fetal exposure to antidepressant drugs, some of which have been linked to congenital malformations and a withdrawal syndrome in infants (77,78). Studies of the

effects of antidepressant drugs in pregnancy are further discussed in the book (1).

Eating disorders are common in young women with type 1 diabetes, who may have unhealthy weight control practices and misuse insulin to help control weight (79,80). Women with type 2 diabetes may have problems with binge eating. Pregnant women with eating disorders are more likely to have hyperemesis, preterm delivery, fetal growth restriction, and postpartum depression (1). Validated detection instruments that can differentiate normative from more dysfunctional behaviors and attitudes are useful in young women with type 1 diabetes (80,81). Important principles of management include *a*) addressing the factors that may have triggered the expression of disordered eating, *b*) involving the family in treatment, *c*) teaching use of regular meal and snack times and responding to hunger and satiety cues, *d*) encouraging nondeprivational approaches to eating, and *e*) using specifically adapted cognitive behavior therapy for women with bulimia nervosa or binge-eating disorder (82,83).

Stress management techniques such as visualization, muscle relaxation, and relaxation breathing provide patients with tools to manage stressors. Psychosocial approaches and support relationships are important if behavior modification or pharmaceutical treatment is needed for cessation of smoking or use of alcohol or illicit drugs during pregnancy. Tricyclic antidepressants are recommended for panic disorders in pregnancy. For women struggling with depression or an eating disorder, referral to a mental health clinician is an important component of care (1).

II. MANAGING DIABETES COMPLICATIONS

A. Metabolic disturbances

1. DKA

Recommendations

- All women with preexisting diabetes who are planning pregnancy or already pregnant should be educated about DKA; prevention with SMBG, MNT, and appropriate insulin therapy; and sick day management. (A)
- Providers should have a high index of suspicion for DKA in diabetic pregnant women with nausea, vomiting, abdominal pain, fever, and poor oral intake. (A)
- Teach the patient to perform urine ketone measurements at times of illness or when persistent glucose levels exceed 200 mg/dl and to promptly report positive values. (E)
- Protocols for management of DKA during pregnancy include correction of volume depletion, insulin infusion, monitoring and correcting electrolyte imbalances, identifying and treating precipitating factors, and continuous fetal monitoring. (A)
- Initial DKA care is best given in intensive or special care units with experience in monitoring of high-risk pregnancies. (E)

The marked increase in insulin resistance and enhanced lipolysis/ketosis associated with pregnancy account for the greater risk of DKA during gestation (57). Although DKA is usually seen in patients with type 1 diabetes, it can also occur in women with type 2 diabetes (84,85). Predisposing factors include infection, vomiting and dehydration, diabetic gastroparesis, omission of insulin doses, and the obstetrical use of β-sympathomimetic drugs and glucocorticoids (57,86,87). DKA jeopardizes both maternal and fetal wellbeing. In pregnancy, 10–30% of cases of DKA have been reported to occur with moderately elevated glucose levels (<250 mg/dl) (57,84). Diabetic pregnant women with nausea, vomiting, and persistent and even moderate hyperglycemia should be evaluated for ketoacidosis. DKA is best managed in critical care units in hospitals with experience in monitoring high-risk pregnancies (87). Treatment protocols for DKA are based on correcting volume depletion, supplying insulin by infusion, carefully monitoring and correcting electrolyte imbalances, and identifying and treating precipitating factors (86). Continuous fetal heart rate monitoring and biophysical tests are used to assess fetal wellbeing in cases occurring after 24 weeks' gestation. Immediate delivery may not be necessary for ominous patterns, since correction of DKA often reverts the patterns to normal. A tabular summary of stepwise management of DKA in pregnancy is presented in the book (1).

2. Maternal hypoglycemia

Recommendations

- Educate and train all women who are planning pregnancy or already pregnant about the recognition and treatment of hypoglycemia, SMBG, and the need to carry glucose and a medical alert identification. (E)
- Glucose (15–20 g) is the preferred treatment for the conscious woman with hypoglycemia, although any form of carbohydrate may be used. If SMBG 15 min after treatment shows continued hypoglycemia, the treatment should be repeated. Once SMBG glucose returns to normal, the woman should consume a meal or snack to prevent recurrence of hypoglycemia. (E)
- Advise women that the risk of severe hypoglycemia increases during early pregnancy. Institution of intensified glycemic control before conception may result in a lower rate of severe hypoglycemia and less hypoglycemia unawareness during pregnancy. (A)
- Balance physical activity and the timing and amount of insulin doses and carbohydrate intake in meals and snacks to minimize iatrogenic hypoglycemia. (E)
- Glucose targets should be raised for patients with hypoglycemia unawareness until the syndrome is reversed by meticulous prevention of hypoglycemic episodes. (E)
- Instruct the spouses, partners, and coworkers of women at risk for hypoglycemia in the appropriate use of glucagon. (E)

Hypoglycemia is the most common and important adverse effect associated with intensive treatment of type 1 diabetes (88) and a limiting factor in achieving optimal glycemic control in insulin-treated type 2 diabetes (89). There is strong evidence that postabsorptive plasma glucose declines by 10 mg/dl during early pregnancy (1) and some evidence that the threshold for secretion of counterregulatory hormones is lower (48–57 mg/dl) during gestation in diabetic women (90,91). It is reasonable to use a threshold of <60 mg/dl (3.3 mmol/l) to define hypoglycemia during pregnancy. Documented, repetitive hypoglycemia is common in early pregnancy (41–68% of patients) (1), as is asymptomatic nocturnal hypoglycemia (92,93). The frequency of severe hypoglycemia was 18% among pregnant women with type 1 diabetes participating in the DCCT, all of whom were treated with intensive glycemic control when pregnant regardless of randomization status. Severe hypoglycemia was independently predicted by its occurrence before pregnancy, but was less common in women

who were in the intensified glycemic control arm compared with the conventional treatment arm before pregnancy (94). Observational studies in Europe report even higher rates of severe hypoglycemia in early pregnancy, with risk predictors including history of hypoglycemia before pregnancy and hypoglycemia unawareness (93,95,96).

Some of the classic signs of hypoglycemia (88) (anxiety, nausea, palpitations, tremor, sweating, warmth, confusion, dizziness, headache, hunger, weakness) may be difficult to discriminate from symptoms of pregnancy (91). Frequent SMBG is needed to detect hypoglycemia and minimize severe consequences (1).

Attenuated sympathetic neural activation causes the clinical syndrome of impaired awareness of hypoglycemia i.e., loss of the warning symptoms that normally allow patients to recognize developing hypoglycemia and take corrective action (88,89,97). Defects in glucose counterregulation and hypoglycemia-associated autonomic failure may be magnified during pregnancy in women with type 1 and long-standing insulin-treated type 2 diabetes (90,91,98,99). Various clinical factors (imperfect insulin replacement, nausea, delayed or missed meals, physical activity, sleep, antecedent hypoglycemia) exacerbate the reduced neuroendocrine responses to hypoglycemia (88,100). Hypoglycemia unawareness is at least partially reversible by several weeks of meticulous avoidance of iatrogenic hypoglycemia (93,101).

Protocols to minimize the occurrence of maternal hypoglycemia include intensive education of patients and significant others, frequent SMBG, proper timing of adequate meals and snacks, correct administration of insulin doses, and careful management of physical activity (102). There is some evidence that use of insulin analogs, especially with CSII, reduces the frequency of maternal hypoglycemia (1). One cup of milk (8 oz, 14 g sugars) or 3–5 glucose tablets (12–20 g) may be used to treat mild hypoglycemia in pregnancy (in order to prevent marked rebound hyperglycemia from excess glucose consumption), with one cup orange juice (22 g sugars) reserved for blood glucose <50 mg/dl (1). With severe hypoglycemia and the patient unable to swallow, a family member or coworker should inject 1 mg glucagon subcutaneously and call an emergency service for help. Once an unresponsive patient is alert and responsive, a snack or meal should be taken to prevent recurrent hypoglycemia.

3. Thyroid disorders

Recommendations

- Screen for thyroid dysfunction/autoimmunity with TSH and thyroid peroxidase antibodies (TPOAb) in all diabetic women before or during early pregnancy. (B)
- If normal TSH, but elevated antibodies: measure TSH at 7–8, 14–16, and 26–30 weeks and follow closely postpartum. (E)
- During pregnancy, treat any TSH elevation (>2.5 μU/ml first half; >3.0 μU/ml second half). Follow closely during the first 20 weeks, when the demands for thyroxine are highest, and readjust as needed to maintain euthyroidism (TSH <2.5 μU/ml first half; <3.0 μU/ml second half). (E)
- To assess thyroxine levels in pregnancy, measure adjusted total T4, since changes in plasma proteins affect the assay for free T4. (E)
- If TSH (<0.03 mU/ml) and T4 levels suggest hyperthyroidism, measure TSH-receptor antibodies (TRAb). (E)
- Treat hyperthyroidism with moderate doses of propylthiouracil to maintain maternal T4 at or just above upper range of normal to minimize drug-induced fetal hypothyroidism. (B)
- Alert the pediatrician about the newborn of a mother with elevated TRAb. (E)

Autoimmune thyroid disease is common (35–40%) in women with type 1 diabetes, and previously undiagnosed patients should be screened for thyroid dysfunction before pregnancy with a sensitive TSH assay and TPOAb titer. The prevalence of hypothyroidism is increased in women with type 2 diabetes compared with reference populations, and some will develop chronic thyroid autoimmunity (103,104). In preconception screening, if the TSH is <0.1 μU/ml or >4.0 μU/ml (reference levels for healthy woman aged 20–49 years) (105–107), evaluate the patient for possible thyroid disease, treatment of which may improve pregnancy outcome (1). If only the TPOAb titer is elevated, TSH should be remeasured in each trimester, since the demands of pregnancy can unmask hypothyroidism (108). Women with elevated thyroid antibodies are also at risk for early fetal loss and postpartum thyroiditis (1). In one study, treatment of antibody-positive euthyroid pregnant women with T4 reduced the rate of miscarriage and premature delivery (109).

Serum TSH levels are reduced by the influence of the thyrotropic activity of human chorionic gonadotropin (108,110). During pregnancy clinical (overt) hypothyroidism is suggested by serum TSH ≥2.5 μU/ml in the first half or ≥3.0 μU/ml in the second half, along with total serum T4 reduced to <7.8 μg/dl (<100 nmol/l) (nonpregnant normative values multiplied by 1.5 due to the rapid increase in T4-binding globulin in pregnancy). Subclinical (mild) hypothyroidism is suspected with normal thyroxine levels but elevated TSH according to pre-, early, or later gestation. Serum free T4 levels are difficult to interpret in pregnancy due to the influence of increased thyroxin binding globulin (TBG) and decreased plasma albumin on the assays (108).

Both overt and subclinical hypothyroidism can adversely affect the course of pregnancy and fetal development (108). Fetal brain development (neuronal multiplication, migration, and architectural organization) is dependent on maternal thyroxine until the second trimester, and later phases of fetal brain development (glial cell multiplication, migration, and myelinization) can also be affected by maternal hypothyroxinemia (1). Overt hypothyroidism that is untreated in pregnancy is clearly linked to major cognitive impairments in offspring. Subclinical hypothyroidism is associated with mild cognitive deficits in the offspring (six population-based studies) (111), with similar findings even in offspring of women with high-normal TSH levels (five studies) (112). Untreated subclinical hypothyroidism is associated with pregnancy loss, placental abruption, and premature delivery, but adequately treated even overt hypothyroidism is associated with normal pregnancy outcome. Either form of hypothyroidism, if untreated, can alter glycemic control and lipid metabolism in diabetes (1).

If hypothyroidism has been diagnosed before pregnancy, an international panel recommends adjustment of the preconception T4 dose to reach a TSH level not higher than 2.5 μU/ml (108). The T4 dose usually needs to be incremented by 4–6 weeks' gestation and may require a 30–50% increase in dosage (108,113). If overt hypothyroidism is diagnosed during pregnancy, the target TSH level for adjustment of thyroid replacement doses is no higher than 2.5 μU/ml in the first

half and <3.0 μU/ml in the second half of pregnancy. Thyroid function tests should be remeasured every 30–40 days. Pending results of clinical trials, the panel recommends T4 replacement in pregnant women with subclinical hypothyroidism, since the potential benefits outweigh the potential risks (108). Ingesting levothyroxine and ferrous sulfate simultaneously may lead to the formation of insoluble ferric-thyroxine complexes resulting in a reduced absorption of thyroxine (114).

Clinical hyperthyroidism is found in 1.7% of patients with type 1 diabetes and 0.3% of those with type 2 diabetes, compared with 0.2% in the reference pregnant population (115). Hyperthyroidism during pregnancy is defined as suppressed TSH (<0.03 μU/ml) and elevated total T4 (>18 μg/dl, >225 nmol/l; values are 1.5 times nonpregnant upper normal) or clearly elevated free T4 levels. Graves' disease is differentiated from gestational hyperthyroidism by a goiter and presence of TRAb in the first half of pregnancy. Gestational hyperthyroidism (often accompanied by hyperemesis) is usually self-remitting, and most cases do not require antithyroid treatment (108).

Careful management of hyperthyroidism is important since thyrotoxicosis increases the risk for maternal and fetal complications (115–119). The coexistence of hyperthyroidism and poorly controlled diabetes in pregnancy may increase the risk of poor perinatal outcome (115). Propylthiouracil is the preferred antithyroid drug in pregnancy, since methimazole use has been associated with fetal cutis aplasia and esophageal/choanal atresia (108,120). Either drug crosses the placenta and can result in fetal hypothyroidism, which is minimized by targeting maternal T4 in the high normal range (1,108,115,117). TRAb found in maternal Graves' disease also cross the placenta and can stimulate or inhibit the fetal thyroid. Fetal goiter can be due to either fetal hypothyroidism from maternal treatment with thiomides or fetal hyperthyroidism from maternal antibody transfer (108). TRAb can be associated with transient neonatal hypo- or hyperthyroidism; there is low risk in the absence of the maternal autoantibodies (1,108,119).

B. Management of cardiovascular risk factors

CVD is the major cause of mortality in women with diabetes. Diabetes itself is an independent risk factor for macrovascular disease, and its common coexisting conditions (obesity, hypertension, dyslipidemia, albuminuria) are also risk factors. Once diabetic patients develop clinical CHD, they have a particularly bad prognosis, which points to the importance of recognition of preclinical stages and preventive therapies (13). Clinical trials have shown the efficacy of reducing cardiovascular risk factors in preventing or slowing CVD (121). Heightened awareness of the degree of cardiovascular risk may allow such prevention or better management of acute atherosclerotic complications in pregnancy. Recent guidelines on primary prevention of CVD in people with diabetes (14) and in women (122) emphasize healthy food intake, physical activity, smoking cessation, and control of weight, blood glucose, blood pressure, and lipids. Most of these approaches, other than modifications sometimes needed in pharmacotherapy, can be used during pregnancy, which offers a time of motivation to learn behavior modifications and management skills that should produce long-lasting health benefits.

1. Screening for CVD

Recommendations

- Evaluation of risk for CVD is best performed before pregnancy. (E)
- Screen for standard cardiovascular risk factors (hypertension, dyslipidemia, albuminuria, smoking, family history of premature CHD) in all diabetic women. (A)
- Screen for evidence of CVD by simple physical examination for arterial bruits, aortic ejection murmur, and absent or asymmetric foot pulses. (E)
- Obtain information on symptoms of CVD and cardiac autonomic neuropathy (CAN). Consider carotid ultrasound testing, ankle/brachial index, heart rate variability with deep breathing, orthostatic blood pressure in patients at high risk. (E)
- Obtain resting ECG before or during pregnancy in patients with diabetes of age ≥35 years. (E)
- Patients with atypical pain, possible angina or anginal equivalent, or other reasons to suspect active CHD, including significant dyspnea or abnormal resting ECG, should have cardiology consultation for consideration of stress ECG, stress echocardiography, or other testing. (E)
- Patients of age ≥35 years *and* duration of type 1 diabetes ≥15 years or duration of type 2 diabetes ≥10 years with excess cardiovascular risk, especially with signs of CAN or carotid/lower extremity vascular disease, should be considered for stress ECG or stress echocardiogram. (E)
- Consider brain natriuretic peptide (BNP) plus echocardiographic imaging to detect systolic or diastolic ventricular dysfunction for excessive dyspnea or suggestive physical exam findings. Obtain cardiology consultation if there is evidence of cardiomyopathy. (E)
- Treat CVD risk factors such as hyperglycemia, hypertension, dyslipidemia, and smoking with interventions adapted for pregnancy. (A)
- Reduce risk for CVD in diabetic women with two oily fish meals per week (of low-risk for excess mercury; fish oil 1 g/day may be substituted). (A)
- Consider anesthesia and mode of delivery if there is evidence of CVD. (E)

The absolute and relative risks for CVD are dramatically increased in young women with type 1 diabetes (123–125) and in those with type 2 diabetes (126,127) compared with a nondiabetic population (1,13,14). Diabetic women are considered a high-risk group for CHD (>2% per year), especially in the presence of other CVD risk factors (126, 128,129). The risk for CVD in diabetic women includes CHD, cardioautonomic neuropathy (130,131), cardiomyopathy/heart failure (132,133), ischemic stroke (134), and peripheral arterial disease (PAD) (135). The rising tide of type 2 diabetes in the young may increase the prevalence of CVD in this group by the time of pregnancy, particularly in those with biomarkers of insulin resistance or chronic inflammation (1). CVD risk assessment and risk factor management should be vigorously applied in diabetic women of reproductive age (136,137). Intensified diabetes treatment reduces the frequency of the various signs of CVD (1). Aspirin therapy is recommended as a primary prevention strategy in women with diabetes over age 40 years at increased cardiovascular risk (2); however, aspirin use in early pregnancy has been associated with increased risk of birth defects arising from vascular disruption of fetal mesenteric vessels (gastroschisis and small intestinal atresia) (1).

Coronary artery disease is often more diffuse, calcified, and extensive in diabetes, yet ischemia may be silent; and CHD may be associated with left ventricular dysfunction (1). A 1999 ADA consensus

panel report on CHD and diabetes proposed that asymptomatic patients at age 35 years or more with two or more standard risk factors or the desire for vigorous exercise should be considered for coronary screening tests (128). However, in view of evidence that the burden of conventional cardiac risk factors is not predictive of presence of ischemia on perfusion imaging, at least in older patients, and that medical management (indicated anyway in people with diabetes at moderate or high CVD risk) may lead to similar outcomes compared with surgical interventions, a 2007 ADA consensus panel recommended against routine CHD screening in people with diabetes (138). The concept of screening asymptomatic diabetic women of reproductive age remains controversial and is inadequately studied (1).

Active or previously treated CHD is reported to occur in 1 of 10,000 pregnancies but in 1 of 350 diabetic pregnant women (139). The frequency of silent ischemia is unknown. In large administrative datasets, diabetes and hypertension were important risk factors for myocardial infarction during pregnancy or within 6 weeks of delivery (1). It is increasingly recognized that CHD presents differently in women than men, which may impact early diagnosis and treatment (122). Subtle symptoms, if present, may include atypical chest pain (or neck, jaw, or shoulder pain), fatigue, dyspnea, and nausea, all of which may be difficult to distinguish from common pregnancy-related symptoms (including gastroesophageal reflux). Abnormal Q-waves, deep T-wave inversions, left-bundle branch block, or nonspecific ST-T wave changes on resting ECG usually trigger evaluation for inducible ischemia (138). Should suspicion arise of CHD on historical or clinical grounds in pregnant women with diabetes, cardiology consultation and consideration of modalities to diagnose ischemia that avoid radiation exposure are recommended (140).

The prevalence of CAN is 11–33% in young adults with diabetes, depending on quality of glycemic control, and may be accompanied by left ventricular hypertrophy and diastolic ventricular dysfunction (1,130). Reduction in variability of heart rate (measured by the R-R interval) is the earliest indicator of CAN (1). The clinical impact of CAN in diabetic adults relates to exercise intolerance, orthostatic hypotension, cardiac arrhythmias, silent myocardial ischemia and painless infarction, intraoperative cardiovascular lability, and increased cardiac events (131). The few studies of CAN in pregnancies complicated by diabetes are cited in the book, along with a table of simple office tests for CAN that can be applied in pregnancy (1).

Heart failure occurs more frequently in diabetic women of reproductive age than in female control subjects of equal age, especially those with diabetic cardiomyopathy or diffuse atherosclerosis and patchy myocardial ischemia (132,133). Diabetic cardiomyopathy may be associated with either systolic or diastolic ventricular dysfunction or both (141). The physiologic volume overload, atrial dilation, disturbed diastolic relaxation pattern, and changes in ventricular dynamics associated with normal pregnancy, and further discussion of assessment and management of diabetic cardiomyopathy, can be found in the book (1). More investigation is needed in this area before evidence-based recommendations can be made.

The risk of ischemic stroke is increased four- to eightfold in relatively young adult women with type 1 (134) or type 2 diabetes (126,142,143) compared with nondiabetic women of similar age, although the absolute risk is low (4% over 20 years of follow-up of women with type 1 diabetes) (144). In large administrative datasets, the frequency of ischemic stroke was 9–25 per 100,000 pregnancies, with the risk of pregnancy-related strokes of all types more likely with maternal diabetes (OR 1.7–2.5 in univariate analysis) (1). Carotid atherosclerosis marked by intima-media thickening or plaque burden on high-resolution B-mode ultrasound is a predictor of both ischemic stroke and CHD in reproductive-age diabetic women (145,146). We lack studies of carotid intima-media thickness in diabetic pregnancy.

PAD of the femoral-popliteal and tibial arteries contributes to serious morbidity and excess mortality in both types of diabetes via tissue damage in the lower extremities and the association of PAD with CHD and ischemic stroke (135,147). Limited data show the frequency of signs of PAD to range 2–12% in diabetic women of reproductive age (126,148), with smoking and long duration of diabetes being important risk factors. More than half of patients with abnormal lower extremity arterial tests do not report claudication, possibly related to the association of PAD with peripheral neuropathy (135,147). The absence of peripheral pulses is insensitive as a sign of PAD; if suspicion is high, evaluation should include measurement of the ankle-brachial index (ABI) (135,149,150). The ABI has been validated against angiographically confirmed disease, and a ratio <0.9 was found to be 95% sensitive and almost 100% specific (148,151). We lack studies of PAD associated with diabetes and pregnancy.

2. Hypertension

Recommendations

- Blood pressure should be measured at every clinical visit. Patients found to have systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$80 mmHg should have blood pressure confirmed on a separate day. Repeat systolic blood pressure $>$130 mmHg or diastolic blood pressure $>$80 mmHg confirms a diagnosis of hypertension in diabetic women. (C)
- Women with diabetes in the preconception period should be treated to a systolic blood pressure $<$130 mmHg and a diastolic blood pressure $<$80 mmHg. (B)
- Patients with systolic blood pressure $>$140 mmHg or diastolic blood pressure $>$90 mmHg should receive pharmacologic therapy safe for anticipated pregnancy in addition to lifestyle and behavioral therapy. Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets. (A)
- Diabetic women with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 may be given lifestyle therapy alone for a maximum of 3 months or concomitant addition of pharmacologic agents safe for pregnancy to achieve target goals before conception. (E)
- During pregnancy in diabetic women with chronic hypertension, pharmacologic therapy should be used to achieve blood pressure target goals of 110–129 mmHg systolic and 65–79 mmHg diastolic in the interest of long-term maternal health and minimizing impaired fetal growth secondary to overtreatment. (E)
- ACE inhibitors and ARBs are contraindicated in gestation and should be stopped when pregnancy is anticipated. Effective contraception should be used by diabetic women treated with these agents. (A)
- Blood pressure medications that are safe for pregnancy should be added se-

quentially until target blood pressure levels are achieved. The agents include methyldopa, long-acting calcium channel blockers, and selected β-adrenergic blockers. (E)
- Hypertensive diabetic pregnant patients may be instructed to avoid excess salt intake but should not be severely salt restricted. Adequate potassium intake should be encouraged. (E)
- All diabetic pregnant women, especially those with hypertension, should be closely monitored for the development of preeclampsia. (A)

Hypertension is a major risk factor for CVD, nephropathy, and retinopathy in diabetic women (122,152). Because of the clear synergistic risks of hypertension and diabetes, the diagnostic cutoff for a diagnosis of hypertension is lower in people with diabetes (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg) than in those without diabetes (2). Epidemiologic evidence supported by randomized clinical trials in nonpregnant diabetic women demonstrate the benefit of controlling blood pressure to <130/80 mmHg, if it can be safely achieved (11,153,154). In addition to lifestyle and behavioral therapies, combinations of two or more drugs are usually needed to achieve the target blood pressure goal (2,11,155).

All categories of hypertensive disorders in pregnancy are more common in diabetic women. Chronic hypertension can be associated with serious perinatal complications (156). The prevalence of chronic hypertension is 10–17% in pregnancies with diabetes, increases with age and duration of diabetes, and predicts increased rates of prematurity and neonatal morbidity, especially when associated with superimposed preeclampsia (1). In women with preexisting diabetes, the incidence of preeclampsia increases from ~18% in women without chronic hypertension or preexisting proteinuria to almost 30% when either or both of these conditions are present (157). Studies of gestational hypertension without albuminuria are inadequate to determine perinatal outcome or to provide consensus recommendations for treatment.

We lack RCTs of antihypertensive therapy in pregnant diabetic women with chronic hypertension, but clinical trials of methyldopa in other pregnant women with chronic hypertension showed that treatment reduced fetal loss and fetal growth restriction, and there was less accelerated hypertension (1,158). The strong evidence for aggressive treatment in the nonpregnant hypertensive diabetic population (152–154) supports the recommendation to control blood pressure to <130/80 during the 9 months of pregnancy as well. Normative blood pressure data show the 50th percentile blood pressure to be 105/63 mmHg at 12–20 weeks' gestation, and the 97.5th percentile to be 128/81 mmHg. There is a U-shaped relationship between blood pressure and pregnancy outcome, with increases in fetal growth restriction when the diastolic blood pressure is <60–65 or >85–90 mmHg, or with mean aterial pressure (MAP) <75 or ≥90 mmHg. Increased rates of stillbirth, preeclampsia, and perinatal mortality occur with midtrimester MAP ≥90 mmHg (1). Treatment of chronic hypertension to blood pressure <110/65 mmHg in pregnancy may be associated with an increase in fetal growth restriction (1,158).

ACE inhibitors and ARBs must not be used in any stage of pregnancy because of their association with embryopathy and fetopathy (1,159). Preferred antihypertensive medications in pregnancy include methyldopa, long-acting calcium channel blockers, and β-adrenergic blockers. Clonidine or prazosin may be used as fourth-line agents (160,161). Methyldopa is a weak antihypertensive agent, but many clinicians prefer it as a first-line agent due to the reassuring long-term follow-up of children exposed in utero. Nondihydropyridine calcium channel blockers such as diltiazem may be preferred over the dihydropyridines in diabetic women because of their tendency to dilate glomerular arterioles and reduce renal albumin excretion, although evidence for the latter effect in pregnancy is only anecdotal. β-Blockers with partial β-agonist activity (acebutolol, carvedilol, labetalol, pindolol) decrease peripheral resistance directly without much effect on heart rate or cardiac output and may be preferred in pregnancy. Atenolol use has been associated with excess fetal growth restriction (1). A clinical trial of continuing thiazide treatment in pregnant women with chronic hypertension showed reduced plasma volume (162).

3. Dyslipidemia

Recommendations

- Measure fasting lipid profile at least annually in women with diabetes and more often if needed to achieve goals. In women with low-risk lipid values (LDL cholesterol <100 mg/dl, <2.6 mmol/l; HDL cholesterol >50 mg/dl, >1.25 mmol/l; and triglycerides <150 mg/dl, <1.7 mmol/l), lipid assessments may be repeated every 2 years. (E)
- Before pregnancy, follow current guidelines for nutritional and pharmacotherapy along with exercise and weight control for diabetic women with dyslipidemia. The primary treatment goal is an LDL cholesterol <100 mg/dl (2.6 mmol/l) in women without overt CVD and <70 mg/dl (1.8 mmol/l) in women with overt CVD. (A)
- Lifestyle modification focusing on the reduction of saturated fat (<7% of energy), *trans* fat (as little as possible), and cholesterol intake (<200 mg/day); weight control; and increased physical activity has been shown to improve the lipid profile in women with diabetes. (A) These treatment principles can be maintained during pregnancy, although the lipid profile will show a physiological change. (E)
- Statin therapy is contraindicated in any stage of gestation and should be discontinued in anticipation of pregnancy. (E)
- Obtain a lipid profile in all pregnant diabetic patients at registration, if not obtained before pregnancy. The purpose is risk assessment, correlation with indexes of cardiovascular, renal, and thyroid disease, and education of patients with dyslipidemia for continuing lifestyle modification and later pharmacologic treatment to sustain long-term health protection. (E)
- Follow-up measurements of the triglyceride level during pregnancy are important in patients with hypertriglyceridemia. (E)
- Cholesterol-lowering drugs except bile acid binding resins are unapproved for use in pregnancy. MNT may be helpful in reducing hypercholesterolemia in pregnancy. Plant sterol containing margarines could be useful as a dietary approach for cholesterol lowering. (E)
- For diabetic pregnant women with triglyceride levels ≥1,000 mg/dl, treatment is indicated to reduce the risk of pancreatitis. Add fish oil capsules to a low-fat diet to attain n-3 fatty intakes of 3–9 g/day. Secondary strategies include medium chain triglycerides, total parenteral nutrition, fibric acids, and niacin. (E)

Lipid disorders are associated with diabetes. Women with diabetes may demonstrate hypertriglyceridemia, hypercholesterolemia,

Table 2—*Stages of the evolution of diabetic nephropathy and common effects on pregnancy*

Stages of kidney damage*	GFR	Albuminuria	Pregnancy effect
Hyperfiltration (a)	>150	<30 mg/day	Unknown
Microalbuminuria 1	>90	30–299 mg/day	Increased preeclampsia
Macroalbuminuria 1	>90	≥300 mg/day	Increased preeclampsia
Early nephropathy 2	60–89	TPE ≥500 mg/day	Increased risk of fetal growth restriction
Moderate CKD 3	30–59	Massive proteinuria	Perinatal complications likely
Severe CKD 4	15–29	Less proteinuria	Delay pregnancy to after transplant
Kidney failure 5	<15		Dialysis

*There may be overlap between GFR and albuminuria groupings. In the second level and beyond, kidney damage is defined as abnormalities on pathologic, urine, blood, or imaging tests (refs. 2 and 190). Table modified from references 2 and 188–190. GFR: creatinine clearance quantified as ml/min per 1.73 m^2. CKD, chronic kidney disease; TPE, urinary total protein excretion.

and elevations in LDL cholesterol, lipoprotein(a), or apolipoprotein B before pregnancy (163,164). Dyslipidemia in type 2 diabetes is characterized by an elevated total triglyceride (>150 mg/dl), low levels of cardioprotective HDL cholesterol (<50 mg/dl), and increased numbers of small-dense particles of LDL without necessarily an increase in LDL cholesterol to >130 mg/dl. Clinical trial results support LDL cholesterol as the primary target of therapy in diabetic dyslipidemia with a goal of <100 mg/dl. When triglyceride levels are ≥200 mg/dl, non–HDL cholesterol becomes a secondary target (<130 mg/dl) of cholesterol-lowering therapy (12–14).

In normal pregnancy the triglyceride level may double by 20 weeks' gestation, and cholesterol, LDL cholesterol, and HDL cholesterol increase by 10–20%, with further progression of all lipid levels until term (165). Triglyceride levels may increase much more in pregnancy complicated by type 2 diabetes, and exaggerated hypertriglyceridemia (>2,000 mg/dl) presents a seriously increased risk for pancreatitis. Prevention of pancreatitis requires anticipatory lipid screening and monitoring. As the triglyceride level can rise rapidly from 1,000 to 2000 mg/dl, treatment is initiated at the 1,000 mg/dl level. Management of hypertriglyceridemia in pregnancy is based on intensified glycemic control, fish oil supplementation, use of medium chain triglyceride emulsions, and pharmacotherapy with fibrates (category C) or extended release niacin (1).

Cholesterol is taken up by placental trophoblasts in the form of lipoproteins through receptor-mediated as well as receptor-independent transport, and there is concentration-dependent efflux of cholesterol to fetal blood from the basolateral surface of the trophoblast (166). Maternal hypercholesterolemia (250–450 mg/dl) is associated with enhanced intimal accumulation of oxidized LDL and fatty streak formation in the fetal aorta, which persists in children of age 2–15 years (167).

MNT is important for reduction of dyslipidemia in pregnancy. The main goals of the food plan should be to limit intake of saturated fat to <7% of calories and cholesterol to <200 mg/day and to replace *trans*-unsaturated fats with monounsaturated or polyunsaturated fat sources (12,14,69). Use of anti-atherogenic diets in nondiabetic pregnant women is effective in reducing the rise in total and LDL cholesterol (168). Statins are contraindicated in pregnancy due to teratogenic effects. For hypercholesterolemia, bile acid binding resins are the only nonabsorbed lipid-lowering agents (category B for pregnancy). These are of limited effectiveness when used alone, yielding a 10–20% reduction in LDL cholesterol (1).

Diabetic women are encouraged to eat at least two meals of oily fish per week to increase n-3 fatty acids, but pregnant women should avoid eating fish potentially high in methylmercury (e.g., swordfish, king mackerel, shark, or tilefish) (1).

C. Diabetic nephropathy

Recommendations

- Determine the level of albuminuria and estimate glomeruler filtration rate (GFR) with serum creatinine before pregnancy in all women with diabetes. (E)
- During early pregnancy, assess urine albumin excretion with a random urine/creatinine ratio. (E)
- In pregnant patients with micro- or macroalbuminuria, measure properly instructed 24-h CrCl, since estimated GFR by the Modification of Diet in Renal Disease (MDRD) study equation is not accurate in gestation. (E)
- To reduce the risk and/or slow the progression of nephropathy (A) and to improve perinatal outcome (E), optimize glucose and blood pressure control.
- Discontinue ACE inhibitors and ARBs in anticipation of pregnancy and use agents as discussed in the section on hypertension in pregnancy. (E)
- In women with overt nephropathy, consult a registered dietitian and restrict protein intake to ~1.1 g · kg body $wt^{-1} \cdot day^{-1}$ (~10% of daily calories, the current adult recommended dietary allowance for protein), but not to <60 g/day. (E)
- Consider referral to a center experienced in the care of diabetic renal disease and pregnancy when either the GFR has fallen to <60 ml/min per 1.73 m^2 or difficulties have occurred in the management of hypertension. (E)

Diabetic nephropathy is the single leading cause of end-stage renal disease and is a strong predictor of mortality from CVD in diabetic women. The classification of albuminuria and estimated GFR levels in diabetic nephropathy and chronic kidney disease and their effects on pregnancy are listed in Table 2 (2,153,169–171).

During normal pregnancy, urinary albumin excretion (UAE) shows a modest increase up to 30 mg/day, or random urine ACR up to 22 mg/g, but total protein excretion increases up to 300 mg/day (1). The diagnosis of microalbuminuria during pregnancy is based on repeated measures of UAE 30–299 mg/day or ACR 30–299 mg/g in the absence of bacteriuria (1,2). Diabetic women with microalbuminuria at baseline can have large increases in both UAE and total protein excretion by the third trimester, but albuminuria usually regresses postpartum. Some of the cases of increased proteinuria are due to the increased rates of preeclampsia (and preterm delivery) predicted by microalbuminuria at baseline in several observational studies of women

with type 1 diabetes (1). The diagnosis of overt diabetic nephropathy during pregnancy is presumed if there is persistent albuminuria (≥300 mg/day) or proteinuria (≥500 mg/day) before 20 weeks' gestation in the absence of bacteriuria or evidence of other renal or urinary tract disorders. Proteinuria in the second half of pregnancy may be due to preeclampsia. Dipstick methods or random urine protein/creatinine ratios are not accurate methods to predict or quantify proteinuria during pregnancy. Patients with overt nephropathy can reach nephrotic levels of proteinuria in the third trimester (3–20 g/day), usually with regression of proteinuria postpartum (1). Diabetic nephropathy during pregnancy is a strong risk factor for fetal growth restriction, superimposed preeclampsia, premature delivery, and stillbirth, all of which may be minimized by optimal control of blood glucose and blood pressure (172).

Estimated GFR based on serum creatinine, age, sex, and race (MDRD formula) is not accurate during pregnancy (173), so measurement of 24-h urine CrCl is recommended in the assessment of nephropathy during pregnancy. During normal pregnancy, GFR increases up to 50%, associated with the physiologic increase in cardiac output and renal blood flow during the first half of pregnancy. Well-controlled diabetic patients without impaired CrCl at baseline can demonstrate the expected rise in CrCl observed in normal pregnancy (1).

During pregnancy CrCl remains stable in three-fourths of nephropathy patients with initial preserved GFR, but declines in two-thirds of patients with significantly reduced GFR in early pregnancy. Progression to kidney failure during pregnancy in women with nephropathy is uncommon, but the published experience in women with severe kidney disease in early pregnancy is limited. Whether pregnancy exacerbates subsequent progression of nephropathy is of interest. In the aggregate of published series, 45% of women with mildly decreased GFR (level 2) in early pregnancy went on to renal failure by 12 years postpartum. However, case-control studies of previously pregnant women with nephropathy compared with never-pregnant patients did not demonstrate an increased risk of renal failure in the parous group over the next 10 years, and the rate of decline of GFR after pregnancy was similar to that expected in nonparous women with nephropathy (1).

Management of hypertension during diabetic pregnancy is summarized in section B.2 and further discussed in the book (1). Observational studies support control of blood pressure at 110–129/65–79 mmHg in pregnant women with nephropathy (172,174,175). ACE inhibitors and ARBs must not be used at any stage of pregnancy. There is only anecdotal evidence that the nondihydropyridine calcium channel blocker diltiazem reduces albuminuria during pregnancy. The use of erythropoietin for severe anemia, hemodialysis, and management of women with renal transplants during pregnancy are discussed in the book (1).

D. Diabetic retinopathy

Recommendations

- Preconception care for all diabetic women should include a dilated and comprehensive eye examination by an opthalmologist or optometrist. Women should be counseled on the risk of development and/or progression of diabetic retinopathy. (B)
- To reduce the risk or slow the progression of retinopathy, optimize glycemic and blood pressure control. (A)
- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (NPDR), or any proliferative diabetic retinopathy (PDR) to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. (A)
- Blood glucose levels should be lowered slowly to near-normal over a 6-month period in preconception patients with severe NPDR or PDR before pregnancy is attempted. (A)
- Dilated eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum. (B)
- Patients with no or minimal retinopathy should be evaluated in the first and third trimesters. Patients with mild retinopathy should be evaluated every trimester. Patients with moderate to severe NPDR or PDR should be evaluated monthly at the discretion of the eye care provider. (E)
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in preconception and pregnant patients with high-risk PDR, clinically significant macular edema, and in some cases of severe NPDR. (A)
- In women with untreated PDR, vaginal delivery has been associated with retinal and vitreous hemorrhage. Assisted second-stage delivery or cesarean delivery should be considered in consultation with an obstetrician and ophthalmologist. (E)

Diabetic retinopathy is responsible for the majority of new cases of blindness among adults. Glaucoma, cataracts, and other disorders of the eye may occur earlier in women with diabetes and should also be evaluated. Intensive diabetes management with the goal of achieving near normoglycemia has been shown to prevent and/or delay the onset of diabetic retinopathy. Controlling blood pressure will also decrease the progression of retinopathy (2).

The short-term risk of progression of retinopathy during pregnancy is approximately double that during the nonpregnant state. Increased frequency of retinal exams is therefore recommended during pregnancy, with intervals determined by retinopathy status. The risk of developing PDR during pregnancy from no apparent retinopathy at baseline is rare, but if retinopathy is present its level of severity early in pregnancy predicts the risk of progression during pregnancy in women with type 1 diabetes. Other factors that increase the risk for progression of established retinopathy during pregnancy include: longer duration/earlier onset of diabetes, elevated first trimester A1C and either persisting poor glycemic control *or* rapid normalization of blood glucose, chronic hypertension, nephropathy, and development of preeclampsia during the same pregnancy. Best outcomes should be achieved when glycemia is optimized before conception. Macular edema seems to cluster with PDR, diabetic nephropathy, and preeclampsia during pregnancy. Information on diabetic retinopathy during pregnancy complicated by type 2 diabetes is fragmentary (1).

The risk of progression of untreated PDR in pregnancy is very high and supports the need for careful preconception retinopathy evaluation and management. Laser photocoagulation should be considered when retinal neovascularization, clinically significant macular edema, or very severe NPDR are identified in pregnancy. Patients with neovascularization should avoid the Valsalva maneuver to reduce the risk of serious hemorrhage. Although there are no controlled studies of the route of delivery on the risk of serious hemorrhage in women with active PDR, it makes sense to avoid maternal pushing in

the second stage of labor by using epidural anesthesia and assisted second-stage or cesarean delivery. Treatment recommendations for nonpregnant individuals should be followed for vitreous hemorrhage or detachment during pregnancy (1).

After pregnancy, progression of retinopathy may continue in 6–20% of patients with type 1 diabetes, with some patients requiring laser photocoagulation postpartum (34). These reports support the need for careful ophthalmologic follow-up for 1 year after gestation. Case control studies demonstrate either similar or lower rates of long-term progression of retinopathy in parous versus nulliparous women, and the rate does not increase in women having more than one pregnancy (1).

E. Diabetic neuropathies

Recommendations

- All patients should be screened for symmetric distal polyneuropathy (DPN) and autonomic neuropathy at least annually, using simple clinical tests. (B)
- Educate all patients about self-care of the feet. For those with DPN, facilitate enhanced foot care education and refer for special footwear. (A)
- Counsel women with diabetes that pregnancy does not appear to increase the risk for development or progression of DPN or autonomic diabetic neuropathies, except for transient but possible severe effects on gastroparesis. (B)
- Advise women with gastroparesis that this complication is associated with a high risk of morbidity and a risk of poor perinatal outcome. Apply standard medications for hyperemesis and nutritional support as needed. (C)
- Advise women with chronic sensorimotor symmetric DPN or cardiovascular autonomic neuropathy that these conditions may be associated with an increased risk of perinatal complications and will require cautious management. (B)
- Assess the presence of clinically diminished counterregulatory responses to hypoglycemia and educate patients to minimize its occurrence. (E)
- Treat symptomatic diabetic women with DPN or cardiovascular or gastrointestinal autonomic neuropathies as appropriate for pregnancy. (E)

The diabetic neuropathies can be heterogeneous with focal or diffuse clinical manifestations in women of reproductive age, with damage to all peripheral nerve fibers—motor, sensory, and autonomic (176,177). Among the most common are chronic sensorimotor symmetric DPN (176) and autonomic neuropathy (130). Cardiac autonomic neuropathy is considered in the section on CVD.

DPN screening tests include pinprick sensation, temperature and vibration perception (using a 128-Hz tuning fork), 10-g monofilament pressure sensation at the distal plantar aspect of both great toes, and assessment of ankle reflexes (176–179). Combinations of more than one test have >87% sensitivity in detecting DPN (2). Loss of perception to filament touch and vibration predict risk of foot ulcers. We need more data on the predictive values of these tests during pregnancy.

There is limited information, mostly derived from isolated case reports, on whether symptoms of sensorimotor or autonomic neuropathy worsen during pregnancy. The effect of diabetic neuropathy on the outcome of pregnancy is difficult to separate from other known risk factors for adverse pregnancy results, such as poor metabolic control, hyperemesis, inadequate nutrition, and coexisting microvascular disease. Of particular importance during pregnancy is the association of autonomic neuropathy with an increased risk of severe hypoglycemia. The presence of gastroparesis is particularly troublesome in that, with hyperemesis of pregnancy, it exacerbates nausea and vomiting. The result can be irregular absorption of nutrients, inadequate nutrition, and aberrant glucose control (1). Many patients with gastroparesis benefit from treatment with prokinetic agents such as metoclopramide, a category B drug considered safe for use throughout pregnancy. Erythromycin, another category B drug (except for the estolate form), may also be helpful in the treatment of gastroparesis (176). Severe cases of diabetic gastroparesis coupled with hyperemesis may require extended total parenteral nutrition (1).

There are few data on treatment of pain from DPN during pregnancy. C-fiber pain, characterized by hyperesthesia and burning, can be treated by topical application of Capsaicin (considered safe in pregnancy) or Clonidine, a category C drug that has not been reported to cause harm in pregnancy. A-fiber pain, a more deeply seated ache that does not usually respond to the aforementioned treatments, may respond to treatment with tricyclic antidepressants, such as amitriptyline or nortriptyline. Both are category D drugs because of the possible risk of teratogenicity, but appear to be relatively safe for use after the first trimester, with some evidence of minimal effects on newborn behavior. Antiepileptic drugs, such as carbamazepine and gabapentin have also been used effectively in the management of diabetic neuropathic pain (176), but as with any antiepileptic drug, use of these medications during pregnancy must take into account their teratogenic potential. In severe cases of DPN pain, methadone may be useful.

Acknowledgments— The authors are grateful for the inspiration provided by patients, for the support of their families during preparation of the statement and the supporting book, and for excellent information/library services provided by Janet Bruman, Nancy Firchow, and Vaughn Flaming.

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Table 3—*Relationships disclosed by authors that could be construed as representing potential conflicts of interest*

Name	Research or educational grant	Speaker honoraria	Consultant; advisory board	Ownership interest
F.M.B.	Harvard	Hospitals	None	None
P.M.C.	NIH	Hospitals	None	None
D.R.C.	NIH	Hospitals	RW Johnson Program	None
L.B.J.	Abbott, Lilly, Lifescan, Medtronic, Pfizer, Novartis	NovoNordisk, Hemacue, Roche, Sanofi-Aventis	None	None
J.L.K.	Lifescan	Lilly	None	None
S.I.K.	NIH	Hospitals	None	None
R.H.K.	Abbott, AstraZenica NIH, Takeda	Abbott, AstraZeneca	None	None
M.N.M.	None	Hospitals	None	None
E.S.O.	None	Hospitals	Bioniche Pharmaceuticals	None
P.P.	NIH, Pfizer	None	None	None
B.M.R.	None	Hospitals	None	None

No conflicts of interest reported: J.M.B., D.L.C., E.P.G., W.H.H., L.D.H., M.I., D.M.R., A.M.T., and M.S.K.

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