OBSTETRICS

Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus

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There is now strong evidence that lifestyle modification can prevent or delay the development of type 2 diabetes mellitus in high-risk individuals. Women with gestational diabetes mellitus are at increased risk for type 2 diabetes and so are candidates for prevention programs. We review literature on type 2 diabetes risk in women with gestational diabetes, examine current recommendations for postpartum and long-term follow-up, and summarize findings from a 2007 expert-panel meeting. We found data to support that women with gestational diabetes have an increase in risk of type 2 diabetes comparable in magnitude with that of individuals with impaired glucose tolerance and/or impaired fasting glucose and that prevention interventions likely are effective in this population. Current recommendations from leading organizations on follow-up of women after delivery are conflicting and compliance is poor. Clinicians and public health workers face numerous challenges in developing intervention strategies for this population. Translation research will be critical in addressing this important public health issue.

Key words: diabetes gestational diabetes, prevention, postpartum screening

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Type 2 diabetes is emerging as a leading cause of death and disability and is straining health care systems.[1-3] Numerous randomized clinical trials have demonstrated that lifestyle modification and pharmacotherapy can prevent or delay the development of type 2 diabetes in high-risk individuals. Specifically, high risk individuals include those with laboratory evidence of impaired glucose tolerance (IGT) (commonly defined as a plasma glucose concentration of 140 mg/dL or greater and less than 200 mg/dL 2 hours after a 75 g glucose challenge) and/or impaired fasting glucose (IFG) (commonly defined as a fasting plasma glucose concentration of 100 mg/dL or greater and less than 126 mg/dL).[4-15]

Because most trials have included only participants with abnormal glycemia, the implications of these studies for high-risk groups not defined by IFG and/or IGT require consideration.[16,17] This issue is especially important because screening for IFG and IGT in asymptomatic individuals is not currently recommended as part of routine clinical care.[18] Because of the urgency of the growing diabetes epidemic, it is not practical to require that prevention trials be conducted in all high-risk groups before expanding prevention recommendations beyond individuals with IFG/IGT. Therefore, it is important to identify other high-risk groups that likely will benefit from prevention interventions.[17] Because women with a history of gestational diabetes mellitus (GDM) are at elevated risk for type 2 diabetes, they represent 1 such high-risk group.

Gestational diabetes, defined as carbohydrate intolerance leading to hyperglycemia with onset or first recognition during pregnancy, affects 2-10% of pregnancies in the United States.[19] Although this carbohydrate intolerance usually resolves after delivery,[20,21] up to one third of affected women have diabetes or impaired glucose metabolism at postpartum screening.[22-26] An estimated 15-50% will develop diabetes in the decades following the affected pregnancy.[27-29] Thus, a history of GDM conveys important information about future risk for diabetes that can be used to identify individuals needing ongoing monitoring and prevention interventions.

We reviewed literature on type 2 diabetes risk in women with a history of GDM, summarized current recommendations for postpartum and long-term follow-up, and reviewed progress toward implementation of those recommendations. We then summarized recommendations and research gaps based on an expert panel meeting convened by the Centers for Disease Control and Prevention (CDC) in 2007 to address postpartum screening and type 2 diabetes prevention in women with a history of GDM.

Type 2 diabetes risk in women with a history of GDM

Whereas some women with GDM will eventually develop autoimmune (type 1

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diabetes) or highly penetrant genetic forms (maturity-onset diabetes of the young) of diabetes, most have preexisting impaired beta cell function and chronic insulin resistance that is characteristic of type 2 diabetes. Women with a history of GDM are at substantially increased risk for future development of type 2 diabetes, providing additional evidence of a common underlying mechanism. In 1 of the few studies using survival analysis (which accounts for censoring within the cohort), the mean annual diabetes risk in a cohort of nearly 7000 women in Australia with a history of GDM was 1.7% and the cumulative 5 year risk was 8.1%. In contrast, the cumulative 5-year risk was 0 % in the nearly 800 women without GDM[28] and the background risk was 0.7% per year among US adults aged 18-78 years.[30]

Non-Caucasian and Hispanic women are at particularly high risk for diabetes after GDM.[31-35] However, even in low-risk populations, a history of GDM is associated with a high relative risk for type 2 diabetes compared with women with unaffected pregnancies; relative risks range from 3 to 20.[28,36-40] In comparison, annualized relative risks for the development of type 2 diabetes in the general population among individuals with IGT, IFG, or both are 3.5 to 8.6, 5.1 to 9.9, and 5.5 to 20.1, respectively.[41] Thus, evidence indicates that a history of GDM is associated with an elevation in diabetes risk that is comparable in magnitude with that in individuals with glucose levels in the prediabetic range.

Current type 2 diabetes screening recommendations for women with GDM

A number of organizations have put forth recommendations for postpartum screening, including the American College of Obstetricians and Gynecologists (ACOG),[42] the American Diabetes Association (ADA),[43,44] and the Fifth International Workshop–Conference on Gestational Diabetes Mellitus Panel[45] (Table 1). The type of screening recommended varies, however, as does the cogency of the justification backing the recommendations. For example, the ADA recommends postpartum screening to reclassify maternal glycemic status[43] and states that either the fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) is appropriate for screening high-risk, asymptomatic individuals, including those with a history of GDM.[44]

ACOG notes that use of the OGTT for postpartum screening of women with GDM will identify women with IGT and so may be more beneficial than FPG "in counseling for future pregnancies." However, ACOG further notes that the benefits of postpartum screening are unproven,[42] a conclusion that is consistent with the 2002 US Preventive Services Task Force recommendations for the general population, which state that insufficient evidence exists to recommend for or against screening asymptomatic adults (www.ahrq.gov/clinic/uspsft/uspsdiab.htm).[18] In contrast, the Fifth International Workshop Panel explicitly recommends that women who had GDM but do not have diabetes immediately postpartum should receive an OGTT 6 to 12 weeks postpartum and considers a fasting plasma glucose level insufficiently sensitive to identify women with diabetes or IGT.[45]

Regarding long-term follow-up of women with a GDM-affected pregnancy, the ADA recommends screening every 3 years if postpartum screening results are normal and annually if postpartum screening indicates IFG or IGT.[43] The Fifth International Workshop recommendations state that women should receive an OGTT at 1 year postpartum and every 3 years thereafter, whereas acknowledging the lack of studies on which to base recommendations for screening frequency.[45]

It is unknown whether screening every 3 years is an optimal schedule, given the need to prevent the development of unrecognized type 2 diabetes before subsequent pregnancies.[46-49] ACOG's Practice Bulletin has no recommendations for long-term screening, other than to suggest that if the postpartum OGTT is normal, the FPG can be used for subsequent follow-up. ACOG's Committee Opinion on Primary and Preventive Care, however, includes recommendations for screening with a fasting glucose as part of periodic assessment (annually or as appropriate) for preventive care in women with a history of GDM.[50]

Compliance with postpartum screening recommendations for women with a GDM-affected pregnancy

Despite the lack of uniformity in recommendations, obstetricians appear to be aware of the importance of postpartum screening. In a survey of AGOG Fellows and Junior Fellows, 74% of 441 respondents reported that they routinely conduct postpartum screening.[51] However, studies suggest the percentage of women actually receiving postpartum screening is low.[22-26] When reviewing studies examining postpartum screening practices in the United States (Table 2),[22-26,52-54] we found no population-based estimates of postpartum screening rates.

In studies conducted in medical centers, the percentage of women screened with any assessment of glycemic status (including random blood glucose or hemoglobin A1c) ranged from 18% to 67%.[24,26,54] The percentage of women receiving a recommended screening test (FPG or OGTT) was lower; as few as 1 in 4 eligible women were screened.[23,52] Less is known about compliance with recommendations for long-term follow-up, but limited data suggest that the percentage of women receiving additional screening after the postpartum period is low. [55]

Prevention interventions for women with a history of gestational diabetes

Evidence is accumulating that progression to type 2 diabetes among women with a history of GDM can be prevented or delayed. In the Diabetes Prevention Program study, a randomized trial of more than 3000 adults with a plasma glucose concentration of 95-125 mg/dL while fasting and 140-199 mg/dL 2 hours after a 75 g oral glucose load (IGT), researchers found that a lifestyle intervention that produced a 7% weight loss and an increase in physical activity of 150 minutes per week reduced the incidence of diabetes by 58%, whereas treatment with metformin reduced the incidence by 31%.[10] Women with a history of

TABLE 1
Recommendations from selected organizations for postpartum screening and long-term follow-up for women with a history of GDM

Recommending organization	Year of last update	Recommended postpartum screening test	Recommended long-term follow-up	Recommended interventions
American College of Obstetrics and Gynecology[42]	2001	No specific recommendation to perform postpartum screening, but if screening is done, ACOG notes that the OGTT identifies women with IGT, "which may be advantageous for counseling for future pregnancies."	"If postpartum testing is normal, subsequent follow-up tests may use the FPG."[42] Periodic assessment of fasting plasma glucose is recommended as part of routine preventive care for women with a history of GDM.[50]	Women with "additional risk factors," such as early-onset GDM or obesity, should receive counseling regarding diet, exercise, and weight management.
American Diabetes Association[43,44]	2004	6 wks or longer postpartum: glycemic status should be assessed.	If postpartum screening results are normal, rescreen at 3 y intervals. If postpartum screening indicates IFG and/or IGT, rescreen annually.	"All patients with a history of GDM should be educated about the benefits of maintaining a normal body weight through MNT and physical activity. Patients should be educated about symptoms of hyperglycemia, and family planning should be encouraged to ensure optimal glycemic regulation prior to subsequent pregnancies. Medications that worsen insulin resistance should be avoided." Women with IFG or IGT postpartum should receive intensive MNT and an individualized exercise program.
Fifth International Workshop–Conference of Gestational Diabetes[45]	2007	After delivery: FPG or random blood glucose 6-12 wks postpartum: OGTT	An OGTT should be performed at 1 y and a minimum of every 3 y thereafter.	Recommend implementation of the Diabetes Prevention Program lifestyle program Also recommend additional research to establish timing and cost-effectiveness of prevention interventions to identify effective ways to deliver the intervention.

MNT, medical nutrition therapy.

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GDM in the lifestyle intervention arm had a reduction in diabetes risk that was similar to that seen in women with no history of GDM and appeared to respond more favorably to metformin[56] This finding may have been related to the younger age of the GDM-affected group; metformin appeared more effective overall in younger than older study participants.[10,56]

Studies of Hispanic women with a history of GDM have demonstrated that pharmacologic treatment of insulin resistance with the thiazolinediones troglitazone (Troglitazone in Prevention of Diabetes [TRIPOD]) or pioglitazone (Pioglitazone in Prevention of Diabetes) was associated with preservation of beta cell function[9] and reduced risk for type 2 diabetes.[8,9] Although these studies were limited to a single ethnic group, similar findings were reported from the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial, a study of more than 5000 men and women from more than 20 countries, in which another thiazolinedione, rosiglitazone, was found to reduce the risk of diabetes by 60%.[57] Therefore, it is unlikely that the bene-

TABLE 2
US studies reporting postpartum screening rates for diabetes among women with a GDM-affected pregnancy

Reference	Study design and setting	Percentage of women who received a postpartum screen for diabetes	Characteristics associated with receiving postpartum screen for diabetes
Russell et al, 2006[22]	Retrospective study at a diabetes clinic, Providence, RI, 2001-2004, n = 344	45%: FPG or OGTT	Hispanic women, compared with white women, attending the postpartum visit. Not associated with age, marital status, education, parity, prior GDM, body mass index, tobacco use, preterm delivery, cesarean section, infant birthweight, health insurance, referral source.
Kim et al, 2006[23]	Retrospective study at a University of Michigan Hospital, Ann Arbor, MI, 1997-2002, n = 577	38%: any type of glucose test[a] 23%: FPG or OGTT	Married, saw endocrinologist after delivery, higher number of visits after delivery. Not associated with prenatal insulin use, total number of prenatal visits, or visit with an obstetrician after delivery.
Smirnakis et al, 2005[24]	Retrospective study at Massachusetts General Hospital and Baystate Medical Center, Boston, MA, 2000-2001, n = 197	67%: any type of glucose test[a] 37%: FPG or OGTT	Higher mean blood glucose values from the fasting and 1 h postglucose load test during pregnancy. Not associated with maternal age, race, primary language, annual household income, insurance status, body mass index, or practice site.
Dinh et al, 2003[52]	Retrospective study at a diabetic care management program, York, PA, 2000-2001, n = 158	34%: any type of test[a]; 24%: FPG or OGTT	Not addressed.
Schaefer-Graf et al, 2002[25]	Retrospective cohort at Los Angeles County and University of Southern California Women's and Children's Hospital, Los Angeles, CA, 1987-1995, n = 4041	46%: OGTT	Younger age, no prior GDM. Not associated with other demographic characteristics, glycemic parameters, or neonatal parameters.
Conway and Langer, 1999[26]	Retrospective cohort at University Hospital in San Antonio, TX, 1995-1997, n = 1017	17.6%: OGTT	Not associated with maternal age, parity, gestational age at diagnosis, or glucose testing characteristics.
Greenberg, 1995[53]	Retrospective cohort at the University of California at San Diego Medical Center, San Diego, CA,1987-1992, n = 238	39%: OGTT	Attending 6 wk postpartum visit, provider ordering test.
Dacus et al, 1994[54]	Retrospective cohort at the Regional Medical Center at Memphis, TN, 1991-1993, n = 230	63%: OGTT[b]	Not stated.

OGTT, 75 g, 2 h glucose test.

[a] Any test included whole blood capillary, random venous glucose, glucose obtained as part of panels of laboratory tests, and hemoglobin A1c, fasting venous glucose, or oral glucose tolerance test.

[b] All 230 women were scheduled for an OGTT at 5-10 weeks postpartum as part of a research study.

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fits of thiazolinediones are confined to Hispanic women. However, current concerns remain regarding the safety of thiazolinediones, particularly with respect to cardiovascular disease and fracture risk.[58-61]

A remaining question is whether women with a history of GDM but with normal postpartum OGTT results should receive less intensive intervention than women with abnormal findings. Women with normal results may

have a lower short-term risk for type 2 diabetes compared with women who have IFG or IGT at the postpartum screening, but likely still have an elevated long-term risk compared with women who did not have GDM. The few existing US-based studies of long-term risk for type 2 diabetes that have separately examined women who have normal glycemia after delivery are limited by the duration of follow-up, which may be too short. For example, in a large cohort of Hispanic women with prior GDM,[34] women were analyzed according to the area under the glucose tolerance curve of their postpartum OGTT. Those who fell into the second or first quartiles had normal glucose tolerance. However, their 5 year cumulative incidence rates of diabetes were 27% and 12%, respectively. Although these rates are lower than the rate of 84% for women in the fourth quartile (all of whom had IGT), they are higher than an 8 year cumulative incidence rate of 3% in a separate study of Mexican American adults with normal glucose tolerance at baseline.[34,62]

Additional studies are needed to further assess diabetes risk in women who do not have IFG or IGT at postpartum screening.

It is difficult to determine from existing studies whether diabetes prevention interventions are effective in women with a history of GDM but normal postpartum glucose tolerance. Most intervention trials conducted thus far have not included individuals with normal glycemia, and duration of follow-up in existing studies may be too short, given the lower risk in this group. For example, in the TRIPOD study, women were followed up for a median duration of 30 months. Women with normal glucose tolerance at baseline were not excluded, but the incidence of diabetes in these women was low, precluding meaningful analysis of the effects of treatment in this group.[8]

Likewise, in the Xenical in the Prevention of Diabetes in Obese Subjects study, orlistat plus a lifestyle intervention significantly reduced the risk of diabetes, compared with lifestyle intervention alone, in subjects with IGT at baseline, but a protective effect was not discernible in the subgroup of obese adults with normal glucose tolerance at baseline. The latter finding is perhaps because individuals with normal glucose tolerance were at relatively low risk for diabetes, and the study did not have adequate power to detect a protective effect in the relatively short follow-up period.[14] Additional research is needed to determine the efficacy of diabetes prevention interventions in women with normal glycemia at their postpartum assessment.

The major organizations previously discussed have addressed diabetes prevention for women with a history of GDM (Table 1). Recommendations from the Fifth International Workshop state that providers and researchers should "support public health initiatives such as . . . the National Diabetes Education and Prevention for GDM Initiative for implementation of the Diabetes Prevention lifestyle program into the public sector."[45] The ADA recommends that all women with a history of GDM should be educated about lifestyle modifications, whereas those with IFG or IGT at postpartum screening should receive intense medical nutrition therapy and an individualized exercise program.[43] The ACOG states that women with additional risk factors (such as early-onset GDM or obesity) should receive counseling regarding diet, exercise, and weight management to prevent or delay type 2 diabetes.[42]

However, evidence suggests that helping women manage their weight and increase their physical activity during the postpartum period will be challenging. Previous trials evaluated education, goal setting, counseling, and follow-up by telephone or mail but had high attrition rates, and participants achieved only modest success in reaching their goals.[63-65] Furthermore, because women of reproductive age may seek care from different types of providers over time, there is no clear mechanism to ensure they receive appropriate follow-up.

Finally, previous randomized trials of lifestyle interventions to prevent diabetes often have used intensive interventions with multiple counseling sessions and multiple years of follow-up; compliance with this type of intervention may be particularly difficult for women with infants or young children. Therefore, interventions previously used in diabetes prevention trials may need to be modified to produce meaningful improvements in future diabetes risk among women with a recent history of GDM.

Comment

In the United States, antepartum screening for GDM is nearly universal,[51,66] offering an opportunity for type 2 diabetes risk assessment that is far-reaching. Screening for GDM may identify up to 31% of parous women who will later develop type 2 diabetes[67] and has the potential added advantage of identifying at-risk women before they develop abnormal glycemia in the nonpregnant state, providing an opportunity for prevention earlier in the process of beta cell decline.

The potential public health impact of achieving universal postpartum screening is also substantial. In the United States, there are approximately 4 million live births each year. If GDM affects 5% of pregnancies (200,000 per year), postpartum screening could identify approximately 8000 women with existing type 2 diabetes and 30,000 with IFG or IGT who might benefit from prevention interventions. An additional 162,000 women with normal postpartum screening results could receive education about lifestyle modifications. From an expert panel meeting convened by the CDC in April 2007, the following recommendations and research gaps were identified.

Recommendations

Postpartum screening

All women with a GDM-affected pregnancy should have their glycemic status assessed at their postpartum visit. The OGTT is more sensitive than an FPG for detecting abnormal glycemia and diagnosing diabetes mellitus. A single set of clear, unambiguous guidelines for postpartum screening that has support from organizations representing clinicians who will be providing this service is needed; attendees at the April 2007 meeting identified ACOG's leadership in this area as critical for facilitating change in obstetrical practice.

Long-term screening

Women with a GDM-affected pregnancy should have their glycemic status assessed on a regular basis after their postpartum visit. A single set of clear, unambiguous guidelines addressing type and frequency of long-term follow-up screening is needed. These guidelines should specify the appropriate follow-up for women with normal and abnormal glycemia at postpartum screening and have support from major organizations representing clinicians who will be providing this service. Factors to consider when developing these guidelines should include the prevention of undiagnosed diabetes in subsequent pregnancies; the sensitivity, specificity, and cost of screening; and patient and provider compliance with the recommended screening procedures. Until guidelines are developed and endorsed by participating organizations, women should be screened every 1-3 years, the frequency depending on the results of their postpartum screen and the likelihood of a future pregnancy.

Obtaining high rates of long-term follow-up for women with a history of GDM will require the involvement of many types of providers, including obstetricians, internists, family practice physicians, diabetes educators, and other midlevel providers. Therefore, efficient mechanisms must be identified for communicating a woman's obstetrical history, including history of GDM, to multiple health care providers and facilities. Patients should be educated about the importance of communicating a history of GDM to their nonobstetrical providers, and nonobstetrical providers should be educated about the importance of previous GDM as a risk factor for type 2 diabetes.

Referral and interventions for diabetes prevention

Women found to have diabetes at their postpartum visit should be referred to the appropriate primary care provider or specialist for treatment. Women with IFG or IGT at their postpartum visit should receive prevention interventions that promote lifestyle modifications such as weight management and increased physical activity. Women with normal fasting glucose and glucose tolerance at their postpartum visit should receive, at a minimum, education about the benefits of weight management and increased physical activity. Women with a history of GDM but a clinical picture that is inconsistent with elevated risk for type 2 diabetes (such as lean body habitus and absence of a family history of type 2 diabetes) may benefit from referral to a specialist for further evaluation. All women with a GDM-affected pregnancy should be educated about the importance of monitoring their glucose metabolism to avoid future pregnancies affected by undiagnosed or inadequately treated type 2 diabetes.

Research gaps

Research is needed to determine how to maximize patient and provider compliance with recommendations for postpartum screening. In particular, studies are needed to determine whether the increased sensitivity of the OGTT, compared with a FPG, is offset by a potential reduction in compliance.[68] In addition, the optimal type and frequency of screening after the postpartum period has not been established.

The degree to which the risk of type 2 diabetes is elevated in women with normal glycemia in the postpartum period is uncertain. Research is needed to quantify the potential benefits of lifestyle modifications and/or pharmacotherapy in this population. Researchers may need to consider study designs using intermediate outcomes, such as rising glucose levels or conversion to IFG or IGT, rather than diabetes.

It is unknown whether and how lifestyle modification interventions used in previous diabetes prevention trials should be modified for women with a recent pregnancy. Studies of diabetes prevention interventions for this population should address how to maximize compliance in this population of women who may be overwhelmed by the demands of motherhood.

The long-term safety and efficacy of pharmacotherapy for diabetes prevention among women with a history of GDM have not been established. Future studies should include in their design consideration of the relatively young age and the likelihood of future pregnancies in this population.

In conclusion, screening pregnant women for GDM offers health care providers a unique opportunity to identify individuals at high risk for type 2 diabetes who are candidates for early treatment and prevention interventions. Identifying high-risk individuals early allows prevention interventions to begin sooner in the process of beta cell decline than would otherwise be possible in the absence of universal screening.

Health care providers and public health workers face numerous challenges in developing and implementing an intervention for this population, and it is likely that meaningful reductions in risk will require a multilevel approach that includes patient and provider education, development of efficient mechanisms for the transfer of medical information among providers, establishment of readily available interventions, and environmental changes that support physical activity and healthy eating. Translation research will be critical in addressing this important public health issue. ■

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