Approach to the Patient with Gestational Diabetes after Delivery

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The diagnosis of gestational diabetes mellitus (GDM) identifies patients with a pancreatic β-cell defect. In some patients, the defect is transient or stable, but in most it is progressive, imparting a high risk of diabetes for at least a decade after the index pregnancy. The β-cell defects in GDM can result from many causes, including genetic variants typical of monogenic forms of diabetes and autoimmunity typical of evolving type 1 diabetes. No specific disease-modifying therapies are available for those patients. The majority of women with GDM have clinical characteristics indicating a risk for type 2 diabetes (T2D). Available evidence indicates that T2D can be prevented or delayed by intensive lifestyle modification and by medications, particularly those that ameliorate insulin resistance. Clinical management should include assessment of glucose tolerance in the postpartum period to detect diabetes or assess diabetes risk. Women who don't have diabetes should be advised about their risk and participate in family planning to prevent subsequent pregnancies with undiagnosed hyperglycemia. All patients should be monitored for rising glycemia indicative of progressive β-cell deterioration. We suggest a combination of fasting glucose and glycosylated hemoglobin measurements for this purpose. Monitoring should be initiated at least annually and should be intensified if glycemia is rising and/or impaired. Lifestyle modification is advised to reduce the risk for T2D. Like monitoring, lifestyle modification should be intensified for rising glycemia and/or development of impaired glucose levels. At present, there is insufficient evidence to recommend medications to prevent T2D. Close follow-up and monitoring will allow initiation of pharmacological treatment as soon as diabetes develops. Children of women with GDM are at increased risk for obesity and diabetes. They should receive education, monitoring, and lifestyle advice to minimize obesity and diabetes risk. **(*J Clin Endocrinol Metab* 96: 3592–3598, 2011)**

The Case

A 28-yr-old Hispanic woman was diagnosed with gestational diabetes mellitus (GDM). This was her first pregnancy. She is obese, with a body mass index of 31 kg/m^2, but has no other medical problems. She has a family history of diabetes mellitus in her mother, ma-

Abbreviations: A1C, Hemoglobin A1C; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; T2D, type 2 diabetes.

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- Recognize the risk of diabetes after gestational diabetes and the spectrum of causes of beta cell dysfunction that underlie that risk
- Select clinical approaches to reducing diabetes risk and assess success of those approaches

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ternal aunt, and brother. She gained 35 pounds during pregnancy and had no pregnancy complications other than obesity and GDM. She had an uncomplicated vaginal delivery of a healthy girl weighing 8 pounds 10 ounces at 39 wk gestation. The mother's 75-g oral glucose tolerance test at 18 wk gestation revealed a fasting glucose of 109 mg/dl, 1-h glucose of 220 mg/dl, and 2-h glucose of 186 mg/dl. She was unable to achieve target glucose levels with diet and exercise, and insulin was begun at 22 wk gestation. Thereafter, the majority of her pre- and postmeal glucose levels met therapeutic targets. Insulin was discontinued immediately after delivery, and her fasting glucose levels were normal before discharge from the hospital. She opted to breast-feed her baby. She wants to have more children eventually, but she would like to discuss contraception options for the immediate future.

Background

This patient was diagnosed with GDM based on glucose intolerance that was first detected during pregnancy (1). She is not alone. Incidence rates of GDM have been in the range of 4–12% over the last decade, and there is evidence that the incidence is increasing (2, 3), perhaps due to rising rates of obesity.

From the physiological standpoint, GDM identifies women whose pancreatic β-cells compensate inadequately for insulin resistance during pregnancy. Available evidence indicates that this β-cell defect is not specific to pregnancy—it exists before and after pregnancy in many, or probably most, cases (4). Thus, GDM can be thought of as detection of an underlying β-cell defect through routine glucose screening in pregnancy. In many cases, the β-cell defect worsens over time, imparting a high risk of diabetes after the index pregnancy. The β-cell defects of GDM result from many causes, including autoimmunity typical of type 1 diabetes, single gene variants typical of maturity onset diabetes of the young or maternally inherited diabetes, and chronic insulin resistance typical of type 2 diabetes (T2D). The majority of women have clinical characteristics suggesting chronic insulin resistance and evolving T2D.

From the clinical standpoint, GDM is associated with increased pregnancy risks to the mother, including higher rates of preeclampsia and operative delivery, and increased perinatal risks to the baby, including higher rates of birth injury and macrosomia (5). GDM also confers long-term health risks for the mother and child. Mothers have a 20–60% risk of developing diabetes within 5–10 yr after their index pregnancy (6). Children have an increased risk of obesity and diabetes during childhood and adolescence (7–11). Hence, postpartum screening and diabetes prevention strategies are critical for both mother and child. Due to space limitations, we will focus this Approach to the Patient on clinical management of the mother and address: 1) current practice guidelines for postpartum screening and monitoring for diabetes; 2) factors associated with increased risk for diabetes; 3) strategies to delay or prevent diabetes; and 4) areas of uncertainty, including a brief discussion of management of children from GDM pregnancies.

What to Do after Hospital Discharge

Postpartum screening for diabetes: when to screen and what to measure

Professional organizations generally agree that diabetes screening for women with GDM should occur around the time of the first postpartum visit. At that time, a small fraction of patients have diabetes and a larger fraction (~25% in some studies) have impaired glucose levels, which portend a particularly high risk of diabetes in the next 5 yr (12). The American Diabetes Association (ADA) recommends screening at 6–12 wk after delivery, and the World Health Organization recommends screening at least 6 wk after delivery. Both organizations suggest a 75-g oral glucose tolerance test (OGTT) (1, 13). The United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommends screening with a fasting glucose at the 6-wk postpartum visit (5). There are currently no official guidelines for the use of hemoglobin A1C (A1C) as a screening test in the postpartum period, when the impact of pregnancy and perinatal blood loss on red cell turnover could alter glucose–A1C relationships. Other measures of glycemic control, such as fructosamine testing, could be considered. Although plasma fructosamine levels are not used for diagnosis of diabetes or included in any official guidelines, they are not affected by pregnancy or blood loss and could be evaluated at the initial postpartum visit to assess average glucose levels over the past 2- to 3-wk period.

Continued monitoring for diabetes after the postpartum period is also important. The ADA recommends reassessment at no greater than 3 yr if glucose levels are normal at the postpartum visit. Reassessment at 1 yr is recommended if postpartum glycemia is impaired. Options for long-term screening include A1C, fasting glucose, and a 75-g OGTT. The diagnosis of diabetes is made if the A1C is at least 6.5%, fasting plasma glucose is at least 126 mg/dl, and/or 2-h plasma glucose is at least 200 mg/dl on a 75-g OGTT (14).

What we recommend

There are really two considerations for the mother. The one that is the focus of the recommendations in the previous paragraph is whether she has diabetes or impaired glucose levels. This can be determined by an OGTT in the postpartum period and A1C measurements thereafter. Finding diabetes indicates a clear need for treatment; finding impaired glucose or A1C levels should heighten efforts at diabetes prevention (see below) and increase the frequency of screening to at least annually. The other important consideration, one that is generally overlooked in "official" recommendations and in clinical practice, is whether the mother's glucose levels are rising. Rising glucose is the best available clinical indicator that β-cell function is falling, and falling β-cell function leads to diabetes (15). We suggest measuring A1C at least annually for several years after the index pregnancy. If it remains stable, the interval between measurements can be lengthened gradually. If A1C rises, even within the normal range, monitoring should continue at least annually, and efforts to halt progression (see below) should be intensified.

In addition to screening for diabetes, close follow-up of women with a history of GDM provides an opportunity for early detection and treatment of metabolic disorders closely associated with obesity and insulin resistance. Thus, we suggest routine monitoring for signs and symptoms of polycystic ovary syndrome, obstructive sleep apnea, nonalcoholic steatohepatitis, hyperlipidemia, and hypertension. Clinical features suggestive of polycystic ovary syndrome include menstrual cycle irregularities, hirsutism, acne, and male pattern baldness. Symptoms of obstructive sleep apnea include daytime sleepiness, snoring, and restless sleep. Elevated serum liver transaminases may suggest nonalcoholic steatohepatitis. Hypertension is diagnosed by routine blood pressure monitoring, and lipid abnormalities are diagnosed by screening fasting lipid levels. Body mass index should be closely followed so that lifestyle modifications can be initiated early to help prevent weight gain.

Factors That May Influence Diabetes Risk

Most, but not all women with a history of GDM have falling β-cell compensation for chronic insulin resistance during the first 5–10 yr after the index pregnancy. In this setting, two general factors influence the risk of diabetes. The first is the level of metabolic deterioration that is present during and soon after pregnancy. In general, women with the highest glucose levels (*e.g.* impaired fasting or 2-h glucose or impaired A1C after pregnancy, women given insulin for hyperglycemia during pregnancy, women diagnosed relatively early in gestation) are closest to diabetes and require relatively little deterioration to "cross the line" to that diagnosis. They are clearly prime targets for aggressive measures to prevent additional deterioration to diabetes. The second general factor that influences diabetes risk is the rate of deterioration. Rising glucose is a clinical indicator of deterioration. Factors that may influence that rate and, thereby, diabetes risk include weight gain, use of progestin-only contraception (16–18), and additional pregnancies (19, 20). The common factor among them is insulin resistance, which should be avoided or treated to minimize diabetes risk.

Contraceptive options

Family planning is important for women with prior GDM to minimize the risk of birth defects that can occur if a woman conceives while hyperglycemic. Contraception could also be important to women who wish to avoid the potential impact of additional pregnancies to increase the diabetes risk. Nonhormonal methods like intrauterine devices and tubal ligation are metabolically neutral and should not impact diabetes risk. Hormonal methods differ in their impact on diabetes risk (16–18, 21). Low-dose estrogen-progestin combination oral contraceptives do not appear to increase the risk of diabetes. Progestin-only preparations have been associated with increased diabetes risk in two settings— during breast-feeding, when estrogen levels are generally low (16), and during chronic use of depo-medroxyprogesterone acetate, an injectable contraceptive that promotes weight gain (17, 18). In both settings, the associations with diabetes risk are from nonrandomized observational studies, so a cause-and-effect relationship has not been established clearly. Nonetheless, we recommend that progestin-only preparations not be the first choice for women with prior GDM. If other clinical considerations make progestin-only contraception the best choice in an individual patient, we recommend careful monitoring of glucose levels.

Breast-feeding

Breast-feeding is associated with reductions in glucose levels in women with recent GDM (22) and with postpartum weight loss, an important modifier of diabetes risk (23). Thus, breast-feeding may have beneficial effects on glucose tolerance for women with recent GDM.

Prevention and Treatment

GDM is detected through routine clinical care. There is some evidence that a history of GDM may impart a higher risk of diabetes than otherwise predicted by glucose intolerance in nonpregnant individuals (24). Thus, women

with GDM represent an important and potentially cost-effective subset of the population for diabetes prevention. As discussed below (see *Controversies and Areas of Uncertainty*), most women with GDM have clinical characteristics suggesting a risk of T2D. Thus, the growing body of clinical trial evidence on how T2D may be delayed or prevented should be relevant to women with GDM. In addition, some of the published diabetes prevention studies have included women with prior GDM, providing clinical evidence specifically relevant to those women (24, 25).

Evidence from diabetes prevention trials suggests that interventions aimed at reducing body fat, through lifestyle modification in the Finnish Diabetes Prevention Study (DPS) (26) and U.S. Diabetes Prevention Program (DPP) (27), or mitigating the adverse metabolic effects of adiposity with thiazolidinediones (25, 28, 29) have the strongest effects to slow or arrest disease progression. Among pharmacological interventions, thiazolidinediones have the largest impact on diabetes risk reduction—in the range of 55–70% compared with placebo. Interventions such as metformin or acarbose that primarily lower glucose produce smaller risk reductions (25–33%) and provide less evidence for slowing of rates of progression in general (30). However, in the DPP (24), metformin had a particularly strong effect to reduce diabetes risk in women with a history of GDM. Thus, the armamentarium for diabetes risk reduction after GDM includes lifestyle modifications to reduce obesity and pharmacological agents such as metformin and thiazolidinediones.

The question of when to use what from this armamentarium has not been the subject of randomized clinical trials. Thus, the best we can do right now is to make recommendations based on our understanding of disease biology and extrapolations from the existing prevention trial data. Lifestyle modification has potential benefits not only in reducing diabetes risk, but also in mitigating other morbidities associated with obesity, and increased physical activity can improve metabolic abnormalities even in the absence of weight loss. Thus, programs to reduce caloric intake and increase physical activity (26, 27) should be the initial step in diabetes prevention after GDM. Although prevention trials using this approach are limited to people who have impaired glucose levels, the very high risk of diabetes in the decade after GDM— even in women who have normal glucose levels right after pregnancy—suggests that lifestyle modification should be prescribed to all women with a history of GDM and clinical characteristics of potential T2D. Whether pharmacological therapy should be prescribed for diabetes prevention is an open question. Our view is that pharmacology should be added only when there is evidence that lifestyle modification has failed to achieve the desired outcome. As discussed above (see *What to Do after Hospital Discharge*), the usual definition of such failure is development of diabetes. Rising glucose or A1C levels provide an earlier indication that lifestyle changes have failed to arrest β-cell deterioration. We have shown that waiting to add drug therapy (specifically, thiazolidinedione) until diabetes develops can arrest β-cell decline, albeit at a lower level of β-cell function than when medications are used for prevention (31). Thus, we favor withholding pharmacological treatment until diabetes develops, keeping in mind that we also favor monitoring of A1C levels at 3- to 6-month intervals once glucose levels are impaired to get a solid handle on rates of deterioration and to diagnose diabetes as early as possible.

Controversies and Areas of Uncertainty

The child

There is good evidence that offspring of mothers with GDM are at increased risk for obesity and diabetes during childhood and adolescence (7–11). However, this field has not yet evolved evidence-based approaches to clinical management. Although prospective studies and randomized trials have not been done, there is evidence from retrospective cohort studies that breast-feeding is associated with decreased childhood obesity and reduced development of T2D during childhood (32, 33), and that breast-feeding for at least 6 months has a protective effect on childhood adiposity among children exposed to diabetes *in utero* (34). Future research is necessary to examine the effects of lifestyle measures to minimize obesity in children exposed to maternal diabetes *in utero*. For now, potential strategies could include promotion of breast-feeding, implementation of lifestyle measures to minimize obesity in early childhood, and regular monitoring of fasting glucose or A1C levels, particularly in overweight and obese children.

Unusual subtypes of GDM

Most of the information presented above is relevant to patients who have clinical characteristics of T2D (*e.g.* obesity, advanced maternal age, high-risk ethnicity). In fact, 10–15% of women with GDM may have other forms of β-cell dysfunction. Some have autoantibodies to islet or β-cell antigens, suggesting evolving type 1 diabetes. The frequency appears to reflect the contribution of type 1 diabetes in the background population (highest in women of European ancestry, lowest in Hispanic and Native American women). Other patients may have maturity onset diabetes of the young or maternally inherited diabetes that is first detected in pregnancy. There is very little high-quality clinical evidence on which to base recommenda-

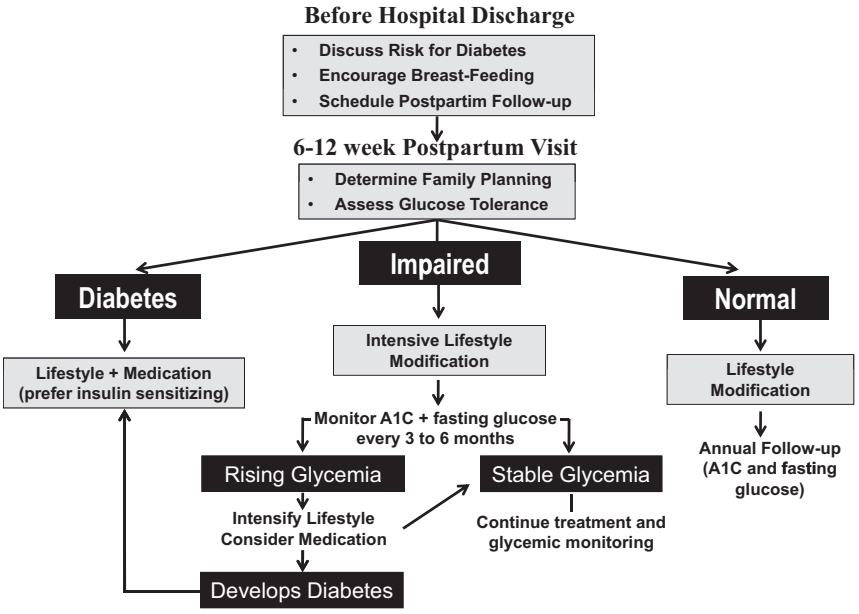

FIG. 1. Diagram depicting management of patients with prior GDM. Postpartum glucose tolerance testing is used to assess current status of glycemic regulation. Thereafter, fasting glucose and A1C measurements are used to determine whether glycemic regulation is stable or deteriorating. Deteriorating glycemic regulation leads to progressively more intense monitoring and interventions aimed primarily at reducing insulin resistance to stabilize or restore β-cell function. The interventions are for women with clinical characteristics suggesting a risk of T2D. See text for other subtypes.

tions for detection and management of such patients. We suggest measuring anti-glutamic acid decarboxylase antibodies in lean women of European ancestry who have GDM and little or no family history of diabetes. No specific diabetes preventatives are currently available for women who are anti-glutamic acid decarboxylase positive, but they may deteriorate rapidly and should be monitored closely for worsening hyperglycemia. Women with a family history suggesting an autosomal dominant or maternally inherited form of diabetes should be considered for genetic testing for maturity onset diabetes of the young or maternally inherited diabetes.

New diagnostic criteria

It appears that the incidence of GDM could double when new diagnostic criteria from the International Association of Diabetes and Pregnancy Study Groups are applied to clinical care. The criteria are based primarily on results from the Hyperglycemia and Adverse Pregnancy Outcomes study (35) and are designed to detect pregnancies with some increased perinatal risks. The new criteria base the diagnosis of GDM on at least one plasma glucose value on a 75-g OGTT that is at or above thresholds of 92 mg/dl (5.1 mmol/liter) fasting, 180 mg/dl (10 mmol/liter) at 1 h, or 153 mg/dl (8.5 mmol/liter) at 2 h. The criteria are slightly lower than prior criteria recommended by the ADA for a 100-g OGTT, and only one abnormal value is required, so the additional cases of GDM will have less severe hyperglycemia than has been the case in the past. Virtually nothing is known about the long-term diabetes risk or approaches to modifying that risk in women who meet the new criteria, but not older ones. At present, it seems prudent to advise lifestyle modifications and monitor glucose or A1C values for developing diabetes, pending long-term studies to define approaches to management.

Returning to the Patient (Fig. 1)

Our patient has several risk factors associated with a high risk of diabetes after GDM: obesity, diagnosis early in pregnancy, high glucose levels on OGTT, and treatment with insulin during pregnancy. Like all women with GDM, she should have assessment of her glucose levels at 6–12 wk postpartum. We suggest an OGTT to define where she sits in the clinical spectrum of glucose tolerance, which will in turn guide the intensity of intervention and follow-up. She should receive early counseling about her increased risk for diabetes and about her child's risk for obesity and diabetes. Family planning and contraceptive options should be discussed, and she should be encouraged to use a highly effective form of contraception. Progestin-only methods should be discouraged because of their association with weight gain and increased diabetes risk. Breast-feeding should be encouraged and may help with postpartum weight loss, an important modifier of diabetes risk. Importantly, breast-feeding may also reduce her baby's future risk for obesity and diabetes.

The patient's obesity and ethnicity suggest that her diabetes risk is for type 2, so she should be counseled about lifestyle modification to reduce obesity. If she proves to have impaired glucose levels at her postpartum evaluation, she would be a strong candidate for the type of intensive lifestyle changes implemented in the DPS (26) and DPP (27). Even if she has normal glucose levels postpartum, she may progress to impaired glucose levels in the next several years. Weight loss should be encouraged, and she should have an assessment of fasting glucose and A1C at least annually until it becomes apparent whether her disease remains stable or progresses with rising glucose or A1C levels. Whether pharmacological treatment at the stage of impaired glucose levels will provide a better long-term

outcome than waiting until diabetes first develops is unknown. We suggest reserving pharmacological therapy for diabetes but diagnosing the disease early through careful monitoring of A1C levels. Based on data from diabetes prevention and early treatment studies, we recommend the use of insulin sensitizers (metformin and/or thiazolidinedione) as initial treatment when diabetes develops. Finally, the patient should be advised that weight loss may reduce her risk of developing GDM if she elects to have more children.

Conclusions

The diagnosis of GDM identifies relatively young women with a significant defect in pancreatic β-cell function. In most of those women, the β-cell dysfunction worsens over time, leading to diabetes. The majority of cases occur on a background of chronic insulin resistance, which appears to be causally involved in worsening of the β-cell defect. Conversely, the β-cell defect can be slowed or stopped by effective treatment of insulin resistance. Weight loss and medications that mitigate insulin resistance show the best promise for delaying or preventing T2D, the dominant form of diabetes that develops after GDM. Current recommendations for postpartum screening and subsequent monitoring are based on categorical definitions of glucose tolerance that are relatively insensitive to the progressive deterioration of β-cell function that leads to diabetes. Clinical management should combine regular evaluation of glycemia (*e.g.* A1C) with measures to reduce insulin resistance (especially weight loss and increased physical activity). The intensity of glycemic monitoring and lifestyle changes should increase if there is evidence of deterioration in glucose or A1C levels. At present, there is insufficient evidence to recommend pharmacological treatment until diabetes develops. At that time, a focus on drugs that enhance insulin sensitivity shows the best promise for slowing or arresting the β-cell disease. Management of diabetes risk in the mother should be coupled with appropriate family planning and with efforts to detect and minimize the development of obesity in her children to arrest the vicious cycle of transgenerational diabetes that may be contributing to the worldwide epidemic of diabetes today.

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