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GUEST EDITORIAL

Lois Jovanovic, MD, FACE, FACP, FACN
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THE IMPORTANCE OF PRECONCEPTION CARE IN WOMEN WITH PREEXISTING DIABETES

Experts agree that updated guidelines for the treatment of diabetes in pregnancy are needed. The American Diabetes Association (ADA) is developing new guidelines to address this, but in the meanwhile, CADRE brings you this issue of *CADRE'S Current Diabetes Practice* to shed light on the argument for more aggressive treatment approaches.

More pregnancies are complicated by diabetes than clinicians realize. Limited data are available, but a recent 12-year retrospective review of New York City birth certificates found that 4.2% of all pregnancies in 2001 were complicated by diabetes. The majority of cases were gestational diabetes mellitus (GDM), while the remainder involved women with preexisting diabetes. Generalization to the US population, with 4,022,000 births in 2002, would indicate that nearly 170,000 pregnancies are complicated by diabetes annually.

When maternal diabetes is left untreated or is undiagnosed during pregnancy, severe fetal complications can occur. The consequences of diabetic embryopathy, which include spontaneous abortion and birth defects such as congenital heart disease, musculoskeletal deformities, and central nervous system deformities, are all sustained during the critical period of organogenesis (the first 6 to 7 weeks of pregnancy) and are a direct result of maternal hyperglycemia during that time.

If metabolic control is achieved prior to conception and maintained throughout

pregnancy, women with diabetes have as good a chance of a positive outcome as anyone else. However, compared with the general population, a woman with inadequately controlled preexisting diabetes has a 2- to 5-fold higher risk of delivering a baby with a significant congenital anomaly. A great deal of this excess risk can be attributed to a lack of preconception planning.

Unfortunately, in the majority of pregnancies complicated by preexisting diabetes, women only present for treatment after conception has occurred. This topic is explored in more detail in a case study presented in the Diabetes Tactics section of this issue of *CADRE'S Current Diabetes Practice*. Other women, however, will recognize that there are special considerations associated with ensuring a healthy pregnancy. It is in hopes of improving our ability to partner with these women that this article proposes several major areas to be addressed before any woman with a history of diabetes (either current diabetes or prior GDM) can be considered in an ideal position to conceive.

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ABOUT THE COUNCIL FOR THE ADVANCEMENT OF DIABETES RESEARCH AND EDUCATION

The Council for the Advancement of Diabetes Research and Education (CADRE) is a nonprofit organization committed to reducing the devastating complications of both type 1 and type 2 diabetes through achievement of tight metabolic control.

To achieve this goal, CADRE provides health care professionals with scientific information and educational programs to enable them to manage and empower their patients with diabetes.

CADRE'S CURRENT DIABETES PRACTICE

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Ensure Glucose Control: "Tight" Is No Longer Tight Enough

During the first 8 weeks of pregnancy, A1C levels are the primary tool available to assess the risk of fetal malformation. Epidemiologic research shows that A1C levels in the normal range (ie, 4% to 6%) during this time period are associated with congenital malformation rates similar to those in nondiabetic pregnancies. Therefore, prior to conception, a woman's A1C level should be as near normal as possible, absent hypoglycemia. This recommendation cannot be stressed strongly enough. The standard A1C target for a nonpregnant patient (<7%) is not a reasonable goal for a woman planning a pregnancy; only an A1C at or near the normal range is.

To achieve this goal, women with pre-existing type 2 diabetes mellitus (T2DM) must stop using all oral antihyperglycemic agents and switch to insulin treatment. Although metformin has been used safely during pregnancy in women with polycystic ovarian syndrome, with some evidence indicating that this treatment helps to reduce spontaneous abortion in this population, metformin use during pregnancy complicated by T2DM has not been studied comprehensively and is not currently recommended.

Alternately, women with T2DM can engage in aggressive prepregnancy lifestyle management (consisting of physical activity and weight loss). However, even if women are successful at achieving glucose control using lifestyle management alone, this may not preclude their need for insulin therapy during pregnancy. Women who are already receiving insulin will often need their regimens fine-tuned and intensified. If the treating health care provider does not have the time, staff, or opportunity to provide this kind of intensive counseling, the woman must be referred to a diabetes center or diabetes educator. Ideally, she should be referred to a clinic that applies a team-centered approach to diabetes care.

Consideration also needs to be given to the insulin selected for treatment. Inhaled insulin and insulins detemir, glargine, and glulisine are labeled as pregnancy category C and are not recommended for use during pregnancy. A more detailed discussion of this issue can be found in the Diabetes Tactics section of this newsletter.

Next, the woman will need to establish a rigorous self-monitoring of blood glu-

If metabolic control is achieved prior to conception and maintained throughout pregnancy, women with diabetes have as good a chance of a positive outcome as anyone else.

cose (SMBG) schedule of testing up to 8 times a day, to include fasting and 1-hour postmeal values at a minimum, as well as premeal, bedtime, and 3:00 AM values as needed. She should be taught to record her results and look for patterns; prior to conception, all SMBG readings should be at target levels. To accomplish this goal, the woman will need easy access to health care staff, sometimes off-hours, for assistance adjusting her insulin regimen.

Both during the preconception period and throughout pregnancy, premeal and fasting glucose target levels should be <90 mg/dL. Prior to conception, an acceptable 1-hour postmeal glucose goal is <150 mg/dL; however, an ideal goal is <120 mg/dL, as this will become the target once pregnancy is confirmed (Table 1). Although these targets are quite stringent, available evidence indicates that adherence will lead to decreased rates of any minor or major negative event associated with diabetic pregnancy.

Any woman with a history of GDM should also have her glucose levels evaluated prior to conception. Ideally, women with a history of GDM should have their glucose levels tracked regularly postpartum. This issue is addressed more fully *Continued*

Table 1. Recommended Blood Glucose Targets for Women With Preexisting Diabetes, Preconception and Postconception

	Preconception	Postconception
Premeal (fasting)	60-90 mg/dL	60-90 mg/dL
1-Hour postmeal	<150 mg/dL	<120 mg/dL
A1C	<6.5%	<5% (to be achieved within first trimester)

by Thomas Buchanan in the Literature Corner in this newsletter. Women with prior GDM should have a fasting plasma glucose (FPG) measurement taken either prior to conception or as soon after conception as possible. Any woman with an FPG in excess of 95 mg/dL postconception already meets the American Diabetes Association criteria for GDM diagnosis and should be evaluated and treated as if she has preexisting diabetes.

Last, in women with preexisting diabetes, the timing of the final preconception A1C test should be synchronized with the last day of the woman's menstrual cycle. If the woman's A1C levels are normal, she has "permission" to try and conceive. If she does not become pregnant, the process should be repeated each month until conception occurs. However, there is no evidence to support the need for several consecutive months of normal A1C tests prior to conception.

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Assess the Woman's Retinopathy Status

The rapid normalization of blood glucose during or prior to pregnancy can trigger the development of diabetic retinopathy. This risk can be reduced by achieving enhanced metabolic control more gradually during the preconception period. Therefore, a baseline dilated retinal exam by an ophthalmologist is an essential part of preconception care. If any retinopathy is found, pregnancy should be delayed until retinal status is stabilized. A woman with no evidence of retinopathy should be counseled on her approximately 10% risk of developing retinopathy during pregnancy.

Assess Blood Pressure and Kidney Function

To prevent the worsening of diabetic nephropathy or retinopathy during pregnancy, preexisting hypertension (blood pressure >120/80 mm Hg) must be addressed. Women with drug-managed hypertension may need to establish new treatment regimens, as some medications, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker drugs, are contraindicated during pregnancy. Calcium channel blockers should generally not be used during the first 12 weeks of pregnancy. Methyldopa and hydralazine are the only blood pressure medications currently considered acceptable for use in pregnancy. Other medications, such as labetalol or nifedipine, should only be used if the expected benefit outweighs the risk.

Women with uncontrolled blood pressure who are not yet pregnant might benefit from the short-term use of ACE inhibitors, as these are among the most effective medications available to lower blood pressure and improve proteinuria. Once blood pressure levels are normalized, the ACE inhibitor should be discontinued and the regimen readjusted. If this course of action is chosen, the woman must be willing to use a highly effective contraceptive method (such as oral contraception) until preconception evaluation confirms that it is relatively safe to conceive.

Women with T1DM or T2DM have substantively different pregnancy-related risks than women with GDM.

Since renal insufficiency can also have serious negative effects on fetal growth and development, a preconception baseline assessment of renal function is essential and should include a 24-hour urine for creatinine clearance, total protein excretion, and microalbuminuria. A woman with renal disease (creatinine clearance <50 mL/minute and/or serum creatinine >2 mg/dL) is at increased risk for fetal morbidity and mortality. Heavy proteinuria (>2 g/24 hours alone, >300 mg/24 hours when accompanied by hypertension) is another cause of poor pregnancy outcomes. In the presence of the latter, pregnancy should be discouraged.

Refer the Woman for a Full Gynecologic Exam

A full obstetric and gynecologic history and exam is the final key component of preconception care. Women should be questioned about menstrual history, infertility, and prior pelvic or reproductive tract infections, as well as previous pre- and perinatal complications, spontaneous abortions, congenital defects, and neonatal complications. Women should also be advised to curtail smoking and alcohol use at this time, as well as to initiate supplementation with a multivitamin containing folate. For more information on nutrition management during pregnancy complicated by diabetes, please see Davida Kruger and Melinda Maryniuk's article in the Practice Pointers section of this issue of *CADRE's Current Diabetes Practice*.

Many health care providers believe erroneously that GDM is a catchall term that describes the condition of a pregnant woman with any type of diabetes. However, women with type 1 diabetes

Continued

mellitus (T1DM) or T2DM have substantively different pregnancy-related risks than women with GDM. It is essential, therefore, that women with preexisting diabetes find an obstetrician/gynecologist (OB/GYN) experienced in the care of her type of diabetes. “Experienced,” in this case, means an OB/GYN who manages more than 5 similar cases a year and is familiar with the pertinent medical literature.


Special Cases: When the Woman Is Already Pregnant

Unfortunately, fewer than half of women with diabetes engage in preconception planning, and the majority of these women present for prenatal care with poorly controlled blood glucose. When faced with this difficult situation, there are several steps that the clinician should take immediately.

Although not highly accurate in detecting birth defects in early pregnancy (<12 weeks’ gestation), fetal sonogram should be used to measure crown-to-rump length. This measurement, in turn, can be correlated with calculated gestational age based on the first day of the woman’s last menstrual period. If crown-to-rump length is shorter than expected, congenital malformations should be suspected. However, physicians must also consider that the fetus may simply be small for gestation or that the woman did not correctly recall the start date of her last menstrual period.

Next, the woman’s A1C level must be measured. If a woman presents beyond her first trimester with poorly controlled A1C levels, it is safe to assume that her A1C levels were uncontrolled during organogenesis as well. With these factors in mind, the physician and patient must work together to determine whether or not to continue the pregnancy. Health care providers should temper their guidance to women with elevated A1C levels, especially when presented with potential fetal sonographic abnormalities. If the woman is considering terminating her pregnancy, it might be best to support this decision.

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Insulin Therapy: Emerging Concepts in Insulin Use and Delivery		
LOCATION	DATE	FACULTY
Dearborn, MI	Wednesday, September 6 2:00 - 3:15 pm	John M. Flack, MD, MPH Wayne State University School of Medicine Detroit, MI
Philadelphia, PA	Wednesday, September 27 10:45 am - 12:00 pm	Paul S. Jellinger, MD, MACE The Center for Diabetes and Endocrine Care University of Miami School of Medicine Hollywood, FL
Melville, NY	Friday, September 29 3:15 - 4:30 pm	William V. Tamborlane, MD Yale University School of Medicine New Haven, CT
Manhattan, NY	Wednesday, October 4 7:45 - 9:00 am	Mary Ann Banerji, MD, FACP SUNY Health Science Center Brooklyn, NY
Tampa, FL	Saturday, October 7 10:45 am - 12:00 pm	Lawrence Blonde, MD, FACP, FACE Ochsner Clinic Foundation New Orleans, LA
San Jose, CA	Thursday, November 9 10:45 am - 12:00 pm	Lawrence Blonde, MD, FACP, FACE Ochsner Clinic Foundation New Orleans, LA
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Atlanta, GA	Thursday, December 14 2:00 - 3:15 pm	Vivian Fonseca, MD Tulane University Health Sciences Center New Orleans, LA

If the woman chooses to terminate her pregnancy, she should be encouraged to begin a protocol of glycemic control and preconception planning in preparation for a subsequent pregnancy. She should be referred for counseling and reminded that the termination of this pregnancy will offer her the opportunity to prepare for a future, healthy pregnancy. Alternately, if she wishes to continue her pregnancy, the physician should immediately implement intensive glycemic control measures. 

Suggested Reading

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DIABETES TACTICS

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URGENT EARLY INTERVENTION IN A PREGNANT PATIENT WITH PREEXISTING DIABETES

Case Presentation

Maria is a 22-year-old Caucasian female with a 20-year history of type 1 diabetes mellitus (T1DM). She has recently switched health care providers and has come to her new physician’s office this morning with the news that she is pregnant.

Based on a pregnancy test, combined with her self-reported last menstrual period (LMP), Maria is at 7 weeks’ gestation. She is 5 feet 7 inches tall and weighs 137 lb, with a body mass index of 21.5 kg/m². Her current insulin regimen consists of 27 U of glargine daily, taken in the evening before bed. Maria does not self-monitor her blood glucose levels (SMBG) regularly, and her most recent A1C measurement was 7.6%. She is also taking an angiotensin-converting enzyme (ACE) inhibitor for previously

There have been no clinical trials of insulin glargine during pregnancy, and case study reports have not been encouraging.

documented proteinuria. A review of Maria’s medical history shows that she has mild retinopathy.

Maria’s medical records over the past several months indicate that she tends to have high fasting plasma glucose (FPG) levels in the morning; this morning, her FPG is 187 mg/dL. Because of this, her prior physician increased her daily glargine dosage from 17 U to its current 27 U, in order to treat what was referred to as an “insulin issue.” However, in conversation today, Maria describes regularly feeling a “blood sugar crash” in the middle of the night. Maria does not measure her blood glucose levels when this occurs, but does tend to overeat in response to this problem.

Maria’s blood pressure is 132/83 mm Hg. Additional laboratory results show her creatinine clearance is 57 mL/minute with protein levels of 320 mg/24 hours. Her white blood cell count is 12,500, with mostly polymorphonuclear cells. Although pregnancy blurs the identification of urinary tract infections based on white blood cell count, Maria’s urine culture is positive for an infection. Her free thyroxine (T₄) level is 0.7 ng/dL (T₄ levels during pregnancy should range from 1.0 to 1.6 ng/dL), her thyroid-stimulating hormone (TSH) level is 4.9 μIU/mL (a normal level during pregnancy is <2.5 μIU/mL), and her C-peptide is undetectable.

Sonogram results show that Maria’s fetus looks smaller than the expected gestational week. Specifically, the crown-to-rump length appears closer to 5 weeks’ gestation.

Analysis

Preconception care is essential for women with preexisting diabetes, both for the protection of the health of the patient and for the viability of her pregnancy. Unfortunately, Maria was unable to address these issues prior to conceiving and is therefore starting at a deficit.

Of particular concern is Maria’s hyperglycemia. Inadequate glycemic control during preconception and the period of

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organogenesis (which is complete by the eighth gestational week) significantly increases the risk of macrosomia, as well as congenital malformations such as neural tube defects (eg, spina bifida, caudal agenesis, anencephaly); cardiac anomalies including septal defects, patent ductus arteriosus, and situs inversus; and renal anomalies such as horseshoe kidney or agenesis. The fact that the sonogram shows the fetus as small for gestational age is a further cause for concern, as this may indicate an increased risk of birth defects. If we take Maria’s reported LMP as fact, we are left with 1 week in the critical period of organogenesis, so immediate action is necessary.

One culprit for Maria’s poor glycemic control may be food chaos. Given her self-described eating patterns, it seems that she is eating too much at night in order to compensate for feelings of low blood sugar. This eating response is causing elevated FPG in the mornings, which led her previous doctor to increase her glargine dosage. This is creating a vicious cycle, wherein the excess insulin causes

Continued

Maria's blood glucose to “crash” at night, which in turn leads her to eat more, and so on. Maria requires an improved insulin dosage to achieve better basal and meal-related boluses.

There have been no clinical trials of insulin glargine during pregnancy, and case study reports to date have not been encouraging, with mothers not achieving glucose control equivalent to NPH and infants showing elevated mean birth weights. Since this fetus is already at an increased risk for birth defects, continuing treatment with glargine raises numerous concerns. Most importantly, the profile of insulin glargine is too flat for this patient; Maria needs less insulin for the period between midnight and 4:00 AM and then increasing amounts from 4:00 AM until at least 10:00 AM. One daily injection of a 24-hour flat insulin will not address her changing needs around the clock.

Maria is also hypertensive; her blood pressure should ideally be lowered to <120/80 mm Hg. This goal is based on new American Diabetes Association T1DM pregnancy guidelines (publication pending). Furthermore, her protein is >300 mg/24 hours, which is associated with poor pregnancy outcomes when accompanied by hypertension. In addition, ACE inhibitors can cause congenital malformations, so this medication will need to be stopped. Last, because epidemiologic evidence indicates that undiagnosed and/or untreated hypothyroidism during pregnancy is associated with fetal loss and adverse fetal outcomes, including diminished IQ scores, her TSH levels should be targeted to <2.5µIU/mL.

Recommendations

This is an emergency situation, and Maria needs to be admitted to the hospital immediately. Her subcutaneous insulin regimen should be switched from glargine to calculated NPH combined with a rapid-acting bolus insulin (lispro or aspart; since no clinical data exist on glulisine use during pregnancy, it is not recommended). Some practitioners might feel reluctant to switch Maria's insulin at this point, but given her poor glucose control on glargine,

Table 1. Calculation of Total Insulin Dose and Dose Regimen for Pregnancy, Weeks 4 to 12

Time	Fraction of Total Insulin Dose*	
	Intermediate-acting insulin (NPH)	Rapid-acting insulin
Before Breakfast	1/6	4/20
Before Lunch	N/A	3/20
Before Dinner	1/6	3/20
Bedtime	1/6	N/A

NA = not applicable.

*Calculate weight in kg x 0.7 = total daily insulin dose; 1/2 of total dose should be given as NPH, 1/2 as rapid-acting insulin.

and the lack of clinical trial data showing the safety and efficacy of glargine in pregnancy, it is best to use an insulin that is well studied in pregnancy. If it is possible, and if Maria's insurance will cover it, the future introduction of an insulin pump should be considered.

To address Maria's FPG of 187 mg/dL and bring her blood glucose down to <100 mg/dL, she is provided with an immediate 3 U of rapid-acting insulin. Each unit of rapid-acting insulin should bring Maria's blood glucose down by approximately 25 mg/dL. If her glucose levels remain high prior to eating, Maria should receive a correction dose of lispro or aspart (approximately 2 U). If Maria's blood glucose is still hovering around 180 mg/dL at dinner time, this process may need to be repeated. Maria should be encouraged to not eat until her glucose level is <90 mg/dL. Maria's new calculated NPH insulin regimen (described below) should also be started at this time, with doses given at 8:00 AM, 4:00 PM, and midnight.

Once Maria's blood glucose has stabilized, the typical insulin dosing schedule for pregnancy complicated by preexisting diabetes can be applied (Table 1). In weeks 4 to 12, this is calculated by multiplying the patient's present pregnant weight in

kilograms (Maria weighs 62.3 kg) by 0.7. Half of the total should be given in 3 doses of NPH, spaced 8 hours apart (typically at 8:00 AM, 4:00 PM, and midnight). The other half should be given as 3 doses of rapid-acting insulin before each meal, divided to provide 4/20 of the total daily dose before breakfast, 3/20 before lunch, and 3/20 before dinner. Maria's total daily insulin requirement is calculated to be approximately 43.6 U. Therefore, each NPH dose will be 7.27 U, which can be rounded to 7 U. In Maria's case, we should also assume that she will require supplemental insulin dosing until her blood glucose levels are corrected and stabilized.

Maria should also be put on a calculated diet, with her blood glucose level tested 8 times a day: before and after each meal, before bed, and at 3:00 AM.

That night, Maria's glucose is 152 mg/dL after dinner and 140 mg/dL at bedtime. She is given her standard dose of 7 U of NPH before bed, but no rapid-acting insulin. Instead, she is woken at 3:00 AM and given rapid-acting insulin. The period from midnight to approximately 3:00 AM can be dangerous because blood glucose levels drop with the pattern of decreased hormonal release experienced normally at this time of night. Alternately, the period from 4:00 AM until about 10:00 AM represents what is known as the “dawn phenomenon,” during which time blood glucose levels tend to rise. This further illustrates why a 24-hour insulin such as glargine is ineffective for a patient like Maria; its flat profile will lead to too much insulin provided between midnight and 3:00 AM, with an inadequate amount available from 4:00 AM onward.

Continued

Preexisting pregnancy <8 weeks' gestation in the context of poor glycemic control is an emergency situation.

Upon waking, Maria's FPG is 252 mg/dL; at this time, she is given her calculated dose of 7 U of NPH and 7 U of rapid-acting insulin, plus an additional 6 U of rapid-acting insulin to correct for hyperglycemia. Again, each unit of rapid-acting correction insulin should bring Maria's blood glucose down by approximately 25 mg/dL; therefore, the extra 6 U should bring her glucose level to 100 mg/dL. It is important to note that the commonly used insulin sensitivity correction factor and its associated rules of 1500 and 1700 have not been studied during pregnancy; alternately, the correction factor described above has been evaluated during pregnancy complicated by diabetes. For more information, please refer to "The art and science of maintenance of normoglycemia in pregnancies complicated by insulin-dependent diabetes mellitus," authored by Jovanovic-Peterson and Peterson; the full citation is listed under Suggested Reading, below.

If Maria's blood glucose remains high after an initial 24-hour treatment period, her NPH injection dose will probably need to be increased to 9 U.

Maria's hypertension also needs to be treated. The blood pressure medications that are safest for the first trimester of pregnancy are hydralazine and methyldopa. She should be started on both (hydralazine 25 mg and methyldopa 250 mg, both qid). The 4 daily doses should be spaced evenly across the day (ie, every 6 hours), not just during waking hours. Since these are short-acting drugs, we will see quickly if they can bring Maria's blood pressure to <120/80 mm Hg over the 6-hour dosing interval. If they cannot, the doses should be increased to 50-mg hydralazine and 500-mg methyldopa. If this still does not work, as low a dose as possible of labetalol or nifedipine should be added. She should also be started on levothyroxine for her thyroid disorder, at a dose of at least 75 µg.

Once discharged, Maria will have to maintain a carbohydrate-controlled diet, perform SMBG 8 to 10 times a day and record her results in a notebook, as well as

give herself 6 daily insulin injections and possibly a correction dose in the middle of the night. Maria will need to be taught carbohydrate counting as a method for adjusting her rapid-acting insulin analogue dose. She will need to see her physician once a week and check in via phone appointments. A diabetes care team must also be assembled, to include an ophthalmologist who can monitor Maria's retinopathy closely.

Take-Home Messages

- Preexisting pregnancy <8 weeks' gestation in the context of poor glycemic control is an emergency situation.
- This patient should not be discharged until her blood glucose levels are normal and she has received adequate self-management training to maintain glucose control on her own.
- There is a good chance that this patient's kidney function will improve if she maintains good glucose and blood pressure control throughout the pregnancy.
- Despite best efforts, there is an increased risk of this baby having birth defects, as well as an approximately 20% risk that the patient's mild retinopathy will progress.
- In situations like this, the best guideline is to use the safest medications available as aggressively as possible. ▲

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STRATEGIES TO PREVENT DIABETES RECURRENCE IN WOMEN WITH PRIOR GESTATIONAL DIABETES

Women who have experienced gestational diabetes mellitus (GDM) are at high risk for subsequent GDM and are also at elevated risk for future diabetes development. A review of the published literature found a cumulative incidence of future diabetes diagnosis in women with prior GDM ranging from 2.6% to over 70% (Figure 1). With this in mind, follow-up care should be started soon after delivery, both to prevent diabetes as well as ensure its prompt diagnosis.

We know that a number of maternal characteristics are associated with increased diabetes risk. These include: non-Caucasian race, obesity, increased maternal age, a family history of diabetes, delivery of a macrosomic infant, the severity of prior GDM, multiple prior pregnancies complicated by GDM, the presence of glutamic acid decarboxylase (GAD) antibodies, and postpartum glucose intolerance. However, to best assess a woman's diabetes risk, it is important to consider the potential original trigger of her GDM (Figure 2).

The Potential Triggers of GDM

Most commonly, GDM occurs against a background of chronic insulin resistance. However, GDM can also be caused by nascent autoimmune diabetes or previ-

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ously undetected monogenic forms of diabetes. GDM with chronic insulin resistance imparts a high risk for type 2 diabetes mellitus (T2DM) and, until adequate biomarkers can be identified, is indicated primarily by obesity. In the absence of obesity, it is important to consider potential autoimmune triggers, which may indicate an elevated risk for type 1 diabetes mellitus (T1DM) or its variant, latent autoimmune diabetes of adulthood (LADA), as well as monogenic forms of diabetes such as maturity-onset diabetes of the young (MODY) and maternally inherited diabetes.

Patients considered at risk for T1DM should be screened for antibodies such as GAD antibodies, antibodies to protein tyrosine phosphatase (IA2), and islet cell antibodies (ICA). Relevant family history suggesting autosomal dominant or maternally inherited diabetes should suggest a monogenic form. Substantial variability exists as regards autoimmune diabetes progression in women at risk for T1DM. Postpartum, patients may experience a return to normal glucose tolerance, continued β -cell deterioration, or the rapid development of T1DM. Thus, aggressive monitoring should be applied.

The majority of GDM, however, is triggered by chronic insulin resistance. As these women are at substantially elevated risk for future T2DM development, particularly in the 5 to 10 years following delivery, comprehensive metabolic monitoring should be initiated within 2 months of delivery. A baseline oral glucose tolerance test (OGTT) should be conducted, with the expectation that some women will present with diabetes and/or impaired glucose tolerance (IGT) at this time. An OGTT is the preferred test in this situation since fasting plasma glucose (FPG) measurements are insensitive for IGT and are less sensitive than OGTT for T2DM identification. Serum or plasma glucose values 2 hours after a 75-gram oral glucose challenge ≥ 200 mg/dL are diagnostic of diabetes (following confirmatory testing), while levels ≥ 140 mg/dL indicate IGT. Repeat OGTT testing should be performed at least once a year. Because many women will have metabolic syndrome characteristics, blood pressure and lipid testing are essential as well.

Clinicians may also want to consider measuring the woman's A1C level. While not a diagnostic test for diabetes or IGT, an initial A1C level can serve as a baseline

comparison for subsequent A1C measurements to determine if overall glycemia is worsening toward diabetes. A1C testing should be considered as an adjunct to OGTT screening—one which, because of the ease of the test, can be performed more frequently.

Preventing or Delaying Diabetes Development in Women With Prior GDM

Although no preventive treatment is currently available for T1DM or LADA, immunomodulatory therapies may eventually offer some benefit. Monogenic forms of diabetes likely antedate pregnancy. While specific disease-modifying therapies have not been identified for MODY, knowledge of the underlying genetics may be important for counseling about future pregnancies. In addition, one subtype of MODY, MODY 2, tends to be nonprogressive, while another subtype, MODY 3, tends to respond well to sulfonylurea therapy.

The Diabetes Prevention Program (DPP) demonstrated that exercise and weight loss can prevent or delay the development of T2DM in obese patients with IGT. The DPP included women with prior GDM, although specific data on this population have not yet been published. With the general DPP outcomes in mind, women should be advised to take proactive steps to reduce their weight and, presumably, their insulin resistance. While the mean weight loss observed in the DPP was relatively modest (~7% of body weight), additional weight loss is likely to impart additional benefits and reduced diabetes risk. Thus, it is recommended that women try to achieve a healthy body weight by engaging in regular exercise and adjusting their eating patterns as needed. Even if they fail to reach normal weight, what weight loss they can achieve and sustain should have beneficial health effects.

If a woman's A1C or glucose levels continue to rise despite weight loss, then it is very likely that her insulin secretion is deteriorating and she is heading for diabetes. While A1C levels cannot be used

Continued

Figure 1. Cumulative Incidence of Type 2 Diabetes Following GDM, Classified by Patient Ethnicity and Length of Follow-up



Adapted from Kim C, et al.
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Women with prior GDM are at substantially elevated risk for future T2DM development, particularly in the 5 to 10 years following delivery.

to diagnose diabetes, levels in the range of 6.0% to 6.5% are often associated with OGTT-diagnosable diabetes. If A1C levels are observed in this range, a woman should have a repeat OGTT. If she does not yet have diabetes, intensification of lifestyle management is appropriate. If diabetes is diagnosed, the clinician should consider drug therapy.

For women with prior GDM, the best evidence for slowing the progressive loss of insulin secretion that causes T2DM and its worsening comes from trials of medications that treat insulin resistance, such as thiazolidinedione drugs or possibly met-

formin. The Troglitazone In Prevention Of Diabetes (TRIPOD) study, and its follow-up, the Pioglitazone In Prevention Of Diabetes (PIPOD) study, demonstrated that Hispanic women with prior GDM treated with an insulin-sensitizing thiazolidinedione drug (troglitazone) experienced a >50% reduction in T2DM occurrence over 30 months of treatment. Women who participated in the follow-up PIPOD study (pioglitazone) experienced β -cell function stabilization over an additional 3 years of treatment. Although not specific to women with prior GDM, the DPP also included a troglitazone treatment arm for approximately 1 year. In this treatment group, the risk of diabetes was reduced by 75% compared with placebo, suggesting that insulin sensitization is an effective strategy for T2DM not only in prior GDM, but in other high-risk groups as well.

Other Postpartum Concerns

Since women with prior GDM are at risk for diabetes, and since conception in the presence of uncontrolled diabetes can lead

to serious fetal birth defects, the use of reliable contraception is important. Research suggests that the risk for fetal birth defects is significantly higher when maternal FPG is >120 mg/dL and/or A1C levels are more than 1% above the normal range. The only way to assure safe glucose levels prior to conception is to plan subsequent pregnancies; therefore, birth control is an essential part of pregnancy planning. This topic is discussed in greater detail in Dr. Lois Jovanovic’s Guest Editorial in this issue of *CADRE’s Current Diabetes Practice*.

Last, it is worth keeping in mind that recent research suggests that, during breast-feeding, both depo-provera and progestin-only oral contraceptives increase diabetes risk. This is an important consideration, as progestin-only oral contraceptives are frequently prescribed to breast-feeding women to prevent loss of milk volume. For this reason, it is best during breast-feeding if an alternate form of contraception, such as the intrauterine device or a barrier method, is used. If patients elect progestin-only methods, their glucose levels should be monitored closely. It is also important to note that breast-feeding per se does not increase maternal or offspring diabetes risk and may, in fact, provide some protection from future diabetes (in mother and offspring) or obesity (in offspring).

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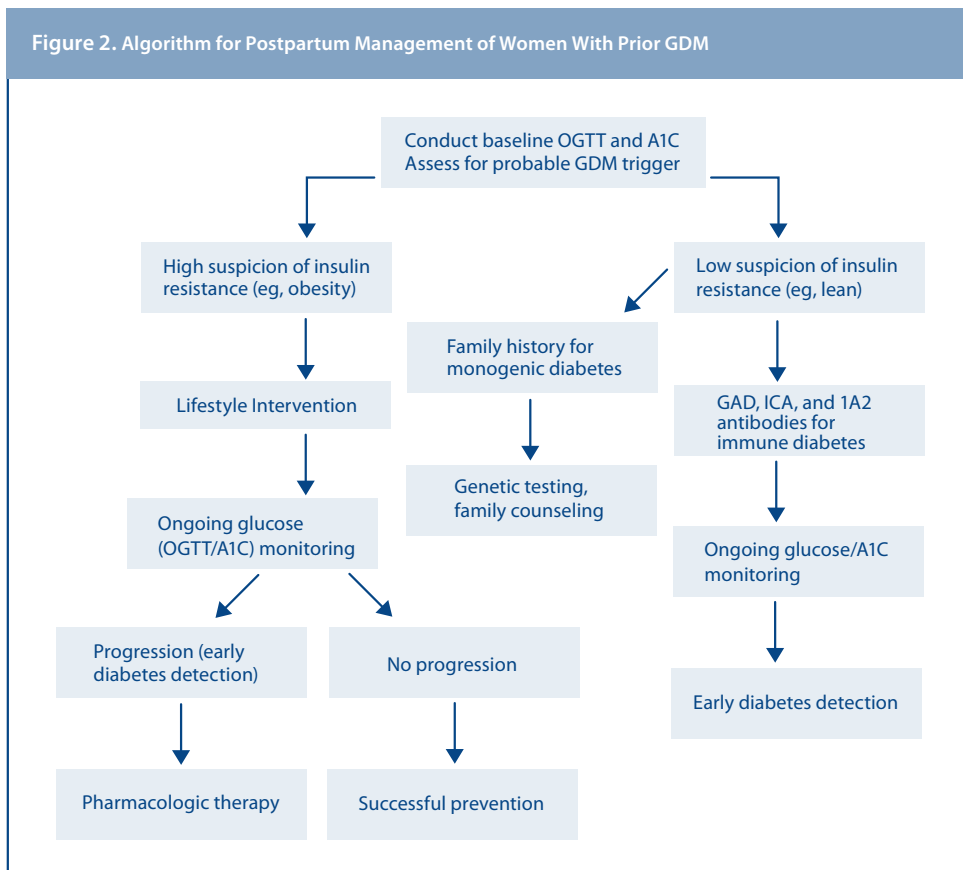
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Continued

Figure 2. Algorithm for Postpartum Management of Women With Prior GDM



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PRACTICE POINTERS

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MEDICAL NUTRITION THERAPY IN PREGNANCY COMPLICATED BY DIABETES

For women with diabetes or a history of gestational diabetes mellitus (GDM), the best time to adopt a healthier lifestyle is in the months or even years preceding conception. Developing good eating habits and working toward a healthy weight during the preconception period make glycemic control easier to maintain, prepare a woman for the challenges of pregnancy and motherhood, and give her baby the best chance for a healthy start in life.

Preconception Glycemic Control

In the preconception period, the primary goal for a woman and her health care provider is to achieve good glycemic control. Ideally, prior to conception, A1C levels should be within normal range (ie, 4% to 6%) or at least no more than 1% above normal levels, with the goal being to target the best glycemic control possible without increased hypoglycemia risk. When preconception and first trimester A1C

levels are in this range, a woman's risk for spontaneous abortion and fetal congenital malformations is similar to that for patients without diabetes. To achieve these target A1C levels, the American Diabetes Association currently recommends preprandial and fasting plasma glucose (FPG) targets of 80 to 110 mg/dL and a 2-hour postprandial glucose (PPG) of <155 mg/dL.

The preconception period is also an excellent time for a woman with diabetes or prior GDM to work with her health care provider or diabetes educator to review self-monitoring of blood glucose (SMBG) skills. It is a good idea for the woman to learn as much as possible about pregnancy-induced insulin resistance, the role of A1C in pregnancy, and the rationale behind strict glycemic control, hypoglycemia risk reduction, and ketone testing.

Intrapartum Glycemic Control

To achieve or maintain optimal glycemic control during pregnancy, a woman with diabetes or GDM will typically need to conduct daily SMBG; some women may need to monitor their blood glucose levels as often as 8 times a day (3 times premeal, 3 times 1-hour postmeal, at bedtime, and nocturnally [3:00 AM]). Educators should emphasize the importance of the 1-hour postmeal measurement (indicative of the

Ideally, prior to conception, A1C levels should be within normal range (ie, 4% to 6%) or at least no more than 1% above normal levels.

peak postmeal insulin response and therefore the most valuable postprandial decrement in pregnancy), because this is not a time when patients with diabetes typically check their blood glucose.

For women with preexisting diabetes, a target range for premeal or FPG of 60 to 99 mg/dL is recommended, as is a 1-hour PPG of 100 to 129 mg/dL. These are the current ADA guidelines. As Lois Jovanovic points out in her Guest Editorial, the ADA is currently revising these guidelines. Health care providers may choose to adjust these goals for women who experience recurrent hypoglycemia or hypoglycemia unawareness. In order to maintain blood glucose levels as close to normal as possible, treating hypoglycemia with 15 g of carbohydrate is not recommended during pregnancy unless blood glucose levels fall below 60 mg/dL. Severe hypoglycemia

Continued

Table 1. Guidelines for Recommended Weight Gain in Pregnancy

	Institute of Medicine (IOM) BMI range (kg/m ²)	World Health Organization (WHO) BMI range (kg/m ²)	Kcal/kg per prepregnancy weight*†	Recommended weight gain (lb)*
Underweight	<19.8	<18.5	36-40	28-40
Normal weight	19.8-26.0	18.5-24.9	30	25-35
Overweight	26.1-29.0	25.0-29.9	24	15-25
Obese	>29.0	≥30.0	not <1800 kcal daily	15
Twins‡	NA	NA	NA	35-45
Triplets‡	NA	NA	NA	45-55

NA = not applicable.

*Recommendations for kcal/kg and weight gain apply only to the IOM BMI criteria; the WHO BMI classification is included for comparison purposes only.

†An additional 150 to 300 kcal/day is recommended in the 2nd and 3rd trimesters.

‡The recommendation is for 150 kcal/day above that for a singleton pregnancy, or an amount that is consistent with targeted weight gain.

Table 2. Recommended Daily Carbohydrate Intake During Pregnancy Complicated by Diabetes

	Preexisting diabetes	GDM
Carbohydrate*	44%-55% of total calories†	40%-45% of total calories
Breakfast	Based on usual intake and blood glucose levels	15-30 g‡
Bedtime snack	15-30 g	15-30 g
Fiber	25-35 g	25-35 g

*Pregnant women should consume a minimum of 175 g of carbohydrates per day.

†Some women can tolerate more carbohydrates, especially if they are experienced in adjusting insulin dose based on carbohydrate intake.

‡May be increased if insulin is added and if patient carefully tracks pre- and postmeal glucose levels.

poses a risk to the mother (eg, seizures, coma, falls, and associated injury) and consequently to the fetus.

A woman with GDM who is unable to maintain target blood glucose levels (FPG ≤ 105 mg/dL, 1-hour PPG ≤ 155 mg/dL, or 2-hour PPG ≤ 130 mg/dL) with diet alone will need to start insulin therapy. Once insulin has been initiated, FPG and PPG targets for preexisting diabetes should be applied.

Preconception and Intrapartum Nutrition

For a woman with diabetes or GDM, a healthy diet is an important component of blood glucose management. It is never too early to consult a registered dietitian (RD) to develop an individualized medical nutrition therapy (MNT) plan that addresses nutritional shortcomings and dietary pitfalls that could affect both fetal and maternal health. Specifically, the health care provider should evaluate the woman's eating patterns to ensure that erratic carbohydrate intake or excess saturated fat consumption is not contributing to excessive glycemic excursions or increased cardiovascular risk. Periodic dietary consultations should continue throughout the preconception period and pregnancy to ensure that changing nutritional needs are assessed and met.

Caloric Requirements

During a single-fetus pregnancy, caloric needs are based on a woman's prepregnancy weight (Table 1). Regardless of a woman's prepregnancy body mass index (BMI), it is essential that she gain at least 6.8 kg (15 lb), to ensure adequate fetal

nutrition. Women carrying twins or triplets should take in an additional 150 kcal/day during the second and third trimesters, adjusted as needed to gain 15.9 to 20.5 kg (35 to 45 lb) or 20.5 to 25 kg (45 to 55 lb), respectively.

All women should distribute their caloric intake across 6 to 8 small meals and snacks throughout the day; this will decrease postprandial hyperglycemia risk. A bedtime snack can help decrease the risk of overnight hypoglycemia.

Specific Nutrient Requirements

To decrease the risk of fetal neural tube defects, a woman should eat foods rich in folic acid such as dark green vegetables, enriched grain products, legumes, oranges, and strawberries, and take 400 μ g of supplemental folic acid each day, to achieve a total daily intake of 600 to 1000 μ g. A woman with a previous neural tube defect pregnancy should take 4 mg of folic acid daily. The daily calcium requirement (1000 mg/day) can be met through diet and supplements, and women should also take an iron supplement (27 mg/day). Most prenatal vitamins will adequately cover these micronutrient requirements.

Carbohydrate

The recommended amount of carbohydrate for a woman with preexisting diabetes will be based on her current meal plan, typical carbohydrate intake, and blood glucose levels. Carbohydrate targets are typically tighter for a woman with GDM. Because the natural hormonal patterns of

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Achieving Glycemic Goals: Consideration of Regimens That Closely Mimic Normal Insulin Patterns

LOCATION	DATE	FACULTY
Los Angeles, CA	Thursday, September 28 9:15 - 10:30 am	Lawrence Blonde, MD, FACP, FACE Ochsner Clinic Foundation New Orleans, LA
Hartford, CT	Thursday, October 12 10:45 - 12:00 pm	Mary Ann Banerji, MD, FACP SUNY Health Science Center Brooklyn, NY
Baltimore, MD	Friday, October 20 9:15 - 10:30 am	John E. Gerich, MD University of Rochester School of Medicine Rochester, NY
Brooklyn, NY	Friday, October 20 4:45 - 6:00 pm	Mary Ann Banerji, MD, FACP SUNY Health Science Center Brooklyn, NY
Minneapolis, MN	Saturday, November 11 9:15 - 10:30 am	TBA
San Antonio, TX	Saturday, December 9 12:30 - 1:45 pm	Julio Rosenstock, MD Dallas Diabetes and Endocrine Center Dallas, TX

pregnancy increase morning blood glucose levels, carbohydrate intake should be restricted at breakfast, particularly in GDM. A woman should choose breakfast foods with a lower glycemic load, such as whole fruit (instead of juice) and whole-grain breads and cereals. Table 2 provides more detailed information on recommended daily carbohydrate intake.

To make sure that an adequate amount of fiber is consumed, a woman should focus on carbohydrates that are also good sources of dietary fiber, such as whole grains, fresh fruits and vegetables, and beans and legumes. Nutritive sweeteners, such as sugar, honey, corn syrup, and sugar alcohols, should be counted as carbohydrate.

Protein and Fat

During pregnancy, a woman's protein intake should be approximately 20% to 25% of her daily caloric intake. To help reduce saturated fat intake, she should be advised to choose lean sources of protein (lean meats, fish, and low-fat dairy products). Because of the risks associated with methylmercury in certain fish, pregnant women should not eat swordfish, king mackerel, or tilefish (golden or white snapper). White albacore tuna should be lim-

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Improving Glycemia Without Weight Gain: Harnessing the Power of Gut and Pancreatic Hormones		
LOCATION	DATE	FACULTY
Atlanta, GA	Friday, September 15 9:15 - 10:30 am	Lawrence Blonde, MD, FACP, FACE Ochsner Clinic Foundation New Orleans, LA
Washington, DC	Saturday, November 4 12:30 - 1:45 pm	Matthew C. Riddle, MD Oregon Health & Science University Portland, OR
Milwaukee, WI	Friday, December 15 7:45 - 9:00 am	Mary Ann Banerji, MD, FACP SUNY Health Science Center Brooklyn, NY

ited to 6 oz per week, but canned light tuna is safe to eat, as are shellfish, salmon, sardines, and haddock.

Fat should make up 30% to 35% of total caloric intake for a woman with preexisting diabetes and <40% for a woman with GDM; saturated fats should be limited to 10% of total calories in all cases.

Alcohol, Caffeine, and Nonnutritive Sweeteners

A pregnant woman should not consume any type of alcohol, and caffeine consumption should be held to ≤ 300 mg/day

(8 oz of regular coffee contains about 135 mg of caffeine, a 12-oz cola has about 35 mg, and 8 oz of black tea has about 50 mg). Although most nonnutritive sweeteners are safe during pregnancy, they should be used only in moderation; saccharin, however, is not recommended, because it can cross the placenta and is cleared very slowly by the fetus.

Conclusion

Clinical trials have demonstrated that preconception and first trimester efforts to achieve good glycemic control can dramatically reduce the incidence of diabetic embryopathy. Meticulous glucose monitoring and insulin adjustment are the cornerstone of these efforts, along with medical nutrition therapy. Preconception and intrapartum nutritional assessment, nutrition education, and meal planning provided by an RD can give a mother-to-be skills and knowledge that will improve her own and her baby's health.

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CADRE would like to thank the faculty of CADRE symposia at the 2006 AACE, ADA, and AADE annual meetings:

AACE 2006

Etie S. Moghissi, MD, FACP, FACE, Moderator
Anthony P. Furnary, MD
Mary Ann Banerji, MD, FACP

ADA 2006

Derek LeRoith, MD, PhD, FACP, Moderator
Lawrence Blonde, MD, FACP, FACE
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AADE 2006

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