Controversies in the diagnosis and treatment of gestational diabetes

LOIS JOVANOVIC, MD*
Director and Chief Scientific Officer, Sansum Medical Research Institute; Clinical Professor of Medicine, University of Southern California

ABSTRACT

Uncontrolled gestational diabetes is associated with infant macrosomia and a lifelong risk of developing diabetes. Prompt diagnosis and aggressive management is therefore critical. All pregnant women should be screened for carbohydrate intolerance. Women with even minor abnormalities in blood sugar levels should be trained to monitor their glucose levels, rigorously control their diet, and use insulin if necessary. Exercise is also very beneficial.

BASIC ISSUES ABOUT GESTATIONAL diabetes are still controversial despite universal agreement about the dangers of this condition to mother and child. Who should be screened for gestational diabetes? What tests should be used? What blood sugar levels best identify women at risk of poor pregnancy outcomes? How aggressively should gestational diabetes be managed?

In this article, we will answer these questions by discussing recent evidence on how best to diagnose and manage gestational diabetes and newly diagnosed type 2 diabetes.

RISKS OF GESTATIONAL DIABETES

Gestational diabetes, defined as glucose intolerance of various degrees first detected during pregnancy, is found in 1% to 12% of pregnancies, depending on the screening criteria and the sample. Among these are the approximately 4% of pregnancies complicated by previously undiagnosed type 2 diabetes.[1]

Maternal glucose passes through the placental barrier but insulin does not. An excess of maternal glucose will stimulate pancreatic action in the fetus, causing hyperinsulinemia, which is frequently followed by insulin resistance, morbid obesity, and metabolic problems such as hypoglycemia, hyperbilirubinemia, erythremia, and respiratory distress. Congenital defects may be more common, and pregnancies complicated by gestational diabetes are also more likely to end in stillbirth.

Infants of mothers with uncontrolled gestational diabetes are likely to be both fatter and larger overall (that is, to have macrosomia), which causes pregnancy complications and increases the need for operative delivery. These children are also much more likely to develop diabetes. Many suffer pancreatic exhaustion from prenatal hyperglycemia. In utero they tend to build up deposits of visceral fat (FIGURE 1), and are prone to develop insulin resistance. For the mother, gestational diabetes also signals a risk of developing gestational diabetes in future pregnancies, nondiabetic fasting hyperglycemia, and overt diabetes.

Screen all pregnant women at 24 to 28 weeks gestation

HOW TO DIAGNOSE GESTATIONAL DIABETES

Whom to screen

Risk factors for gestational diabetes are obesity or overweight, physical unfitness, age older than 25 years, and a family history of diabetes. Black, Latina, Native American, and Asian women are at higher risk than women of other ethnic groups. Guidelines published in 1997 by the American Diabetes Association[2]

*Disclosure: The author indicates that she has received research support from and serves as a consultant and a speaker for Eli Lilly and Ortho Nordisk, which make products for diabetes care.

MRI can reveal fetal macrosomia in gestational diabetes

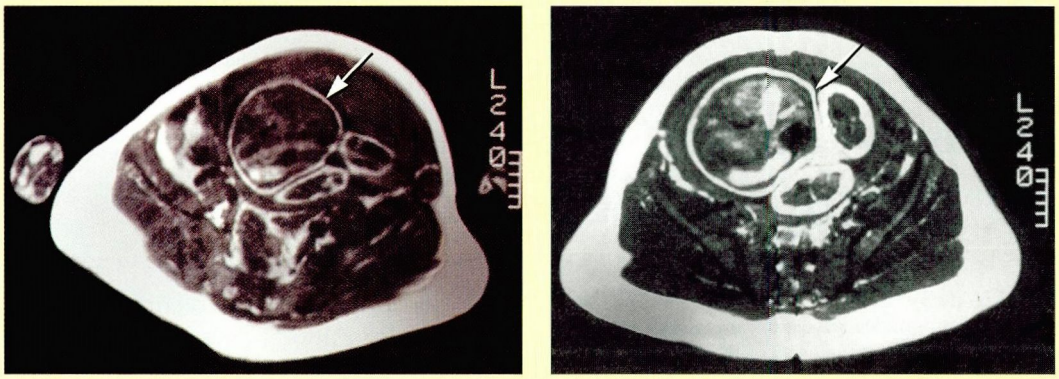

FIGURE 1. Left, a magnetic resonance image of a woman with well-controlled gestational diabetes, taken at the maternal umbilicus at 38 weeks of gestation. The fetus (arrow) weighed 3,900 g at birth and was normal for percent body fat. **Right,** Another woman, with poorly controlled gestational diabetes at 38 weeks of gestation. This fetus weighed 3,940 g at birth, had 50% of its neonatal weight composed of fat, and had all of the stigmata of the infant of a diabetic mother.

FROM JOVANOVIC-PETERSON L, CRUES J, DURAK E, PETERSON CM. MAGNETIC RESONANCE IMAGING IN PREGNANCIES COMPLICATED BY GESTATIONAL DIABETES PREDICTS INFANT BIRTHWEIGHT RATIO AND NEONATAL MORBIDITY AM J PERINATOL 1993; 10:432–437

For screening, we use the 50-gram glucose challenge test

sought to reduce the number of unnecessary screenings by developing protocols to identify women in low-risk groups who need not be screened.

However, we and many other experts disagree with this strategy, because about 1% to 2% of women with no risk factors develop diabetes, and because applying the ADA guidelines adds needless complexity to the screening process. We therefore recommend screening all pregnant women at 24 to 28 weeks of gestation. (Women in the high-risk categories should be screened as soon as pregnancy is confirmed.)

How to screen

A number of screening options are available, including the 100-gram oral glucose tolerance test (GTT), the 75-gram GTT, and the 50-gram glucose challenge test. Glycosylated hemoglobin is not the preferred method for screening and diagnosing gestational diabetes. Our data show that women with poor responses to the 50-gram challenge test are at high risk for having macrosomic infants even though they may not meet the generally accepted standard for gestational diabetes.[3] Therefore we perform the 50-gram test; any woman with a plasma glucose level higher than 140 mg/dL at 1 hour is diagnosed with gestational diabetes. (All women with carbohydrate intolerance first diagnosed during pregnancy should be treated as though they have gestational diabetes; those whose condition does not resolve after delivery are probably those with previously undiagnosed type 2 diabetes.)

TREATING GESTATIONAL DIABETES

Women with poor clearance of glucose after the challenge test should be trained to monitor their glucose levels and control their diet, with insulin added if necessary. In addition, exercise is a very promising treatment for gestational diabetes. Only minimal control of gestational diabetes is needed to prevent stillbirth, but a more rigorous level of control is needed to prevent macrosomia and diabetic fetopathy.

The euglycemic diet

On the euglycemic diet (TABLES 1 AND 2), 75% to 80% of women with gestational diabetes can achieve normal glycemia. The diet reduces caloric intake to just above the ketonuric threshold; women close to their ideal body

Sample dietary plan for a woman with gestational diabetes

Mrs. P, a 42-year-old Mexican-American woman in her 12th week of pregnancy, should be placed on the euglycemic diet because her blood sugar level 1 hour after the 50-gram glucose challenge test was 210 mg/dL, indicating that she has developed gestational diabetes.

Mrs. P stands 5 feet 2 inches (1.57 meters) tall and her pre-pregnant weight was 218 pounds (99 kg). Using the formula body mass index = (weight in kg) ÷ (height in m)^2, we calculate that her BMI is 40. She was therefore at about 160% of her ideal body weight (BMI < 25) before she was pregnant.

We use her present pregnant weight to calculate her daily dietary calorie allowance. The third row in TABLE 1 shows that she should consume 12 calories/kg x present pregnant weight (103 kg) = 1,236 calories. No more than 40% (494 calories) may be from carbohydrates.

We use TABLE 2 to calculate the calories allowed at each meal. Mrs. P will be allowed only 137 calories at breakfast (only 49 of which may be from carbohydrates). Her lunch and dinner will each be 343 calories (148 of them from carbohydrates). Snacks at midmorning and late evening will each be 69 calories, and snacks at mid-afternoon and early evening will each be about 137 calories.

Mrs. P will need careful coaching to keep to this plan, and she should be encouraged to keep a detailed diet journal. She may also be started on insulin if her blood sugars do not normalize.

mass index may consume only 30 calories per kilogram of their pregnant weight and heavier women consume fewer. To reduce postprandial glucose peaks, the diet restricts carbohydrate consumption to less than 40% of total calories, allowing 40% or more of calories to be fat and the remaining 20% to be protein. Because high cortisol levels interfere with glucose clearance in the morning and are particularly high during pregnancy, breakfast is very small and very low in carbohydrates. We ask our patients to keep a detailed diet diary.[4]

Blood glucose monitoring

Patients are taught to use blood glucose monitoring strips and reflectance meters to monitor their blood sugar. Because the peak postprandial response best predicts the risk of macrosomia, patients check their glucose levels in the morning and 1 hour after each meal. Those who are taking insulin monitor their preprandial levels as well.

Insulin

Women on the euglycemic diet must begin more aggressive treatment if their capillary whole blood glucose levels rise above 120 mg/dL more than twice in a 2-week period. (This capillary glucose level is equivalent to a plasma whole blood level of 140 mg/dL). If they are not yet on insulin, they must begin taking it. If they are taking insulin, their dosage must be increased. Women whose fasting levels rise above 90 mg/dL (equivalent to

TABLE 1

Total calories in the euglycemic diet

PERCENT OF IDEAL BODY WEIGHT	TOTAL CALORIES
80% to 120%	30 calories/kg present pregnant weight (PPW)
121% to 150%	24 calories/kg PPW
> 151%	12 to 15 calories/kg PPW

TABLE 2

Calorie distribution for the euglycemic diet

TIME	MEAL	FRACTION OF TOTAL CALORIES	PERCENT OF TOTAL DAILY CARBOHYDRATES
8:00 AM	Breakfast	2/18	10
10:30 AM	Snack	1/18	5
12:00 PM	Lunch	5/18	30
3:00 PM	Snack	2/18	10
5:00 PM	Dinner	5/18	30
8:00 PM	Snack	2/18	5
11:00 PM	Snack	1/18	10

TABLE 3

Calculating the daily dose of insulin for gestational diabetes

WEEKS OF GESTATION	DAILY INSULIN DOSE (UNITS)
Weeks 1–18	0.7 × present pregnant weight in kg (PPW)
Weeks 18–26	0.8 × PPW
Weeks 26–36	0.9 × PPW
Weeks 36–40	1.0 × PPW

TABLE 4

Sample insulin schedule

TIME	FRACTION OF TOTAL DOSE*	
	NPH (45% OF TOTAL)	LISPRO (55% OF TOTAL)
Before breakfast	28.5%	22%
Before lunch	None	16.5%
Before dinner	None	16.5%
Bedtime	16.5%	None

*Doses are adjusted frequently according to glucose levels

Exercise may cure gestational diabetes

a plasma whole blood level of 105 mg/dL) must also be started on insulin.

For women who require insulin, we frequently use a combination of human NPH (neutral protamine Hagedorn) insulin and lispro insulin, a novel analog of human insulin that has recently been shown to be safe and effective in pregnant women (TABLES 3 and 4). Lispro is absorbed and acts faster than regular insulin and so can be taken as few as 15 minutes before eating to blunt peak postprandial response, whereas regular insulin must be taken up to an hour and a half before a meal.

Because lispro is not a human insulin, clinicians initially feared that it would trigger an antibody response and that when bound to antibodies, it might cross the placental barrier to exacerbate fetal hyperinsulinemia. However, a randomized trial in pregnant women found little cross-reactivity and no evidence that it crosses the placenta. The lispro group had fewer hyperglycemic and hypoglycemic episodes than the ordinary insulin group, meaning that lispro should probably become the treatment of choice for gestational diabetes.[5] A case report[6] of two infants with birth defects after their mothers were treated with lispro is anecdotal but nonetheless has raised concerns which are being addressed in a large European trial.

Exercise

Exercise is effective as an adjunct treatment for ordinary diabetes, and we have conducted a randomized trial that suggests that it cures gestational diabetes.[7] We use an arm cycle machine with a firm backrest, which allows a seated woman to perform vigorous upper body exercise without triggering the uterine irritation, contractions, or fetal distress associated with many other types of weight-bearing exercise. Although many women with gestational diabetes are overweight and physically unused to exercise, we have found that the possibility of stopping or delaying the need for insulin injections strongly motivates many.

In our trial, after 6 weeks of diet and exercise, the exercising group developed better cardiovascular fitness, normal fasting glucose levels, and significantly lower peak postprandial glucose levels. Many achieved normal glucose levels and were able to maintain good glycemic control without using insulin.

Oral hypoglycemic agents contraindicated

First-generation hypoglycemic agents such as sulfonylurea cross the placenta and thus may cause fetal hyperinsulinemia. These agents are in use in Mexico, and a study of Mexican women who gave birth in the United States described a minor malformation syndrome in the infants characterized by ear malformations.[8] However, in vitro studies are suggesting that some second-generation agents may not cross the placental barrier.[9]

BENEFITS OF SCREENING AND TREATMENT

In Santa Barbara County in 1985, the rate of infant macrosomia was 18%. The following year, we began universal screening of pregnant women with the glucose challenge test,

followed by appropriate treatment. By 1992, the macrosomia rate fell to 7%. Over the same period, the frequency of cesarean sections fell from 30% to 20%. We calculated that the cost of screening, educating, and treating the additional women (those who had poor responses to the challenge test but not the GTT) was $233,650 per year. In contrast, the cost of the cesarean deliveries and intensive care that would have been required for the additional macrosomic infants was estimated at $833,870 per year.[10] These figures support our contention that maintaining normal blood sugar during all pregnancies complicated by glucose intolerance produces normal, healthy babies and is cost-effective.

REFERENCES

1. **Jovanovic L, editor.** Medical Management of Pregnancy Complicated by Diabetes. Alexandria (Va): American Diabetes Association, 2000.
2. **Metzger B, Coustan D.** Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 1998; 21 (Suppl 2):B161–B167.
3. **Bevier WC, Fischer R, Jovanovic L.** Treatment of women with an abnormal glucose challenge test (but a normal oral glucose tolerance test) decreases the prevalence of macrosomia. Am J Perinatol 1999; 16:269–275.
4. **Jovanovic L.** Time to reassess the optimal dietary prescription for women with gestational diabetes [editorial]. Am J Clin Nutr 1999; 70:3–4.
5. **Jovanovic L, Ilic S, Pettitt DJ, et al.** Metabolic and immunologic effects of insulin lispro in gestational diabetes. Diabetes Care 1999; 22:1422–1427.
6. **Diamond T, Kormas N.** Possible adverse fetal effect of insulin lispro. N Engl J Med 1997; 337:1009.
7. **Jovanovic-Peterson L, Durak EP, Peterson CM.** Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes. Am J Obstetr Gynecol 1989; 161:415–419.
8. **Piacquadio K, Hollingsworth DR, Murphy H.** Effects of in-utero exposure to oral hypoglycaemic drugs. Lancet 1991; 338:866–869.
9. **Elliott BD, Schenker S, Langer O, et al.** Comparative placental transport of oral hypoglycemic agents in humans: a model of human placental drug transfer. Am J Obstet Gynecol 1994; 171:653–660.
10. **Jovanovic-Peterson L, Bevier W, Peterson CM.** The Santa Barbara County Health Care Services program: birth weight change concomitant with screening for and treatment of glucose-intolerance of pregnancy: a potential cost-effective intervention. Am J Perinatol 1997; 14:221–228.

ADDRESS: *Lois Jovanovic, MD, Director and Chief Scientific Officer, Sansum Medical Research Institute 2219 Bath Street, Santa Barbara, California 93105; e-mail lois@sansum.org.*