

Gestational Diabetes Mellitus: The Case for Euglycemia

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A B S T R A C T

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable degree with onset or first recognition during the present pregnancy. When maternal glucose is not normalized, the outcome of pregnancy is not normal. Identifying the woman at risk for an abnormal outcome of pregnancy is based on maternal blood glucose (BG) levels. Once identified, the goal of therapy for the woman with GDM is to normalize the metabolic milieu. Although fetal macrosomia is a result of maternal hyperglycemia, waiting until the fetus shows signs of overgrowth from glucose-mediated overnutrition is not optimal. Although there are no randomized, double-blind, placebo-controlled trials to prove that normoglycemia can prevent or reverse diabetic fetopathy, the prudent strategy is to achieve and maintain normoglycemia in all pregnancies with universal BG testing and targeted treatment to minimize the risk of glucose-mediated complications.

R É S U M É

Le diabète gestationnel est une intolérance au glucose dont le degré varie et qui s'installe ou que l'on diagnostique pendant une grossesse. Lorsque la glycémie n'est pas normalisée, l'issue de la grossesse n'est pas normale. Pour savoir quelles femmes sont exposées à une issue anormale de la grossesse, on se fonde sur la glycémie pendant la grossesse. Lorsqu'on a repéré les femmes qui sont exposées au diabète sucré gestationnel, le but du traitement est de normaliser le milieu métabolique. L'hyperglycémie chez la mère produit une macrosomie fœtale, mais attendre que le fœtus montre des signes de croissance exagérée en raison d'un apport de glucose trop élevé n'est pas la meilleure façon de procéder. Même si aucune étude à double insu, avec répartition aléatoire et contrôlée contre placebo n'a été menée pour prouver qu'une glycémie normale peut prévenir ou renverser une fœtopathie diabétique, il est prudent de voir au maintien d'une glycémie normale chez toutes les femmes enceintes en faisant systématiquement des épreuves et en administrant un traitement au besoin pour réduire au minimum le risque de complications liées au glucose.

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INTRODUCTION

The goal of therapy for women with gestational diabetes mellitus (GDM) is to normalize the metabolic milieu of the mother to result in a normal, healthy infant. Therapeutic decisions should be designed to decrease the morbidity and mortality of the mother and of the fetus. To this end, many have suggested that because macrosomia is a marker for diabetic fetopathy, when there is evidence of fetal overgrowth, decisions about early delivery can be made solely based on sonographic indications that the fetus is large for gestational age. To date, there is no randomized, double-blind, placebo-controlled trial to prove that normalization of maternal glycemia can prevent or reverse diabetic fetopathy. Therefore, obstetricians have turned to testing for fetal overgrowth as the mainstay of the management of pregnancies complicated by GDM. Unfortunately, this strategy demands that the fetus at risk must first manifest overgrowth before treatment decisions are made. However, while waiting for the definitive study, the evidence that maternal glycemia does impact on fetal outcome is mounting. This review presents evidence suggesting that until there is a proven test to identify the pregnancies at risk for untoward outcome, all women with GDM need to perform self-monitoring of blood glucose (SMBG) to guide treatment decisions about insulin therapy (1).

MATERNAL AND NEONATAL OUTCOMES

Maternal mortality is no longer an issue, given the levels of control achieved in most healthcare settings; however, maternal morbidity is still high if cesarean section is required. Therefore, treatment goals also need to be directed toward decreasing the rate of cesarean section. Unfortunately, the mere label of "GDM" has increased the rate of cesarean section (2). However, when the criteria for performing a cesarean section have been based solely on fetal size and degree of maternal hyperglycemia, the rate of cesarean section has been reduced to that of the general population (3). Furthermore, women with a history of GDM are at an increased risk for subsequent type 2 diabetes. Some report that up to 50% of women with a history of GDM will develop type 2 diabetes within 5 years of the index pregnancy (4).

The literature also supports the opinion that there is a need to rely on maternal blood glucose (BG) levels to achieve the best outcome for the infant. Langer and colleagues tested the hypothesis that stringent glycemic control, verified BG data, adherence to an established criterion for insulin initiation and achievement of near normoglycemia result in the reduction of adverse outcomes (5). The group of women with GDM who were managed with intensive therapy experienced rates of macrosomia, cesarean section, metabolic complications, shoulder dystocia, stillbirth, neonatal intensive care unit days and respiratory complications that were lower than the rates in a group of women with GDM who were not managed intensively and were comparable to the rates of controls without diabetes. The authors concluded

that intensified management based on patient-monitored BG levels and treatments based on these BG determinations are associated with enhanced perinatal outcome. Thus, their management strategy clarifies the relationship between glycemic control and neonatal outcome.

The most common and significant neonatal complication clearly associated with GDM is macrosomia: an oversized baby with birth weight >90th percentile for gestational age and sex, or a birth weight >2 standard deviations above the normal mean birth weight. Extrapolation of the studies performed in women with pregestational type 1 and type 2 diabetes to the fetal overgrowth observed in the infants of women with GDM suggests that macrosomia associated with GDM is directly related to maternal BG levels (6-8). The logical leap to treatment strategies would then be to prevent hyperglycemia in all women with GDM and to make decisions about the initiation of insulin therapy based solely on the presence of maternal hyperglycemia (9). However, not only is the concept that macrosomia is directly related to maternal hyperglycemia controversial, the notion that normalizing maternal BG could prevent macrosomia is also strongly debated (10). Furthermore, the definition of normoglycemia during pregnancy has not been adequately reported due to difficulty measuring BG excursions in the home setting.

GLYCEMIC CONTROL IN GDM

Initial attempts to normalize the 24-hour BG profile of pregnant women with diabetes were all conducted in hospitalized patients (11). When BG meters became available for outpatient surveillance of BG control, normalization programs could be continued at home (12). However, the number and timing of the BG determinations have not been adequately studied. Furthermore, reports of macrosomia despite normoglycemia (10) perpetuated the philosophy that there is an urgency to deliver the infant early to avoid fetal overgrowth, perceived to be unaffected by glycemic control (13). Perhaps the debate remains because many of the reports claiming that neonatal complications occur despite excellent metabolic control fail to measure postprandial BG levels (6-8). The Diabetes in Early Pregnancy (DIEP) study, a multicentre trial comparing pregnant women with type 1 diabetes to pregnant controls without diabetes throughout pregnancy, was designed to answer questions related to causes of spontaneous abortions and malformations (14-17). Investigators also looked at variables associated with macrosomia (6,16). The DIEP study showed that 1-hour postprandial BG levels predicted the 28.5% of macrosomic infants born to women with diabetes (6). Combs and colleagues confirmed these findings, also in a population of women with type 1 diabetes, as they associated macrosomia with higher postprandial BG concentrations obtained between weeks 29 and 32 of gestation (7). de Veciana and colleagues reported that insulin-requiring women with GDM who only monitored preprandial BG had

a 42% risk of macrosomia whereas those who also monitored BG 1 hour after eating decreased their risk of neonatal macrosomia to near normal, or 12% (8). However, in the latter report, the women most likely all had pregestational, undiagnosed type 2 diabetes, because their glycosylated hemoglobin (A1C) level at the time of diagnosis was markedly elevated and much higher than typically found in women with GDM (8). Demarini and colleagues added to the evidence that maternal postprandial BG monitoring is important (17). They showed that when the postprandial BG levels of women with diabetes were <6.67 mmol/L, the infants had a significantly lower rate of hypocalcemia than infants born to women with diabetes who had higher postprandial BG levels (17).

The advent of continuous glucose monitoring has only recently been applied to the study of ambient glucose levels in pregnant women with diabetes. To date, there is only 1 report using a continuous glucose sensor in 10 women with GDM (18). Jovanovic showed that continuous glucose monitoring detects postprandial glucose elevations not detected by intermittent fingerstick BG determinations (18). Perhaps “macrosomia despite normoglycemia” is in reality “macrosomia because of undetected hyperglycemia.”

To truly resolve the controversy surrounding the impact of hyperglycemia on the outcome of pregnancies in women with diabetes, normal BG ranges during pregnancy need to be established, and the levels of glycemia in pregnancies of women without diabetes need to be related to degrees of fetal overgrowth in a normal population. The definition of normoglycemia in pregnancy has not been re-addressed for more than 2 decades. The 2 available reports combined only studied 20 pregnant women without diabetes during the third trimester with hourly BG determinations over a 24-hour period (12,19). Both papers suggested that “normal” maternal BG levels were lower than BG levels in women who were not pregnant, and both reported FBG at 3.05 to 3.61 mmol/L with no BG level >6.67 mmol/L, even 1 hour after a high-carbohydrate meal. Although some clinicians have used these BG levels as goals in the treatment of pregnant women with diabetes in an attempt to minimize the risk of neonatal macrosomia, others have recommended waiting until there are more definitive data before potentially increasing the risk of hypoglycemia while attempting to lower maternal BG levels to “normal.” Clinicians want confirmatory evidence that normal maternal BG levels are this low and proof that higher BG levels increase the risk of fetal overgrowth (20,21).

Finally, evidence based on maternal diurnal BG levels during the third trimester in normal pregnancies of women without diabetes suggests that these BG levels are related to fetal growth. Parretti and colleagues carefully selected 51 women who, by all criteria, were normal—i.e. term delivery of a single infant with normal fetal growth, normal glucose challenge test (GCT) (50 g of oral glucose administered anytime during the day, regardless of timing of last meal, with 1-hour plasma glucose level <7.8 mmol/L), not obese, not

hypertensive, and able to have an unmodified lifestyle (22). These women monitored their BG levels every 2 weeks from 28 to 38 weeks of gestation, with timed meals at 8:00 AM, 12:00 PM (noon) and 8:00 PM and BG levels measured before each meal and 1 and 2 hours after meals (in addition to every 2 hours in the afternoon and during the night with a remarkable 96.9% compliance). Fetal parameters were also measured in detail; the fetuses were evaluated by ultrasound scan at 22, 28, 32 and 36 weeks of gestation. The authors showed that overall daily mean BG level is indeed lower in pregnant women than in women who are not pregnant: the mean FBG during the third trimester was 3.11 mmol/L. Most noteworthy was that the mean peak postprandial BG response occurred 1 hour postprandially and never exceeded 5.84 mmol/L. This 1-hour peak was significantly correlated with fetal abdominal circumference. By 32 weeks' gestation, there was a positive correlation between fetal abdominal circumference and BG levels 1 hour after breakfast, 1 and 2 hours after lunch, and 1 and 2 hours after dinner. A negative correlation between the head circumference:abdominal circumference ratio and 1-hour postprandial BG levels was also observed. This longitudinal study finally provides the true definition of normoglycemia during the third trimester of pregnancy. In addition, it relates the postprandial BG level to parameters of fetal growth and shows that there is a continuum, even in the normal range, of degrees of hyperglycemia and overgrowth. Coincidentally, the BG levels reported in this study are similar to those in the papers that are now more than 2 decades old (12,19,22). The observation that the 1-hour peak postprandial BG level correlates with the fetal abdominal circumference lends credence to the notion that unless the peak postprandial BG response is blunted, the rate of macrosomia in pregnant women with diabetes will not be affected.

Some have argued that as long as BG level is measured postprandially, the issue of testing 1 hour vs. 2 hours after meals may not be critical. Moses and colleagues compared the outcome of 166 pregnancies of women with GDM who tested BG 1 hour postprandially with a target BG level of <8.0 mmol/L to the outcome of pregnancies of 101 women with GDM who tested BG 2 hours postprandially with a target BG level of <7.0 mmol/L (23). Therapy was adjusted to maintain BG levels below the targets, as defined by the group assignment. There were no significant demographic differences between the 2 groups. The neonatal birth weight, percentage of women requiring insulin and the total daily dose of insulin were similar in both groups. The authors concluded that for women with GDM, BG monitoring either 1 hour or 2 hours postprandially led to similar outcomes. This suggests that women may choose the most convenient time for their postprandial BG monitoring.

Even if the tools and techniques available today make it onerous to achieve and maintain normoglycemia, treatment modalities must be derived to safely achieve this goal. Only then will glucose-mediated macrosomia be eliminated (24).

The need for BG monitoring to guide therapeutic decisions for all pregnant women is supported by a report from Bevier and colleagues (25). In their study, they showed that treating even minor elevations of maternal BG improves outcome. They studied 103 women who had a positive 1-hour GCT, but a negative 100-g 3-hour oral glucose tolerance test (OGTT). The women were randomly assigned to either the experimental or control group, with the women in the experimental group receiving dietary counselling and conducting SMBG. A1C was significantly higher in the women in the control group, and birth weight (measured in grams or gender-specific percentile), specific for gender, ethnicity and gestational age, was significantly higher in the infants of mothers in the control group. The rate of cesarean section was also higher in the women in the control group (25).

Measurement of maternal BG level to guide therapy is also cost effective. Based on the hypothesis that untreated elevated BG levels result in an increased prevalence of macrosomia, Jovanovic-Peterson and colleagues designed a study to evaluate the impact of a treatment program for pregnant women with impaired glucose tolerance (IGT) on birth weight and cost in the Santa Barbara County Health Care Services, Santa Barbara, California, United States (US) (3). In 1985, 18% of 4364 births had birth weight >90th percentile and the rate of cesarean section was 30% of total births (3). In 1986, the authors initiated a program to treat all pregnant women with IGT who had a positive GCT (>4.95 mmol/L after a 50-g oral glucose load), even if they had a negative OGTT (≤ 1 of the results above the cutoffs after a 100-g glucose load). All pregnant women with IGT were placed on a 40% carbohydrate, 1800-kcal diet and taught to monitor their capillary whole BG. Insulin therapy was initiated if FBG was >4.5 mmol/L and/or 1-hour postprandial BG was >6.67 mmol/L. By the early 1990s, the rate of macrosomia had decreased to 7%, and the rate of cesarean section had decreased to 20%. The cost to Santa Barbara County Health Care Services to educate and treat the additional women with IGT was US \$233 650.00. Assuming that, without this program, there would have been an additional 398 macrosomic infants, with some requiring cesarean delivery and intensive neonatal care, total potential savings could be an estimated US \$833 870.00 per year or US \$1950.00 per woman with IGT.

Kitzmilller and colleagues also showed that intensive management, defined as SMBG with insulin therapy decisions based on BG concentrations, results in a cost savings with their analysis of care for GDM (26). Reimbursed average charges in the Northern California managed care market in 1996 were used to establish the direct costs, and the direct costs were then applied to the elements of care and pregnancy outcomes of 3 GDM management programs in Northern California, Southern California and New England, US, using prospectively collected data. Most striking was their report of the utility of postprandial BG monitoring for the care of insulin-requiring women with GDM. Incremental cost

effectiveness of postprandial BG monitoring in the Southern California controlled trial was US \$35.00 per patient in input costs per cesarean section averted and US \$25.00 per patient in input costs per neonatal intensive care unit day prevented. The benefit:cost ratio of the difference in input and outcome costs was 2.98 in favour of postprandial BG monitoring in the Southern California study.

CONCLUSION

Until there is evidence to absolutely prove that maternal hyperglycemia may be ignored when the fetal growth patterns appear normal on the ultrasonogram, it is prudent to achieve and maintain normoglycemia in every pregnancy complicated by GDM. The definition of normoglycemia includes both preprandial and postprandial BG concentrations. Decisions concerning the need for insulin therapy should be based on the success or lack of success in achieving BG targets with optimal dietary intervention. Unfortunately, the controversy still exists and the only way to end the debate is to conduct a randomized, double-blind trial aimed at demonstrating whether identification and management of maternal hyperglycemia in women with GDM are associated with significant improvement in neonatal and maternal outcomes.

REFERENCES

1. Jovanovic L (ed.). *Medical Management of Pregnancy Complicated by Diabetes*. 3rd ed. Alexandria, VA: American Diabetes Association; 2000.
2. Naylor CD, Sermer M, Chen E, et al. Selective screening for gestational diabetes mellitus. *N Engl J Med*. 1997;337:1591-1596.
3. 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.
4. Schaefer-Graf UM, Buchanan TA, Xiang AH, et al. Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. *Am J Obstet Gynecol*. 2002;186:751-756.
5. Langer O, Rodriguez DA, Xenakis EM, et al. Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol*. 1994;170:1036-1047.
6. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol*. 1991;164:103-111.
7. Combs CA, Gunderson E, Kitzmilller JL, et al. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care*. 1992;15:1251-1257.
8. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med*. 1995;333:1237-1241.
9. Jovanovic-Peterson L, Peterson CM. Rationale for prevention

- and treatment of glucose-mediated macrosomia: a protocol for gestational diabetes. *Endocrine Practice*. 1996;2:118-129.
10. Visser GHA, van Ballegooie E, Sluiter WJ. Macrosomy despite well-controlled diabetic pregnancy [letter]. *Lancet*. 1984; 1:283-285.
 11. Jovanovic L, Peterson CM, Saxena BB, et al. Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. *Am J Med*. 1980;68:105-112.
 12. Jovanovic L, Druzin M, Peterson C. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med*. 1981;71:921-927.
 13. Kjos SL, Henry OA, Montoro M, et al. Insulin-requiring diabetes in pregnancy: a randomized trial of active induction of labor and expectant management. *Am J Obstet Gynecol*. 1993; 169:611-615.
 14. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med*. 1988;319:1617-1623.
 15. Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med*. 1998; 318:671-676.
 16. Jovanovic L, Metzger BE, Knopp RH, et al. The Diabetes in Early Pregnancy Study: β -hydroxybutyrate levels in type 1 diabetic pregnancy compared with normal pregnancy. *Diabetes Care*. 1998;21:1978-1984.
 17. Demarini S, Mimouni F, Tsang RC, et al. Impact of metabolic control of diabetes during pregnancy on neonatal hypocalcemia: a randomized study. *Obstet Gynecol*. 1994;83:918-922.
 18. Jovanovic L. The role of continuous glucose monitoring in gestational diabetes. *Diabetes Technol Ther*. 2000;2(suppl 1):S67-S71.
 19. Gillmer MDG, Beard RW, Brooks FM, et al. Carbohydrate metabolism in pregnancy. Part I. Diurnal plasma glucose profile in normal and diabetic women. *Br Med J*. 1975;3:399-402.
 20. Ostertag S, Jovanovic L, Lewis B, et al. Insulin pump therapy in the very low birth weight infant. *Pediatrics*. 1986;78:625-630.
 21. Jovanovic L. Response to Fraser. Third trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth [letter]. *Diabetes Care*. 2002;25:1104-1105.
 22. Parretti E, Mecacci F, Papini F, et al. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies. Correlation with sonographic parameters of fetal growth. *Diabetes Care*. 2001;24:1319-1323.
 23. Moses RG, Lucas EM, Knights S. Gestational diabetes mellitus. At what time should the postprandial glucose level be monitored? *Aust N Z J Obstet Gynaecol*. 1999;39:457-460.
 24. Jovanovic L. What is so bad about a big baby? *Diabetes Care*. 2001;24:1317-1318.
 25. 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.
 26. Kitzmiller JL, Elixhauser A, Carr S, et al. Assessment of costs and benefits of management of gestational diabetes mellitus. *Diabetes Care*. 1998;21(suppl 2):B123-B130.