OBSTETRICS

Does gestational diabetes affect fetal growth and pregnancy outcome in twin pregnancies?

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BACKGROUND: Women with twin pregnancies are at increased risk for fetal growth restriction, which might be attributed to the limited maternal resources that are being shared by >1 fetus. Based on that, it may be hypothesized that the fetal effects of gestational diabetes mellitus (GDM) with respect to accelerated fetal growth may be less pronounced in twin gestations or alternatively may even have a beneficial role in decreasing the risk of fetal growth restriction in these pregnancies. However, available data are conflicting and are limited by the fact that many of the complications associated with GDM are less relevant for twin gestations, and that all women with GDM included in previous studies were monitored and treated to control maternal blood glucose levels.

OBJECTIVE: We sought to assess the impact of GDM and milder degrees of glucose intolerance on fetal growth and pregnancy outcome in twin pregnancies.

STUDY DESIGN: This was a retrospective cohort study of all women with twin pregnancies who underwent screening for GDM in a single tertiary referral center from October 2003 through December 2014. The diagnosis of GDM during the study period was based on the 2008 Canadian Diabetes Association (CDA) guidelines, which involve universal screening with a 50-g glucose challenge test (GCT) followed by a diagnostic 2-hour 75-g oral glucose tolerance test (OGTT). Fetal growth and pregnancy outcome were compared among 4 groups of women with increasing degree of glucose intolerance: (1) GCT-NEGATIVE, negative 50-g GCT; (2) OGTT-NEGATIVE, positive 50-g GCT followed by a negative 75-g OGTT; (3) GDM-IADPSG, positive 50-g GCT followed by a positive 75-g OGTT according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria but not the 2008 CDA criteria—because these women were not considered to have GDM during the study period they were not subjected to any form of treatment; and (4) GDM-CDA, positive 50-g GCT followed by a positive 75-g OGTT according to the 2008 CDA criteria.

RESULTS: Overall 1393 women were eligible for the study: 1021 (73.3%) in the GCT-NEGATIVE group, 184 (13.2%) in the OGTT-NEGATIVE group, 99 (7.1%) in the GDM-IADPSG group, and 89 (6.4%) in the GDM-CDA group. There was a continuous relationship between the degree of glucose intolerance and fetal growth as reflected by a right shift of the distribution curve of birthweight percentiles and a greater likelihood of high birthweight percentile: OGTT-NEGATIVE = odds ratio (OR), 1.5; 95% confidence interval (CI), 1.07—2.2; GDM-IADPSG = OR, 1.7; 95% CI, 1.1—2.6; and GDM-CDA = OR, 1.9, 95% CI, 1.3—3.1 (using the GCT-NEGATIVE group as reference). Fetuses of women with glucose intolerance were more likely to experience asymmetric growth as reflected by an elevated abdominal circumference to head circumference ratio.

CONCLUSION: GDM and milder degrees of glucose intolerance in twin pregnancies are associated with an increased risk of asymmetric overgrowth in a manner that is related to the degree of glucose intolerance.

Key words: gestational diabetes, multiple gestations, twins

Introduction

Gestational diabetes mellitus (GDM) has traditionally been defined as an abnormal glucose tolerance that is first identified during pregnancy[1-3] and has been shown to be associated with adverse maternal and neonatal outcome when untreated,[4-6] including accelerated fetal growth, macrosomia, and short- and long-term complications.[5-7]

Women with twin pregnancies are at increased risk for pregnancy complications including preterm birth, hypertensive complications, as well as fetal growth restriction.[8-11] The mechanisms responsible for the higher rate of fetal growth restriction in twin pregnancies are complex, but one of the factors that may play a role is the limited maternal resources that are being shared by >1 fetus.[12-14] Based on that, it may be hypothesized that the fetal effects of the mild hyperglycemia associated with GDM with respect to accelerated fetal growth may be less pronounced in twin gestations or alternatively may even have a beneficial role in decreasing the risk of fetal growth restriction in these pregnancies.

This question regarding the effects of GDM on fetal growth and pregnancy outcome in twins has been addressed by a relatively small number of studies of small sample size that produced conflicting results,[15-25] and the interpretation of these studies is further limited by several factors. First, one of the major difficulties in studying the effects of GDM on pregnancy outcome in twins is that many of the complications associated with GDM are less relevant for twin gestations due to the lower gestational age at delivery, increased risk for hypertensive complications, and high rate of malpresentation and cesarean delivery. Thus, adverse outcomes such as macrosomia and shoulder dystocia are rare in twin gestations, while other complications that have been reported by previous studies such as cesarean delivery, preeclampsia, and neonatal complications such as hypoglycemia and jaundice are more common in twins irrespective of

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TABLE 1
Canadian Diabetes Association and International Association of the Diabetes and Pregnancy Study Groups 75-g oral glucose tolerance test thresholds for diagnosis of gestational diabetes mellitus

	2008 CDA	IADPSG
Strategy	2 Steps	1 Step
Screening test	1-h 50-g GCT	None
Screen negative	<140 mg/dL (7.8 mmol/L)	
Screen positive (followed by OGTT)	140–185 mg/dL (7.8–10.2 mmol/L)	
Diagnostic of GDM	≥185 mg/dL (10.3 mmol/L)	
Definitive test	Fasting 2-h 75-g OGTT	
Fasting threshold	≥95 mg/dL (5.3 mmol/L)	≥92 mg/dL (5.1 mmol/L)
1-h threshold	≥191 mg/dL (10.6 mmol/L)	≥180 mg/dL (10.0 mmol/L)
2-h threshold	≥160 mg/dL (8.9 mmol/L)	≥153 mg/dL (8.5 mmol/L)
Diagnosis of GDM	≥2 Abnormal values	≥1 Abnormal values

CDA, Canadian Diabetes Association; *GCT*, glucose challenge test; *GDM*, gestational diabetes mellitus; *IADPSG*, International Association of the Diabetes and Pregnancy Study Groups; *OGTT*, oral glucose tolerance test.
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GDM. We believe that focusing on fetal growth as the primary outcome can overcome this limitation as fetal growth is not affected by prematurity and may therefore reliably reflect the presence of fetal hyperglycemia and hyperinsulinemia in these pregnancies even in cases of preterm deliveries.

The second factor that limits the interpretation of available studies relates to the fact that all women with GDM included in these studies were monitored and treated to control maternal blood glucose levels, thereby leading to masking or at least underestimation of the true impact of GDM on pregnancy outcome in these cases.[5,6,26] Since randomizing women with GDM to receive no treatment would be considered unethical given the presence of level I evidence regarding the benefits of treatment in these cases, the only way to address this limitation would be by assessing pregnancy outcome in women with evidence of glucose intolerance that is below the level that is consistent with the diagnosis of GDM. Therefore, in the current study we included a subgroup of women who did not meet 2008 Canadian Diabetes Association (CDA) criteria for the diagnosis of GDM[27] (which were used to diagnose GDM during the study period) but did meet the more recent International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria for the diagnosis of GDM,[28] which are lower than the thresholds recommended by the CDA (Table 1).

The aim of the current study was to assess the impact of GDM and milder degrees of glucose intolerance on fetal growth and pregnancy outcome in twin pregnancies while trying to overcome the limitations described above.

Materials and Methods

Study population

This was a retrospective cohort study of all women with twin pregnancies who underwent screening for GDM in a single tertiary referral center (Sunnybrook Health Sciences Center, Toronto, Ontario, Canada) from October 2003 through December 2014. Women with any of the following conditions were excluded from the study: pre-GDM, incomplete or nonstandard screening for GDM (eg, women who had the 2-hour 75-g oral glucose tolerance test [OGTT] with no prior screening with a nonfasting 1-hour 50-g glucose challenge test [GCT] or following a normal 50-g GCT finding), delivery <28 weeks of gestation (based on the assumption that any adverse effects of GDM will be minimal <28 weeks of gestation), complicated monochorionic-diamniotic twins (ie, twin-to-twin transfusion syndrome, selective intrauterine growth restriction, or twin-anemia-polycythemia sequence), monochorionic-monoamniotic twins, stillbirth or reduction of ≥1 fetuses, or genetic or structural fetal anomalies. The study was approved by the institutional research ethics board.

Definitions

The 2008 CDA guidelines for the screening and diagnosis of GDM were followed throughout the study period[27] (Table 1). These guidelines are based on a 2-step screening strategy. The first step involves universal screening at 24-28 weeks of gestation using the 1-hour 50-g GCT. The results of the 50-g GCT are interpreted as a negative screen, positive screen, or diagnostic for GDM (Table 1). Patients with positive screen go on to have the diagnostic fasting 2-hour 75-g OGTT. The test is interpreted as positive for GDM if at least 2 of the values exceed their corresponding thresholds (Table 1).

The IADPSG recommendations for the screening and diagnosis of GDM are based on a 1-step approach using a fasting state 2-hour 75-g OGTT (Table 1), and the test is interpreted as positive for GDM if ≥1 of the values surpasses the corresponding threshold[28] (Table 1). All 3 thresholds of the 75-g OGTT recommended by the IADPSG are lower than those in the 2008 CDA recommendations (Table 1).

All women diagnosed with GDM at our center are followed by a team that consists of a specialist in maternal fetal medicine, endocrinologist, diabetes nurse, and nutritional consultant experienced in the management of diabetes in pregnancy. Patients with GDM are seen in the diabetes clinic every 1-2 weeks from the time of diagnosis up to delivery. All patients monitor blood glucose levels 4 times a day using a glucometer. When patients do not meet the target glucose levels (fasting <95 mg/dL [<5.3 mmol/L] and 2-hour postprandial <121 mg/dL