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ORIGINAL ARTICLE

Glycemic control in twin pregnancies with gestational diabetes: are we improving or worsening outcomes?

Nathan S. Fox[1,2], Rachel S. Gerber[3], Daniel H. Saltzman[1,2], Simi Gupta[1,2], Ariel Y. Fishman[4], Chad K. Klauser[1,2], and Andrei Rebarber[1,2]

[1]*Maternal Fetal Medicine Associates, PLLC, New York, NY, USA,* [2]*The Department of Obstetrics, Gynecology, and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA,* [3]*The Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA, and* [4]*The Sy Syms School of Business, Yeshiva University, New York, NY, USA*

Abstract

Objective: To estimate the association between glycemic control and adverse outcomes in twin pregnancies with gestational diabetes (GDM).

Study design: A cohort of patients with twin pregnancies and GDM were identified from one maternal–fetal medicine practice from 2005 to 2014. Patients with prepregnancy diabetes were excluded. First, outcomes were compared between patients with GDMA1 and GDMA2 (gestational age at delivery, birthweight, small for gestational age (SGA, birthweight <10th percentile), preeclampsia, and cesarean delivery). Then, finger stick glucose logs were reviewed and correlated with the risk of SGA and preeclampsia. Abnormal finger stick values were defined as: fasting ≥90 mg/dL, 1-h postprandial ≥140 mg/dL, 2-h postprandial ≥120 mg/dL.

Results: Sixty-six patients with twin pregnancies and GDM were identified (incidence 9.1%). Comparing the 43 patients with GDMA1 to the 23 patients with GDMA2, outcomes were similar, aside from patients with GDMA1 having lower birthweight of the smaller twin (2184 ± 519 g versus 2438 ± 428 g, $p = 0.040$). The risk of preeclampsia was not associated with glycemic control. Patients with SGA had lower mean fasting values (83.3 ± 5.5 versus 87.2 ± 7.7 mg/dL, $p = 0.033$), and a lower percentage of abnormal fasting values (24.0% versus 36.9%, $p = 0.040$), abnormal post-breakfast values (9.9% versus 27.1%, $p = 0.003$), and total abnormal values (20.1% versus 27.7%, $p = 0.055$).

Conclusion: In twin pregnancies with GDM, improved glycemic control is not associated with improved outcomes, and is associated with a higher risk of SGA. Prospective trials in twin pregnancies should be performed to establish goals for glycemic control in twin pregnancies.

Keywords

Gestational diabetes, glycemic control, preeclampsia, small for gestational age, twins

History

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Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, with an incidence of approximately 6–7% [1–3]. GDM and hyperglycemia is associated with several adverse pregnancy outcomes including preeclampsia, macrosomia, birth injury, and cesarean delivery [4–7]. Recently, several large trials have demonstrated that screening for, and treatment of, GDM is significantly associated with improved outcomes [5,8]. Based on this, screening and treatment of GDM is currently recommended with target finger stick capillary glucose values of fasting <90 (or 95) mg/dL, 1-h postprandial <140 mg/dL, and 2-h postprandial <120 mg/dL, with pharmacologic intervention as necessary to achieve euglycemia [1,3].

In the US, 3.3% of all live births are twins [9]. In twin pregnancies, several physiologic changes are amplified [10,11], which may impact the ideal glycemic control as compared to singleton pregnancies. However, the two large randomized trials evaluating screening and treatment of GDM either did not include twin pregnancies [8], or only included a small number of twins and did not separately analyze the data [5]. Furthermore, several of the risks associated with GDM in singleton pregnancies are not applicable to the same degree in twin pregnancies. For example, macrosomia and macrosomia-related outcomes such as birth injury are not prevalent in twin pregnancies. Therefore, it is currently unknown if treatment of GDM in twin pregnancies is beneficial at all, nor is it known what should be considered ideal glycemic control in twin pregnancies.

The objective of this study was to estimate the association between glycemic control and pregnancy outcomes in twin pregnancies with GDM.

Address for correspondence: Nathan S. Fox, MD, Maternal Fetal Medicine Associates, PLLC, 70 East 90th Street, New York, NY 10128, USA. Tel: 212-722-7409. Fax: 212-722-7185. E-mail: nfox@mfmnyc.com

Materials and methods

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, the charts of all patients with twin pregnancies delivered by a single maternal-fetal medicine practice between June 2005 (when our electronic medical record was established) and June 2014 were reviewed. Baseline characteristics and pregnancy outcomes were obtained from our computerized medical record. We included all patients with a diagnosis of GDM. Patients with prepregnancy diabetes were excluded. We also excluded patients with major fetal anomalies discovered before or after birth, as well as patients with twin-to-twin transfusion. Over the course of the study period, our GDM screening protocol was per standard recommendations [1]. All patients with twin pregnancies underwent a 1-h glucose challenge test (GCT) with a 50 g non-fasting oral glucose load between 24 and 28 weeks gestation, or earlier as indicated (obesity, polycystic ovarian syndrome, history of GDM, family history of diabetes). During the study period, all patients with a GCT of 130 mg/dL or higher underwent a 100 g 3-h oral glucose tolerance test (OGTT). GDM was diagnosed if 2 of 4 values were abnormal on the OGTT, based on Carpenter and Coustan cutoffs: fasting $\geq$95 mg/dL, 1 h $\geq$180 mg/dL, 2 h $\geq$155 mg/dL, 3 h $\geq$140 mg/dL [12]. Once diagnosed, all patients with GDM underwent nutritional counseling regarding a diabetic diet and began monitoring their finger stick capillary blood glucose 4 times daily (fasting, after breakfast, after lunch, and after dinner). Patients were given the option of testing 1 or 2 h postprandial. Glycemic goals were fasting <90 mg/dL, 1-h postprandial <140 mg/dL, and 2-h postprandial <120 mg/dL [3]. Patients who could not achieve adequate control (defined as approximately 2/3 normal values) with dietary intervention were started on either glyburide or insulin. These patients were considered as having GDMA2. Typically, our first-line agent would be glyburide unless the glucose levels were so high that it was assumed glyburide would fail, or if the patient preferred insulin over glyburide.

All patients with twin pregnancies in our practice undergo serial growth ultrasounds every 2–4 weeks, and weekly biophysical profile testing beginning at 32 weeks, or more frequently as indicated. Dichorionic twin pregnancies are delivered at 38 weeks and monochorionic twin pregnancies are delivered at 37 weeks, or earlier as indicated. In our practice, neither the frequency of ultrasound nor the timing of delivery is routinely changed in twin pregnancies due to a diagnosis of GDM.

We first compared baseline characteristics and pregnancy outcomes between patients with GDMA1 and GDMA2. Pregnancy outcomes included gestational age at delivery, birthweight, birthweight percentiles, and preeclampsia. To define birthweight percentiles for gestational age, we used standard tables for singleton pregnancies [13]. We chose singleton tables as they are the standard tables used for twins in the United States in defining growth restriction and determining neonatal outcomes [14–16].

To estimate the association between glycemic control and pregnancy outcomes, we then did two case–control analyses. First, we compared glycemic control between patients who did and did not develop preeclampsia. Then, we compared glycemic control between patients with and without small for gestational age (SGA), defined as having a twin with a birthweight less than the 10th percentile for gestational age. To assess glycemic control, we compared mean fasting values, and the percent of abnormal values (fasting, after breakfast, after lunch, after dinner, and total). Since postprandial values were either 1-h or 2-h, we did not assess mean postprandial values.

Chi square, Fisher's exact test, Student's *t*-test, and partial correlations were used, as appropriate (IBM SPSS for Windows 22.0, Armonk, NY, 2013; Stata Statistical Software: Release 11, College Station, TX 2009). For the case–control analyses, we used logit regression to calculate a partial correlation, treating preeclampsia or SGA, respectively, as dependent variables, to compare differences in glycemic control between the groups. We also used logit regression to analyze the effect of controlling for differences in baseline characteristics between the groups.

Results

During the time of the study, there were 725 patients with twin pregnancies, 66 (9.1%) of whom had GDM and were included in the analysis. Forty-three (65.2%) patients had GDMA1 and 23 (34.8%) patients had GDMA2. The numbers of glucose measurements were: fasting 2781 (42.1 measurements per patient), after breakfast 2605 (39.5 measurements per patient), after lunch 2530 (38.3 measurements per patient), after dinner 2429 (36.8 measurements per patient), for a total of 10 345 measurements (156.7 measurements per patient).

The baseline characteristics are shown in Table 1. There were no baseline differences between patients with GDMA1 and GDMA2, aside from a higher mean body mass index (BMI) in the GDMA2 group. Pregnancy outcomes are shown in Table 2. There was no difference between the groups in regards to gestational age at delivery. Mean birthweights were smaller in the GDMA1 group, but this did not translate into a significantly higher incidence of birthweight less than the 10th or less than the 5th percentile.

The comparison of glycemic control between patients who did and did not develop preeclampsia is shown in Table 3. There was no difference in the glycemic control between the groups. The comparison of glycemic control between patients with and without SGA is shown in Table 4. SGA was associated with improved glycemic control. Patients with SGA had lower mean fasting values (83.3 ± 5.5 versus 87.2 ± 7.7 mg/dL, $p = 0.033$), and had a lower percentage of abnormal fasting values (24.0% versus 36.9%, $p = 0.040$), abnormal post-breakfast values (9.9% versus 27.1%, $p = 0.003$), and total abnormal values 20.1% versus 27.7%, $p = 0.055$), although this p value was insignificant as it was slightly above 0.05.

For the analyses in both Tables 3 and 4, we performed a regression analysis to control for differences in baseline between the groups (maternal age, chorionicity, IVF, multifetal reduction, race, nulliparity, history of GDM, maternal BMI, chronic hypertension, anticoagulation, and GDM type (A1 versus A2). We performed a second regression analysis

Table 1. Baseline characteristics in twin pregnancies with gestational diabetes, based on severity.

	Gestational diabetes, A1 $N = 43$	Gestational diabetes, A2 $N = 23$	p value
Maternal age	36.5 ± 7.1	33.9 ± 6.1	0.139
Advanced maternal age (≥35)	60.5%	43.5%	0.187
Chorionicity			
Monochorionic-diamniotic	18.6%	17.4%	0.903
Dichorionic-diamniotic	81.4%	82.6%	
In-vitro fertilization	81.4%	73.9%	0.479
Multi-fetal reduction	7.0%	0.0%	0.546
Non-White race	32.6%	34.8%	0.855
Nulliparity	79.1%	60.9%	0.114
History of gestational diabetes	2.3%	13.0%	0.118
Pre-pregnancy BMI (kg/m^2)	24.0 ± 4.8	27.5 ± 6.2	0.016
Pre-pregnancy obesity	14.0%	21.7%	0.419
Chronic hypertension	4.7%	4.3%	0.955
Anticoagulation	2.3%	13.0%	0.118

Table 2. Pregnancy outcomes in twin pregnancies with gestational diabetes, based on severity.

	Gestational diabetes, A1 $N = 43$	Gestational diabetes, A2 $N = 23$	p value
Gestational age at delivery	35.8 ± 2.0	36.3 ± 1.5	0.383
Birthweight larger twin	2499 ± 523 g	2766 ± 450 g	0.056
Birthweight smaller twin	2184 ± 519 g	2438 ± 428 g	0.040
Either twin birthweight <10th percentile	53.5%	43.5%	0.438
Either twin birthweight <5th percentile	34.9%	17.4%	0.135
Preeclampsia	19.5%	22.7%	0.764
Cesarean (all patients)	72.1%	73.9%	0.874
Cesarean (labored)	29.4% (5/17)	40% (4/10)	0.573

Table 3. Correlation between preeclampsia and glycemic control in patients with twin pregnancies and gestational diabetes.

	Preeclampsia $N = 13$	No preeclampsia $N = 50$	p value	Adjusted p value*
Mean fasting blood glucose (g/dL)	83.9 ± 8.6	85.7 ± 6.6	0.426	0.126
Mean proportion of abnormal fasting blood glucose measurements (%)	29.5%	30.9%	0.857	0.459
Mean proportion of abnormal post-breakfast blood glucose measurements (%)	20.3%	17.9%	0.716	0.832
Mean proportion of abnormal post-lunch blood glucose measurements (%)	15.9%	18.5%	0.624	0.457
Mean proportion of abnormal post-dinner blood glucose measurements (%)	23.8%	27.7%	0.508	0.352
Mean proportion of abnormal blood glucose measurements (total %)	22.9%	24.1%	0.805	0.395

Abormal blood glucose values: Fasting, >90 g/dL; 1-h after meals, >140 g/dL; 2-h after meals, >120 g/dL.
*Adjusted for maternal body mass index and type of GDM (A1 versus A2).

controlling for all baseline differences in a step-wise regression using all variables with a p value of < 0.10. We then performed a third regression controlling for variables we thought were clinically relevant, which were maternal BMI and type of GDM (A1 versus A2). In all three analyses, the results were not materially different from the unadjusted analysis, and the results of the third regression analysis are shown in Tables 3 and 4.

Comments

In this study, we found that improved glycemic control in twin pregnancies with GDM was not associated with improved outcomes, and was in fact associated with an *increased* risk of SGA. Patients with GDMA2 did not have worse outcomes compared to those who were well controlled by diet alone throughout pregnancy. In fact, the patients who achieved euglycemia by dietary control had babies with smaller mean birthweights. Furthermore, when we examined actual glucose values, we did not find a correlation between poor glycemic control and preeclampsia, but we did find a correlation between *improved* glycemic control and SGA. This indicates that the goals for glycemic control in twin pregnancies need to be reconsidered, as strict glycemic control may not be improving outcomes and may in fact be increasing the risk of SGA. Therefore, when caring for a patient with twin pregnancy and GDM, it may not be prudent to encourage her to achieve euglycemia by dietary modifications or pharmacologic intervention, or the optimal definition of euglycemia in twin pregnancies might need to be changed. This has the potential to change the paradigm of GDM screening and management in twin pregnancies altogether.

Table 4. Correlation between birthweight and glycemic control in patients with twin pregnancies and gestational diabetes.

	SGA* $N = 33$	No SGA* $N = 32$	p value	Adjusted p value†
Mean fasting blood glucose (g/dL)	83.3 ± 5.5	87.2 ± 7.7	0.033	0.030
Mean proportion of abnormal fasting blood glucose measurements (%)	24.0%	36.9%	0.040	0.038
Mean proportion of abnormal post-breakfast blood glucose measurements (%)	9.9%	27.1%	0.003	0.003
Mean proportion of abnormal post-lunch blood glucose measurements (%)	18.0%	17.9%	0.982	0.7910
Mean proportion of abnormal post-dinner blood glucose measurements (%)	27.2%	27.1%	0.991	0.922
Mean proportion of abnormal blood glucose measurements (total %)	20.1%	27.7%	0.055	0.053

Abormal blood glucose values: Fasting, >90 g/dL; 1-h after meals, >140 g/dL 2-h after meals, >120 g/dL.
*SGA, small for gestational age, defined as either twin with a birthweight less than the 10th percentile for gestational age.
†Adjusted for maternal body mass index and type of GDM (A1 versus A2).

Prior studies that demonstrated improved outcomes with treatment of GDM either did not include twin pregnancies [8] or included very few twin pregnancies [5]. Therefore, treatment of GDM in twin pregnancies is not based on Level I evidence, and the optimal glycemic control is currently unknown in twin pregnancies. Furthermore, it is also unknown whether the screening for, and treatment of, GDM in twin pregnancies is associated with any benefit at all. It is plausible that optimal glycemic control would differ for singleton and twin pregnancies. After all, twin pregnancies have altered physiology and require increased caloric intake. Additionally, the adverse outcomes associated with hyperglycemia in singleton pregnancies do not always apply to twin pregnancies, namely macrosomia and birth injury, which is frequently a complication of macrosomia. Not only do twins have very low rates of macrosomia, twin pregnancies are at a very high risk of fetal growth restriction [17–20], and restricting calories or medicating patients to achieve euglycemia could plausibly increase this risk. We have previously shown the risks of poor weight gain in twin pregnancies [21] and suspect that strict glycemic control may have the same effect on twin pregnancies. Preeclampsia, which is prevalent in twin pregnancies, is reduced with the treatment of GDM in singleton pregnancies. However, we did not see an association between improved glycemic control and a lower risk of preeclampsia.

Prior studies have indicated that GDM is not associated with adverse perinatal outcomes in patients with twin pregnancies. Okby et al. compared outcomes between 341 patients with twins and GDM to 4428 patients with twins and no GDM and found no increased risk of low Apgar scores or perinatal mortality [22]. In fact, twins with GDM had significantly lower rates of low Apgar scores and perinatal mortality. There is less data regarding outcomes in twin pregnancies based on severity of GDM (GDMA1 versus GDMA2), or outcomes based on glycemic control in patients with GDM, which is one of the reasons our study was undertaken.

Our study has limitations. First, it is retrospective and observational. Ideally, the optimal study would be a large prospective study that could randomize patients with twin pregnancies to screening and treatment of GDM versus no screening of GDM, or randomize patients with GDM to various treatment protocols. This would be the best way to answer the question of how to manage twin pregnancies with GDM. Our data only suggest that the current treatment strategy of treating twin pregnancies similar to singleton pregnancies might need to be reconsidered. Second, there may have been other unmeasured differences between the groups such as certain baseline characteristics or various weight gain patterns prior to and after the diagnosis of GDM that could have contributed to birthweight. Third, due to the prevalence of GDM in twin pregnancies, we only had 66 patients with twins and GDM. Therefore, we did not perform a power analysis and accept that we are underpowered to prove that glycemic control is not associated with improved outcomes. Larger studies would need to be conducted to prove this. However, despite our sample size we still found a significant association between improved glycemic control and SGA. Therefore, our data suggest that glycemic control in twin pregnancies needs to be revisited in properly designed studies, and the use of singleton norms in twin pregnancies is possibly incorrect.

In conclusion, in twin pregnancies with GDM, improved glycemic control is not associated with improved outcomes, and may be associated with a higher risk of SGA. Prospective trials in twin pregnancies should be performed to establish the goals for glycemic control in twin pregnancies.

Declaration of interest

The authors report no conflicts of interest.

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