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Perinatal Outcomes in Twin Pregnancies Complicated by Gestational Diabetes

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Abstract

Background—Gestational diabetes in singleton pregnancies increases the risk of large for gestational age infants, hypertensive disorders of pregnancy, and neonatal morbidity.[1,2,3,4] Compared to singleton gestations, twin gestations are at increased risk for fetal growth abnormalities, hypertensive disorders and neonatal morbidity.[5] Whether gestational diabetes further increases the risk of these outcomes is unclear.

Objectives—We sought to determine the relation between gestational diabetes and the risk of preeclampsia, fetal growth abnormalities, and NICU admission in a large cohort of twin pregnancies.

Study Design—We used a retrospective cohort of all twin deliveries at our institution from 1998 to 2013. We excluded pregnancies delivered before 24 weeks, monochorionic-monoamniotic twins, and patients with pre-existing diabetes for a final cohort of 2,573 twin deliveries. Gestational diabetes was defined as two abnormal values on a 100 gram, three-hour glucose challenge test as defined by Carpenter Coustan Criteria or a one-hour value 200mg/dL after a 50 gram glucose test.[1] Multivariable Poisson regression models were used to estimate associations between gestational diabetes and preeclampsia, small for gestational age, large for gestational age and admission to the NICU, after adjustment for pre-pregnancy body mass index, maternal race,

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maternal age, parity, use of *in vitro* fertilization, pre-pregnancy smoking, and chronic hypertension as confounders.

Results—The unadjusted incidence of gestational diabetes was 6.5% (n=167). Women with gestational diabetes were more likely than women without gestational diabetes to be 35 years or older, living with obesity, and have conceived with *in vitro* fertilization. Preeclampsia was more common among twin pregnancies complicated by gestational diabetes: 31% compared to 18% in twin pregnancies without gestational diabetes (aRR= 1.5; 95% CI, 1.1, 2.1). A diagnosis of small for gestational age infant was less common among women with gestational diabetes (17%) compared to women without gestational diabetes (24%), although results were imprecise aRR= 0.8 (0.5, 1.1). There was no association between gestational diabetes and large for gestational age or NICU admission. Among women with gestational diabetes who reached 35 weeks, 62% (n=60) required medical management.

Conclusions—Gestational diabetes is a risk factor for preeclampsia among twin pregnancies. Close blood pressure monitoring and patient education are critical for this high risk group. The association between gestational diabetes and neonatal outcomes in twin pregnancies is less precise, although it may be protective against a small for gestational age infant. Prospective studies to determine if glycemic control decreases risk of preeclampsia in twin pregnancies with gestational diabetes are needed.

Keywords

Gestational diabetes; diabetes; twin gestation; multifetal gestation; chorionicity; preeclampsia

Introduction

In singleton pregnancies, diagnosing and treating gestational diabetes decreases maternal and neonatal risks.[1–4,6–9] A meta-analysis of randomized trials demonstrated a reduction in preeclampsia, birthweight greater than 4000 grams, and shoulder dystocia with appropriate management of gestational diabetes in singletons.[10] While the management of gestational diabetes in twins is assumed to be the same as for singleton pregnancies, the maternal and neonatal risk of gestational diabetes in twin pregnancies remains incompletely characterized.[11,12]

Twin pregnancies have a markedly increased baseline risk of preeclampsia and prematurity compared to singletons.[5] Thus, it is possible that gestational diabetes does not meaningfully increase the risks of these complications above their baseline risk. Additionally, a number of studies have demonstrated an increased risk of small for gestational age infants (SGA) in twins pregnancies complicated by gestational diabetes compared to twin pregnancies without diabetes. Thus, it is possible that the risks of gestational diabetes in twin pregnancies vary considerably from that of singletons.[10,13,14]

The existing literature of perinatal outcomes of twin pregnancies complicated by gestational diabetes has yielded mixed results.[11,12,15–24] Some studies have demonstrated an increased risk of preeclampsia in twin pregnancies complicated by gestational diabetes.[11,15,16,18] Others have not found such a relationship.[12,17] The impact on fetal growth and risk of small

or large for gestational age (LGA) has similarly been inconsistent.[12,19–24] The published studies on gestational diabetes in twin pregnancies have a number of limitations that might contribute to these disparate findings. First, many studies lack information about important confounders such as pre-pregnancy body mass index and chorionicity.[18,21,25] Given placental factors are implicated in the etiology of gestational diabetes, hypertensive disorders and fetal growth, chorionicity is a particularly important variable to consider.[26–28] Second, existing studies have used singleton growth charts rather than twin specific curves to classify twin growth.[29] Singleton curves overestimate SGA and underestimate LGA, and thus may obscure an association between gestational diabetes and fetal growth abnormalities.[30] Finally, many of the published studies took place outside of the United States, where the diagnostic criteria used to diagnose gestational diabetes vary from those commonly used in the United States (US).[12,15,16,18,19,23]

Given these considerations, we sought to examine how gestational diabetes is associated with preeclampsia, fetal growth abnormalities and neonatal intensive care unit (NICU) admission in a well characterized US twin cohort. We chose these outcomes given they are clinically relevant in twins.

Materials and Methods

Study Population

Our study cohort is drawn from all women delivering twin gestations at our institution from 1998 to 2013. Our Institutional Review Board approved this study. We used an institution-wide database to identify twin deliveries. Detailed data derived from medical records coding, medical record abstraction, and the electronic birth record are maintained in this delivery database.[31] Database administrators review variable frequencies for outlying values and investigate them by abstraction from the medical record. We obtained chorionicity (first filled in from placental reports and then from ultrasound reports if placental pathology was not available), type of assisted reproductive technology, and management of gestational diabetes (diet versus medical—insulin versus oral hypoglycemic agent) from medical record abstraction. Gestational age at Magee-Womens Hospital is estimated using last menstrual period or date of conception confirmed or revised with early ultrasound. Based on the American College of Obstetricians and Gynecologists guidelines at the time, last menstrual period or conception dating was changed to the first trimester ultrasound estimate if the discrepancy from last menstrual period was greater than 7 days. For a second trimester ultrasound the dating was changed if the discrepancy was greater than 10 days. We excluded monochorionic monoamniotic twins, all pregnancies that delivered before 24 weeks gestation, and pregnancies with pre-existing diabetes.

Gestational Diabetes

We screened for gestational diabetes using a 50 gram oral glucose test. A positive screening test was defined as a value of 135mg/dL or more. A positive screen was followed by a three hour 100 gram oral glucose challenge test. We defined gestational diabetes as two abnormal values on the 100 gram test as defined by Carpenter Coustan Criteria. Women with a one-hour value >200mg/dL after a 50 gram glucose test were also diagnosed

with gestational diabetes. We characterized diabetes management for twin pregnancies that reached 35 weeks' gestation, a gestational age by which we hypothesized that most women would have started medical management. Importantly, at Magee-Womens Hospital all gestational diabetes is managed by a single maternal fetal medicine group with a consistent management approach. Gestational diabetes is managed with dietary changes unless more than 3 values are abnormal in a week (fasting greater than 95mg/dL or one-hour post prandial greater than 140mg/dL). If medical management is required women are given the option for glyburide, metformin, or insulin.

Outcome Definitions

Outcomes of interest included preeclampsia, small and large for gestational age birth, and neonatal intensive care unit admission. The diagnosis of preeclampsia was based on ICD-9 coding. We validated this diagnosis in a subset of charts. We defined small for gestational age and large for gestational age as either twin less than 10% or greater than 90% on the National Institutes of Child Health and Human Development (NICHD) twin growth curve.[30] We defined NICU admission as admission to the NICU of either infant.

Statistical Analysis

To estimate the independent association between gestational diabetes and the perinatal outcomes of interest we used multivariable modified Poisson models with a log link and robust standard errors.[32] We used theory based causal diagrams to identify confounders that we included in all models.[33] Confounders included pre-pregnancy body mass index, maternal race/ethnicity, chorionicity, maternal age, parity, use of *in vitro* fertilization, tobacco use prior to pregnancy, and pre-existing hypertension. After modeling, we estimated risk differences and 95% confidence intervals via marginal standardization.[32]

Results

Our study population included 2,573 twin deliveries—2,034 (81%) dichorionic twin deliveries and 539 (19%) monochorionic/diamniotic twin deliveries. The mean gestational age at delivery was 35.4 weeks. A total of 167 (6.5%) women were diagnosed with gestational diabetes. The mean gestational age at diagnosis was 25.0 weeks. The incidence of gestational diabetes did not meaningfully vary by chorionicity (6.6% among dichorionic twins, 5.9% monochorionic/diamniotic twins). Women with gestational diabetes were more likely than women without gestational diabetes to be nulliparous, living with obesity, advanced maternal age, have private insurance, and have conceived using *in vitro* fertilization (Table 1). The mean gestational age at delivery did not differ by gestational diabetes status—35.4 weeks in women without gestational diabetes versus 35.5 weeks in women with gestational diabetes. The stillbirth rate overall was 1.6% (n=42) and did not vary by gestational diabetes status (1.6% among women without gestational diabetes and 1.3% among women with gestational diabetes).

The perinatal complications of interest were common in this twin cohort. Nearly 1 in 5 women with twin pregnancies were diagnosed with preeclampsia (n=494) and roughly 1 in 4 women had at least one small for gestational age infant (n=593). Almost half had at least one

twin admitted to the NICU (n=1190). A total of 9% (n=236) of women had at least one large for gestational age twin.

The unadjusted incidence of preeclampsia among twin pregnancies was 19% (n=494). Preeclampsia was more common among twin pregnancies complicated by gestational diabetes (31%) compared with twin pregnancies without gestational diabetes (18%) (Table 2). After adjusting for confounders, gestational diabetes was associated with 10 additional cases of preeclampsia (95% CI: 1.5–18) per 100 twin deliveries compared with not having gestational diabetes. The adjusted RR was 1.5 (95% CI: 1.1, 2.1).

The unadjusted incidence of small for gestational age of either twin was 23% (n=593). Having a small for gestational age infant was less common among women with gestational diabetes (17%) compared to women without gestational diabetes. In adjusted analysis, gestational diabetes was associated with 5.4 fewer cases of SGA per 100 twin pregnancies; however, results were imprecise with wide confidence intervals (95% CI: −12, 1.5). The adjusted RR was 0.8 (95% CI: 0.5, 1.1) Gestational diabetes was not associated with LGA and NICU admission in adjusted analyses (Table 2).

Management of Gestational Diabetes in Twins

A total of 107 women with gestational diabetes were still pregnant at 35 weeks and 91% (n=97) had data about how their gestational diabetes was managed in the chart. A total of 62% (n=60) of these women required medical management of their diabetes with either insulin, glyburide, or metformin. Among women with available data, 68% used insulin to manage their diabetes. Women with diet controlled gestational diabetes were more likely to be nulliparous, have conceived by *in vitro* fertilization, and have a normal BMI (Table 3). The unadjusted incidence of preeclampsia among twin pregnancies with gestational diabetes that were still pregnant at 35 weeks was 33% (n=32). Preeclampsia was less common among twin pregnancies with diabetes that required medical management (28%) compared with twin pregnancies with diet controlled gestational diabetes (41%).

Discussion/Comment

Principal Findings

In a well-characterized cohort of twin pregnancies, we found that women with gestational diabetes had an elevated risk for preeclampsia compared with twin pregnancies without gestational diabetes. Additionally, gestational diabetes was associated with fewer cases of small for gestational age infant. These associations remained after controlling for important confounders including parity, chorionicity, body mass index, and maternal age. We did not observe an association between gestational diabetes and LGA or admission to the NICU. Notably, over half of the women diagnosed with gestational diabetes that were still pregnant at 35 weeks required medical management.

Results

While a number of studies have demonstrated an association between gestational diabetes in twin pregnancies and preeclampsia, this association has not been consistent across all

studies.[11,12,14–18,34] Notably, a large population based study in Canada (3,901 deliveries) did not detect an association between gestational diabetes in twins and hypertensive disorders.[12] The screening and diagnostic criteria for gestational diabetes in this study differ from the screening and diagnostic criteria we used. It is possible that the less sensitive screening cutoff and the diagnostic differences in the Canadian study contribute to our different findings. Additionally, there are marked differences in demographics between our populations, particularly with regards to race and BMI.

Our finding of a possible protective effect against SGA in twin pregnancies complicated by gestational diabetes is consistent with a number of other studies.[12,20,21,23] We used a twin specific definition of SGA which may contribute to the modest effect size we saw.[30] Finally, many studies report an increased risk of NICU admissions among twin pregnancies complicated by gestational diabetes that we did not demonstrate.[11,20,21,35] Variations in these findings are more difficult to interpret given NICU admission criteria vary significantly by institution. Lastly, we found that the majority of women with gestational diabetes and twin pregnancies required medical management. Data on medical management in twins is limited with only one other report of a total of 66 women limiting comparisons between studies.[14] Importantly, our finding in twins is in contrast to singleton pregnancies where roughly 15–30% of singleton pregnancies with gestational diabetes require medical management.[36]

Clinical Implications

Our data have a number of clinical implications. First, our data suggest that the rate of gestational diabetes is not meaningfully different between women with dichorionic twins and monochorionic diamniotic twins. Second, women with twin pregnancies who develop gestational diabetes should be re-counseled about the risk of preeclampsia, educated about the signs and symptoms of preeclampsia, and potentially be given a blood pressure cuff to monitor blood pressures at home. Finally, women diagnosed with gestational diabetes should be counseled that roughly half of women who are diagnosed with diabetes will require medical management if they remain pregnant to 35 weeks.

Research Implications

In singleton pregnancies complicated by gestational diabetes, glycemic control decreases the risk of maternal and neonatal complications. While we found that women who required medical management of gestational diabetes had a lower rate of preeclampsia than women with diet controlled gestational diabetes, the retrospective nature of our work and the lack of granular glycemic data do not allow us to examine the modifying impact of glycemic control on perinatal outcomes. It is possible that there is tradeoff between decreasing maternal risk of preeclampsia and increasing risk of SGA that warrants further prospective study. Understanding the impact of glycemic control and blood sugar targets on important perinatal outcomes could help guide treatment goals and practices in this population, as they may differ from singletons.

Strengths & Limitations

A major strength of our study is that we used a well-characterized cohort from a single institution with consistent approaches to the diagnosis of gestational diabetes and other pregnancy complications. Given this, we were able to exclude women with pre-existing diabetes and account for important confounders such as chorionicity. This has not been done in prior studies. We also used twin specific growth curves. Given the high rate of SGA among twins when using singleton curves this is an important step in characterizing the risk of gestational diabetes. Our study also has important limitations. First the association between gestational diabetes and small for gestational age infant is imprecise with a wide confidence interval. Second, the racial and ethnic background of our sample is not representative of the demographics of the United States as a whole. Furthermore, we lacked information on important neonatal outcomes beyond size such as hypoglycemia and jaundice. These neonatal outcomes are critical to get a more comprehensive picture of the impact of gestational diabetes in twin pregnancies. Finally, we did not have detailed information about glycemic control as noted above and while indications for medical management were standardized, treatment regimens were not and likely evolved during the study time.

Conclusions

Our study suggests that gestational diabetes in twin pregnancies is a risk factor for preeclampsia and may reduce the risk of small for gestational age. Future prospective studies are needed to examine the impact of glycemic control on the totality of perinatal outcomes. It is possible that glycemic control may mitigate the risk of preeclampsia, but contribute to the risk of small for gestational age infants among twins. Further understanding the impact of glycemic control on these outcomes will help guide treatment goals and practices in this population.

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AJOG at a Glance

Why was this study conducted

- The association between gestational diabetes and important maternal and neonatal outcomes among twins is not well characterized.
- Many existing studies lack important information on confounders including prepregnancy weight and chorionicity.

What are the key findings?

- Gestational diabetes was associated with 10 additional cases of preeclampsia per 100 twin births when controlling for confounders.
- Gestational diabetes was protective against small for gestational age without increasing the proportion of infants born large for gestational age. Our estimates, however, are imprecise.
- More than half of women with gestational diabetes required medical management.

What does this study add to what is already known?

- The rate of gestational diabetes is similar between dichorionic and monochorionic diamniotic twins.
- Gestational diabetes is a risk factor for preeclampsia in twin pregnancies. Women with gestational diabetes should be educated about the signs and symptoms of preeclampsia and monitored carefully.
- The impact of gestational diabetes on fetal growth is less clear and warrants evaluation in larger cohorts.

Table 1.

Characteristics of People Delivering Twins by Gestational Diabetes Status, 2003–2013 (n=2,573)

Characteristic	No Gestational Diabetes (n=2406)	Gestational Diabetes (n=167)
Race-ethnicity		
Non-Hispanic white	1920 (80)	138 (83)
Non-Hispanic black	396 (16)	13 (7.0)
Hispanic	23 (1.0)	1 (1.0)
Non-Hispanic other	67 (3.0)	15 (9.0)
Prepregnancy BMI category		
Underweight	81 (3.0)	4 (2.0)
Normal weight	1213 (50)	55 (33)
Overweight	596 (25)	42 (25)
Obese	516 (22)	66 (40)
Age (y)		
Less than 35	1,861 (77)	101 (60)
Greater than or equal to 35	545 (23)	66 (40)
Parity		
Nulliparous	1,090 (45)	87 (52)
Multiparous	1,316 (55)	80 (48)
Smoking prior to pregnancy		
No	2,069 (86)	150 (90)
Yes	337 (14)	17 (10)
Insurance		
Private	1665 (69)	132 (79)
Medicaid, self-pay, or other	738 (31)	35 (21)
In Vitro Fertilization		
No	2,041 (85)	116 (69)
Yes	365 (15)	51 (31)
Preexisting hypertension		
No	2,297 (95)	157 (94)
Yes	109 (5.0)	10 (6.0)
Birthweight at Delivery (grams)		
Twin A Mean (SD)	2338 (655)	2403 (604)
Twin B Mean (SD)	2285 (671)	2315 (623)

Table 2.

Association between select adverse outcomes and gestational diabetes in twins, 2003–2013 (n=2,573)

Outcome	Gestational diabetes	Population at risk, n	Cases, n (%)	Unadjusted Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)	Adjusted number of excess cases per 100 births (95% CI)
Preeclampsia						
	No	2406	440 (18)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	167	54 (31)	1.7 (1.3, 2.3)	1.5 (1.1, 2.1)	10 (2, 17)
SGA of either infant						
	No	2406	565 (24)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	167	28 (17)	0.7 (0.5, 1.0)	0.8 (0.5, 1.1)	−5.4 (−12, 1.5)
LGA of either infant						
	No	2406	218 (9)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	167	18 (11)	1.2 (0.7, 1.9)	1.0 (0.6, 1.7)	0.2 (−4.3, 4.9)
NICU admission of either infant						
	No	2406	1105 (46)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	167	85 (51)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	8.4 (−3.7, 21)

*Adjusted for pre-pregnancy BMI, maternal race, maternal age, parity, use of *in vitro* fertilization, pre-pregnancy smoking and chronic hypertension

**When the estimate is a negative value, it is the adjusted number of prevented cases per 100 births.

Table 3.

Characteristics of People Delivering Twins with Gestational Diabetes Stratified by Management Strategy

Characteristic	Diet Alone (n=37)	Diet and Medicine (n=60)
Race-ethnicity		
Non-Hispanic white	31 (84)	49 (82)
Non-Hispanic black	1 (2.5)	4 (6)
Hispanic	1 (2.5)	0 (0.0)
Non-Hispanic other	4 (11)	7 (12)
Prepregnancy BMI category		
Underweight	1 (3.0)	0 (0)
Normal weight	15 (42)	18 (30)
Overweight	9 (25)	15 (25)
Obese	12 (33)	27 (45)
Age (y)		
Less than 35	22 (59)	39 (65)
Greater than or equal to 35	15 (41)	21 (35)
Parity		
Nulliparous	24 (65)	25 (42)
Multiparous	13 (35)	35 (58)
Smoking prior to pregnancy		
Yes	4 (11)	5 (8)
No	33 (89)	55 (92)
Insurance		
Private	30 (81)	46 (77)
Medicaid, self-pay, or other	7 (19)	14 (23)
In Vitro Fertilization		
No	22 (59)	44 (73)
Yes	15 (41)	16 (27)