Original Research

Preterm Birth or Small for Gestational Age in a Singleton Pregnancy and Risk of Recurrence in a Subsequent Twin Pregnancy

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OBJECTIVE: To evaluate whether a history of preterm birth or small for gestational age (SGA) in a singleton pregnancy is associated with an increased risk of recurrence of the same condition in a subsequent twin pregnancy.

METHODS: Retrospective cohort study of twin pregnancies delivered in one maternal–fetal medicine practice from 2005 to 2014. Patients with a history of singleton preterm birth at less than 37 weeks of gestation were compared with patients with a history of singleton term birth and nulliparous patients. A similar analysis was performed for a history of SGA (birth weight less than 10%).

RESULTS: Six hundred forty-seven twin pregnancies were included. The prior singleton gestational age at delivery was significantly positively correlated with the twin gestational age at delivery ($P<.001$), and the prior singleton birth weight was significantly positively correlated with the birth weight of the larger twin ($P<.001$) and the smaller twin ($P<.001$). The rate of twin preterm birth before 32 weeks of gestation was 3.5% in patients with a prior term birth, 9.2% in nulliparous patients, and 26% in patients with a prior preterm birth ($P<.001$). The rate of SGA in patients with a prior birth not complicated by SGA was 42.1%, in nulliparous women it was 54.4%, and in patients with a history of SGA it was 65.2% ($P=.007$). On regression analysis, prior preterm birth and SGA of a singleton pregnancy were independently associated with recurrence of the same condition in a subsequent twin pregnancy.

CONCLUSION: Prior preterm birth and SGA in a singleton pregnancy increase the risk of the same condition in a subsequent twin pregnancy. We postulate that the extrinsic mechanism responsible for the pathophysiology of adverse outcomes in twin pregnancies overlaps with that in singleton pregnancies.

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LEVEL OF EVIDENCE: II

The incidence of twin pregnancy in the United States has grown from 1.9% of live births in 1980 to 3.3% in 2011.[1] Twins are at increased of morbidity and mortality when compared with singletons resulting from the high incidence of preterm birth and small for gestational age (SGA) in this population. In the United States, 57.3% of twins are born preterm (less than 37 weeks of gestation) and 11.3% are born before 32 weeks of gestation.[2] This leads to an increased incidence of low birth weight and complications from prematurity in twins. Furthermore, even when adjusted for gestational age, twins have an increased incidence of SGA with studies reporting an incidence of 15–25%.[3–5] Based on more contemporary data, we have recently reported an even higher incidence of SGA with 47% of patients delivering a neonate less than the 10th percentile for gestational age and 27% of patients delivering a neonate less than the fifth percentile for gestational age.[6]

In singleton pregnancies, there is an established relationship between outcomes of prior pregnancies on future pregnancies. Specifically, patients with a prior preterm birth are at increased risk for recurrent preterm birth and this association is stronger with earlier gestational ages at the prior preterm

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birth.[7–9] Similarly, patients with prior SGA neonates or fetal growth restriction are at increased risk of recurrence as well.[10–12] In regard to the relationship between twin and singleton pregnancy outcomes, most research has focused on the effect or a prior twin adverse outcome on a future singleton pregnancy outcome. For example, there is debate in the literature whether a prior twin preterm birth is or is not a risk factor for subsequent preterm birth in a singleton pregnancy.[8,13–15]

There are fewer data regarding the risk of a prior singleton pregnancy outcome on subsequent twin pregnancy outcomes and much of these data are derived from statewide registries[16,17] as opposed to single centers.[18] Furthermore, the data on this question do not include patients with twin pregnancies and no previous pregnancies. The objective of our study was to evaluate whether a history of preterm birth or SGA in a singleton pregnancy is associated with an increased risk of recurrence of the same condition in a subsequent twin pregnancy.

MATERIALS AND METHODS

After Biomedical Research Alliance of New York institutional review board approval was obtained, the charts of all patients with twin pregnancies 22 weeks of gestation or greater 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 excluded pregnancies complicated by twin–twin transfusion syndrome, major fetal anomalies, and patients with monochorionic–monoamniotic placentation.

We reviewed the obstetric history of all our twin pregnancy patients. For patients who were not nulliparous, we used the most recent singleton pregnancy outcome for analysis. If the patient's most recent pregnancy was a twin pregnancy, they were excluded from analysis. We recorded the prior singleton gestational age at delivery as well as whether that delivery was preterm, defined as delivery at less than 37 weeks of gestation from any cause. We also recorded the prior singleton birth weight as well as whether that pregnancy was complicated by SGA, defined as a birth weight less than the 10th percentile for gestational age.[19] We estimated the association of these prior singleton pregnancy outcomes with preterm birth and SGA in the index twin pregnancy. We analyzed several gestational age outcomes, including mean gestational age at delivery and delivery at less than 37, less than 34, less than 32, and less than 28 weeks of gestation as well as mean birth weight of the larger twin, mean birth weight of the smaller twin as well as a birth weight less than the 10th percentile for gestational age and a birth weight less than the fifth percentile for gestational age. To define birth weight percentiles for gestational age in twins, we used standard tables for singleton pregnancies.[19] We chose singleton tables because they are the standard tables used for twins in the United States in defining growth restriction and determining neonatal outcomes.[6,20–22] For patients whose prior singleton birth was 20–23 6/7 weeks of gestation, we did include them as having a prior preterm birth, but we did not consider the birth weight in regard to SGA and excluded these pregnancies from the SGA analysis.

Gestational age was determined by last menstrual period and confirmed by ultrasonography in all patients. The pregnancy was redated if there was a greater than 5-day discrepancy up to 14 weeks of gestation or a greater than 7-day discrepancy after 14 weeks of gestation. If the pregnancy was the result of in vitro fertilization (IVF), gestational age was determined from IVF dating. In our practice, patients with twin pregnancies are managed according to a standard protocol, regardless of their obstetric history. We do not administer progesterone to twins with a prior singleton preterm birth. All patients with twin pregnancies in our practice undergo serial growth ultrasonograms every 2–4 weeks and weekly biophysical profile testing beginning at 32 weeks of gestation or more frequently as indicated. Dichorionic twin pregnancies are delivered at 38 weeks of gestation and monochorionic twin pregnancies are delivered at 37 weeks of gestation, or earlier as indicated.

Pearson correlation and one-way analysis of variance were used when appropriate (Stata 11). Accompanying each analysis of variance, we also conducted Bartlett's test for equal variances, which showed variances to be unequal ($P<.01$ for all variables), so we used the Kruskal-Wallis test for analysis and to analyze whether means differed by categories. This test, because it is nonparametric, does not require that variances are equal between categories nor does it presume the data are normally distributed.

To estimate the independent association between prior pregnancy history and outcomes, we performed a logistic regression analysis controlling for advanced maternal age (35 years or older at delivery), obesity (body mass index [calculated as weight (kg)/[height (m)]^2] 30 or higher), chorionicity, IVF, multifetal reduction, maternal race, prior loop electrosurgical excision procedure or cone biopsy, gestational diabetes, preeclampsia, anticoagulation, and uterine

anomaly. The regression was done in a backward stepwise fashion including variables with a significance to the level of <.10.

RESULTS

Over the course of the study period, we delivered 702 patients with twin pregnancies at 22 weeks of gestation or greater. Fifty-five patients were excluded (12 monochorionic–monoamniotic, six with twin–twin transfusion syndrome, nine with major fetal anomalies, and 28 whose previous pregnancy was a twin pregnancy), leaving 647 patients for analysis. The characteristics of the population are shown in Table 1.

Four hundred twenty-three (65.4%) patients were nulliparous, 201 (31.1%) patients had a prior singleton term birth, and 23 (3.6%) patients had a prior singleton preterm birth. The gestational age at delivery of the prior singleton pregnancy was significantly correlated with the gestational age at delivery of the index twin pregnancy (Pearson correlation coefficient 0.431, $P<.001$). The association of a prior singleton preterm birth with twin pregnancy preterm birth is shown in Table 2. Patients with a prior term singleton birth had the lowest risk of twin preterm birth followed by nulliparous patients, and patients with a prior singleton preterm birth had the highest risk of twin preterm birth. The results were significant for all definitions of twin preterm birth measured.

One hundred ninety-five (30.1%) patients had a prior singleton birth without SGA, and 23 (3.6%) patients had a prior singleton birth with SGA (six patients with a prior singleton birth at 20–23 6/7 weeks of gestation were excluded from this analysis). The prior singleton birth weight was significantly correlated with the birth weight of the larger twin (Pearson correlation coefficient 0.353, $P<.001$) as well as with the birth weight of the smaller twin (Pearson correlation coefficient 0.326, $P<.001$). The association of prior singleton pregnancy with SGA with twin pregnancy outcomes is shown in Table 3. Patients with a prior singleton pregnancy without SGA had the lowest risk of twin SGA followed by nulliparous patients, and patients with prior singleton pregnancy with SGA had the highest risk of twin SGA. The results were significant for all definitions of SGA measured.

On logistic regression analysis controlling for advanced maternal age, obesity, chorionicity, IVF, multifetal reduction, maternal race, prior loop electrosurgical excision procedure or cone biopsy, gestational diabetes, preeclampsia, anticoagulation, and uterine anomaly, a prior preterm birth of a singleton pregnancy was independently associated with twin pregnancy preterm birth at less than 37 weeks of gestation, less than 32 weeks of gestation, and less than 28 weeks of gestation. Similarly, on regression analysis, a prior singleton pregnancy with SGA was independently associated with twin SGA less than 10% as well as twin SGA less than 5%. The results of the regression analysis are shown in Table 4.

Table 1. Characteristics of the Population

Characteristic	n (%)
No. of patients	647
Advanced maternal age (35 y or older at delivery)	296 (45.7)
Prepregnancy obesity	56 (8.7)
Chorionicity	
Dichorionic–diamniotic	561 (86.7)
Monochorionic–diamniotic	86 (13.3)
In vitro fertilization	421 (65.1)
Multifetal reduction	46 (7.1)
Caucasian	557 (86.1)
Prior LEEP or cone biopsy	27 (4.2)
Gestational diabetes	58 (9.0)
Preeclampsia	102 (15.8)
Anticoagulation	27 (4.2)
Uterine anomaly	20 (3.1)

LEEP, loop electrosurgical excision procedure.

DISCUSSION

In this study we found that preterm birth or SGA in a singleton pregnancy was associated with a significantly increased risk of recurrence of the same condition in a twin pregnancy. Patients with twin pregnancies and a prior singleton preterm birth were at the highest risk of preterm birth followed by nulliparous patients followed by patients with a prior singleton term birth. Similar results were found for SGA. Therefore, when caring for twin pregnancies, those with a prior adverse singleton pregnancy outcome should be considered the highest risk and those with a prior good singleton pregnancy outcome should be considered the lowest risk with nulliparous patients falling in the middle. This has potential implications for management of twin pregnancies and provides insight into the pathophysiology of preterm birth and SGA in twin pregnancies. For example, patients with a prior spontaneous singleton preterm birth can reduce their risk of recurrent preterm birth in a subsequent singleton pregnancy with progesterone supplementation.[23] However, multiple studies have shown that progesterone supplementation in twin pregnancies, for the sole indication of twin pregnancy, does not reduce the risk of preterm birth.[24–27] Our findings suggest that there

Table 2. Outcomes in Twin Pregnancies Based on Most Recent Singleton Pregnancy Outcome

Outcome	Prior Term Singleton (n=201)	Nulliparous (n=423)	Prior Preterm Singleton (n=23)	P*
Twin gestational age at delivery	36.3±2.1	35.5±2.8	33.8±3.7	<.001
Twin delivery (wk of gestation)				
Less than 37	109 (54.2)	260 (61.5)	20 (87.0)	.007
Less than 34	19 (9.5)	90 (21.3)	8 (34.8)	<.001
Less than 32	7 (3.5)	39 (9.2)	6 (26.1)	<.001
Less than 28	3 (1.5)	13 (3.1)	3 (13.0)	.019

Data are mean±standard deviation or n (%) unless otherwise specified.
* *P* shown for Kruskal-Wallis χ^2 with correlation for rank-ties. One-way analysis of variance or χ^2 for trend.

may be a subset of twin pregnancies with an additional risk of preterm birth related to a previous preterm birth, and it may be appropriate to study the effectiveness of progesterone supplementation in those twin pregnancies specifically. There is plausibility to this theory because progesterone has shown some effectiveness in other subsets of twin pregnancies at highest risk of preterm birth such as those with a short cervix.[28] Furthermore, given that 65.1% of our twin cohort was the result of IVF (which is similar to the national average), for patients undergoing assisted reproduction who have a history of a prior singleton preterm birth, it would be particularly important to utilize methods that would minimize the risk of multiple pregnancy such as single embryo transfer, if feasible. Whether patients with a prior singleton preterm birth and an early twin pregnancy should be counseled to reduce to singleton pregnancy is unknown. However, they should be counseled that their risk of preterm birth is high. In our study, women with such a history had 26% risk of delivering before 32 weeks of gestation.

In regard to SGA, we have previously reported that SGA is common in twin pregnancies and that several risk factors commonly associated with SGA in singleton pregnancies such as maternal age, maternal weight, assisted reproduction, thrombophilia, and gestational hypertension were not associated with SGA in twin pregnancies.[6] This suggested that the pathophysiology of SGA in twin pregnancies differs from that in singleton pregnancies. However, our findings in this study suggest that there may be overlap between the causes of SGA in singleton pregnancies and twin pregnancies. This suggests that although fetal growth needs to be monitored in all twin pregnancies, perhaps those with a history of SGA in a singleton pregnancy need to be monitored more closely.

Our findings are in agreement with prior research. Ananth et al[16] used data from maternally linked data of women in Missouri from 1989 to 1997 and found that a prior singleton preterm birth was associated with an increased risk of preterm birth in a subsequent twin birth with a hazard ratio of 1.8 (95% confidence interval [CI] 1.6–2.1). They did a similar analysis for SGA using data from 1978 to 1997 and found similar results with a pairwise odds ratio of 2.3 (95% CI 1.89–2.8).[17] Their studies, however, did not include patients with no prior births and also are limited by the nature of the data obtained from birth certificates. Facco et al[18] analyzed data from a single center in 1995–2005 and also found that a prior singleton preterm birth was associated with an increased

Table 3. Outcomes in Twin Pregnancies Based on Most Recent Singleton Pregnancy Birth Weight

Outcome	Prior Singleton, No SGA (n=195)	Nulliparous (n=423)	Prior Singleton, SGA (n=23)	P*
Any twin birth weight				
Less than 10%	82 (42.1)	228 (54.4)	15 (65.2)	.007
Less than 5%	35 (17.9)	140 (33.4)	9 (39.1)	<.001
Birth weight (g)				
Larger twin	2,639±483	2,441±545	2,297±373	<.001
Smaller twin	2,368±464	2,143±551	2,090±345	<.001

SGA, small for gestational age (birth weight less than 10%).
Data are n (%) or mean±standard deviation unless otherwise specified.
* *P* value shown for Kruskal-Wallis χ^2 with correlation for rank ties. One-way analysis of variance or χ^2 for trend.

Table 4. Regression Analysis Estimating the Association Between Pregnancy History and Outcomes in Twin Pregnancies

Outcome	OR (95% CI)	Adjusted OR* (95% CI)
Association between prior singleton preterm birth		
Twin delivery (wk of gestation)		
Less than 37	4.607 (1.355–15.667)	4.660 (1.352–16.063)
Less than 34	2.520 (1.042–6.091)	2.335 (0.917–5.946)
Less than 32	4.435 (1.668–11.792)	4.340 (1.444–13.046)
Less than 28	5.700 (1.536–21.148)	6.141 (1.589–23.731)
Association between prior singleton SGA		
Any twin birth weight		
Less than 10%	2.607 (1.056–6.436)	2.908 (1.128–7.502)
Less than 5%	2.957 (1.186–7.374)	2.732 (1.058–7.054)

OR, odds ratio; CI, confidence interval; SGA, small for gestational age (birth weight less than 10%).
* Stepwise logistic regression controlling for: advanced maternal age, obesity, chorionicity, multifetal reduction, race, prior loop electrosurgical excision procedure or cone, gestational diabetes, preeclampsia, anticoagulation, uterine anomaly.

risk of preterm birth in a subsequent twin pregnancy (adjusted odds ratio 3.03, 95% CI 1.3–8.7). They also did not include data from nulliparous patients and did not study the effect of prior SGA.

Strengths of our study include the large cohort of patients with twin pregnancies managed in a single center over 9 years. Additionally, the use of our own electronic medical records to obtain information about the patients as opposed to birth certificate data or patient recall increases the accuracy of the data used in our analysis. We were also able to control for several other variables associated with preterm birth and SGA, allowing us to estimate the independent association between pregnancy history and outcomes in twin pregnancies. Because all pregnancies either had IVF or their dating confirmed by ultrasonography, we are confident that our birth weight percentiles and gestational ages at delivery are accurate, which is critical to studies regarding preterm birth and SGA. Our study is limited by its retrospective design. However, pregnancy history is not amenable to randomization. We are also limited by the fact that the definition of SGA as a birth weight less than the 10th percentile is merely a marker for true fetal growth restriction. We are also limited by the inability to distinguish between a prior spontaneous preterm birth compared with a prior indicated preterm birth. Although in some cases this distinction was clear, in many others, it was not and we could not make this determination with confidence in all cases. Therefore, we included all cases with a prior preterm birth. It is also possible that our findings are unique to our population demographics and further studies in other populations could be done to confirm our findings.

In conclusion, prior preterm birth and SGA in a singleton pregnancy increase the risk of the same condition in a subsequent twin pregnancy. It is possible that that the extrinsic mechanism responsible for the pathophysiology of adverse outcomes in twin pregnancies overlaps with that in singleton pregnancies. Future studies could focus on similar pathophysiologic causes of preterm birth as well as therapies designed to reduce the risk of recurrent adverse outcomes in twin pregnancies.

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