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Risk of Preterm Delivery and Growth Restriction in Twins Discordant for Structural Anomalies

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Abstract

Objective—To determine whether twin gestations with an anomalous fetus are at increased risk of preterm delivery (PTD) or intrauterine growth restriction (IUGR) compared to twins with two normal fetuses.

Study Design—Retrospective cohort of twins undergoing ultrasound 15–22 weeks gestation. Groups were defined by the presence of one twin with a major anomaly (discordant) or by twins with no major anomalies (normal). The primary outcomes were PTD (<37 weeks) and IUGR (<10th percentile).

Results—Of 1,977 twin pregnancies, 66 had a twin with a major anomaly. Preterm delivery occurred in 42 (63.6%) discordant twins, compared to 1271 (66.5%) normal twins (risk ratio (RR) 1.0, 95% confidence interval (CI) 0.8–1.2). IUGR was diagnosed in 15 (22.7%) normal co-twins, compared to 406 (21.3%) presenting twins in normal twins (RR 1.1, 95% CI 0.7–1.7).

Conclusion—Twins discordant for major anomalies are not at increased risk of PTD or IUGR compared to twins with no major anomalies.

Keywords

anomalies; intrauterine growth restriction; multiple gestation; preterm delivery

Introduction

Twin gestations are at increased risk for preterm delivery, intrauterine growth restriction, and structural anomalies.^{1–4} The presence of an anomaly in one twin not only impacts the survival and outcome of the affected twin, but potentially of the normal co-twin as well. Structural anomalies are known to increase the risk of preterm delivery and intrauterine growth restriction in singleton gestations.^{4, 5} Prior studies have demonstrated that preterm delivery is increased with cleft lip/palate, genitourinary anomalies, congenital diaphragmatic hernia, neural tube defects, heart defects, gastroschisis and omphalocele.⁵ The concern

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therefore is that the presence of one anomalous fetus will adversely impact the outcome of the normal co-twin by exacerbating the risk of preterm delivery and growth restriction. This possibility presents both provider and parents with the dilemma of how to manage a pregnancy where twins are discordant for structural anomalies.

Prior studies are conflicting as to whether the presence of one anomalous fetus impacts the risk of preterm delivery or growth restriction.⁶⁻⁹ We therefore sought to estimate the risk of preterm delivery and growth restriction of the normal co-twin in pregnancies complicated by twins discordant for structural anomalies.

Materials and Methods

This is a retrospective cohort study of all patients who underwent routine second trimester (15–22 weeks) ultrasound for anatomic survey at a single, tertiary care center. Institutional review board approval was obtained. Data was collected prospectively by dedicated nurses from 1990–2008. Each patient undergoing ultrasound in our center receives a standardized handout requesting information regarding pregnancy complications, delivery complications and neonatal outcomes, to be filled out and returned after delivery. The coordinator called the patient, and in cases where the patient could not be reached, the physician, if the form was not returned within 4 weeks of the delivery date.

Patients were included in this study if they carried a twin gestation; singleton gestations, intrauterine fetal demise, and higher order multiple gestations were excluded. Twin pregnancies complicated by monoamniocity (due to its rarity), twin-twin transfusion syndrome, structural anomalies in both the fetuses, and pregnancies resulting in selective reduction were also excluded. Gestational age was determined by last menstrual period (LMP) if known and concordant with ultrasound (within 7-days of first trimester ultrasound or 14-days of second trimester ultrasound) or by the earliest ultrasound when the LMP was unknown or discordant. Chorionicity was determined at the earliest ultrasound available. First trimester diagnosis of chorionicity was based on the number of gestational sacs, amnions and yolk sacs present or the presence of a lambda sign.¹⁰ Second trimester determination of chorionicity was based on gender discordance, presence of two placental masses, and characteristics of the intertwin dividing membrane (twin peak sign, T-sign, thickness of membrane).¹¹ Final diagnosis of chorionicity was determined by an attending dedicated to obstetric ultrasound.

An anomaly was defined as a defect in the structure of an organ which resulted from a specific primary abnormality of development.¹¹ Major anomalies were considered defects of organogenesis;¹¹ examples of major anomalies include neural tube defects, congenital heart defects, abdominal wall defects, and renal agenesis. Markers of aneuploidy, such as nuchal thickness, echogenic intracardiac focus and hypoplastic nasal bone were not considered structural anomalies. The exposure group was defined as a twin pregnancy with at least one major anomaly in one fetus and an anatomically normal co-twin. The unexposed group was defined as a twin pregnancy where neither twin had a major anomaly.

The primary outcomes of this study were the incidence of preterm delivery and intrauterine growth restriction (IUGR). Preterm delivery was defined as delivery less than 37 weeks and zero days gestation. Because complications of prematurity are more common and severe at earlier gestations, secondary analyses of preterm delivery less than 34 and 28 weeks were performed. IUGR was defined as birth weight less than the 10th percentile for gestational week at delivery based on the Alexander growth standard.¹² To compare growth restriction between groups, the normal co-twin of the exposed group was compared to the presenting twin of the unexposed group. Additionally, secondary analyses of IUGR defined as birth

weight less than the 5th percentile for gestational age were performed. Some suggestion has been made that twin outcomes vary by presentation;^{13, 14} therefore, the IUGR analysis was also performed controlling for presentation and comparing the normal co-twin to the non-presenting twin.

Because prior studies examining the impact of fetal anomalies on the risk of preterm delivery demonstrate a differential effect based on the type of anomaly, a subanalysis was performed to examine the impact of types of anomalies on preterm delivery. Anomalies were considered as high risk when a prior study associated it with an odds ratio greater than two.⁵ High risk anomalies considered in the subanalysis were central nervous system malformations, urogenital malformations, heart defects, and body wall defects.

The incidence and types of anomalies in the exposed group were described. Subjects with one anomalous twin were compared to subjects with two normal twins using descriptive and univariate statistics using unpaired Student's t test or Mann-Whitney U test, as appropriate, for continuous variables and χ^2 test or Fisher's exact test, as appropriate, for dichotomous variables. Continuous variables were tested for normality visually and with the Kolmogorov-Smirnov test. Stratified analyses were used to identify potentially confounding variables in the outcome-exposure association. Multivariable logistic regression models were then developed to better estimate the effect the presence of an anomalous co-twin on preterm delivery and IUGR. Potential confounders were added to the model based on biologic plausibility (chorionicity, race, hypertensive disorders, diabetes) and statistical significance in the unadjusted analysis. Covariates were retained in the model if they changed the effect size around the primary covariate by >10%. The statistical analysis was performed using STATA, version 10, Special Edition (College Station, TX).

Results

Over an 18-year period, 2,445 twin pregnancies were identified at our institution, 97 of which were complicated by twins discordant for major anomalies. After excluding miscarriages (n=34), monoamniotic twins (n=15), pregnancies where both twins were anomalous (n=2), twin-twin transfusion syndrome (n=45), and pregnancies with incomplete outcomes data (n=372), 1,977 pregnancies remained for analysis. After applying exclusion criteria, 27 cases of twins discordant for anomalies were excluded (5 for undergoing termination, the remainder for missing data). Of the included cases, 66 cases of twins discordant for major anomalies were identified. Twins discordant for major anomalies and normal twin pairs were similar with respect to maternal age, race, chorionicity, tobacco use, preeclampsia, and diabetes (Table 1).

Table 2 lists the type of anomalies present in the cohort. Nine affected fetuses had multiple anomalies. Anomalies were most common in the central nervous system, followed by cardiac malformations and urogenital anomalies.

Compared to twins with no anomalies, twins discordant for major anomalies had a similar gestational age at delivery (median 35.7 (interquartile range 33.4–37.4) versus 36.0 (interquartile range 34.3–37.3) weeks, $p=0.43$) (Table 3). The risk of delivery prior to 37 weeks was similar between the two groups (risk ratio (RR) 1.0, 95% confidence interval (CI) 0.8–1.2). After adjusting for confounding factors (chorionicity, diabetes, and preeclampsia), the risk remained similar (adjusted odds ratio (AOR) 0.8, 95% CI 0.4–1.6). The risk of preterm delivery prior to 34 weeks (AOR 1.2, 95% CI 0.6–2.5) and 28 weeks (RR 1.0, 95% CI 0.2–4.0) was also similar between the two groups.

Because some anomalies place a fetus at higher risk for preterm delivery than others, a subanalysis was performed including only the highest risk anomalies (n=41): central nervous

system malformations, urogenital malformations, heart defects, and body wall defects. No increased risk of preterm delivery less than 37 weeks (AOR 0.6, 95% CI 0.3–1.4) was seen in this subgroup or less than 34 weeks (AOR 1.0, 95% CI 0.4–2.8) (data not shown). Only one preterm delivery less than 28 weeks occurred in this subgroup.

When comparing the normal co-twin of the discordant pair to the presenting twin of the unaffected pair, birth weights are similar (median 2488g (interquartile range 1901–2770g) versus 2469g (interquartile range 2060–2809g), $p=0.60$) (Table 4). The risk of an infant weighing less than the tenth percentile (normal co-twin versus presenting twin of the normal pair and normal co-twin versus non-presenting twin of the normal pair) was similar between the two groups (RR 1.1, 95% CI 0.7–1.7 and RR 1.0, 95% CI 0.6–1.8, respectively). Only one normal co-twin weighing less than the fifth percentile was identified in the group discordant for anomalies (RR 0.3, 95% CI 0.1–2.2). The results were similar when stratified by chorionicity and by presentation (data not shown).

Comment

Twin pregnancies complicated by one anomalous fetus are not at increased risk for preterm delivery compared to twin pregnancies where both fetuses are normal. Furthermore, birth weight of the normal co-twin is similar to the presenting twin in normal pregnancies; the risk of IUGR in the normal co-twin is similar to normal twin pregnancies.

Two prior case control studies noted that the risk of preterm delivery was unaffected by the presence of one structurally anomalous fetus.^{8, 15} In contrast, two retrospective cohort studies have found an increase in the risk of preterm delivery in twin pregnancies complicated by a fetus with a congenital malformation.^{6, 9} Malone et al, in a retrospective cohort of 92 twin pregnancies (14 with anomalous co-twins compared to 78 normal twins), noted a 19.6% attributable risk increase in preterm delivery in pregnancies complicated by an anomalous fetus.⁹ They also noted a difference in birth weight between anomalous twins and unaffected twins; however, this was possibly due to a difference in gestational age at delivery. It is also not clear whether the fetus with structural anomalies was included in the mean birth weight calculation, which would bias towards a smaller birth weight since structural anomalies are frequently associated with growth restriction. The retrospective cohort study by Alexander et al, which included 982 twins with 56 affected pairs, found a significant difference in the risk of preterm delivery, but several practices limit generalizability.⁶ In this cohort, routine antenatal ultrasonography was not done and therefore most twin pregnancies were not diagnosed until the late second or early third trimester. Lastly, data regarding chorionicity, a potentially important confounding factor, was not available in either cohort.

Another large retrospective cohort by Chang et al found no increased risk of preterm delivery in pregnancies with one anomalous fetus compared to twin pregnancies with no structural malformations.⁷ However, the inclusion of twin-twin transfusion as a major anomaly (as opposed to excluding twin-twin transfusion, as in our study) significantly limits the interpretation of this study as twin-twin transfusion is a disorder of the placenta that affects both twins and has implications for the timing of delivery.

One of the strengths of our study is its relatively large sample size, with almost 2000 twin pregnancies included in the sample, enabling us to examine a fairly rare exposure (twin pregnancies with congenital anomaly in one twin). A *post-hoc* power analysis demonstrated that we have 85% power to detect a 2-fold increase in the risk of preterm delivery less than 34 weeks and 80% power to detect a 2-fold increase in the risk of IUGR (assuming a Type I error of 0.05), differences which we think are clinically significant. Additionally, this is a

unique cohort with prospectively collected patient-level information, allowing us to examine confounding factors such as chorionicity.

One concern when interpreting this study is the possibility of selection bias; approximately 11% of subjects did not have outcomes data available. These subjects were less likely than those included in the study to have a fetus affected by major anomaly and were slightly more likely to be black, but were similar with regards to other demographics, including chorionicity (data available upon request). Given the small number of subjects not included and their largely similar characteristics to the study population, this is unlikely to represent a large source of bias.

In this cohort, practitioners had knowledge of the anomaly present in the affected fetus; although this would not have affected the risk of spontaneous preterm delivery, knowledge of anomalies and their associated potential risks for fetal demise may have influenced the risk of iatrogenic preterm delivery in the exposure group. We do not have information regarding the reason for preterm delivery in this cohort and are not able to examine differences regarding spontaneous versus iatrogenic preterm delivery. However, the majority of practitioners will be aware of antenatally diagnosed anomalies and may act on this information. Therefore, our cohort is representative of actual clinical practice, making our study clinically relevant.

Despite our large sample size, we were unable to examine the influence of individual types of anomalies on the risk of preterm delivery. Specifically, the influence of polyhydramnios caused by the anomalous twin on the risk of preterm delivery and growth restriction of the normal-co-twin is of interest. Unfortunately, due to the small number of anomalies associated with polyhydramnios we are unable to comment on this point.

Although prior studies have raised concerns regarding the impact of one structurally anomalous twin on the intrauterine environment, our study does not confirm these prior findings. Our data suggest that the presence of one anomalous fetus does not negatively impact the outcome of the second twin by increasing the risk of preterm delivery or IUGR. Patients can be reassured that the presence of one fetus with a major anomaly does not place the normal co-twin at increased risk of complications beyond that normally experience by twin gestations.

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Table 1

	No Anomaly (n=1911)	Discordant for Anomaly (n=66)	p
Age	30.8 ± 6.0	29.7 ± 6.1	0.05
Gravidity	2.6 ± 1.5	2.9 ± 2.3	0.10
Prior Preterm Birth	107 (5.8%)	5 (8.1%)	0.46
Race			0.30
White	1213 (63.5%)	48 (72.7%)	
Black	400 (20.9%)	10 (15.2%)	
Other	298 (15.6%)	8 (12.1%)	
Twin Type			0.37
Dichorionic	1467 (77.3%)	40 (67.8%)	
Monochorionic, Diamniotic	421 (22.12%)	18 (30.5%)	
Unknown	20 (1.0%)	8 (12.1%)	
Tobacco Use	186 (9.7%)	6 (9.2%)	0.49
Diabetes	127 (6.7%)	3 (4.5%)	0.10
Preeclampsia	398 (20.9%)	9 (13.6%)	0.15
Presenting Twin Anomalous	-	32 (48.5%)	-

Table 2

Organ System	Number of Anomalies *	Types of Anomalies
Central Nervous System	27	Ventriculomegaly Anencephaly Holoprosencephaly Spina bifida Arachnoid cyst Exencephaly Hydrocephalus Dandy Walker malformation Anophthalmia
Cardiac	14	Hypoplastic left heart Cardiac rhabdomyoma Ebstein's anomaly Double outlet right ventricle AV canal defect Membranous VSD Tetralogy of Fallot Cardiac arrhythmia Pericardial effusion
Urogenital	11	Multicystic dysplastic kidney disease Renal agenesis Absent bladder
Abdominal Wall Defect	10	Omphalocele Gastroschisis Body stalk anomaly
Musculoskeletal	5	Hemivertebrae Short-limbed dwarf Ossification defects
Craniofacial	2	Cleft lip/palate
Chest	2	Congenital diaphragmatic hernia
Trisomy	2	Trisomy 21 Trisomy 18
Other	5	Cystic hygroma Ascites

* Several fetuses had more than one anomaly, thus the total number of anomalies is greater than the number of cases.

Table 3

Risk of preterm delivery by presence of anomalous twin

	No Anomaly (n=1911)	Discordant for Anomaly (n=66)	RR (95% CI)	AOR (95% CI)	P
Median Gestational Age at Delivery (wks)	36.0	35.7	-	-	0.43
Interquartile Range for Gestational Age at Delivery (wks)	34.3-37.3	33.4-37.4	-	-	-
Delivery <37 weeks	1271 (66.5%)	42 (63.6%)	1.0 (0.8-1.2)	0.8 [‡] (0.4-1.6)	0.61
Delivery <34 weeks	410 (21.4%)	21 (31.8%)	1.5 (1.0-2.1)	1.2 [‡] (0.6-2.5)	0.53
Delivery <28 weeks	58 (3.0%)	2 (3.0%)	1.0 (0.2-4.0)	-	0.99

p values refer to the adjusted odds ratios.

* Compares normal co-twin to presenting twin of no anomaly group

[‡] Adjusted for diabetes, preeclampsia, chorionicity[‡] Adjusted for diabetes, chorionicity

- Calculation not applicable, or unable to calculate due to small sample size

Table 4

Risk of IUGR by presence of anomalous twin

	No Anomaly (n=1911)	Discordant for Anomaly (n=66)	RR (95% CI)	AOR (95% CI)	p
Median Birth Weight (g) *	2469	2488	-	-	0.60
Interquartile Range for Birth weight (g) *	2060-2809	1901-2770	-	-	-
IUGR * <10 th	406 (21.3%)	15 (22.7%)	1.1 (0.7-1.7)	1.1 [†] (0.6-1.9)	0.78
IUGR * <5 th	106 (7.9%)	1 (2.5%)	0.3 (0.1-2.2)	-	0.21

p values refer to the adjusted odds ratios.

* Compares normal co-twin to presenting twin of no anomaly group

[†] Adjusted for diabetes