Growth Restriction as a Determinant of Outcome in Preterm Discordant Twins

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OBJECTIVE: To estimate the influence of intrauterine growth restriction (IUGR) on the outcome of preterm discordant twins.

METHODS: Medical records of preterm twins born at 24–34 weeks of gestation between 1995 and 2000 were reviewed. *Significant discordancy* was defined as more than 15% difference in birth weight. *Small for gestational age* (SGA) was defined as birth weight less than 10th percentile, according to a twin-adjusted gestational age nomogram. The smaller twins of 96 discordant twin pairs were evaluated. The SGA-discordant group included the smaller twin of a discordant pair who was also SGA (n = 46); the appropriate-for-gestational-age (AGA)-discordant group included the smaller twin of a discordant pair who was appropriate for gestational age (n = 50).

RESULTS: Maternal age, incidence of maternal hypertension, antenatal steroids, and gestational age at delivery were similar between groups. Delivery for suspected fetal compromise complicated significantly more pregnancies in the SGA-discordant group than in the AGA-discordant group (45.6% versus 16%, P = .005), as did respiratory distress syndrome (RDS) (37% versus 8%, P < .05) and intraventricular hemorrhage (21.7% versus 6%, P = .024). Mortality or severe neonatal morbidity (defined as severe RDS, intraventricular hemorrhage grades 3–4, or necrotizing enterocolitis) were significantly higher among neonates in the SGA-discordant group than in the AGA-discordant group (19.5% versus 6%, P = .04). The risk for major morbidity was 7.7-fold greater in the SGA-discordant than in the AGA-discordant group, adjusted for gestational age.

CONCLUSION: Growth restriction in preterm discordant twins is associated with a 7.7-fold increased risk for major neonatal morbidity. Therefore, discordant twins with IUGR require closer monitoring than discordant twins without IUGR. (Obstet Gynecol 2005;105:80–4. © 2005 by The American College of Obstetricians and Gynecologists.)

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Growth discordance within twin gestations has been associated with adverse perinatal outcomes.[1,2] The management of these pregnancies, including antenatal surveillance and early delivery, continues to be a controversial issue. Discordancy may occur between 2 appropriate-for-gestational-age (AGA) infants, and conversely, small-for-gestational-age (SGA) twins may be of similar birth weight. In a cohort of more than 10,000 severely discordant twins, born in the United States between 1995 and 1997, the smaller twin's birth weight was below the 10th percentile in 60% of the pairs, and in 40% the smaller twin was AGA.[3]

The impact of intrauterine growth restriction (IUGR) may have synergistic adverse effects on the outcome of discordant twins, but studies evaluating the clinical significance of IUGR in discordant twins are sparse. It is not known whether the adverse events frequently observed in a discordant small twin should be attributed to the discordancy, to the lower birth weight, to prematurity, or whether all factors play a part.

Birth weight differences of more than 15% have been shown to be increasingly more likely to be associated with growth restriction.[4] Thus, these 2 important contributors to perinatal outcome, weight discordance and IUGR, are linked. Talbot et al[5] evaluated the clinical significance of size discordancy in preterm twins and concluded that size discordancy in preterm twins, as an isolated finding, is not a risk factor for increased mortality and morbidity. Adegbite et al[6] showed that the risk of neurologic handicap was 24-fold higher in the discordant than in the concordant twin pairs and was independent of growth restriction. The purpose of this study was to estimate the influence of intrauterine growth restriction on the outcome of preterm discordant twins.

MATERIALS AND METHODS

All medical records of preterm twins born at 24–34 weeks of gestation at the Chaim Sheba Medical Center between January 1, 1995 to December 31, 2000 were reviewed. Data were collected from the neonatal ward records and maternal hospital files and entered into a

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computerized database. All pregnancies were dated by an early ultrasound scan.

Weight discordancy was defined as more than 15% difference in birth weight. The percentage of discordancy was determined by dividing the weight difference between the twins (in grams) by the weight of the larger twin (in grams) and multiplying by 100. *Small for gestational age* (SGA) was defined as birth weight less than the 10th percentile, whereas *appropriate for gestational age* (AGA) was defined as birth weight between the 10th and 90th percentile, according to a twin-adjusted gestational age nomogram.[7] This nomogram was based on 520 twin pregnancies delivered at our institution between 1984 and 1996.

After exclusion of pregnancies resulting in infants with major congenital anomalies, a total of 96 sets of preterm discordant twins met the criteria for evaluation in the final analysis. The smaller twin in each pair of 96 discordant twins was evaluated. The SGA-discordant group included the smaller twin of a discordant pair who was also SGA (n = 46). The AGA-discordant group included the smaller twin of a discordant pair who was appropriate for gestational age (n = 50).

Maternal characteristics, pregnancy complications, and neonatal parameters of morbidity and mortality were compared between the 2 groups. Data regarding age, parity, mode of conception, chorionicity (based on an early ultrasonographic scan), and mode of delivery were collected from maternal hospital charts. In addition, information was collected regarding the presence of pregnancy complications: hypertensive or preeclamptic disorders in pregnancy, placental pathologies (abruption or placenta previa), preterm premature rupture of membranes (PROM), usage of tocolysis, and delivery due to nonreassuring fetal condition. Neonatal characteristics included gestational age at birth, birth weight, gender, birth order of the twins, prenatal steroid exposure, and 5-minute Apgar score.

Outcome variables examined included neonatal death, respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis. A composite outcome parameter of mortality and major neonatal morbidity was created, which included death, severe RDS (need for mechanical ventilation for more than 24 hours), intraventricular hemorrhage grade 3–4 (as defined by appropriate findings on head ultrasonography), and necrotizing enterocolitis (as defined by characteristic radiographic findings accompanied by bloody stools).

Continuous variables were compared between the SGA- and AGA-discordant groups with a 2-tailed Student t test, while categorical variables were compared with the Pearson χ^2 test or a 2-tailed Fisher exact test, as appropriate. Stepwise unconditional logistic regression analyses (SPSS 11.0, SPSS Inc, Chicago, IL) were performed, with the composite outcome of major morbidity as the dependent variable, while discordancy status (SGA-discordant or AGA-discordant), maternal age, infant gender, gestational age at delivery, birth weight, discordancy percentage, pregnancy-induced hypertension, and antenatal steroid exposure were the independent variables. Because of missing data, this comparison was performed on 95 of the 96 infants. Using this logistic regression model, we compared the estimated odds ratio (OR) and its 95% confidence interval (CI) for major morbidity for a SGA-discordant twin relative to an AGA-discordant twin while controlling for the variables mentioned. Statistical significance was defined as $P < .05$. The study was approved by the ethics committee of the Chaim Sheba Medical Center.

Table 1. Maternal and Obstetric Data

	SGA (n = 46)	AGA (n = 50)	*P*
Maternal age (y)	30.6 ± 5.1	31.2 ± 4.8	.52
Nulliparity	63 (29)	56 (28)	.48
IVF pregnancy	13 (6)	22 (11)	.25
Monochorionicity (n/total for whom chorionicity is known)	13 (4/31)	12 (4/33)	.37
Pregnancy-induced hypertension	8.7 (4)	14 (7)	.41
Preterm PROM	10.9 (5)	18 (9)	.32
Placental abruption	8.7 (4)	2 (1)	.14
Antenatal corticosteroids	63 (29)	64 (32)	.91

SGA, small for gestational age; AGA, appropriate for gestational age; IVF, in vitro fertilization; PROM, premature rupture of membranes.
Data are expressed as mean ± standard deviation or % (n).

RESULTS

During the 6-year study period, a total of 329 preterm twin pairs, between 24–34 completed weeks of gestation, were born at Sheba Medical Center. Of these, 96 pairs fulfilled the inclusion criteria as mentioned previously. Of the 96 sets of preterm discordant twins analyzed, in 46 pairs the smaller twin was SGA (group A), and in 50 pairs the smaller twin was AGA (group B). Maternal demographic data, as well as pregnancy and delivery characteristics, are presented in Table 1.

The groups were similar with regard to maternal age, parity, mode of conception, and chorionicity (information regarding chorionicity was available for 64 of 96 sets of twins). In addition, there were no significant differences in the incidence of maternal morbidities, including pregnancy-induced hypertension, preterm PROM, placental abruption, and prenatal corticosteroid exposure.

Table 2. Birth and Baseline Neonatal Characteristics

	SGA (n = 46)	AGA (n = 50)	P
Gestational age at delivery (wk)	32.2 ± 2.1	32.4 ± 2.2	.71
Birth weight (g)	1,135 ± 322	1,524 ± 310	< .01
Percentage of discordancy	31.9 ± 12.5	20.8 ± 4	< .01
Female infants (%)	58.7	54	.64
Smaller second twin	58.7 (27)	60 (30)	.89
Cesarean delivery	60.9 (28)	54 (27)	.49
Delivered for suspected fetal compromise	45.6 (21)	16 (8)	< .01
5-min Apgar < 7	13 (6)	2 (1)	.037

SGA, small for gestational age; AGA, appropriate for gestational age.
Data are expressed as mean ± standard deviation, %, or % (n).

Table 3. Major Neonatal Outcomes

	SGA (n = 46)	AGA (n = 50)	P
RDS	37 (17)	8 (4)	< .01
IVH	21.7 (10)	6 (3)	.024
PVL	4.3 (2)	2 (1)	.5
Sepsis	4.3 (2)	6 (3)	.71
NEC	4.3 (2)	0	.14
Mortality	10.9 (5)	6 (3)	.38
Major morbidity/mortality*	19.5 (9)	6 (3)	.04

SGA, small for gestational age; AGA, appropriate for gestational age; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis.
Data are expressed as % (n).
* Composite outcome of death, severe RDS necessitating mechanical ventilation for more than 24 hours, IVH grades 3–4, and NEC.

As expected, the groups were different with respect to mean birth weight, with the SGA-discordant group being lighter, as well as the degree of discordancy. The mean gestational age at delivery, male/female ratio, and the birth order of the smaller twin were similar. Moreover, the groups were similar in their mode of delivery, although significantly more pregnancies in the SGA-discordant group were delivered for suspected fetal compromise than in the AGA-discordant group (45.6% versus 16%, respectively, $P = .005$). In addition, significantly more neonates in the SGA group had low Apgar score at 5 minutes than in the AGA group (13% versus 2%, respectively, $P = .037$). Birth and baseline neonatal characteristics are presented in Table 2.

When examining neonatal complications, we found the following: The incidence of RDS was significantly higher among the SGA-discordant than among AGA-discordant twins (37% versus 8%, respectively, $P < .05$). Intraventricular hemorrhage, mostly grades 1 and 2, was also more frequent in the SGA-discordant than in the AGA-discordant small twins (21.7% versus 6%, respectively, $P = .024$). There was no difference in the incidence of necrotizing enterocolitis, periventricular leukomalacia, and sepsis, and the neonatal mortality rate was similar in the 2 groups.

The composite outcome of mortality or severe neonatal morbidity (defined as severe RDS, intraventricular hemorrhage grades 3–4, or necrotizing enterocolitis) was significantly higher among neonates in the SGA-discordant group than in the AGA-discordant group (19.5% versus 6%, $P = .04$). From the logistic regression results, it can be concluded that, when controlling for gestational age, the risk for major neonatal morbidity is 7.7 times higher for a SGA-discordant twin than for an AGA-discordant twin (OR 7.7, 95% CI 1.15–52.13, $P = .035$). Other independent variables, including birth weight, infant gender, antenatal steroid exposure, pregnancy-induced hypertension, discordance percentage, and maternal age, which were initially entered into the logistic regression model, did not show any significant contribution to the model and were therefore not included in the final model. Neonatal outcome variables are summarized in Table 3. Logistic regression data are summarized in Table 4.

A subgroup analysis of SGA-discordant versus AGA-discordant newborns in the very-premature subgroup (24–30 weeks of gestation), as well as the less-premature subgroup (31–34 weeks of gestation), revealed similar results. The incidence of RDS and intraventricular hemorrhage remained higher in the SGA group than in the AGA group in both subgroups (Table 5).

DISCUSSION

Discordancy among preterm twins has long been considered a complicating factor with increased risks for perinatal morbidity and mortality. For these reasons the presence of discordancy may prompt elective preterm delivery in an attempt to prevent death and decrease morbidity. Nevertheless, some discordant twins present 2 fetuses that are appropriately grown (although, by definition, one twin is at a lower weight percentile than its sibling), whereas others may present one twin that is significantly growth restricted. Still another possibility is a twin pair in which both are significantly growth restricted. Therefore, twin weight discordancy and IUGR should be investigated separately.

The results presented in this work demonstrate that SGA-discordant preterm twins are at increased risk of significant perinatal morbidity and mortality, when compared with AGA-discordant preterm twins adjusted for gestational age (OR 7.7, 95% CI 1.15–52.13). Significantly more neonates in the SGA-discordant group de-

Table 4. Influencing Factors on Mortality and Major Morbidity: Results of Logistic Regression Model

	β	Significance	Odds Ratio	95% Confidence Interval
Gestational age	−0.569	0.001	0.566	0.418–0.767
AGA/SGA discordancy status	2.046	0.035	7.739	1.149–52.129

SGA, small for gestational age; AGA, appropriate for gestational age.
Dependent variable: mortality or major morbidity, defined as death, severe respiratory distress syndrome, intraventricular hemorrhage grades 3–4, and necrotizing enterocolitis.

veloped RDS and intraventricular hemorrhage compared with the AGA-discordant group.

There is conflicting evidence in the literature regarding accelerated pulmonary maturation in the SGA infant. Previous investigators have found decreased rates of RDS in SGA infants,[8,9] while others have found no difference[10–12] or even increased rates of RDS.[13,14] We have previously demonstrated, along with others, that preterm SGA infants face increased risks of mortality and morbidity because of growth restriction alone, when other variables are controlled for.[12] Nevertheless, studies evaluating the concept of growth restriction in twins are few. We chose to investigate this question by looking at the outcome of discordant twins with and without growth restriction.

Previous investigators have determined that size discordancy, as an isolated finding, is not a perinatal risk factor.[4,15–17] Hseieh et al[15] attempted to determine the risk of discordancy alone when gestational age and birth weight were controlled for. This group concluded that birth weight and gestational age at delivery, but not weight discordancy, were significant predictors for an adverse event. Blickstein et al[17] compared term, discordant, but not growth-restricted twin pairs to term and AGA twin pairs without discordancy. They concluded that discordancy by itself is not a risk factor when the twin pair has reached term and the lighter twin weighs at least 2,500 grams.

Our findings demonstrate that growth restriction in preterm discordant twins is an independent risk factor for major neonatal morbidity or mortality. Our results are strengthened by another recent study by Blickstein et al,[3] which evaluated the neonatal mortality rate among discordant twins classified according to the birth weight of the smaller twin. The authors showed significantly higher neonatal mortality among twin pairs in whom the smaller twin was SGA.

In contrast to our findings, other studies did not demonstrate an association between IUGR and perinatal outcomes in discordant twins. Demissie et al[18] analyzed the database of twin births in the United States for the period 1995–1997. Twins who were SGA and also discordant were at the highest risk of dying in utero, but there was no increased risk for neonatal mortality. This study did not investigate parameters of morbidity and, therefore, cannot account for differences in perinatal outcome other than death.

Amaru et al[19] classified 1,318 twin pairs according to the presence of discordancy and growth restriction and concluded that discordancy places twins at increased risk for some adverse perinatal outcomes, whether they are AGA or SGA. However, the most serious morbidities and neonatal mortality did not show an independent relationship with discordancy. Fraser et al[20] examined neonatal morbidity in 315 liveborn twin pairs and found that IUGR was not associated with adverse neonatal outcome. Both Amaru and Fraser used singleton norms to define IUGR.

We believe that, to evaluate the intrauterine growth of twins, it is more appropriate to use twin-specific growth curves. This is due to the fact that twin growth curves tend to show decreased growth velocity compared with singletons starting at 30–32 weeks. Therefore, their failure to find an impact related to growth restriction may stem from the fact that they were actually dealing with appropriately grown twins. The importance of the present study is its attempt to establish the impact of growth restriction on perinatal outcome in preterm discordant twins. We have shown that, in pregnancies with SGA-discordant twins, the timing of delivery was more

Table 5. Major Neonatal Outcomes in Two Distinct Gestational Age Subgroups

	Neonatal Outcome, 24–30 wk			Neonatal Outcome, 31–34 wk		
	SGA (n = 9)	AGA (n = 9)	*P*	SGA (n = 37)	AGA (n = 41)	*P*
RDS	100 (9)	22.2 (2)	.002	21.6 (8)	4.8 (2)	.027
IVH	33.3 (3)	22.2 (2)	.6	19 (7)	2.4 (1)	.01

SGA, small for gestational age; AGA, appropriate for gestational age; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage.
Data are expressed as % (n).

often determined as a result of suspected fetal compromise than with AGA-discordant twins' pregnancies. Furthermore, growth restriction in preterm discordant twins was associated with higher morbidity and complications in the neonatal period.

In summary, we argue that the presence of growth restriction in preterm discordant twins necessitates close observation and monitoring in the antenatal, as well as the postnatal period, because these preterm infants are at increased risk for decompensation and adverse outcome. Such monitoring may consist of repeated ultrasound examinations, including estimation of fetal growth and blood flow Doppler studies and fetal heart rate monitoring, while hospitalization may be considered when closer monitoring is deemed necessary.[21]

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