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Is Growth-Discordance in Twins a Substantial Risk Factor in Adverse Neonatal Outcomes?

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To evaluate whether growth discordance is an independent risk factor in the neonatal outcome of the smaller twin, all medical records of twin pregnancies delivered between 26 and 41 weeks during a 5-year period (January 2004–December 2008) were reviewed. Among the 49 selected twins, weight discordance was 15–20% in 7 infants, 21–30% in 16 infants, 31–40% in 16 infants and > 40% in 10 infants. No significant differences between the four groups were found with regards to obstetric complications and neonatal disease. Occurrence of birthweight below the 10th percentile and rate of admission to the neonatal intensive care unit significantly increased as intra-pair birthweight difference increased ($p = .03$). The > 40% discordant group had a significantly lower gestational age ($p = .03$), lower birthweight ($p = .007$) and a significantly higher mortality rate (4/10 versus 3/39 $p = .04$) in comparison with the other discordant groups. Multiple logistic regression analysis showed that birthweight was the single independent and consistent factor associated with elevated risks of mortality. For every 250 g increase in birthweight, the risk for mortality decreased by about 84% [RR 0.16(CI 0.00-0.70)]. Gestational age was the most reliable predictor for major neonatal complications. For every 1-week increase in gestational age a significant decreased risk for all outcomes was found. Discordance alone should not be considered as a predictor for adverse neonatal outcome. Neonatal outcome in discordant twins appears to be related to gestational age and birthweight rather than to the degree of discordance.

■ **Keywords:** birthweight discordance, neonatal outcome, twin pregnancy

The frequency of multiple pregnancy and specifically related complications has significantly increased over the last few years. Discordant birthweight is a well-documented phenomenon, which occurs in as many as 10–29% of twin gestations, depending on its definition (Appleton et al., 2007; Blickstein & Lancet, 1988). Levels pointing to significant discordance are generally considered around 15–25% birthweight difference, whereas lower differences are considered physiological and related to individual genetic variations (Blickstein et al., 1987).

Birthweight discordance has been associated with perinatal death (Sonntag et al., 1996; Tobe et al., 2010), postnatal morbidity (Demmissie et al., 2002; Vergani et al., 2004) and developmental problems (Adegbite et al., 2004). This issue has not been fully explained and some authors argue that discordant growth is not an independent risk factor for fetal or neonatal morbidity and mortality (Cohen et al., 2001; Yinon et al., 2005), since the latter could depend on intrauterine growth restriction (Machado et al., 2009; Yinon et al., 2005), low birthweights, and preterm delivery (Cooperstock et al., 2000; Vergani et al., 2004), which are strongly associated with twin discordance. The present study was aimed at evaluating whether discordance is an independent risk factor for adverse neonatal outcome in the smaller twin of twin pregnancies.

Materials and Methods

All medical records of twin pregnancies delivered between 26 and 41 completed gestation weeks during a 5-year period (January 2004-December 2008) were reviewed.

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TABLE 1
Main Maternal Data

	Group I 15–20% (n = 7)	Group II 21–30% (n = 16)	Group III 31–40% (n = 16)	Group IV > 40% (n = 10)	p
Nulliparas	3 (43)	12 (75)	9 (56)	7 (70)	NS
Monochorionicity	2 (29)	2 (12)	7 (43)	5 (50)	I-II vs III-IV = 0.03
Preeclampsia	0	4 (25)	6 (37)	2 (20)	NS
Diabetes	1 (14)	3 (19)	1 (6)	0	NS
Cesarean section	5 (71)	9 (56)	8 (50)	8 (80)	NS

Note: For each discordance group, number (percentage) of observations of several maternal conditions is reported.

Cases with fetal abnormalities, and with twin-twin transfusion syndrome (TTTS) were excluded. Discordance was defined as a difference in weight ≥ 15% and was calculated as a percentage from the birthweight of the heavier twin; discordance (%) = 100 (birthweight difference/birthweight of the heavier twin; Blickstein, 1991).

Intra-pair birthweight percentage differences were stratified into the following four groups: 15–20%, 21–30%, 31–40%, > 40%. These groups were chosen on the basis of their potential clinical relevance to neonatal outcome and growth restriction as highlighted in previous studies (Blickstein & Lancet, 1988; Branum & Schoendorf, 2003). According to twin weight charts (Gielen et al., 2008) infants were classified as follows: less than the 10th percentile (small for gestational age; SGA), 10–90th percentile (appropriate for gestational age; AGA) and > 90th percentile (large for gestational age; LGA). Gestational age (GA) was calculated based on the date of the last menstrual period and by an early ultrasound scanning; when the last menstrual period was uncertain, pregnancy date was based on the earliest ultrasound scan.

The following variables were evaluated in the four groups: incidence of pregnancy induced hypertension (preeclampsia or gestational hypertension), diabetes, preterm premature rupture of membranes (pPROM), chorionicity (based on the earliest ultrasound examination), parity, route of delivery and the birth order of the twins. GA, birthweight (BW), gender, and Apgar score were also recorded. Neonatal morbidities selected as outcome variables included the following: respiratory distress syndrome (RDS) defined on the basis of standard clinical and radiological diagnosis or surfactant requirement, bronchopulmonary dysplasia (BPD), defined as the requirement of oxygen therapy associated with an abnormal chest radiograph at the 28th day of life (Bancalari & Claure, 2006), intraventricular hemorrhage (IVH; Papile et al., 1978), cystic periventricular leukomalacia (De Vries et al., 1992), sepsis, patent ductus arteriosus requiring treatment (Harling et al., 2010) necrotizing enterocolitis (Bell et al., 1978), neonatal jaundice requiring phototherapy or exchange transfusion, and mortality. Admission and length of stay (LOS) into the neonatal intensive care unit (NICU) were also recorded.

The relationship between different BW categories and neonatal outcomes was then evaluated.

Statistical Analysis

The comparison between groups was carried out by unpaired t test or Mann-Whitney U test for continuous variables and by Fisher's exact probability test for categorical variables. Multiple logistic regression analysis was

TABLE 2
Perinatal Data

	Group I 15–20% (n = 7)	Group II 21–30% (n = 16)	Group III 31–40% (n = 16)	Group IV > 40% (n = 10)	p
GA (weeks) *	34 ± 3.4 (28–38)	33 ± 3.7 (26–41)	33 ± 3.7 (27–39)	30 ± 2.3 (28–35)	I-II-III vs. IV = 0.03
BW (g) *	1690 ± 430 (1080–2150)	1423 ± 478 (630–2230)	1246 ± 450 (655–2200)	779 ± 258 (500–1200)	I-II-III vs. IV = 0.007
GA< 37 weeks ^	6 (86)	14 (87)	13 (81)	10 (100)	NS
SGA ^	2 (29)	6 (37)	12 (75)	10 (100)	II vs. IV = .03
Male gender ^	2 (29)	5 (31)	5 (31)	5 (50)	NS
Second-born twin ^	2 (29)	10 (62.5)	12 (75)	9 (90)	I vs. IV = .03
Apgar < 4 at 1 min ^	2 (29)	6 (37)	5 (31)	7 (70)	NS
Apgar < 7 at 5 min ^	1 (14)	4 (25)	4 (25)	7 (70)	NS

Note: * Mean values ± standard deviation (range) are reported.
^ Number (percentage) of observations is reported.
BW, birthweight; GA, gestational age; SGA, small for gestational age.

TABLE 3
Main Clinical Data

	Group I 15–20% (n = 7)	Group II 21–30% (n = 16)	Group III 31–40% (n = 16)	Group IV > 40% (n = 10)	p
NJ ^	2 (29)	5 (31)	10 (62)	8 (80)	NS
RDS ^	1 (14)	3 (19)	5 (31)	5 (50)	NS
BPD ^	0	1 (6)	4 (25)	3 (30)	NS
IVH 3° ^	0	0	0	2(20)	NS
Sepsis ^	1 (14)	2 (12)	3 (19)	3 (30)	NS
NEC ^	0	0	0	1 (10)	NS
PDA ^	1 (14)	3 (19)	5 (31)	5 (50)	NS
NICU admission ^	4 (57)	8 (50)	12 (75)	10 (100)	I-II vs. IV = .03
NICU LOS*	36 ± 19	47 ± 34	56 ± 39	44 ± 38	NS
Mortality ^	0	2 (12)	1 (6)	4 (40)	I-II-III vs. IV = .04

Note: ^ Number (percentage) of observations is reported.
* Mean values ± standard deviation are reported.
BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NJ, neonatal jaundice requiring phototherapy; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome.

used to assess the independent effect of discordance and of other potential predictors (GA, BW, SGA, male gender) on neonatal outcome of the smaller twin. The effect of BW was evaluated in increments of 250-g units, the effect of GA was tested in 1-week intervals, while the effect of discordance was evaluated for increment of 10% units. The odds ratio (OR), as an estimate of the relative risk of an event (such as mortality and major neonatal complications) was calculated using logistic regression analysis and 95% confidence intervals (95% CI) were computed. Probability values < 0.05 were considered significant.

Results

During the 5-year period, 448 twin pregnancy deliveries and 54 pairs of discordant twins (12%) were observed. After excluding two pairs with twin-to-twin transfusion syndrome, two pairs with incomplete data, and one pair with a major anomaly (anencephaly), 49 pairs of twins were enrolled in the study. Among the 49 selected twins, weight discordance was 15–20% in seven infants, 21–30% in sixteen infants, 31–40% in sixteen infants and > 40% in ten infants.

Main maternal data are reported in Table 1. No difference in pregnancy complications was observed in the four groups. The rate of monochorionic placentation was similar between the four groups. However, when grouping severe (Groups III and IV) and mild (Groups I and II) discrepancies a significantly higher occurrence of monochorionic placentation was found for severe discrepancies (12 out of 26 vs. 4 out of 23; $p = .03$).

Neonatal data of smaller twins are reported in Table 2. GA and BW were significantly lower in Group IV ($p < .05$). The number of preterm infants was similar between the groups, and all newborns in Group IV were born before 37 weeks. Occurrence of SGA infants significantly increased as intra-pair BW difference increased ($p = .03$). A higher incidence of Apgar Score < 4 at 1 minute and < 7 at 5 minutes was observed in the Group IV. A significantly higher number of second-born twins was found in Group IV in comparison with Group I ($p = .03$)

Table 3 reports main clinical data regarding smaller twins. None of the infants included in the study were affected by cerebral parenchimal damage. A higher percentage of each adverse event was found for Group IV even if the level of difference was not statistically significant. Rate of admission to the NICU significantly increased as intra-pair birthweight difference increased ($p = .03$). Seven out of the 49 (14.3%) smaller infants died. Looking in detail at mortality, the > 40% discordant group had a significantly higher rate when compared with the other discordant groups combined (4/10 versus 3/39 $p = .04$). All dead infants were SGA and six of them were second-born.

In univariate analysis, GA, BW, SGA infants, and discordance resulted as significantly associated with mortality ($p = .03$). GA and BW were strongly associated with all the neonatal morbidities ($p = .006$), while discordant BW was significantly associated only with RDS, BPD and PDA ($p = .04$). The multiple logistic regression analysis showed that BW is the single independent and consistent factor associated with an increased risk of mortality. The risk of mortality fell by about 84% for every 250g increase in birthweight [RR 0.16 (CI 0.00–0.70)]. With regard to major neonatal complications, multiple logistic regression showed that GA is the most reliable predictor. For every 1-week increase in GA a significant decreased risk for all adverse outcomes was found [RDS: RR 0.36 (CI 0.20–0.66), BPD: RR 0.47 (CI 0.28–0.78), IVH: RR 0.69 (CI 0.53–0.91), PDA: RR 0.25 (CI 0.11–0.59), sepsis: RR 0.61 (CI 0.44–0.86)].

Discussion

Controversies about the exact definition of weight discordance in twin pregnancies are still ongoing. Up to now, the

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critical degree of birthweight discordance that differentiates normal from pathological conditions has not been definitely established, and the threshold for clinically significant discordance has not been universally defined. Several authors suggest that an intra-pair weight difference < 15% should be considered physiological (Blickstein & Lancet, 1988; O'Brien el al., 1986). Most authors believe that 25% is the difference level above which discordance should be considered as abnormal and might reflect some significant degree of growth restriction (Blickstein & Keith, 2004). Our study evaluates neonatal morbidity and mortality along several degrees of weight discordance in twin pregnancies, excluding cases with associated fetal abnormalities and TTTS that might have biased results of previous investigations (Copperstock et al., 2000; Amaru et al., 2004).

We did not find any maternal factor that may be related to discordant growth in twins as it was previously reported (Hartley et al., 2002).

Moreover, our results indicate that high birthweight discordance in twins is associated with a risk of preterm birth and low birthweights, as suggested in previous reports (Cooperstock et al., 2000; Branum & Schoendorf, 2003), although a birthweight discordance higher than 40% is required before the effects become statistically significant.

With regard to the relationship between discordance and SGA, we found a significant increase from 75% to 100% of SGA incidence when birthweight difference increased from > 30% to > 40%, closely resembling findings of O'Brien et al. (1986), who reported that approximately two-thirds of pregnancies were associated with an SGA infant when birthweight discordance was 30% or higher. Our data confirm that intra-pair weight discordance is associated with other morbidity factors, that is, fetal growth restriction, preterm delivery and low birthweight. Logistic regression analysis allowed us to better evaluate the role of several factors as predictors for adverse neonatal outcome. Thus our results show that discordance cannot be considered as an efficient predictor for adverse neonatal outcome.

We found that discordance > 40% is associated with a higher incidence of major neonatal pathologies, but logistic regression analysis shows that the only independent predictor for neonatal morbidity is gestational age.

Our study also shows that birthweight discordance was associated with an increased risk of neonatal mortality in smaller twins only for a discordance degree higher than 40%, analogous with the findings of Branum and Schoendorf (2003), who obtained similar results for discordance > 25%.

By means of multivariate logistic regression analysis we found that birthweight is the strongest and most consistent risk factor for neonatal mortality. With regard to the rate of admission to the NICU, it was found to increase with increasing levels of discordance, with higher rates seen for discordance higher than 30%. The increase in the rate of admission was statistically significant only for discordance higher than 40%. However, in the latter, it should be taken into account that we found a significantly higher rate of premature and low birthweight infants.

Data on fetal growth and blood flow Doppler were not available in many of our cases. Thus monitoring the fetal growth and blood flow Doppler could define, in further studies, the influence of placental pathology and the impact of intrauterine growth restriction on the outcome of pregnancies with extremely weight-discordant twins (Neilson & Alfirevic, 2010).

Despite the relatively small sample of twins enrolled in our study, we believe that our data are exceptional as 80% of our population was represented by premature newborns and levels of discordance were carefully classified, while data about extreme twin weight discordance (> 40%) were separately evaluated. Our results suggest that twin discordant pregnancies should be diagnosed early and closely monitored. Severely discordant twin pairs in which the smaller twin was also small for gestational age are at an increased risk of neonatal death. Identification of this group is a mandatory step in the management of birthweight discordance in twin gestations. However, we believe that a preterm delivery should not be suggested only on the basis of discordant growth since it does not efficaciously predict an adverse neonatal outcome that appears to be determined more particularly by gestational age and birthweight.

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