Birthweight Discordance in Twins and the Risk of Being Heavier for Respiratory Distress Syndrome

Fuat Emre Canpolat, Murat Yurdakök, Ayse Korkmaz, Sule Yigit, and Gülsevin Tekinalp

Neonatology Unit, Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey

Twin pregnancies are becoming common as a result of increased assisted reproduction. Studies have shown that the smaller twin of a pair is at greater risk of morbidity and mortality. Our aim was to determine if there is a relation between birthweight discordancy and neonatal morbidity and mortality and to test the occurrence of respiratory distress syndrome (RDS) in discordant twins. For 5 years all twins admitted to our intensive care unit were included in the study. Discordance was calculated as the difference between twins' weights divided by the heavier weight. Diagnosis of RDS was made by typical clinical and radiographic methods. Multiple logistic regression was performed with gender, weight order and birth order as the independent variables and RDS as the dependent variable. Two hundred and sixty-six twin pairs with a mean gestation of 33 weeks and a mean birthweight of 1890 g were evaluated. Multiple logistic regression revealed that being the heavier twin was a more important risk factor for RDS (odds ratio 4.5; 95% confidence interval 2.2–9.2) than being the male or second-born twin. Based on neonatal outcomes a birthweight discordance equal or greater than 20% in twin pairs was accepted as the discordance criterion. Discordant and concordant groups were statistically different in neonatal mortality, necrotizing enterocolitis, polycytemia and hypoglycemia. Our data demonstrated that being the heavier twin is a risk factor for RDS and a birthweight difference of 20% or more in twin pairs should be accepted as discordance.

Birthweight discordant twins are associated with higher rates of adverse neonatal outcomes, including low birthweight, very low birthweight, neonatal intensive care unit admissions, neonatal oxygen requirement, and hyperbilirubinemia (Amaru et al., 2004). The high perinatal mortality rate in twins is largely associated with the increased rate of low birthweight babies from preterm deliveries and growth restricted pregnancies (Dashe et al., 2000; Kiely, 1990). Perinatal mortality has differed widely among studies. According to a systematic review of these studies total mortality in naturally conceived twins (147/3392, 4.3%) is greater than singletons (45/5641, 0.8%; relative risk 1.68, 95% confidence intervals [CI] 1.11–2.55; Helmerhorst et al., 2004). Twin growth discordance is an indicator of aberrant twin growth. The criterion used for birthweight discordance has ranged from 15% to 25% in previous studies. (Blickstein et al., 1987; Erkkola et al., 1985; Hollier et al., 1999). However, there is a need to determine a cutoff point that best identifies the fetus or neonate at risk for death or morbidity.

Twin pregnancies are becoming increasingly common, and an increased number of twins who are admitted to the neonatal intensive care units are born prematurely (Dunn & Macfarlane, 1996). The increasing twin rate is partly due to a higher incidence of assisted reproduction and an increase in maternal age at conception (Spellacy et al., 1990). Twins are known to be at increased risk of intrauterine morbidity and of premature delivery (Ghai & Vidyasagar, 1988) therefore multiple pregnancies are usually monitored closely. Several studies have shown that the smaller twin of a pair is at greater risk of intrauterine death, especially as growth discrepancy increases (Chen et al., 1993). Early delivery is therefore often planned in order to save the smaller twin, but early delivery is associated with greater risk of infant respiratory problems. Respiratory distress syndrome (RDS) is also the major cause of morbidity and mortality in preterm deliveries. RDS is an acute illness usually of preterm infants, developing within 4 to 6 hours of birth, characterized by a rapid respiratory rate (> 60 breaths/minute), respiratory distress (intercostal, subcostal and sternal retraction or indrawing), expiratory grunting and cyanosis. On the chest radiograph, there is a typical appearance of reticulogranular mottling with air bronchograms, but in severe cases the lungs may be completely white due to fluid retention in the airspaces and widespread atelectasis. The basic etiology of RDS is surfactant deficiency.

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Address for correspondence: Fuat Emre Canpolat, Hacettepe University, Ihsan Dogramaci Childrens' Hospital, Neonatology Unit, 06100 Hacettepe, Ankara, Turkey. E-mail: femrecan@hacettepe.edu.tr, femrecan@gmail.com

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Approximately 2% to 3% of infants develop respiratory distress soon after birth, 50% of the infants born between 26 and 28 weeks of gestation develop RDS, whereas fewer than 20% to 30% of premature infants at 30 to 31 weeks have the disorder. Central nervous system hemorrhage, intraventricular hemorrhage and patent ductus arteriosus represent significant clinical problems affecting the care of infants with RDS. Careful fetal monitoring, treatment of maternal diseases, tocolysis and maternal glucocorticoids have decreased the incidence of RDS (Rodrigues et al., 2002)

The aim of this study was to test the hypothesis that there is a difference in the occurrence of RDS in the neonatal period between heavier and lighter twins, and to determine the risk of neonatal morbidity and mortality associated with birthweight discordancy in these twin pairs.

Materials and Methods

Subjects

All twins who were admitted to the neonatal intensive care unit at Hacettepe Childrens' Hospital between January 1, 2000 and October 31, 2004 were identified from the admission records. Twin pairs were excluded if one or both was stillbirth, if one had a major congenital anomaly, and if there was twin-to-twin transfusion syndrome. Twins who were not admitted to the intensive care unit were excluded as these infants' birthweights were more than 2500 g and they were discharged from hospital in a few days. The following demographic details were obtained for the remaining twins from the medical records: age of gestation (by early ultrasound scan and/or Ballard score), type of gestation (assisted reproduction or normal), gender, birthweight, mode of delivery, birth order and Apgar score at 5 minutes.

Babies were considered to have RDS if they had tachypnea, grunting and cyanosis in the first day of life, required mechanical ventilation including continuous positive airway pressure and oxygen in the first four hours of life and had typical radiographic findings on chest X-rays (Rodrigues et al., 2002). Diagnosis of necrotizing enterocolitis (NEC) were made according to Bell's criteria (Chandler & Hebra, 2000). Bronchopulmonary dysplasia (BPD) was defined as an infant with oxygen dependency at a postnatal age of 28 or postconceptional age of 36 weeks (Bancalari & Gerhardt, 1986). An upper limit of central venous hematocrit of 65% was used in the clinic. Hypoglycemia was defined as a plasma glucose of less than 40–45 mg/dL in a term or premature infant. Only neonates with positive blood cultures were considered to be neonatal sepsis, clinical suspection without cultures were excluded. Duration of hospitalization was calculated for each infant because twins are sometimes discharged from hospital separately. Neonatal mortality was defined as mortality between the 7th and the 28th day of life. Early neonatal mortality was defined as mortality in the first week of life which is related to perinatal factors rather than neonatal mortality. Birthweight discordance was calculated by subtracting the birthweight of the smaller twin from the weight of the larger twin, and dividing the difference by the birthweight of the larger twin and multiplying that by 100 (Yalçin et al., 1998).

Statistical Analysis

All statistical data were analyzed with SPSS for Windows® Version 11.5 Data System on a personal computer. Multiple logistic regression was performed with gender, weight order and birth order as the independent variables and RDS as the dependent variable. Chi-square, test of significance between two percentages and t tests are also used to compare other data. Mann–Whitney test was used for comparing Apgar scores. A p value of less than .05 was considered significant.

Results

Two hundred and sixty-six eligible twin pairs were born at Hacettepe University Hospital during the 5-year duration of the study. Their mean gestation was 33 weeks (range 24–38) and mean birthweight was 1890 g (range 600–3200). Two hundred and seventy-six infants (51%) were male, with 86 male–male pairs, 76 female–female pairs and 104 mixed pairs. The median Apgar score was 9 (range 3–10) at 5 minutes. One hundred and ninety twin pairs' (71%) parents were assisted for reproduction. The mode of delivery was cesarean section in 243 (91%) twins, and vaginal in 23 (9%). These characteristics are summarized in Table 1.

Twins were divided into three groups according to their birthweight discordance: Group A (n = 24 twin, total 48 infants), when discordance was equal or

Table 1

Demographics and Clinical Characteristics of Twin Pairs

Demographics and characteristics	
Gestational age (week)	33.3 ± 3
Birthweight 1 (g, first-born twin)	1895 ± 540
Birthweight 2 (g, second-born twin)	1880 ± 560
Mode of delivery (vaginal/cesarean)	23/243
Gender, male	276 (%51)
Deaths	21
First-born infants	10
Second-born infants	11
Heavier infants	7
Lighter infants	14
RDS	55
First-born	24
Second-born	31
Heavier	26
Lighter twin	6
Both twins	23
Assisted reproduction	190 (%71)

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greater than 30%; Group B (n = 30 twin, total 60 infants) in which discordance was between 20 and 30%; and Group A+B (n = 54 twin, a total of 108 infants) when discordance was equal or greater then 20%. Mortality rates, RDS, NEC, BPD, polycytemia, hypoglycemia, sepsis and duration of hospitalization were compared between these groups. Diagnosis of diseases were made for each infant and all infants were included in the analysis. There were no differences between these three groups on the aforementioned indices, except for hypoglycemia ($p < .05$). These results are summarized in Table 2. These comparisons were made to test for differences between discordance of birthweights greater than 20% with those greater than 30%.

All twins were divided into two groups (discordant or concordant) based on a birthweight difference of 20% or more for discordance and less then 20% for concordance. The comparison of these groups is shown in Table 3. Groups were statistically different in the number of NEC cases, neonatal mortality, polycytemia and hypoglycemia. Other parameters of neonatal outcome tended to be worse in the discordant group (except RDS) but this difference was not significant. Because of these results, a birthweight discordance of equal or more than 20% in twin pairs was accepted as discordance (Table 4).

Table 2

The Clinical Outcome Difference Between Discordant Twin Pairs*

	Group A (D > 30%) n = 24, 48 twins	Group B (D < 30%, D > 20%) n = 30, 60 twins	Group A+B (D > 20%) n = 54, 108 twins	p
Neonatal mortality (7–28 day)	4 (8.3%)	4 (6.6%)	8 (7.4%)	*ns*
Apgar 5th minute	8.8	8.9	8.9	*ns*
RDS				
Larger twin	2 (8.3%)	3 (10%)	5 (9.2%)	*ns*
Smaller twin	1 (4.1%)	2 (6.6%)	3 (5.5%)	*ns*
NEC	2 (8.3%)	2 (6.6%)	4 (7.4%)	*ns*
BPD	3 (12.5%)	3 (10%)	6 (11.1%)	*ns*
Polycytemia	5 (20.8%)	5 (16.6%)	10 (16%)	*ns*
Hypoglycemia	12 (50%)	10 (33.3%)	22 (40.7%)	< .05
Sepsis	3 (12.5%)	4 (13.3%)	7 (12.9%)	*ns*
Hospitalization (days)	17.1	16.4	14.6	*ns*

Note: D = discordance.

Both significant in Group A vs. B and A vs. A+B.

RDS = respiratory distress syndrome, NEC = necrotizing enterocolitis, BPD = bronchopulmonary dysplasia.

ns = nonsignificant

*Chi-square test and test of significance between two percentages were used for analysis. Mann–Whitney test was used for Apgar scores. Logistic regression used for interaction.

Table 3

The Clinical Outcome Difference Between Discordant and Concordant Twin Pairs*

	Discordant, D > 20% n = 54, 108 twins	Concordant, D < 20% n = 212, 424 twins	p
Neonatal mortality (7–28 days)	8 (7.4%)	13 (3.1%)	.0349
RDS			
Larger twin	5 (9.2%)	21 (9.9%)	*ns*
Smaller twin	3 (5.5%)	3 (1.4%)	.0396
NEC	4 (7.4%)	5 (2.3%)	.0421
BPD	6 (11.1%)	16 (7.5%)	*ns*
Polycytemia	10 (18.5%)	24 (11.3%)	.0385
Hypoglycemia	22 (40.7%)	46 (21.6%)	.0326
Sepsis	7 (12.9%)	18 (8.4%)	*ns*
Hospitalization (days)	14.6	12.5	*ns*

Note: *Chi-square test, test of significance between two percentages and t tests were used. p values were results of significance between two percentages.

Multiple logistic regression revealed that being the heavier twin was the most important risk factor for RDS in our patients (odds ratio [OR] 4.5; 95% CI 2.2–9.2). Our statistical data demonstrated that being the male twin (OR 1.2; 95% CI 0.6–2.2) or being the second-born twin (OR 1.3; 95% CI 0.6–2.4) was related with risk of RDS but not as strong as being the heavier one.

Discussion

Perinatal mortality has been reported as 4 to 10 times greater in twins compared with singletons (Hawrylyshyn et al., 1982; Kovacs et al., 1989). The high perinatal mortality rate in twins is largely associated with the increased rate of low birthweight babies from preterm deliveries and growth-restricted pregnancies (Kiely, 1990). Some studies had shown that neonatal outcome in twin pregnancies associated with discordant growth depends on gestational age and fetal growth retardation. Only a few studies have found negative impacts of being the heavier twin, which, in this study, is related to short-term respiratory problems. One of these studies which included 124 twin pairs found a risk for need of oxygen in the first 4 hours of life for the heavier twin (Webb & Shaw, 2001). This report has suggested that the larger twin may be at increased risk of short-term respiratory distress (Webb & Shaw, 2001), and this may be exacerbated by the use of antenatal steroids which are known to be less effective in preventing respiratory distress in twins than in singletons (Turrentine et al., 1996). Some studies of singleton growth-retarded infants have shown a decreased incidence of RDS compared with nongrowth-retarded singletons (Procainoy et al., 1980). Some authors hypothesized that this was secondary to improved surfactant production due to chronic intrauterine stress,

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Table 4

A Total of All Mortalities (Early Neonatal 0–7 Days and Neonatal 7–28 Days) and Relation to 'Discordance'

	D < 20%				D > 20%			*p*
Discordance %	< 5	5–10	10–15	15–20	20–25	25–30	> 30	
Mortality, *n*	3	5	3	4	4	5	7	
Total	15 (3.5%, *n* = 424, 212 twins)				16 (14.8%, *n* = 108, 54 twins)			**< .05**

Note: D = Discordance

but this theory is not supported in current reports and discussions (Thompson et al., 1992).

Studies on singleton pregnancies in the past have suggested that in utero growth retardation may protect against acute respiratory distress. Gluck and Kulovich (1973) showed an improved lecithin/sphyngomyelin ratio in these pregnancies, the theory being that chronic intrauterine stress increased endogenous steroid production. Other case-control studies have shown the opposite effect (Thompson et al., 1992). However, the strongest predictor of respiratory distress in newborns is gestational age.

In twin pregnancies there is usually a disparity in birthweights between twins. It is possible therefore that the risk of respiratory distress may be different for each infant in each twin pair. Gender and birth order are the other major factors which may also affect the risk of neonatal respiratory illness. Male infants are slightly larger on average and more susceptible to respiratory distress (Ghai & Vidyasagar, 1988), and the second-born twin is at higher risk of intrapartum hypoxia and abnormal delivery (Chen et al., 1993). We found that although the risk of serious respiratory illness is unlikely in the heavier twin, there is an increased risk of RDS over the smaller twin. In this study the twins acted as each other's controls for gestation and maternal factors (e.g., corticosteroids), which may affect risk of respiratory disease. Whether the effect of weight order on respiratory status was due to more respiratory illness in the heavier twin or less in the lighter twin could be investigated further by comparison with a singleton control group.

Birthweight discordance of more than 20% in twins seems to be significant because of its effect on neonatal outcome in our data. Obstetricians nowadays can measure estimated fetal weight successfully by ultrasound scanning. A detection of discordance between twins of 20% or more should be monitored closely especially for the smaller twin. A further perinatal study with a large number of twin pregnancies, (except twin–twin transfusion syndromes, including early intrauterine death or stillbirths) should investigate for maternal problems, perinatal outcomes, intrapartum or postpartum deaths and other complications in discordant twins. A study on discordant twins concluded that the definition of discordant growth in twin gestations should be categorized with respect to gestational age since the level of discordance may have differing effects on neonatal morbidity and mortality depending on the stage of pregnancy (Yalçin et al., 1998). Further studies should also compare gestational differences between discordant twins.

Our data therefore support a high risk in RDS for the heavier twin, which was more significant than being either second-born or male. Based on our findings of differences in neonatal outcomes, the authors suggest that a birthweight discordance of at least 20% in twin pairs be used as the criterion for 'discordance'.

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