

Birth weight discordant twins have increased prenatal mortality and neonatal morbidity: an analysis of 1,132 twins

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Abstract

Background: Multiple pregnancies have increased significantly over the past decades. Birth weight discordance (BWD) is a common problem between twins, but its association with an increased morbidity and mortality is still unclear. The aim of this study was to determine the frequency of BWD among twins and to evaluate its impact on perinatal morbidity.

Methods: Retrospective study of 1,132 twins born in a tertiary perinatal center, over a period of 8 years (2003-2010), that were divided in two groups: concordant (intrapair birth weight difference $\leq 20\%$) or discordant ($> 20\%$). The two groups were compared in terms of epidemiological and obstetric data, mode of delivery, perinatal morbidity and mortality.

Results: During the study period, multiple gestation occurred in 2% of cases, of which 96% were twins. BWD was found in 212 (19%) twins. Multivariate analysis demonstrated that maternal age ≥ 35 years and hypoxic-ischemic placental infarction were risk factors for the occurrence of BWD. The discordant group showed a significantly higher incidence of congenital skeletal and central nervous system malformations, a higher rate of hospitalization in the neonatal intensive care unit and a longer duration of hospitalization. The percentage of those requiring assisted ventilation, pulmonary surfactant, parenteral nutrition and central venous catheters was significantly higher in the discordant group compared with the concordant one. The rate of stillbirth was significantly higher in the discordant group (3% versus 1%); mortality was also higher (3% versus 2%), but this difference was not statistically significant ($p = 0.405$).

Conclusion: BWD was associated with increased prenatal mortality and neonatal morbidity. Diagnosis and management of pregnant women with this fetal condition in tertiary perinatal centers may improve the prognosis of these infants.

Keywords

Birth weight, morbidity, mortality, multiple pregnancy, premature birth, twins.

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Introduction

The incidence of multiple pregnancies has increased significantly over the last decades [1-4] mainly due to older maternal age and to the wider use of assisted reproduction techniques [1, 2, 4]. It is known that twin gestations are associated with higher perinatal morbidity and mortality [5]. Moreover, when twins have discordant fetal growth there is an increased risk of further complications, such as stillbirth, fetal growth restriction, malformations, and preterm birth [2-6].

There is no consensus regarding the threshold of birth weight discordance (BWD) that is associated with an increased risk of complications. However, the American College of Obstetricians and Gynecologists (ACOG) considers a 15-25% difference in weight among twins to be discordant [3, 7]. Discordance of at least 20% occurs in approximately 15-25% of twin pairs and nearly 5% of twin gestations experience severe discordance (> 30-35%) [2, 7]. Despite several reports that have associated BWD with poor perinatal outcome [2, 5, 8], some studies suggested that the majority of twins with BWD do well despite the weight difference [2, 5, 9]. In addition, most previous studies were based on obstetric databases and few have analyzed the neonatal complications systematically.

The purpose of this study was to determine the frequency of BWD among twins delivered in a tertiary hospital and to evaluate its impact on perinatal morbidity and mortality.

Methods

Study design

Retrospective analysis of all consecutive twin pregnancies delivered at a gestational age of more

than 23 weeks at our center between January 2003 and December 2010. The cases were identified through the institution birth registry and detailed information was obtained by analysis of hospital records. Triplets or higher order deliveries were excluded.

Inter-twin BWD was defined as a difference > 20% using the following formula: [(birth weight of larger twin - birth weight of smaller twin)/birth weight of larger twin] x 100.

The population of dichorionic twins was described separately.

We also stratified discordant twins into minor groups and compared the following variables:

- intrapair birth weight differences (severely discordant twins [$> 35\%$] versus mildly discordant twins [21-35%]);
- chorionicity (monochorionic versus dichorionic twins);
- intrapair birth size difference (larger versus smaller twin).

The study was approved by the institution's review board.

Clinical variables definition

Epidemiological, obstetric, perinatal morbidity and mortality data were recorded. Chorionicity was determined by ultrasound examination in the antenatal or by anatomopathological analysis in the postnatal period. Gestational age was calculated based on the date of the last menstrual period, and confirmed by an ultrasound scan performed during the first trimester (showing a difference of no more than seven days). When the date of the last menstrual period was uncertain, pregnancy dating was based on biometry of the largest values. Prematurity was defined as a gestational age of less than 37 weeks. Intrauterine growth restriction was defined as an estimated fetal weight below the 10th percentile. Birth weight was also classified based on the 10th percentile for the respective gestational age and gender according to the Fenton growth chart. Congenital malformations were diagnosed by ultrasound examination during the antenatal or postnatal period or by clinical examination of the neonate. Infants were followed up until hospital discharge.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Continuous variables were

described as mean \pm standard deviation (SD) for normally distributed variables or as median (25th-75th percentile) for those non-normally distributed. Categorical variables are expressed as a number (n) and percentage (%). Differences between groups were assessed using t-Student and Mann-Whitney U tests for quantitative variables comparisons and chi-square tests were performed for discrete variables comparisons. Multiple regression analysis was used to determine strength of the association between maternal and prenatal significant variables and BWD.

A p-value of < 0.05 was considered as statistically significant.

Results

A total of 26,153 deliveries were conducted at our center during the study period, of which 589 (2%) were multiples. Triplets and higher order deliveries were excluded (n = 23). Among the 566 pairs of twins, 106 (19%) were discordant. The weight discordance was associated with lower gestational age (mean/mode: 33/35 versus 34/37 weeks, $p < 0.001$), lower birth weight (mean/mode: 1,815/1,400 g versus 2,132/1,870 g, $p < 0.001$) and higher percentage of newborns small for gestational age (30% versus 10%, $p < 0.001$).

Maternal demographics and prenatal complications in twin gestations

Maternal age ≥ 35 years, use of assisted reproductive techniques (in-vitro fertilization, intra-cytoplasmic sperm injection, ovarian stimulation, or others), infertility, and pregnancy-induced hypertension were significantly more frequent in the discordant group.

We found that the incidence of intrauterine growth restriction was higher in the discordant group. Stillbirth occurred in 3% in the discordant group and in 1% in the concordant group ($p < 0.05$) (**Tab. 1**).

Placenta characteristics

On microscopic examination of the placentas, vascular-thrombotic lesions (hypoxic-ischemic placental infarction) were significantly more frequent in the discordant group. The groups were similar in chorionicity, in velamentous umbilical cord insertion and in the incidence of chorioamnionitis (**Tab. 2**).

Table 1. Maternal demographics and prenatal complications in twin gestations (n = 566).

Variable	Discordant twin gestation (n = 106)	Concordant twin gestation (n = 460)	p-value
Maternal age ≥ 35 years	32%	20%	< 0.05
Multipara	48%	49%	n.s.
Use of assisted reproductive techniques ^a	35%	22%	< 0.05
Infertility	34%	21%	< 0.01
Tobacco use	13%	14%	n.s.
Primary hypertension	2%	2%	n.s.
Diabetes mellitus	1%	0%	n.s.
Pregnancy-induced hypertension	15%	8%	< 0.05
Infection ^b	1%	2%	n.s.
Gestational diabetes	7%	8%	n.s.
Threatened preterm labor	50%	46%	n.s.
Intrauterine growth restriction	29%	6%	< 0.001
Stillbirth	3%	1%	< 0.05

^a In-vitro fertilization, intra-cytoplasmic sperm injection, ovarian stimulation or others; ^b TORCH infections or others; n.s. = not significant ($p > 0.05$).

Table 2. Placenta characteristics of twin gestations (n = 566).

Variable	Discordant twin gestation (n = 106)	Concordant twin gestation (n = 460)	p-value
Dichorionicity	71%	74%	n.s.
Hypoxic-ischemic placental infarction	12%	3%	< 0.001
Velamentous umbilical cord insertion	21%	18%	n.s.
Chorioamnionitis	13%	13%	n.s.
Umbilical cord knot/tangle	6%	5%	n.s.

n.s. = not significant ($p > 0.05$).

Perinatal risk factors for the occurrence of birth weight discordance

Multivariate stepwise logistic regression analyses showed that there were two risk factor associated with the occurrence of BWD, which included

maternal age ≥ 35 years (odds ratio [OR] = 0.552; 95% confidence interval [CI]: -1.806-2.911) and hypoxic-ischemic placental infarction (OR = 0.390; 95% CI: -2.1-2.88) (**Tab. 3**).

Neonatal complications and outcome

Cesarean deliveries occurred more frequently in the discordant group. This group showed also a significantly higher incidence of congenital skeletal and central nervous system malformations. There was no difference in the incidence of digestive or reno-pelvic malformations between the two groups. Multiple regression analysis demonstrated that the use of assisted reproductive techniques was not associated with congenital malformations (OR = 1.165; 95% CI: -4.602-6.931; $p = 0.888$). The occurrence of neonatal respiratory distress syndrome, sepsis, persistence of ductus arteriosus and anemia was significantly higher in the discordant group. This group also had higher requirement of pulmonary surfactant and increased probability of mechanical ventilation, parenteral nutrition and central venous catheter. The admission in neonatal intensive care occurred in 68% of BWD compared to 50% in the concordant group ($p < 0.01$). Average hospital stay was also higher in BWD: 21 days versus 11 days ($p < 0.01$). Neonatal mortality was higher in the discordant group (3% versus 2%), but this difference was not significant ($p = 0.40$) (**Tab. 4** and **Tab. 5**).

Comparison of fetal and neonatal morbidity in dichorionic twins

Considering only the population of dichorionic twins, the impact of BWD on prenatal mortality and perinatal morbidity was mostly maintained (**Tables 6 to 9**).

Comparison and significant differences in neonatal morbidity in discordant twins

Intrapair birth weight differences (severe versus mild discordance)

Congenital abnormalities of the digestive system (7% versus 1%, $p < 0.05$), platelet transfusion (11% versus 2%, $p < 0.05$) and non-invasive mechanical ventilation (32% versus 11%, $p < 0.01$) occurred significantly more often in severely discordant babies. Mechanical invasive ventilation was significantly more often in mildly

discordant babies (35% versus 14%, $p < 0.05$). Respiratory distress syndrome (45% versus 29%), intraventricular hemorrhage (15% versus 4%), anemia (16% versus 14%) and sepsis (27% versus 25%) occurred also more often in mildly discordant babies but these differences were not statistically significant. Prematurity occurred equally in both groups (93%).

Table 3. Logistic regression analysis for risk factors for the occurrence of birth weight discordant twins.

Risk factors	Odds ratio	p-value	95% confidence interval
Maternal age ≥ 35 years	0.552	< 0.001	-1.806-2.911
Use of assisted reproductive techniques ^a	1.459	n.s.	1.634-4.553
Pregnancy-induced hypertension	0.683	n.s.	-1.848-3.214
Hypoxic-ischemic placental infarction	0.390	< 0.001	-2.1-2.88
Congenital malformations	1.099	n.s.	-3.235-5.433

^aIn-vitro fertilization, intra-cytoplasmic sperm injection, ovarian stimulation or others; n.s. = not significant ($p > 0.05$).

Table 4. Comparison of clinical characteristics at birth between birth weight discordant and concordant twins (n = 1,132).

Variable	Discordant twins (n = 212)	Concordant twins (n = 920)	p-value
Prematurity	80%	74%	n.s.
Male gender	55%	54%	n.s.
Cesarean section	81%	68%	< 0.001
Small for gestational age	30%	10%	< 0.001
Congenital skeletal malformations	4%	1%	< 0.01
Congenital central nervous system malformations	3%	1%	< 0.01
Congenital digestive malformations	1%	1%	n.s.
Congenital reno-pelvic malformations	2%	3%	n.s.

n.s. = not significant ($p > 0.05$).

Table 5. Comparison of neonatal outcome between birth weight discordant and concordant twins (n = 1,132).

Variable	Discordant twins (n = 212)	Concordant twins (n = 920)	p-value
Asphyxia	3%	1%	n.s.
Respiratory distress syndrome	27%	18%	< 0.01
Bronchopulmonary dysplasia	2%	2%	n.s.
Patent ductus arteriosus	7%	4%	< 0.05
Necrotising enterocolitis	1%	1%	n.s.
Sepsis	18%	11%	< 0.01
Intraventricular hemorrhage	5%	3%	n.s.
Anemia	9%	5%	< 0.05
Pulmonary surfactant	15%	10%	< 0.05
Invasive mechanical ventilation	19%	11%	< 0.01
Non-invasive mechanical ventilation	12%	7%	< 0.05
Vasoactive drugs	6%	5%	n.s.
Parenteral nutrition	29%	14%	< 0.001
Central venous catheter	16%	8%	< 0.001
Platelet transfusion	0%	1%	n.s.
Red blood cells transfusion	1%	1%	n.s.
NICU admission	68%	50%	< 0.001
NICU stay > 7 days	59%	38%	< 0.001
Neonatal death	3%	2%	n.s.

NICU: Neonatal Intensive Care Unit; n.s. = not significant (p > 0.05).

Table 6. Placenta characteristics of twin dichorionic gestations (n = 415).

Variable	Dichorionic discordant twin gestation (n = 76)	Dichorionic concordant twin gestation (n = 339)	p-value
Hypoxic-ischemic placental infarction	20%	8%	< 0.01
Velamentous cord insertion	18%	15%	n.s.
Chorioamnionitis	13%	13%	n.s.
Umbilical cord knot/tangle	0%	1%	n.s.

n.s. = not significant (p > 0.05).

Table 7. Maternal demographics and prenatal complications in twin dichorionic gestations (n = 415).

Variable	Dichorionic discordant twin gestation (n = 76)	Dichorionic concordant twin gestation (n = 339)	p-value
Maternal age ≥ 35 years	33%	21%	< 0.05
Multipara	45%	48%	n.s.
Use of assisted reproductive techniques ^a	46%	29%	< 0.01
Infertility	43%	27%	< 0.01
Tobacco use	13%	15%	n.s.
Primary hypertension	1%	2%	n.s.
Diabetes mellitus	1%	0%	n.s.
Pregnancy-induced hypertension	9%	9%	n.s.
Infection ^b	0%	1%	n.s.
Gestational diabetes	17%	8%	< 0.05
Threatened preterm labor	55%	46%	n.s.
Intrauterine growth restriction	27%	7%	< 0.001
Stillbirth	3%	1%	< 0.05

^aIn-vitro fertilization, intra-cytoplasmic sperm injection, ovarian stimulation or others; ^bTORCH infections or others; n.s. = not significant (p > 0.05).

Table 8. Comparison of clinical characteristics at birth between dichorionic birth weight discordant and concordant twins (n = 830).

Variable	Dichorionic discordant twins (n = 152)	Dichorionic concordant twins (n = 678)	p-value
Prematurity	78%	72%	n.s.
Male gender	55%	53%	n.s.
Caesarean section	80%	67%	< 0.01
Small for gestational age	27%	10%	< 0.001
Congenital skeletal malformations	3%	1%	< 0.05
Congenital central nervous system malformations	2%	1%	< 0.01
Congenital digestive malformations	1%	1%	n.s.
Congenital reno-pelvic malformations	3%	3%	n.s.

Table 9. Comparison of neonatal outcome between dichorionic birth weight discordant and concordant twins (n = 830).

Variable	Dichorionic discordant twins (n = 212)	Dichorionic concordant twins (n = 920)	p-value
Asphyxia	3%	1%	n.s.
Respiratory distress syndrome	25%	17%	< 0.05
Bronchopulmonary dysplasia	1%	3%	n.s.
Patent ductus arteriosus	6%	4%	n.s.
Necrotising enterocolitis	1%	1%	n.s.
Sepsis	15%	10%	n.s.
Intraventricular hemorrhage	3%	3%	n.s.
Anemia	5%	5%	n.s.
Pulmonary surfactant	14%	9%	< 0.05
Invasive mechanical ventilation	14%	10%	n.s.
Non-invasive mechanical ventilation	13%	6%	< 0.01
Vasoactive drugs	5%	5%	n.s.
Parenteral nutrition	26%	14%	< 0.001
Central venous catheter	14%	8%	< 0.05
Platelet transfusion	0%	1%	n.s.
Red blood cells transfusion	1%	1%	n.s.
NICU admission	64%	47%	< 0.001
NICU stay > 7 days	74%	72%	n.s.
Neonatal death	3%	2%	n.s.

NICU: Neonatal Intensive Care Unit; n.s. = not significant (p > 0.05).

Chorionicity

The monochorionic discordant twins had significantly lower birth weight (1,634 g versus 1,889 g, $p < 0.01$) and higher frequency of intraventricular hemorrhage (10% versus 3%, $p < 0.05$), anemia (19% versus 5%, $p < 0.01$), neonatal intensive care admission (80% versus 64%, $p < 0.05$) and mechanical ventilation (29% versus 15%, $p < 0.05$), when compared with the dichorionic discordant group.

Intrapair birth size differences

The smaller baby presented significantly higher incidence of skeletal malformations (3% versus 1%, $p < 0.05$). Respiratory distress syndrome (21% versus 19%), patent ductus arteriosus (6% versus 4%), pulmonary surfactant (12% versus 10%), invasive mechanical ventilation (13% versus 12%), non-invasive mechanical ventilation (9% versus 7%), central venous catheter (10% versus 9%), platelet transfusion (1% versus 0%), NICU admission (55% versus 53%), NICU stay > 7 days (44% versus 40%), and neonatal death (3% versus 2%) were more frequent in the smaller baby but this differences were not statistically significant.

Discussion

In literature, the occurrence of BWD among multiple births is fairly common, but its clinical significance is still controversial. For this study, and according with the ACOG, a threshold of 20% was defined. The frequency of discordant twins was 19%, which is similar to the reported rates of 15-30% [2, 5].

In our study, maternal age ≥ 35 years and hypoxic-ischemic placental were risk factor for the occurrence of BWD. These factors are closely related with placental dysfunction, which may lead to intrauterine growth restriction and twin birth weight discordance [8].

In accordance with several other studies, we found a significantly higher incidence of fetal mortality in the discordant group. As described by Assunção et al., the higher incidence of reported congenital malformations (skeletal and central nervous system) can be associated with a higher frequency of intrauterine death of the affected fetus [1].

Neonatal mortality was also higher, but the difference was not statistically significant. One potential explanation is that this study, even with more than 1,000 twins, can be underpowered to detect a difference in subgroups.

Some authors have suggested that induced preterm delivery – and not discordant growth *per se* – has a more important influence on neonatal outcome [5]. Indeed, the discordant group showed a significantly lower gestational age when compared to the concordant group. This association might be explained by increased obstetric intervention in discordant twins, causing preterm delivery.

The incidence of most common neonatal complications was higher in the discordant group,

especially concerning respiratory and infectious diseases, such as respiratory distress syndrome and sepsis. Also, the higher incidence of neonatal intensive care unit admission and the longer duration of hospitalization suggested that the severity of complications suffered by discordant twins was worse.

A significantly lower gestational age and birth weight in discordant group are probably the main causes of the high incidence and severity of respiratory disease. As a result, the percentage of those requiring pulmonary surfactant and mechanical ventilation so as the incidence of patent ductus arteriosus and anemia was significantly higher in the discordant group, which probably contributes to the poor respiratory outcome.

Moreover, respiratory system diseases can lead to respiratory failure and hypoxic organ damage, especially hypoxic encephalopathy.

Although there were no significant differences in the incidence of asphyxia and intraventricular hemorrhage between the concordant and discordant group, these complications were more frequent in the latter. The association of these diseases with central nervous system sequelae, such as long-time adverse cognitive function and even death, is a serious problem. So, after birth regular screening of craniocerebral injury and cognitive development as well as monitoring of physical growth should be a concern.

Conventionally, a cut-off of 15-20% birth weight discordance is considered to be significant, but it seems more clinically relevant to detect more severe birth-weight discordance [9, 10]. In fact, in our study, we found an increased frequency of congenital abnormalities of the digestive system, platelet transfusion and non-invasive mechanical ventilation, in severely discordant (> 35%) when compared with mildly discordant twins (21-35%). Unexpectedly, mildly discordant twins showed higher incidence of invasive mechanical ventilation. Although not statistically significant, respiratory distress syndrome, intraventricular hemorrhage, anemia and sepsis were more frequent in this group. It is possible that these conditions may have determined respiratory failure. Another possible explanation for this contradictory finding is the retrospective data collection and the effect of recent years advances in neonatology care, especially in terms of assisted ventilation.

In our study, perinatal risk factors and neonatal complications differed in chorionicity. Similar to other series, we found worse outcomes in

monochorionic than dichorionic twins [1, 11-13]. The finding that monochorionic twins were of lower birth weight than dichorionic twins suggest that monochorionic placentation itself has an effect on intrauterine growth. Hemodynamic imbalance caused by placental vascular anastomoses are commonly cited as the underlying mechanism [10, 14]. The finding of high prevalence of anemia in monochorionic discordant twins also suggest that placental vascular anastomoses is a mechanism of discordance in this type of twins [10, 14]. Low birth weight is related to intraventricular hemorrhage, which can explain the higher prevalence of intraventricular hemorrhage in monochorionic discordant group in our study.

Several studies in twins have shown that the larger twin has an increased risk of severe neonatal morbidity, particularly respiratory distress syndrome, compared to the smaller twin, due to induced pre-term delivery [6]. In our study, this association was not seen. Instead, the smaller twin showed higher incidence of congenital skeletal malformations.

This is not a randomized controlled trial, therefore it is open to selection bias. Additionally, our data should be interpreted with care due to the retrospective nature of the study. We acknowledge that one of the weaknesses of this review is the focus on short-term outcomes.

Conclusion

Birth weight discordance in twins is a common growth problem.

The results of our study provide evidence that great discordance, monochorionic discordant twins and smaller twin are associated with worse perinatal outcomes.

BWD was associated with increased prenatal mortality and perinatal morbidity, even considering only dichorionic twins. This emphasizes the need for early diagnosis of discordance in order to place differentiated prenatal and appropriate peripartum surveillance [15], potentially reducing perinatal mortality and morbidity.

Since most of these complications can affect growth and development of infants, pediatricians should detect and treat the short-term complications of discordant twins as early as possible. Multicenter studies are required to address the optimal management in these high-risk pregnancies.

Declaration of interest

The Authors declare that they have no conflict of interest regarding the publication of this article.

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