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Pathologic Basis for the Definition of Discordant Growth in Dichorionic Twins

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Keywords
Twin gestation · Discordance · Placental pathology · Maternal vascular malperfusion

Abstract
Objective: The aim of the current study was to identify the optimal cutoff that should define discordance in dichorionic twin gestations through correlation with abnormal placental pathology as a specific measure of fetal growth restriction of the smaller twin. ***Methods:*** We performed a retrospective cohort study of all women with dichorionic twin pregnancies who gave birth in a single center between 2002 and 2015. We investigated the association between the level of growth discordance and maternal vascular malperfusion (MVM) pathology in the placenta of the smaller twin, with and without adjustment for whether the smaller twin is small for gestational age (SGA). ***Results:*** A total of 1,198 women with dichorionic twin gestation met the study criteria. The rate of MVM pathology in the placenta of the smaller twin increased with the level of discordance and was most obvious for discordance ≥25% (rate of MVM 12.0% compared with 2.8% in cases with discordance <10%, adjusted relative risk [aRR] 3.71, 95% confidence interval [CI] 1.97–6.99). When the analysis was adjusted for SGA of the smaller twin, discordance was independently associated with MVM pathology only when growth discordance was ≥25% (aRR 2.18, 95%-CI 1.01–4.93), while SGA was strongly associated with MVM pathology irrespective of the level of discordance. ***Conclusion:*** Our findings suggest that discordant growth in dichorionic twins should raise the concern of fetal growth restriction of the smaller twin, irrespective of whether the smaller twin is SGA, only when the discordance s ≥25%. The association of lower levels of discordance with abnormal placental pathology is mainly driven by the confounding effect of SGA of the smaller twin.

Introduction

Twin gestations, accounting for approximately 3% of pregnancies in the USA [1, 2], are associated with an increased risk of pregnancy complications and perinatal mortality and morbidity compared with singleton gestations [3–5]. Specifically, up to 30% of twins are affected by fetal growth restriction [6–8].

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Intertwin growth discordance has been associated with an increased risk of neonatal mortality and morbidity of the smaller twin [9–15]. The rationale underlying this association in dichorionic twins is that an intertwin discordance that exceeds the expected normal genetic variation in growth potential, which has been estimated to be <10% in the case of dichorionic twins [16, 17], might indicate growth restriction of the smaller twin, with the larger twin serving as a naturally occurring control. However, the interpretation of growth discordance in dichorionic twin gestations in clinical practice is limited by the conflicting data on the optimal cutoff used to define discordant growth, and on whether discordant growth is clinically relevant even when the smaller twin is not small for gestational age (SGA, defined as birth weight below the 10th percentile for gestational age) [17, 18].

One important explanation for the conflicting data described above is that many of the previous studies addressing discordant growth did not account for important confounding factors such as chorionicity, twin-to-twin transfusion syndrome, and congenital structural and genetic anomalies [9, 15, 16]. Another important explanation is that in most available studies the optimal discordance cutoff was identified through correlation with neonatal mortality and morbidity attributed to growth restriction of the smaller twin. However, neonatal mortality and morbidity are not specific for fetal growth restriction and are especially confounded by prematurity [19, 20], which is frequent in twin gestations [21] and may thus mask the effects of impaired fetal growth on neonatal outcomes. Thus, given that intertwin growth discordance is commonly used by care providers for clinical decision-making such as closer monitoring and timing of delivery, there is an important need for additional studies to address the knowledge gaps regarding the management of twin pregnancy affected by growth discordance while overcoming the limitations described above and through correlation of discordance with outcomes that are more specific to fetal growth restriction.

Given that the main concern clinicians face when managing discordant growth in dichorionic twins is that it may indicate fetal growth restriction of the smaller twin, it seems reasonable to correlate discordance with underlying placental pathology (instead of neonatal mortality and morbidity) as a more direct and specific measure of placental insufficiency mediating fetal growth restriction of the otherwise normal fetus [22, 23]. To date such data relating growth discordance with placental pathology are limited. In a prospective study of 668 twin pairs [12], growth discordance was associated with abnormal placental pathology in dichorionic but not in monochorionic twins. However, the authors of that study did not explore the optimal cutoff for discordance and instead used a fixed cutoff of 20%. In addition, the interpretation of that study is limited by the lack of distinction between different types of placental pathology and by lack of adjustment for whether the smaller twin was SGA.

Thus, the aim of the current study was to (1) identify the optimal cutoff that should define discordance in dichorionic twin gestations and (2) to determine whether discordance in dichorionic twins is clinically relevant even when the smaller twin is not SGA, through correlation of growth discordance with abnormal placental pathology.

Methods

Study Population

We conducted a retrospective cohort study of all women with dichorionic twin pregnancies who gave birth in a single tertiary referral center (Sunnybrook Health Sciences Center, Toronto, ON, Canada) between January 2002 and December 2015. Pregnancies complicated by any of the following conditions were excluded: gestational age at birth <24$^{0/7}$ weeks, structural or genetic fetal abnormalities, stillbirth or reduction of one or both fetuses, or incomplete or missing data. The current study was approved by the Institutional Research Ethics Board (#353-2014).

Data Collection

Cases were identified using the institutional perinatal database. Data were extracted from the electronic medical records including demographic and obstetrical characteristics, chorionicity, validation of gestational age by first trimester ultrasound, pregnancy complications, gestational age at birth, neonatal sex, and birth weight.

According to our departmental policy, all placentas of multifetal gestations were routinely sent for pathologic examination during the study period. The placental pathology reports of all twin gestations that met the study criteria were reviewed in detail for information on placental weight, and macroscopic and microscopic abnormalities of the placenta and umbilical cord.

Classification of Placental Findings

Our standard protocol for placental examination was described in detail elsewhere [24–26]. Briefly, within 24 h after delivery, the placenta, membranes and cord were fixed in formalin. Macroscopic evaluation of the placenta, membranes, and umbilical cord included determination of chorionicity and amnionicity, and assigning each placenta (or placental portion in the case of fused placenta) to the larger and smaller twin based on labeling of the cords at the time of birth. For each, gross parenchymal lesions or attached clots were noted, together with the number of umbilical cord vessels, placental cord insertion site (central, marginal or velamentous), and hyper- or hypocoiled cord. Subsequently, at least 6 placental tissue samples were embedded in paraffin blocks for microscopic assessment. Samples were obtained from membranes,

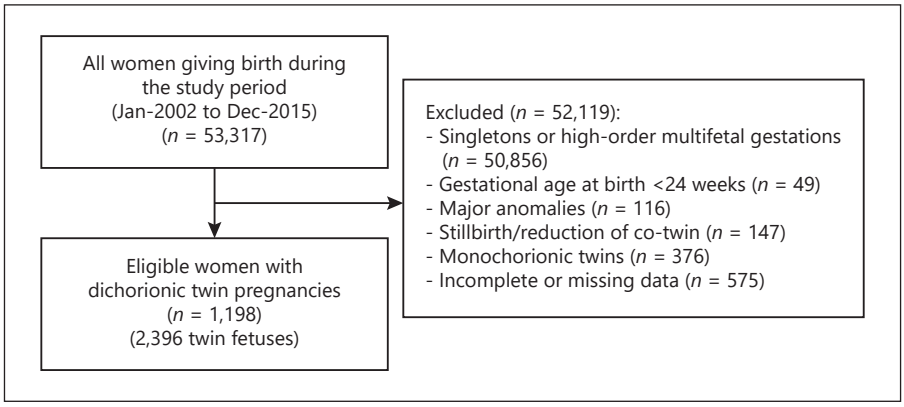

Fig. 1. Selection of the study group.

umbilical cord, and centrally and marginally located tissue that appeared abnormal on gross examination and up to 3 samples from normally appearing placental tissue. Placental abnormalities for each fetus were classified according to the criteria suggested by Redline [27] and the 2014 Amsterdam Placental Workshop Group [28].

In the current study, we chose to focus on maternal vascular malperfusion (MVM) placental pathology given its strongest association with impaired fetal growth in unselected singleton pregnancies [24, 29, 30]. Lesions associated MVM with included small placenta (defined as placental weight <10th percentile [30]), decidual vasculopathy, acute atherosis, and villous changes such as villous infarcts, increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and accelerated villous maturation. Since isolated MVM lesions are often found in uncomplicated pregnancies, we used a composite of at least 2 MVM lesions (≥2 MVM) as a more specific measure of MVM pathology.

Definitions

Small for gestational age (SGA) was defined as birth weight <10th percentile for gestational age based on a birth weight-based Canadian reference of Kramer et al. [31] Birth weight discordance was calculated as follows: ([birth weight of larger twin] – [birth weight of smaller twin])/[birth weight of larger twin] x 100%. Stillbirth was defined as fetal death occurring before or during labor.

Data Analysis

In the first step, we plotted the rate of MVM placental pathology associated with the smaller twin as a function of discordance level as a continuous variable. This allowed us to determine the relationship between discordance level and MVM placental pathology and identify potential discordance thresholds above which the risk of MVM placental pathology increases.

In the second step, we assessed this relationship from a practical and clinical perspective by determining the risk MVM placental pathology in the smaller twin as a function of discordance as a dichotomous variable, using each of the following discordance cutoff values: <10 (reference), ≥10, ≥15, ≥20, ≥25, and ≥30%. Multivariable log-binomial regression analysis was used to determine the association between discordance (using the corresponding cutoff) and the risk of MVM pathology, expressed as adjusted relative risk (aRR) and 95% confidence interval (95%-CI). Models were adjusted for maternal age, hypertensive disorders of pregnancy (defined as gestational hypertension or preeclampsia), gestational age at delivery, and neonatal sex.

To determine whether the association of discordance with MVM placental pathology is independent of whether the smaller twin is SGA, we stratified the analysis described above by SGA status of the smaller twin, that is, the association of discordance (as a

Table 1. Baseline characteristics

Characteristic	Value
N	1,198
Maternal age, years	34.2±5.2
Maternal age >35 years	447 (37.3)
Chronic hypertension	18 (1.5)
Pregestational diabetes	6 (0.5)
Nulliparity	737 (61.5)
Hypertensive disorders of pregnancy[a]	150 (12.5)
Gestational diabetes	92 (7.7)
Gestational age at delivery, weeks	34.6±3.3
Preterm delivery <37 weeks	720 (60.1)
Preterm delivery <34 weeks	307 (25.6)
Preterm delivery <32 weeks	213 (17.8)
Preterm delivery <28 weeks	68 (5.7)
Discordance, %	9.8 (4.7–17.0)
Discordance <10	611 (51.0)
Discordance ≥10	587 (49.0)
Discordance ≥15	368 (30.7)
Discordance ≥20	220 (18.4)
Discordance ≥25	125 (10.4)
Discordance ≥30	70 (5.8)
Female sex[b]	1,192 (49.8)
Birth weight, g[b]	2,260±669
SGA[b]	506 (21.1)

SGA, small for gestational age (birth weight below 10th percentile for gestational age). Data are presented as mean ± SD, median (interquartile range), or *n* (%). [a] Gestational hypertension or preeclampsia. [b] Unit of analysis is fetus (*n* = 2,396) rather than pregnancy.

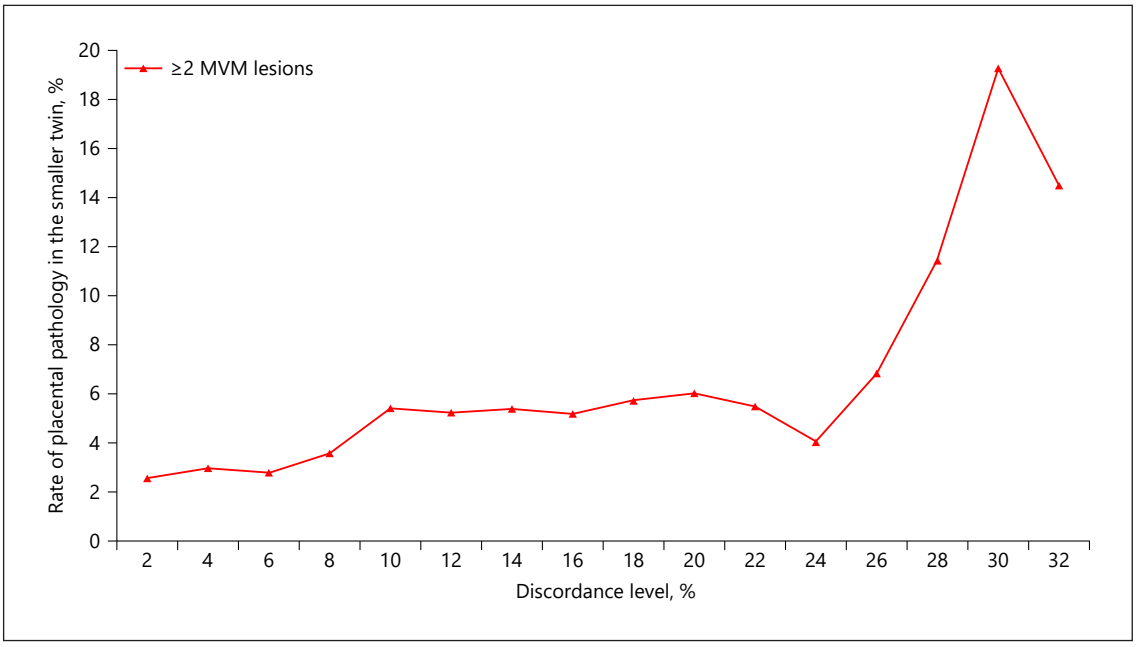

Fig. 2. Rate of MVM placental pathology in the smaller twin by discordance level as a continuous variable. The rate of MVM pathology (≥2 MVM lesions) is presented as a function discordance level. MVM, maternal vascular malperfusion.

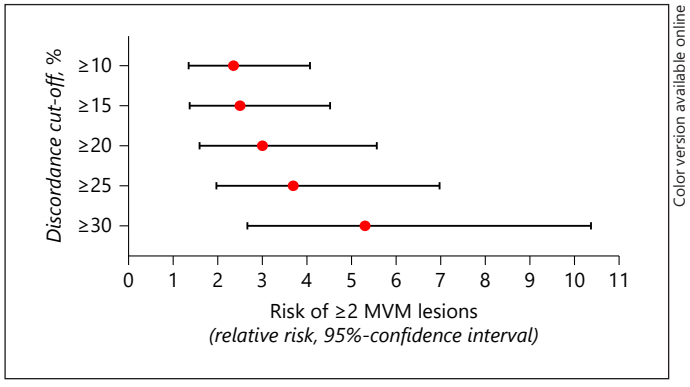

Fig. 3. Association of discordance cutoff with MVM placental pathology in the smaller twin. Values reflect the results of multivariable log-binomial regression analysis to determine the association between discordance (using the corresponding cutoff) and MVM placental pathology. Models are adjusted for maternal age, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension), gestational age at delivery, and neonatal sex and are presented as aRR (95%-CI). aRR, adjusted relative risk; CI, confidence interval; MVM, maternal vascular malperfusion.

dichotomous variable) with MVM placental pathology was determined for cases in which the smaller twin is SGA, and, separately, for cases in which the smaller twin is not SGA. In addition, we addressed this question by comparing the association between discordance and MVM placental pathology, with versus without adjustment for SGA of the smaller twin.

Data were analyzed using SPSS statistical software Version 24.0 (Armonk, NY: IBM Corp.). Significance was set to a two-sided p value of <0.05.

Results

Characteristics of the Study Population

Of a total of 53,317 women who gave birth in our center during the study period, 1,198 had a dichorionic twin gestation (2,396 twin fetuses) that met the study criteria (Fig. 1). The characteristics of the study group are presented in Table 1. Mean gestational age at delivery was 34.6 ± 3.3 weeks. Median birth weight discordance was 9.8% (interquartile range 4.7–17.0%). The proportion of pregnancies meeting each of the prespecified discordance cutoff values ranged from 49% for discordance ≥10% to 5.8% for discordance ≥30% (Table 1).

Relationship between Discordance and Maternal Vascular Malperfusion Placental Pathology in the Smaller Twin

The relationship between discordance level (as a continuous variable) and the rate of MVM placental pathology in the smaller twin is presented in Fig. 2. The rate of MVM pathology increased by approximately 2-fold (2.6

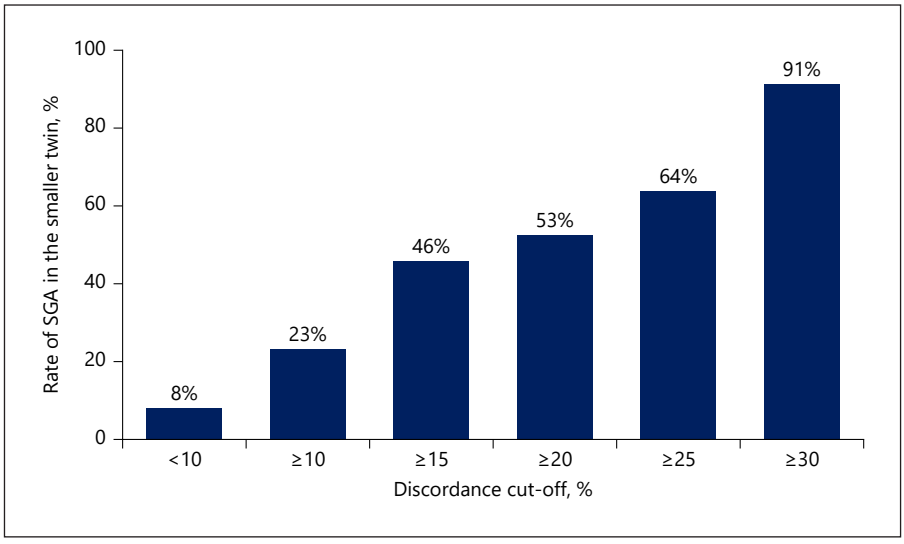

Fig. 4. Rate of SGA in the smaller twin by discordance cutoff. SGA; small for gestational age.

Table 2. Risk of MVM placental pathology in the smaller twin by discordance cutoff

Discordance cutoff	*N*	Risk of ≥2 MVM lesions		
		rate, *n* (%)	crude RR (95%-CI)	adjusted RR (95%-CI)[a]
<10%	611	17 (2.8)	Reference	Reference
≥10%	587	41 (7.0)	**2.51 (1.44–4.36)**	**2.35 (1.35–4.08)**
≥15%	368	27 (7.3)	**2.64 (1.46–4.77)**	**2.50 (1.38–4.52)**
≥20%	220	20 (9.1)	**3.27 (1.74–6.12)**	**3.00 (1.61–5.58)**
≥25%	125	15 (12.0)	**4.31 (2.21–8.40)**	**3.71 (1.97–6.99)**
≥30%	70	11 (15.7)	**5.65 (2.76–11.57)**	**5.28 (2.68–10.40)**

CI, confidence interval; MVM, maternal vascular malperfusion; RR, relative risk. Significant associations are emphasized in bold font. [a] Values reflect the results of multivariable log-binomial regression analysis to determine the association between discordance (using the corresponding cutoff) and MVM placental pathology. Models are adjusted for maternal age, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension), gestational age at delivery, and neonatal sex, and are presented as adjusted RR (95% CI).

to ~5%) when discordance exceeded 10%, and remained relatively stable until increasing sharply at a discordance level of 25%.

We next analyzed this relationship from a clinical perspective by determining the association of discordance as a dichotomous variable with MVM placental pathology in the smaller twin (Table 2). The rate of MVM placental pathology was lowest in pregnancies with discordance <10% (2.8%) and increased gradually with the cutoff value used to define discordance up to 15.7% in the discordance ≥30% group (aRR 5.28, 95%-CI 2.68–10.40) (Table 2). The increase in the risk of MVM pathology with increasing discordance cutoff followed an exponential pattern, as illustrated in Fig. 3. Is the association of discordance with MVM placental pathology independent of whether the smaller twin is SGA?

The rate of SGA in the smaller twin increased with discordance level, ranging from 8% (for a discordance of <10%) to 91% (for a discordance of ≥30%) (Fig. 4). Given this correlation between discordance and SGA of the smaller twin, the association between discordance and MVM placental pathology may be confounded by SGA of the smaller twin. To determine whether discordance is associated with MVM placental pathology irrespective of SGA status of the smaller twin, we stratified the analysis by SGA status of the smaller twin (Fig. 5 and online suppl. Table 1; see www.karger.com/doi/10.1159/000514328 for all online suppl. material). In cases where the smaller

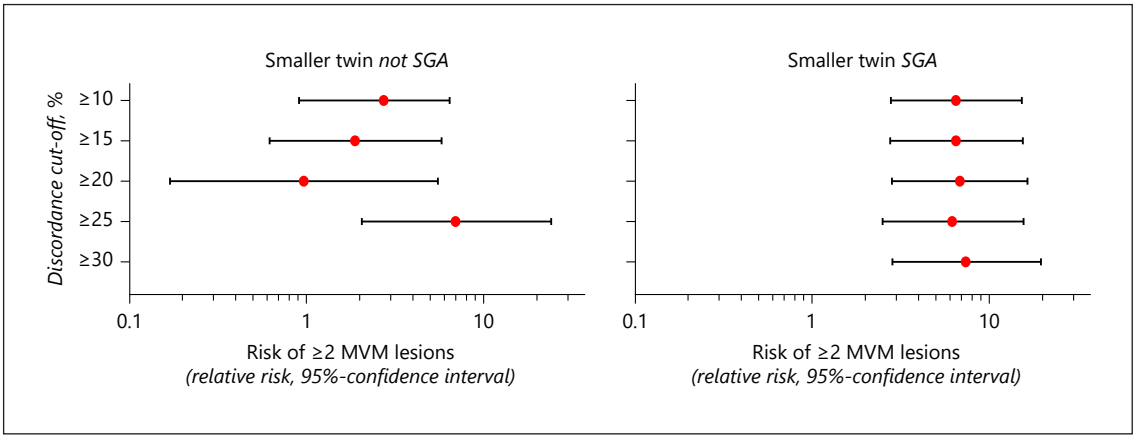

Fig. 5. Association of discordance cutoff with MVM placental pathology in the smaller twin by SGA status of the smaller twin. Values reflect the results of multivariable log-binomial regression analysis to determine the association between discordance (using the corresponding cutoff) and MVM placental pathology. Models are adjusted for maternal age, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension), gestational age at delivery, and neonatal sex, and are presented as aRR (95%-CI). MVM, maternal vascular malperfusion; SGA, small for gestational age; aRR, adjusted relative risk; CI, confidence interval.

Table 3. Association of discordance with MVM placental pathology in the smaller twin with and without adjustment for SGA status of the smaller twin

Variables included in the model (%)	Association of discordance with ≥2 MVM lesions [RR (95% CI)][a]	Association of SGA with ≥2 MVM lesions [RR (95%-CI)][a]
SGA of smaller twin		**3.11 (1.86–5.22)**
Discordance ≥10	**2.51 (1.44–4.37)**	
Discordance ≥10 + SGA of smaller twin	1.79 (0.99–3.32)	**2.54 (1.46–4.40)**
Discordance ≥15	**2.64 (1.46–4.77)**	
Discordance ≥15 + SGA of smaller twin	1.47 (0.76–2.82)	**3.65 (1.80–7.39)**
Discordance ≥20	**3.27 (1.74–6.12)**	
Discordance ≥20 + SGA of smaller twin	1.64 (0.80–3.35)	**3.73 (1.69–8.24)**
Discordance ≥25	**4.31 (2.21–8.40)**	
Discordance ≥25 + SGA of smaller twin	**2.18 (1.01–4.93)**	**2.97 (1.24–7.10)**
Discordance ≥30	**5.65 (2.76–11.57)**	
Discordance ≥30 + SGA of smaller twin	**2.52 (1.03–6.16)**	**3.16 (1.24–8.06)**

CI, confidence interval; MVM, maternal vascular malperfusion; RR, relative risk; SGA, small for gestational age. Significant associations are emphasized in bold font. [a] Values reflect the results of multivariable log-binomial regression analysis to determine the association of discordance (using the corresponding cutoff) with MVM placental pathology, with versus without adjustment for SGA of the smaller twin, and are expressed as adjusted RR (95% CI).

twin was not SGA, there was no significant association between discordance and MVM pathology until a discordance cutoff of ≥25%. In cases where the smaller twin was SGA, the association of discordance with MVM pathology was significant, but changed only minimally with the level of discordance (Fig. 5; online suppl. Table 1). These findings suggest that much of the association of discordance with MVM placental pathology is attributed to a confounding effect of SGA of the smaller twin which is more common as discordance increases. This is further illustrated in Table 3 where the association between discordance, and MVM pathology was adjusted for SGA of the smaller twin. In contrast to the findings in Table 2 where discordance was significantly associated with MVM pathology at any level of discordance, discordance was no longer associated with MVM placental pathology

when the model was adjusted for SGA of the smaller twin until a discordance cutoff of ≥25% (Table 3). In contrast, the association of SGA with MVM pathology remained relatively stable (RR ranging between 2.54 and 3.73) even after adjustment for discordance (Table 3). These findings suggest that SGA of the smaller twin is a more important determinant of MVM placental pathology and that discordance is not an independent predictor of MVM placental pathology until a discordance level of ≥25%.

Discussion

Main Findings

The aim of the current study was to identify the optimal cutoff in size difference that should define discordance in dichorionic twin gestations, and determine whether discordant growth should raise concern of fetal growth restriction of the smaller twin even when the smaller twin is not SGA. Through correlation of growth discordance with MVM placental pathology in the smaller twin as a measure that is specific for placenta-related fetal growth restriction, we found that the optimal definition of pathologic growth discordance is ≥25%, based on the following observations: (1) we found a sharp increase in the risk of MVM placental pathology when discordance level approached 25% and (2) when the risk of MVM placental pathology is adjusted for SGA of the smaller twin, discordance was independently associated with MVM placental pathology only when a cutoff of ≥25% was used to define discordance. The association of growth discordance below the cutoff of 25% with MVM placental pathology was mainly driven by the confounding effect of SGA of the smaller twin which in turn is a more important determinant of MVM placental pathology.

Interpretation of the Results in the Context of Previous Observations

The main rationale for using discordant growth in dichorionic twins as a risk factor for adverse perinatal outcomes, that in turn justifies closer antenatal surveillance and iatrogenic preterm delivery, is that it might indicate growth restriction of the smaller twin, with the larger twin serving as a naturally occurring control. However to date, data on the optimal cutoff that should be used to define discordant growth in twins have been conflicting [18] with recommendations currently ranging from 15 to 30% [15–17, 32]. One potential explanation for this controversy is the fact that many studies failed to account for important confounding factors such as chorionicity, complications related to monochorionic twins such as twin-to-twin transfusion syndrome, structural or genetic anomalies of the smaller twin, and SGA of the smaller twin [9, 15, 16, 18]. Another consideration is that most studies thus far used neonatal mortality and morbidity outcomes to identify the optimal discordance cutoff. Though such an approach may seem reasonable given that our main goal is to predict adverse neonatal outcomes, it is limited by the fact that many of these measures of neonatal mortality and morbidity are not specific for fetal growth restriction and are mainly attributed to prematurity [19, 20]. Consequently, the discordance cutoff values proposed by these studies may not be the optimal cutoff values for the detection of undiagnosed growth restriction of the smaller twin. In the current study, we identified an optimal discordance cutoff through correlation with MVM placental pathology, as a more specific measure of placental insufficiency mediating fetal growth restriction.

Data on the association of growth discordance with abnormal placental pathology in twins are thus far limited. Most available studies have focused exclusively on monochorionic twin gestations or on the relationship between growth discordance and umbilical cord abnormalities [33–35]. Mallozzi Eberle et al. [36] in a small study of 99 dichorionic twin gestations, found that discordant growth of >20% was associated with MVM pathology in the smaller twin. In another study of 157 dichorionic twins, Redline et al. found that discordant growth of >15% was associated with fetal vascular malperfusion but not with MVM pathology [22]. However, both studies were significantly underpowered due to small sample sizes. More recently, Kent et al. [12] in a prospective study of 527 women with dichorionic twins, reported that discordant growth (defined as discordance ≥20%) was associated with a higher rate of placental abnormalities in the smaller twin compared with concordant pairs, though the authors did not distinguish between the different types of placental pathologies. Moreover, none of these studies attempted to identify an optimal discordance cutoff that is associated with placental pathology, and instead used an arbitrary fixed cutoff. In addition, none of the studies adjusted the findings for whether or not the smaller twin showed any evidence of growth restriction. In the current study, we addressed these methodological limitations with a large cohort of dichorionic twins and found that the optimal discordance cutoff for the prediction of MVM placental pathology in the smaller twin is ≥25%, irrespective of whether or not the smaller twin is growth restricted.

Strengths and Limitations

One limitation of the current study is that despite the relatively large sample size, the number of cases with discordance >30% with MVM placental pathology was relatively small, and our cohort was not large enough to allow us to identify the optimal discordance cutoff with greater precision (e.g., using 2% instead of 5% intervals). Still, our study had several points of strength. The large sample size allowed us to adjust the finding for potential confounding variables including SGA of the smaller twin. This study was limited to dichorionic twins, thereby avoiding the confounding effect of complications related to monochorionic twins. At the same time, it should be emphasized that our conclusions are not generalizable to all twins. Another point of strength is that all placentas were assessed in a single center using a standardized protocol.

Conclusion

Intertwin growth discordance is often used by care providers for clinical decision-making such as intensified monitoring which results in increased resource utilization and may lead to iatrogenic preterm delivery. Therefore, a robust cutoff to define clinically meaningful discordance is required so to minimize the impact of false-positive interventions. In the current study, we found that growth discordance in dichorionic twins should be considered as an independent risk factor for MVM placental pathology associated with growth restriction of the smaller twin, irrespective of whether the smaller twin is SGA, only when discordance level is ≥25%. The association of lower levels of growth discordance with MVM placental pathology is mainly driven by the confounding effect of SGA of the smaller twin which is a more important determinant of MVM placental pathology. Further studies are needed to validate this cutoff through correlation with other measures that are specific for fetal growth restriction such as Doppler abnormalities, biochemical and molecular markers in the placental and cord blood, and neonatal anthropometry, such as skinfold thickness and ponderal index.

Statement of Ethics

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The current study was approved by the institutional Research Ethics Board (#353-2014). This was a retrospective study. Data were retrieved from the electronic database (2002–2015). All data which were retrieved were done without any identifiers. Hence, no written informed consent was needed, as also approved by our Ethics Committee.

Conflict of Interest Statement

The authors report no conflict of interests.

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Dr. Melamed holds the Waugh Family Chair in Twin Fetal Medicine Research at the Sunnybrook Health Sciences Center and the University of Toronto.

Author Contributions

Eran Ashwal: data analysis and drafting of the manuscript. Liran Hiersch: data management and manuscript editing. Howard Berger: data management and manuscript editing. Amir Aviram: data analysis and manuscript editing. Arthur Zaltz: manuscript editing. John Kingdom: manuscript editing. Jon Barrett: manuscript editing. Nir Melamed: project development and manuscript editing.

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