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The association of hypertensive disorders of pregnancy with small for gestational age and intertwin birthweight discordance

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Abstract

Available evidence shows conflicting results regarding the association between hypertensive disorders of pregnancy (HDPs)/preeclampsia (PE) and small for gestational age (SGA) and birthweight discordance (BWD). This retrospective study of 2131 twin pregnancies aimed to evaluate the association of HDPs/PE with the presence of SGA and BWD. The eligible pregnancies were categorized into four study groups: concordant pairs without SGA fetuses, discordant pairs without SGA fetuses, concordant pairs with SGA fetuses, and discordant pairs with SGA fetuses. We applied binary logistic regression models to compare the incidence of HDPs/PE and multinomial logit regression models to evaluate the severity of PE between the study groups. The models were adjusted for potential confounders. Increases in HDPs were observed in concordant (aOR, 2.33; 95% CI: 1.46–3.73) and discordant (aOR, 3.50; 95% CI: 2.26–5.43) pregnancies with SGA fetuses but not in discordant pregnancies without SGA fetuses (aOR, 1.42; 95% CI: 0.81–2.49); increases in PE were also found in concordant (aOR, 1.87; 95% CI: 1.08–3.23) and discordant (aOR, 3.75; 95% CI: 2.36–5.96) pregnancies with SGA fetuses but not in discordant pregnancies without SGA fetuses (aOR, 1.34; 95% CI: 0.71–2.52). Discordant pregnancies with SGA fetuses were associated with severe PE (aRRR, 3.48; 95% CI: 1.79–6.77), whereas concordant pregnancies with SGA fetuses were associated with only mild PE (aRRR, 2.54; 95% CI: 1.33–4.88). Our results suggest that SGA is associated with the development of HDP/PE, while discordant growth is associated with the severity of PE. These associations need to be further investigated using estimated fetal weight (EFW).

1 | INTRODUCTION

Due to the rising maternal age of child bearing and the intensive use of assisted reproductive technology (ART), the incidence of twin pregnancies has increased worldwide.[1,2] Compared with singletons, twin pregnancies carry higher risks of complications during pregnancy, such as gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDPs), fetal growth restriction (FGR), and fetal loss.[3,4]

HDPs are the leading cause of maternal-fetal morbidity and mortality. The risk of HDPs in twin pregnancies is estimated to

be at least two times higher than that in singletons.[5–8] Based on known evidence, the pathophysiology of HDPs involves maternal, placental, and fetal factors.[9–11] Accumulated evidence in singletons has revealed that HDPs, especially preeclampsia (PE), are closely related to fetal growth retardation.[12–15] The evidence in twin pregnancies is limited, however. Intertwin growth discordance is a unique term used to assess the growth of twin fetuses in clinical practice. Discordant growth is deemed abnormal growth, which is usually accompanied by fetal growth restriction (FGR). The American College of Obstetrician and Gynecologist (ACOG) suggests a cutoff of 20% to define significant growth discordance,[16] while the National Institute for Health and Care Excellence (NICE) guidance suggests 25%.[17] Previous studies of the association between discordant growth and HDP/PE showed conflicting results.[18–23] This heterogeneity may be due to several limitations, such as limited study size, lack of chorionicity confirming, and use of singleton-based birthweight reference to define small for gestational age (SGA). In addition, the collinear feature impeded the interpretation of previous results. In fact, there still exist some pregnancies complicated with discordant growth but without FGR/SGA. Whether these pregnancies are associated with the development of HDPs remains unclear.

In this regard, the aim of this study was to determine the association between HDPs and birthweight discordance (BWD) and SGA among twin pregnancies.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective cohort study was performed at the Women and Children's Hospital in Foshan, China. All electronic medical records of women, who gave birth to twin fetuses during the period from January 2012 to December 2018, were systematically reviewed. This study was approved by the Ethics Committee of the Hospital.

2.2 | Study populations

All patients with twin fetuses born living at gestational age beyond 26 weeks were considered for inclusion. The exclusion criteria in the current study included congenital anomalies except persistent ductus arteriosus in cases of preterm birth, twin-to-twin transfusion (TTTS), monoamniotic twins, and those with unknown chorionicity, fetal loss before 26 weeks of gestational age, intrauterine death, and twin pregnancies after multifetal reduction. We also excluded pregnant women complicated with chronic hypertension with or without superimposed preeclampsia.

2.3 | Study variables

Information on the included pregnancies was extracted from electronic medical records, including marital status, maternal age, body mass index (BMI), use of assisted reproductive technology (ART), parity, chorionicity, gestational age at birth, complications during pregnancy, and birthweight. Chorionicity was determined by sonographic examination at the first attendance to the obstetric department and was confirmed by placental pathologic findings after birth, if available. The gestational age was calculated from the date of embryo transfer for IVF/ICSI pregnancies (+14 days) and based on the last menstrual period for spontaneous pregnancies and was confirmed by sonography in the first trimester. Maternal BMI was calculated by dividing weight (in kilograms) by height (in meters squared) and was categorized as underweight (BMI < 18.5 kg/m^2), normal weight (18.5–23.99 kg/m^2), overweight (24–27.99 kg/m^2), and obese (≥28 kg/m^2) based on the standard of the Working Group on Obesity in China.[24] A diagnosis of gestational diabetes mellitus (GDM) was made by oral 75 g glucose tolerance test (OGTT) between 24 and 28 weeks (fasting plasma glucose ≥5.1 mmol/l or 1-hour plasma glucose ≥10.0 mmol/l or 2-hour plasma glucose ≥8.5 mmol/l). HDPs included gestational hypertension and preeclampsia (PE), which were diagnosed based on the criteria developed by ACOG.[25] Gestational hypertension was defined as a new development of a blood pressure of ≥140/90 mmHg after 20 weeks of gestation in the absence of proteinuria. A diagnosis of PE was made when a blood pressure of ≥140/90 mmHg and proteinuria of ≥300 mg/24 h were simultaneously found. Severe PE was also defined if one or more of the following features were found as follows: systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥110 mmHg, thrombocytopenia (platelet count <100,000/μl), impaired liver function (abnormal elevated blood concentration of liver enzymes), persistent epigastric, or right upper quadrant pain, kidney injury (serum creatinine concentration >1.1 mg/dl or twice baseline creatinine), pulmonary edema, and presence of neurological symptoms. SGA was defined when the birth weight was below the 10th percentile for gestational age and sex based on twin birthweight curves in Chinese twins.[26,27] BWD was defined as the percentage of intertwin birthweight difference ≥20%. The percentage of intertwin birthweight difference was calculated by dividing the actual birthweight difference by the weight of the larger twin and multiplying by 100.

2.4 | Study groups

Based on BWD and SGA, we grouped the included pregnancies into concordant pairs without SGA fetuses, discordant pairs without SGA fetuses, concordant pairs with SGA fetuses, and discordant pairs with SGA fetuses.

TABLE 1 Characteristics of study groups

Variables	Concordance without SGA fetuses (*n* = 1,733)	Discordance without SGA fetuses (*n* = 128)	Concordance with at least one SGA fetus (*n* = 140)	Discordance with at least one SGA fetus (*n* = 130)	*p*-value
Maternal age	31.1 ± 4.2	31.2 ± 3.8	30.9 ± 4.1	30.7 ± 4.9	.663
Married	1663 (96.0)	122 (95.3)	136 (97.1)	126 (96.9)	.864
Maternal BMI					
Underweight	241 (13.9)	18 (14.1)	26 (18.6)	25 (19.2)	.112
Normal weight	1099 (63.4)	80 (62.5)	93 (66.4)	83 (63.9)	
Overweight	312 (18.0)	20 (15.6)	18 (12.9)	20 (15.4)	
Obesity	81 (4.7)	10 (7.8)	3 (2.1)	2 (1.5)	
Nulliparity	1169 (67.5)	99 (77.3)	100 (71.4)	98 (75.4)	.031
ART conceived pregnancies	1252 (72.2)	107 (83.6)	95 (67.9)	87 (66.9)	.010
Monochorionic pregnancies	257 (14.8)	15 (11.7)	32 (22.9)	27 (20.8)	.015
Fetal sex combination					
Male-male	588 (33.9)	33 (25.8)	47 (33.6)	40 (30.8)	.348
Female-female	486 (28.0)	33 (25.8)	41 (29.3)	40 (30.8)	
Male-female	659 (38.0)	62 (48.4)	52 (37.1)	50 (38.5)	
GDM	380 (21.9)	27 (21.1)	30 (21.4)	30 (23.1)	.982
Gestational age at delivery, wks	36.0 ± 1.7	35.5 ± 2	35.6 ± 2.3	35.7 ± 1.6	.003
HDPs	148 (8.5)	16 (12.5)	25 (17.9)	32 (24.6)	<.001
Gestational hypertension	49 (2.8)	5 (3.9)	11 (7.9)	10 (7.7)	.001
PE	114 (6.6)	12 (9.4)	17 (12.1)	28 (21.5)	<.001
Severity of PE					
Mild PE	60 (3.5)	4 (3.1)	12 (8.6)	16 (12.3)	<.001
Severe PE	54 (3.1)	8 (6.3)	5 (3.6)	12 (9.2)	

Note: Abbreviations: ART, assisted reproductive technology; GDM, gestational diabetes mellitus; HDPs, hypertensive disorders of pregnancy; PE, preeclampsia.

2.5 | Statistical analysis

All statistical analyses were performed using Stata, version 15.1. The baseline characteristics and outcomes were compared between the four study groups. Continuous variables with an approximately Gaussian distribution are presented as the mean ± standard deviation (SD) and were analyzed by analysis of variance (ANOVA). To assess the severity of PE between study groups, a Kruskal-Wallis test was used. Categorical variables are presented as frequencies and accompanying percentages and analyzed by the chi-square test or Fisher's exact test, when appropriate. We applied binary logistic regression models to examine the association between HDPs and PE and the study groups. Models stratified by chorionicity were also established. Since the assumptions of the ordered logit/proportional odds model were not met, we used multinomial logit regression models to examine the association between study groups and the severity of PE (non-PE, mild PE, or severe PE), in which non-PE was considered the base outcome. Multivariable models were established to control for common confounders, including maternal age, nulliparity, ART, chorionicity, gestational age at birth, and maternal BMI, which were also adopted in a previous study[22]. We performed the reduced models were adjusted for gestational age and the full models further adjusted for maternal age, nulliparity, ART, chorionicity, and maternal BMI. Concordant pairs without SGA fetuses were regarded as references in all regression models. The effect estimates were reported as odds ratios (ORs) for binary logistic regression models and relative risk ratios (RRRs) for multinomial logit regression models. All *p*-values were two-tailed, and *p*-values <.05 were considered statistically significant. The power analysis was done post hoc using PASS 11.0. An effect size, calculated by dividing the sample size into chi-square for multiple proportions, was used in the power calculation.

3 | RESULTS

3.1 | Study population

The characteristics of the included twin pregnancies are shown in Table 1. A total of 2131 twin pregnancies were included in this study. There were 1733 concordant pairs without SGA fetuses, 128 discordant pairs without SGA fetuses, 140 concordant pairs with at least one SGA fetus, and 130 discordant pairs with at least one SGA fetus (Figure 1). The overall prevalence of pregnancies with SGA fetuses and BWD was 12.7% and 12.1%, respectively. There were significant differences in nulliparity (p = .031), chorionicity (p = .015), and use of ART (p = .010) between the four study groups. No differences were found in maternal age, BMI, marital status, fetal sex, or incidence of GDM. Gestational age at birth was significantly different between the four groups (p = .003). The incidence of HDPs was

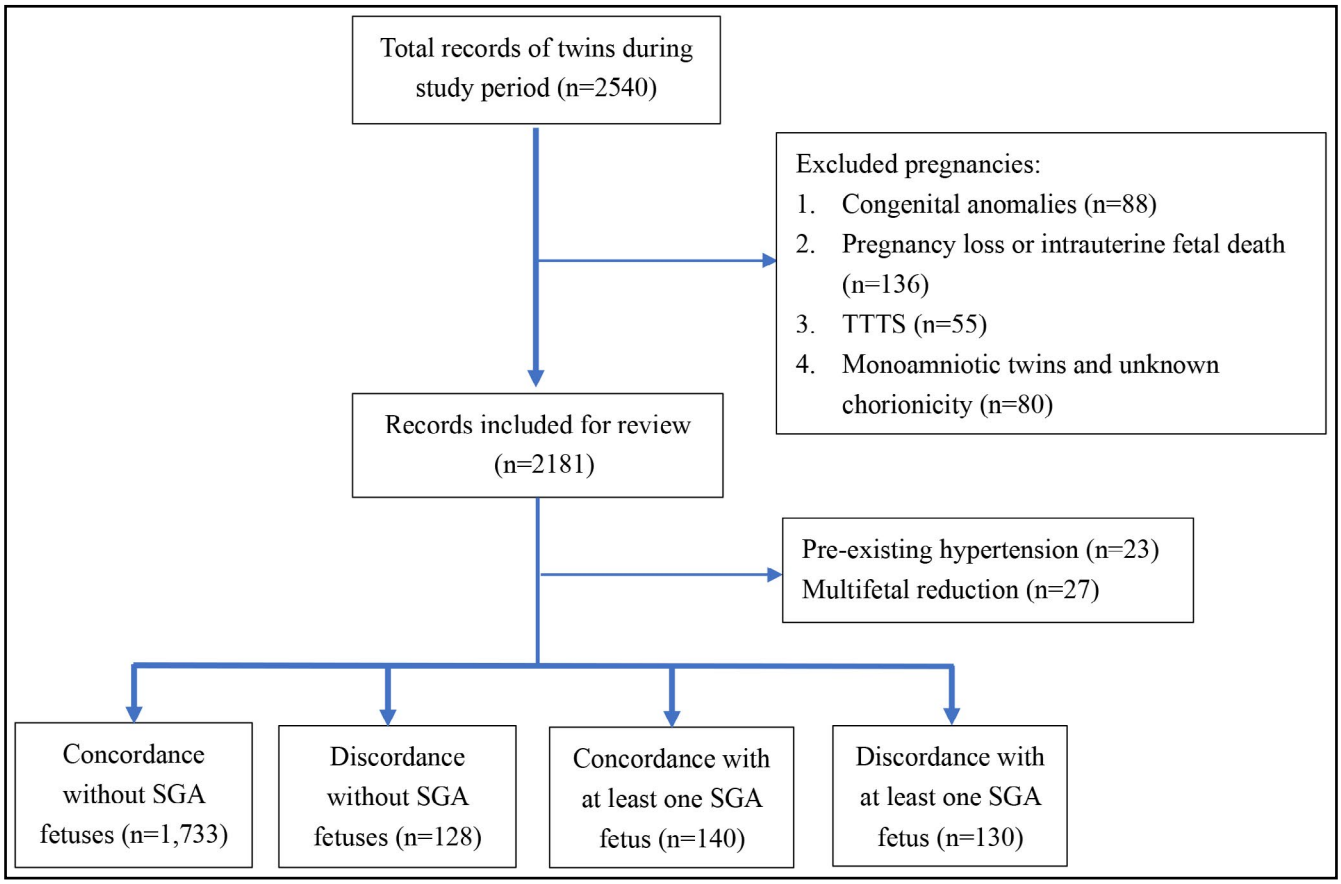

FIGURE 1 Flow chart of pregnancy selection

highest among discordant pregnancies with SGA fetuses (24.6%), followed by concordant pregnancies with SGA fetuses (17.9%), discordant pregnancies without SGA fetuses (12.5%) and concordant pregnancies without SGA fetuses (8.5%). When regarding PE and gestational hypertension separately, we observed differences in these outcomes (p = .001 for gestational hypertension and p < .001 for PE). The severity of PE was also different between study groups after the Kruskal-Wallis test (p < .001). The post hoc power analysis achieved a power of 100% with a significance level of 5% to detect effect sizes of 0.147 and 0.143 in HDPs and PE using three degrees of freedom, respectively.

3.2 | Association between discordant growth and SGA and gestational hypertensive disorders/preeclampsia

Table 2 shows the association between the study groups and the development of HDPs and PE. In the evaluation of HDPs, we obtained a crude OR of 1.53 (95% CI: 0.88–2.65) for discordant pairs without SGA fetuses, an OR of 2.33 (95% CI: 1.46–3.70) for concordant pairs with at least one SGA fetus and an OR of 3.50 (95% CI: 2.27–5.39) for discordant pairs with at least one SGA fetus, compared with concordant pairs without SGA fetuses in a univariate logistic model. In the full model controlled for confounders, significant aORs were observed among pregnancies complicated with SGA fetuses, irrespective of discordant growth. However, discordant pairs without SGA fetuses were not associated with HDPs (aOR, 1.42; 95% CI: 0.81–2.49). These fully adjusted odds ratios were similar to those adjusted only for gestational age.

In the evaluation of PE, significantly increased crude ORs were found in concordant pairs (OR, 1.96; 95% CI: 1.14–3.37) and discordant pairs (OR, 3.90; 95% CI: 2.46–6.17) with SGA fetuses. Discordant pairs without SGA fetuses were not associated with PE (OR, 1.47; 95% CI: 0.79–2.74). The multivariable model also obtained similar results.

3.3 | Stratified analyses by chorionicity

We performed stratified analyses by chorionicity, as shown in Table 3 and Table 4. In dichorionic-diamniotic (DCDA) twin pregnancies, we found increased HDPs in both SGA pregnancies with (aOR, 3.44, 95% CI: 2.10–5.63) and without (aOR, 2.38; 95% CI: 1.41–4.04) growth discordance; the increased PE was observed only in discordant pregnancies with SGA fetuses (aOR, 3.74; 95% CI: 2.22–6.28). In monochorionic-diamniotic (MCDA) twin pregnancies, an increase in HDPs (OR, 4.04; 95% CI: 1.46–11.15) and PE (OR, 3.79; 95% CI: 1.28–11.23)) was observed only in pregnancies with concurrent SGA and discordant growth.

3.4 | Association between discordant growth and SGA fetuses and severity of PE

In the multinomial logit regression model with full adjustment for confounders (Table 5), we found that concordant pregnancies with SGA fetuses were almost 2.5 times more likely to exhibit mild PE (adjusted RRR, 2.54; 95% CI: 1.33–4.88) but unlikely to exhibit severe PE (adjusted RRR, 1.09; 95% CI: 0.42–2.83). Discordant pregnancies with SGA

TABLE 2 Binary logistic analyses of HDPs and PE between study groups

	Unadjusted model		Reduced model[a]		Full model[b]	
Outcomes	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
HDPs						
Concordance without SGA fetuses	Reference	–	Reference		Reference	–
Discordance without SGA fetuses	1.53 (0.88–2.65)	.130	1.48 (0.85–2.58)	.161	1.42 (0.81–2.49)	.215
Concordance with at least one SGA fetus	2.33 (1.46–3.70)	<.001	2.27 (1.42–3.62)	.001	2.33 (1.46–3.73)	<.001
Discordance with at least one SGA fetus	3.50 (2.27–5.39)	<.001	3.43 (2.22–5.30)	<.001	3.50 (2.26–5.43)	<.001
PE						
Concordance without SGA fetuses	Reference		Reference		Reference	
Discordance without SGA fetuses	1.47 (0.79–2.74)	.227	1.40 (0.75–2.62)	.290	1.34 (0.71–2.52)	.362
Concordance with at least one SGA fetus	1.96 (1.14–3.37)	.015	1.88 (1.09–3.25)	.023	1.87 (1.08–3.23)	.026
Discordance with at least one SGA fetus	3.90 (2.46–6.17)	<.001	3.80 (2.40–6.02)	<.001	3.75 (2.36–5.96)	<.001

[a]adjusted for gestational age at birth.

[b]adjusted for maternal age, nulliparity, use of ART, chorionicity, gestational age at birth and maternal BMI.

TABLE 3 Binary logistic analyses of HDPs and PE between study groups in dichorionic twin pregnancies (n = 1800)

Outcomes	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)[a]	p-value
HDPs				
Concordance without SGA fetuses	Reference	–	Reference	–
Discordance without SGA fetuses	1.52 (0.84–2.73)	.167	1.41 (0.78–2.56)	.260
Concordance with at least one SGA fetus	2.44 (1.45–4.09)	.001	2.38 (1.41–4.04)	.001
Discordance with at least one SGA fetus	3.43 (2.11–5.58)	<.001	3.44 (2.10–5.63)	<.001
PE				
Concordance without SGA fetuses	Reference		Reference	
Discordance without SGA fetuses	1.38 (0.70–2.73)	.354	1.27 (0.64–2.53)	.496
Concordance with at least one SGA fetus	1.95 (1.05–3.60)	.034	1.80 (0.97–3.36)	.064
Discordance with at least one SGA fetus	3.86 (2.31–6.46)	<.001	3.74 (2.22–6.28)	<.001

[a]adjusted for maternal age, nulliparity, use of ART, gestational age at birth and maternal BMI.

TABLE 4 Binary logistic analyses of HDPs and PE between study groups in monochorionic twin pregnancies (n = 331)

Outcomes	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)[a]	p-value
HDPs				
Concordance without SGA fetuses	Reference	–	Reference	–
Discordance without SGA fetuses	1.64 (0.35–7.75)	.530	1.63 (0.33–8.06)	.550
Concordance with at least one SGA fetus	1.98 (0.69–5.65)	.203	2.06 (0.71–5.95)	.183
Discordance with at least one SGA fetus	3.74 (1.42–9.82)	.007	4.04 (1.46–11.15)	.007
PE				
Concordance without SGA fetuses	Reference		Reference	
Discordance without SGA fetuses	2.17 (0.45–10.42)	.332	1.94 (0.39–9.71)	.420
Concordance with at least one SGA fetus	2.02 (0.63–6.42)	.235	2.04 (0.63–6.57)	.231
Discordance with at least one SGA fetus	4.03 (1.44–11.32)	.008	3.79 (1.28–11.23)	.016

[a]adjusted for maternal age, nulliparity, use of ART, gestational age at birth and maternal BMI.

fetuses were almost four times more likely to exhibit mild PE and almost 3.5 times more likely to exhibit severe PE (adjusted RRR, 3.48; 95% CI: 1.79–6.77). The results were similar to those from the reduced model.

4 | DISCUSSION

The current study found that twin pregnancies complicated with SGA fetuses were associated with HDPs and PE, irrespective of growth discordance. However, pregnancies without SGA fetuses were not associated with HDPs or PE. Dichorionic pregnancies with SGA fetuses, irrespective of discordant growth, were associated with HDPs and PE. However, in monochorionic pregnancies, only concurrence of SGA and discordant growth was associated with HDPs and PE. In the evaluation of the severity of PE, discordant pregnancies with SGA fetuses were associated with severe PE.

The association between fetal growth retardation and the development of HDPs is well established in singleton pregnancies.[28–32]

TABLE 5 Multinomial logistic analyses of PE severity between study groups

Outcome	Unadjusted model		Reduced model[a]		Full model[b]	
	Crude RRR (95% CI)	*p*-value	Adjusted RRR (95% CI)[a]	*p*-value	Adjusted RRR (95% CI)[b]	*p*-value
Mild PE vs. None PE						
Concordance without SGA fetuses	Reference		Reference	–	Reference	
Discordance without SGA fetuses	0.93 (0.33–2.60)	.891	0.94 (0.33–2.63)	.903	0.92 (0.33–2.58)	.871
Concordance with at least one SGA fetus	2.63 (1.38–5.02)	.003	2.65 (1.39–5.06)	.003	2.54 (1.33–4.88)	.005
Discordance with at least one SGA fetus	4.23 (2.35–7.61)	<.001	4.26 (2.37–7.67)	<.001	4.11 (2.27–7.42)	<.001
Severe PE vs. None PE						
Concordance without SGA fetuses	Reference		Reference		Reference	
Discordance without SGA fetuses	2.07 (0.96–4.45)	.063	1.88 (0.87–4.07)	.110	1.76 (0.80–3.84)	.158
Concordance with at least one SGA fetus	1.22 (0.48–3.10)	.678	1.07 (0.41–2.76)	.892	1.09 (0.42–2.83)	.862
Discordance with at least one SGA fetus	3.53 (1.83–6.80)	<.001	3.39 (1.75–6.56)	<.001	3.48 (1.79–6.77)	<.001

[a]adjusted for gestational age at birth.

[b]adjusted for maternal age, nulliparity, use of ART, chorionicity, gestational age at birth and maternal BMI.

In fact, FGR and PE share a similar placental pathology. Alerted trophoblastic invasion of the maternal endometrium results in placental hypoperfusion and subsequent placental ischemia/hypoxia. On the one hand, this pathophysiologic change triggers the production and massive release of various cytokines into maternal circulation and causes endothelial dysfunction and inflammatory upregulation, which finally results in elevated blood pressure. On the other hand, inadequate perfusion caused by disrupted spiral remodeling decreases the nourishment and oxygen supply to the developing fetus and blocks fetal growth.[33,34]

Aside from the weight percentile of individual fetuses, the intertwin growth difference is a routinely used to evaluate the development of twin fetuses. In the present study, the prevalence of BWD was 12.1%, which was lower than that reported previously in China (17.6%) by Qiao et al.[22] This difference may be explained by the lower proportion of MCDA twins (15.3%) in the current study population compared with that (23.3%) in the previous study.[22] Monochorionic twins are at higher risk of discordant growth than dichorionic twins, mainly because of the shared placenta.[35] Discordant growth is usually accompanied by growth restriction. To avoid the collinear feature between SGA and BWD in the analyses, we categorize the pregnancies into four groups based on SGA status and BWD. Importantly, we found that SGA pregnancies with or without BWD were more likely to have HDPs and PE than the reference group, whereas discordant pregnancies without SGA were not. This finding suggested that discordant growth was not necessarily related to the occurrence of HDPs/PE, which confirmed the previous finding of Giorgione et al.[21] They found that SGA was associated with HDPs and PE, whereas BWD >25% was not. In this regard, twin pregnancies with FGR should be considered candidates for close monitoring for blood pressure, regardless of intertwin growth discordance. Inconsistent with current results, Fox et al [20] and Sparks et al[36] reported no difference in the incidence of FGR between twin pregnancies with and without HDPs. Unfortunately, these studies used a singleton-based birthweight reference to define FGR rather than a twin-based reference. Proctor et al[37] reported that the association of HDPs with FGR was stronger and more consistent using a twin-based reference than using a singleton-based reference, which was also confirmed by Kalafat et al.[38] A study by Qiao et al[22] demonstrated that the association between growth discordance >20% and PE existed only in dichorionic twin pregnancies and not in monochorionic pregnancies. In our stratified analyses by chorionicity, we added evidence that discordant pregnancies without SGA fetuses were not associated with HDPs or PE, regardless of dichorionic, or monochorionic twin pregnancies. In contrast, a population-based study by Jahanfar et al[23] demonstrated associations between BWD >30% and PE and GH, although they were unable to adjust these results to chorionicity. Even though they performed a subgroup analysis in sex-discordant twins, which was considered a proxy for chorionicity, the associations persisted.

Few studies have evaluated the severity of PE among discordant twin pregnancies. Qiao et al[22] revealed increased odds ratios of mild and severe PE in discordant dichorionic twins in binary logistic models. Since the severity of PE was defined as an ordered variable, we considered the ordinal nature of the response variable

and initially adopted an ordered logit model. However, it was found that the assumptions of the ordered logit/proportional odds model were not met (likelihood-ratio test, p = .0122); therefore, a multinomial logit model was used instead. Not surprisingly, both concordant and discordant pregnancies with SGA fetuses were observed to be associated with mild PE. Interestingly, only the coexistence of BWD and SGA showed an association with severe PE. Based on these findings, we speculated that discordant growth might reflect the severity of PE.

Using sonographic estimated fetal weight (EFW) as a predictor for the development of PE remains controversial. A recent study by Erkamp et al[39] found no improvement in diagnostic performance for identifying singletons with high risks of HDPs using the second- or third-trimester EFW <10th percentile. No evidence is available on using EFW to predict HDPs/PE among twin pregnancies to date. The generalization of current results to EFW has yet to be determined. Since the EFW percentage difference increases across gestation in dichorionic twins, as reported by Amyx et al,[40] the cut point of EFW-based discordant growth deserves to be further discussed.

The strengths of this study included a relatively large sample size, the confirmation of chorionicity, the use of twin birthweight reference to define SGA, and similar results in different regression models, which made our results more robust. Several limitations should be noted when interpreting our results, however. First, the main limitation involves the retrospective design, which impeded the identification of the temporal sequence of growth discordance and HDP. We used birthweight to avoid measuring error of EFW by ultrasound and missing a diagnosis of discordant growth, although EFW might have more clinical implications. The associations between EFW and the development of HDPs and the diagnostic performance to predict PE should be confirmed in the future. In addition, the lack of outcome of early- and late-onset PE was another limitation. Furthermore, the number of monochorionic pregnancies was relatively small for the comparison of the study groups. Finally, the present study was based on a single-center, which would limit the generalization of the current results.

In conclusion, twin pregnancies with SGA fetuses are associated with an increased incidence of HDPs and PE, irrespective of birthweight discordance. Discordant pregnancies with SGA fetuses were more likely to exhibit severe PE. The evidence of generalization of these associations to sonographic EFW is warranted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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REFERENCES

1. Smits J, Monden C. Twinning across the developing world. *PLoS ONE*. 2011;6(9):e25239.
2. Adashi EY, Gutman R. Delayed childbearing as a growing, previously unrecognized contributor to the national plural birth excess. *Obstet Gynecol*. 2018;132(4):999-1006.
3. Hiersch L, Okby R, Freeman H, et al. Differences in fetal growth patterns between twins and singletons. *J Matern Fetal Neonatal Med*. 2018;33:1-201.
4. Walker AR, Waites BT, Caughey AB. Twins versus singleton pregnancies: outcomes in small for gestational age late preterm deliveries. *J Matern Fetal Neonatal Med*. 2018;33:1-6.
5. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Hidden high rate of pre-eclampsia in twin compared with singleton pregnancy. *Ultrasound Obstet Gynecol*. 2017;50(1):88-92.
6. Day MC, Barton JR, O'Brien JM, Istwan NB, Sibai BM. The effect of fetal number on the development of hypertensive conditions of pregnancy. *Obstet Gynecol*. 2005;106(5 Pt 1):927-931.
7. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol*. 2000;182(4):938-942.
8. Laine K, Murzakanova G, Sole KB, Pay AD, Heradstveit S, Räisänen S. Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: a population-based register study. *BMJ open*. 2019;9(7):e029908.
9. Giannakou K, Evangelou E, Papatheodorou SI. Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies. *Ultrasound Obstetrics Gynecol*. 2018;51(6):720-730.
10. Garrido-Gomez T, Dominguez F, Quiñonero A, et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology. *Proc Natl Acad Sci USA*. 2017;114(40):E8468-e8477.
11. Narang K, Szymanski LM. Multiple gestations and hypertensive disorders of pregnancy: what do we know? *Curr Hypertens Rep*. 2020;23(1):1.
12. Nakimuli A, Starling JE, Nakubulwa S, et al. Relative impact of pre-eclampsia on birth weight in a low resource setting: a prospective cohort study. *Pregnancy hypertension*. 2020;21:1-6.
13. Wainstock T, Sergienko R, Sheiner E. Who is at risk for preeclampsia? risk factors for developing initial preeclampsia in a subsequent pregnancy. *J Clin Med*. 2020;9(4):1103.
14. Nurgaliyeva GT, Semenova YM, Tanysheva GA, Akylzhanova ZE, Bologan I, Manabayeva GK. Epidemiology of pre-eclampsia in the Republic of Kazakhstan: maternal and neonatal outcomes. *Pregnancy hypertension*. 2020;20:1-6.
15. Mayrink J, Souza RT, Feitosa FE, et al. Incidence and risk factors for Preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. *Sci Rep*. 2019;9(1):9517.
16. Practice bulletin no. 169: multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol*. 2016;128(4):e131-e146.
17. National Collaborating Centre for Women's and Children's Health (UK). *Multiple pregnancy: The management of twin and triplet pregnancies in the antenatal period* | Information for the public. London: RCOG Press. 2011.
18. Ferrazzani S, Merola A, De Carolis S, Carducci B, Paradisi G, Caruso A. Birth weight in pre-eclamptic and normotensive twin pregnancies: an analysis of discordance and growth restriction. *Human Reprod*. 2000;15(1):210-217.
19. Wu D, Huang L, He Z, Huang X, Fang Q, Luo Y. Preeclampsia in twin pregnancies: association with selective intrauterine growth restriction. *J Matern Fetal Neonatal Med*. 2016;29(12):1967-1971.

20. Fox NS, Saltzman DH, Oppal S, Klauser CK, Gupta S, Rebarber A. The relationship between preeclampsia and intrauterine growth restriction in twin pregnancies. *Am J Obstet Gynecol*. 2014;211(4):422.e421-425.
21. Giorgione V, Bhide A, Bhate R, Reed K, Khalil A. Are Twin Pregnancies Complicated by Weight Discordance or Fetal Growth Restriction at Higher Risk of Preeclampsia? *J Clin Med*. 2020;9(10): 3276.
22. Qiao P, Zhao Y, Jiang X, et al. Impact of growth discordance in twins on preeclampsia based on chorionicity. *Am J Obstet Gynecol*. 2020;223(4):572.e571-572.e578.
23. Jahanfar S, Lim K. Adverse maternal outcomes and birth weight discordance in twin gestation: British Columbia, Canadian data. *Int J Women's Health*. 2017;9:871-878.
24. Wang Y, Mi J, Shan XY, Wang QJ, Ge KY. Is China facing an obesity epidemic and the consequences? *Int J Oes*. 2007;31(1):177-188.
25. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122(5):1122-1131.
26. Zhang B, Cao Z, Zhang Y, et al. Birthweight percentiles for twin birth neonates by gestational age in China. *Sci Rep*. 2016;6:31290.
27. Dai L, Deng C, Li Y, et al. Population-based birth weight reference percentiles for Chinese twins. *Ann Med*. 2017;49(6):470-478.
28. Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension? *J Perinatol*. 2009;29(10):680-684.
29. Mateus J, Newman RB, Zhang C, et al. Fetal growth patterns in pregnancy-associated hypertensive disorders: NICHD Fetal Growth Studies. *Am J Obstet Gynecol*. 2019;221(6):635.e631-635.e616.
30. Odegård RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. *Obstet Gynecol*. 2000;96(6):950-955.
31. Xiao R, Sorensen TK, Williams MA, Luthy DA. Influence of pre-eclampsia on fetal growth. *J Matern Fetal Neonatal Med*. 2003;13(3):157-162.
32. Mitani M, Matsuda Y, Makino Y, Akizawa Y, Ohta H. Clinical features of fetal growth restriction complicated later by preeclampsia. *J Obstet Gynaecol Res*. 2009;35(5):882-887.
33. Nirupama R, Divyashree S, Janhavi P, Muthukumar SP, Ravindra PV. Preeclampsia: Pathophysiology and management. *J Gynecol Obstet Hum Reprod*. 2021;50(2):101975.
34. Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. *Am J Obstet Gynecol*. 2006;195(1):40-49.
35. González-Quintero VH, Luke B, O'Sullivan MJ, et al. Antenatal factors associated with significant birth weight discordancy in twin gestations. *Am J Obstet Gynecol*. 2003;189(3):813-817.
36. Sparks TN, Nakagawa S, Gonzalez JM. Hypertension in dichorionic twin gestations: how is birthweight affected? *J Matern Fetal Neonatal Med*. 2017;30(4):380-385.
37. Proctor LK, Kfouri J, Hiersch L, et al. Association between hypertensive disorders and fetal growth restriction in twin compared with singleton gestations. *Am J Obstet Gynecol*. 2019;221(3):251.e251-251.e258.
38. Kalafat E, Abiola A, Thilaganathan B, Bhide A, Khalil A. The association between hypertension in pregnancy and preterm birth with fetal growth restriction in singleton and twin pregnancy: use of twin versus singleton charts. *J Clin Medicine*. 2020;9(8).
39. Erkamp JS, Jaddoe VWV, Duijts L, et al. Population screening for gestational hypertensive disorders using maternal, fetal and placental characteristics: a population-based prospective cohort study. *Prenat Diagn*. 2020;40(6):746-757.
40. Amyx MM, Albert PS, Bever AM, et al. Intrauterine growth discordance across gestation and birthweight discordance in dichorionic twins. *Am J Obstet Gynecol*. 2020;222(2):174.e171-174.e110.

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