OBSTETRICS

Association between hypertensive disorders and fetal growth restriction in twin compared with singleton gestations

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BACKGROUND: Hypertensive disorders of pregnancy (including preeclampsia or gestational hypertension) are associated with fetal growth restriction in singleton pregnancies, an association that may be attributed to abnormal placentation as the shared etiology between these conditions. Given that the pathogenesis of these conditions in twin pregnancies may involve mechanisms other than abnormal placentation, it is unclear whether a similar association between hypertensive disorders of pregnancy and fetal growth restriction is present in twins. Data on the relationship between hypertensive disorders of pregnancy and fetal growth restriction in twins are limited and conflicting. This controversy may be attributed to limitations of existing studies including the use of a singleton-based birthweight reference to define fetal growth restriction in twins and the lack of a positive control group of singleton gestations.

OBJECTIVE: The objective of the study was to determine the association between hypertensive disorders of pregnancy and fetal growth restriction in dichorionic twin gestations, using both a singleton- and a twin-based birthweight reference, and to compare this association with that observed in singleton gestations.

STUDY DESIGN: We performed a retrospective cohort study of all women with dichorionic twin or singleton gestations giving birth in a single tertiary center during 2003–2015. Fetal growth restriction was defined in separate analyses as birthweight <10th percentile for gestational age using either a singleton- or a twin-based birthweight reference. The association between hypertensive disorders of pregnancy and fetal growth restriction was determined separately for twin and singleton gestations and was expressed as adjusted relative risk with 95% confidence interval.

RESULTS: A total of 1520 twin and 48,943 singleton gestations were included. In singleton gestations, hypertensive disorders of pregnancy were associated with an increased risk of fetal growth restriction (16.6% vs 7.4%, adjusted relative risk, 2.07, 95% confidence interval, 1.87–2.30). In twins, there was no association between hypertensive disorders of pregnancy and fetal growth restriction when a singleton-based reference was used to define fetal growth restriction. However, when using a twin-based reference to define fetal growth restriction, hypertensive disorders of pregnancy in twin gestations were associated with a similar increase in the risk of fetal growth restriction to that seen in singletons (11.8% vs 4.7%, adjusted relative risk, 2.37, 95% confidence interval, 1.69–3.34). Findings were similar with regard to the reverse association between fetal growth restriction and hypertensive disorders of pregnancy: in women with twin gestations, the increase in the risk of hypertensive disorders of pregnancy in pregnancies complicated by fetal growth restriction of 1 twin was similar to that observed in singletons only when a twin-based reference was used to define fetal growth restriction (twins: 21.3% vs 9.8%, adjusted relative risk, 2.15, 95% confidence interval, 1.63–3.06; singletons: 8.8% vs 3.7%, adjusted relative risk, 2.19, 95% confidence interval, 1.95–2.44).

CONCLUSION: The association between hypertensive disorders of pregnancy and fetal growth restriction in dichorionic twins is similar in magnitude to that observed in singletons so long as appropriate birthweight references are applied. Therefore, women with a twin gestation complicated by one of these conditions should be closely monitored for the other. Our findings suggest that the use of a twin-based reference to diagnose fetal growth restriction in twin gestations may be more informative and clinically relevant than using a singleton-based reference.

Key words: fetal growth restriction, gestational hypertension, multifetal gestations, preeclampsia, twins

Twin gestations, accounting for more than 3% of pregnancies in the United States[1,2] and are associated with an increased risk of pregnancy complications compared with singleton gestations. Specifically, twin gestations are 2- to 4-fold more likely than singleton gestations to be complicated by hypertensive disorders of pregnancy (HDP; including preeclampsia and gestational hypertension),[3–9] and up to 30% of twins are affected by fetal growth restriction (FGR).[10–13]

In singleton gestations, HDP and FGR are closely related, so women with one of these complications are at an increased risk of developing the other.[14–17] This association is attributed to the fact that both conditions are thought to share placental insufficiency as the common underlying etiology.[18–25]

In twin gestations, the pathogenetic mechanisms underlying HDP and FGR may differ from those involved in singletons. HDP in twins has been attributed to the increased placental mass rather than to abnormal placentation.[26–28] Similarly, the excess risk of FGR in twins is thought to reflect inability of the placenta to meet the increased demands of 2 fetuses within the same uterine environment or to a physiological adaptive response to the competitive uterine environment,[29–34] as opposed to placental insufficiency.[35] Therefore, some have questioned whether the well-established association between HDP and FGR in singleton gestations similarly applies to twins.

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AJOG at a Glance

Why was this study conducted?

Hypertensive disorders of pregnancy are associated with fetal growth restriction (FGR) in singleton pregnancies, an association that may be attributed to abnormal placentation as the shared etiology between these conditions. Given that the pathogenesis of these conditions in twin pregnancies may involve mechanisms other than abnormal placentation, it may be questioned whether a similar association is present in twins.

Key findings

Hypertensive disorders of pregnancy in dichorionic twin gestations were associated with an increased risk of FGR, an increase that was similar in magnitude to that observed in singleton gestations. However, this association was observed only when a twin-based birthweight reference was used to diagnose fetal growth restriction.

What does this add to what is known?

Available data on this topic are limited and conflicting. The current study overcomes limitations of previous studies by using appropriate birthweight reference to define FGR and by using a positive control group of singleton gestations.

This question is both scientifically and clinically important because it may shed light on our understanding of the pathophysiology of these common complications and may inform care providers regarding the risk that women with twins and HDP will develop FGR and vice versa. These considerations may influence the strategy for surveillance of the relatively large proportion of women with twins affected by any of these conditions.

Currently data on the relationship between HDP and FGR in twins are limited and conflicting. While several authors found that HDP in twin gestation are not associated with FGR,[36,37] others reported varying degree of association between the 2 conditions.[38–40] This controversy may be attributed to limitations of existing studies such as small sample size, differences in study population, differences in the outcome measures (FGR vs growth discordance), and the lack of a positive control group of singleton gestations, which would allow for a direct comparison of the magnitude of association of FGR with HDP between twin and singleton gestations.

Another important limitation relates to the fact that most available studies used singleton-based birthweight references to define FGR in twins, which are known to have lower birthweight on average than singletons starting at approximately 28 weeks, given the slower growth of twins during the third trimester.[41] Therefore, the use of a singleton-based reference for twin gestations results in a high baseline rate of FGR, even in uncomplicated twin gestations, which can potentially mask any further increase in the risk of FGR related to HDP. For example, a 5% increase in the risk of FGR would be more obvious when the baseline rate of FGR is 10% (ie, 15% vs 10%, reflecting a relative increase of 50%) compared with 40% (ie, 45% vs 40%, reflecting a relative increase of 12.5%).

We identified only 2 studies that used a twin-based reference,[38,40] but neither of these studies conducted a separate analysis of the association between HDP and FGR using a singleton-based reference to show that it is the use of a twin-based reference that is responsible for the conflicting findings reported by others.[36,37]

The aim of the current study was to determine the association between HDP and FGR in dichorionic twin gestations while overcoming the limitations described in the previous text by using both a singleton- and a twin-based birthweight reference and by comparing this association with that observed in singleton gestations.

Materials and Methods

Study population

We conducted a retrospective cohort study of all women with a dichorionic twin or singleton gestation who gave birth at a single tertiary centre (Sunnybrook Health Sciences Center, Toronto, Canada) between October 2003 and February 2015. Pregnancies complicated by any of the following conditions were excluded: gestational age at birth $<24^{0/7}$ weeks, chronic (preexisting) hypertension, monochorionic twins (as the mechanisms of FGR in these pregnancies differ from those involved in FGR in dichorionic twins), structural or genetic fetal abnormalities, stillbirth or reduction of 1 or both fetuses, or missing data. The current study was approved by the institutional Research Ethics Board.

Data collection

Data were obtained from the Sunnybrook perinatal database and included the following information: demographic characteristics, medical and obstetrical history, chorionicity for twin gestations, pregnancy complications, gestational age at birth, labor and delivery outcomes, birthweight, and neonatal outcomes.

Exposure and outcomes

Given that the association of HDP and FGR in singleton gestations is attributed to a shared etiology (ie, placental insufficiency) rather than to causation, it would be valid to evaluate the association between these 2 conditions using either of them as the exposure, that is, evaluating the risk of FGR in pregnancies with vs without HDP as well as the risk of HDP in pregnancies with vs without FGR.

In the current study, we used both approaches to get as much understanding as possible of the association between the 2 conditions in twin gestations. Thus, in the first step of the analysis, the primary exposure of interest was HDP, defined as preeclampsia or gestational hypertension. Secondary exposure was early-onset HDP, defined as

HDP associated with preterm birth before $34^{0/7}$ weeks.[42–45]

The primary outcome in this analysis was FGR, defined as birthweight below the 10th percentile for gestational age using a Canadian singleton-based birthweight reference[46] and, for twin gestations, using an additional twin-based birthweight reference.[47]

In the second step of the analysis, we switched the exposure and outcomes variables. The primary exposure was FGR (birthweight below the 10th percentile for gestational age using a singleton- or a twin-based birthweight reference) of 1 or both twins within each twin pair. The outcome of interest in this analysis was HDP.

Definitions

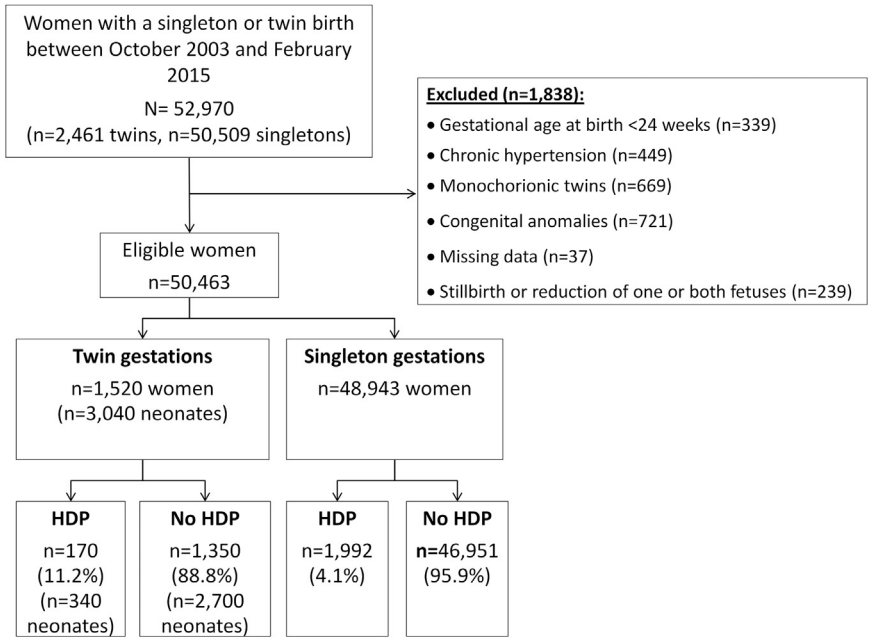
The diagnosis of HDP in Ontario is based on the guidelines published by the Canadian Hypertensive Disorders of Pregnancy Working Group.[4] Gestational hypertension is defined as hypertension that develops for the first time after $20^{0/7}$ weeks' gestation, and preeclampsia is defined as gestational hypertension with a new onset of proteinuria or involvement of 1 of the following organ systems: central nervous system, cardiorespiratory, hematological, renal, hepatic or fetoplacental.[4]

Gestational age was based on the last menstrual period or embryo transfer in in vitro fertilization pregnancies and was confirmed by a first-trimester ultrasound in all cases. Chorionicity was established at a first-trimester ultrasound and confirmed by placental pathology.

Data analysis

Baselines characteristics and outcomes were compared between the groups using the χ^2 and Student t test for categorical and continuous variables, respectively. Multivariable log binomial regression analysis was used to determine the association between HDP and FGR (expressed as adjusted relative risk [aRR] and 95% confidence interval [95% CI]) while adjusting for the following potential confounding variables that were identified a priori: maternal age, nulliparity, and fetal sex.

FIGURE 1
Selection of the study groups



HDP, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension).

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Models for twin neonates were generated using generalized estimating equations to account for the correlation within twin pairs. Three separate analyses were performed: (1) in singleton gestations, using a singleton-based reference[46] to define FGR; (2) in twin gestations, using the same singleton-based reference[46] to define FGR; and (3) in twin gestations, using a twin-based reference to define FGR.[47]

Data were analyzed using SPSS statistical software version 24.0 (IBM Corp, Armonk, NY). Significance was set to a 2-sided value of $P < .05$.

Results

Characteristics of the study population

A total of 1520 women with twins and 48,943 women with singletons met the inclusion criteria (Figure 1). The baseline characteristics of the study population are presented in Table 1. Women in the twins group were older and were more likely to be nulliparous and to give birth prematurely. Twin gestations were more likely to be complicated by HDP and FGR compared with singleton gestations (Table 1).

Risk of FGR in pregnancies complicated by HDP

We first compared the risk of FGR between women with and without HDP (Table 2). In singleton gestations, HDP was associated with an increased risk of FGR (aRR, 2.07, 95% CI, 1.87–2.30). In twin gestations, there was no association between HDP and FGR when a singleton-based reference was used to define FGR. However, when using a twin-based reference to define FGR, HDP in twin gestations was associated with a similar increase in the risk of FGR (aRR, 2.37, 95% CI, 1.69–3.34) to that observed in singletons (Table 2).

This pattern was even more pronounced for the association between early-onset HDP and FGR (Table 3). In twin gestations, there was no association between HDP and FGR when a singleton-based reference was used to define FGR. However, when using a twin-based reference to define FGR,

TABLE 1
Baseline characteristics of the twins and singletons groups

Characteristic	Dichorionic twins (n = 1520)	Singletons (n = 48,943)	*P* value
Maternal age, y	34.1 ± 5.3	32.8 ± 5.0	**< .001**
>35	568 (37.4%)	14,374 (29.4%)	**< .001**
Nulliparity	953 (62.7%)	24,797 (50.7%)	**< .001**
Gestational age at delivery, wks	34.7 ± 3.3	38.5 ± 2.6	**< .001**
<37	914 (60.1%)	4595 (9.4%)	**< .001**
<34	395 (26.0%)	2306 (4.7%)	**< .001**
HDP	170 (11.2%)	1992 (4.1%)	**< .001**
Gestational hypertension	95 (6.3%)	1458 (2.9%)	**< .001**
Preeclampsia	75 (4.9%)	534 (1.1%)	**< .001**
HDP delivered at <34 wks	36 (2.4%)	407 (0.8%)	**< .001**
Neonatal characteristics[a]			
Fetal female sex	1505 (49.5%)	23,717 (48.5%)	.395
Birthweight percentile, singleton reference[b]	33.5 ± 23.4	50.1 ± 26.5	**< .001**
Birthweight <10th percentile	647 (21.3%)	3782 (7.7%)	**< .001**
Birthweight <5th percentile	268 (8.8%)	1382 (2.8%)	**< .001**
Birthweight percentile, twin reference[c]	58.6 ± 27.1	N/A	N/A
Birthweight <10th percentile	168 (5.5%)	N/A	N/A
Birthweight <5th percentile	85 (2.8%)	N/A	N/A

Data are presented as mean ± SD or n (percentage). Significant *P* values are emphasized in bold font.

HDP, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension); *N/A*, nonapplicable.

[a] Unit of analysis for neonatal outcomes in the twins group is neonate (n = 3040); [b] Using the Canadian singleton reference of Kramer et al.[46]; [c] Using the twin reference of Min et al.[47]

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early-onset HDP in twin gestations was associated with a similar increase in the risk of FGR to that observed in singletons (aRR, 4.93, 95% CI, 3.18-7.63 vs aRR, 4.57, 95% CI, 3.41−6.17, respectively) (Table 3).

These findings are further illustrated graphically in Figure 2, in which the rate of FGR at each gestational week was compared between women with and without HDP. In singleton gestations, the rate of FGR at any given week was higher in women with HDP vs women without HDP (Figure 2A). In twin gestations, this pattern was not observed when using a singleton-based reference to define FGR, in part because of the high baseline rate of FGR in the control (no HDP) group during the third trimester (Figure 2B). However, when a twin-based reference was used to define FGR, the relation between HDP and FGR in twin gestations (Figure 2C) was more similar to that observed in singletons (Figure 2A).

Risk of HDP in pregnancies complicated by FGR

We next questioned whether women with twins and FGR of 1 or both fetuses are at an increased risk of HDP, a risk that is well established in singleton gestations affected by FGR (Table 4). Women with singleton gestations affected by FGR were at an increased risk of HDP (aRR, 2.19, 95% CI, 1.95−2.44). In women with twin gestations, the increase in the risk of HDP in pregnancies complicated by FGR of only 1 twin was similar to that observed in singletons only when a twin-based reference was used to define FGR (aRR, 2.15, 95% CI, 1.63−3.06) but not when FGR was defined using a singleton-based reference (Table 4). Women with twin gestations complicated by FGR of both twins were at the highest risk of HDP (aRR, 4.18, 95% CI, 2.12−8.23) (Table 4).

Comment

Main findings

The aim of the current study was to determine the association between HDP and FGR in dichorionic twin gestations. Our main findings are as follows: (1) HDP in dichorionic twin gestations is associated with an increased risk of FGR, an increase that is similar in magnitude to that observed in singleton gestations; (2) women with dichorionic twin gestations complicated by FGR are at an increased risk of HDP, and the risk appears to follow a dose-response relationship: it is similar in magnitude to that observed in singleton gestations when only 1 twin is affected by FGR and is greater when both twins are affected by FGR; and (3) the associations described

TABLE 2
Risk of FGR in pregnancies complicated by HDP in the twin and singleton groups

Definition of FGR	Rate of FGR in women with HDP, n (%)	Rate of FGR in women without HDP, n (%)	Risk of FGR in women with HDP vs without HDP,[a] aRR (95% CI)
Birthweight <10th percentile			
In singletons (using a singleton reference[b])	331/1992 (16.6%)	3451/46,951 (7.4%)	**2.07 (1.87–2.30)**
In twins (using a singleton reference[b])	83/340 (24.4%)	564/2700 (20.9%)	1.15 (0.94–1.41)
In twins (using a twin reference[c])	40/340 (11.8%)	128/2700 (4.7%)	**2.37 (1.69–3.34)**

Significant associations are emphasized in bold font. Denominators reflect the number of singleton and twin fetuses in the HDP and no-HDP groups.

aRR, adjusted relative risk; *CI*, confidence interval; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension).

[a] Values reflect the results of multivariable log binomial regression analysis and are expressed as adjusted relative risk (95% confidence interval). The dependent variable is FGR (birthweight below the 10th percentile according to the corresponding reference) and the independent variable is HDP. Models are adjusted for maternal age, nulliparity, and fetal sex. Models for twin neonates were generated using generalized estimating equations to account for the correlation within twin pairs; [b] Using the Canadian singleton reference of Kramer et al.[46]; [c] Using the twin reference of Min et al.[47]

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in the previous text are observed only when a twin-based birthweight reference is used to diagnose FGR. The use of a singleton-based reference to diagnose FGR in twin gestations results in a potentially erroneous high baseline rate of FGR in uncomplicated twin gestations, which appears to mask the relation between HDP and FGR.

Interpretation of the results in the context of previous observations

While the association between HDP and FGR is well established in singleton gestations, data on whether this association also exists in twin gestations are limited and conflicting.[14–17] Fox et al,[36] in a retrospective study of 578 women with twin gestations, found no association between preeclampsia and FGR. The rate of preeclampsia in their cohort was 14.9%, and the rate of FGR (birthweight <10th percentile according to a singleton-based reference) was similar between women with and without preeclampsia (48.8% vs 50.2%, $P = .8$).

Sparks et al,[37] in a more recent retrospective study of 474 women with dichorionic twin gestations, reported on the rate of FGR (birthweight <10th percentile according to a singleton-based reference) in women with and without HDP or chronic hypertension. Similar to the study of Fox et al, they found no difference in the rate of FGR between women with and without HDP (47.1% vs 42.1%, $P = .6$). However, the interpretation of these studies is limited by the relatively small sample size and by the lack of a positive control group of women with singleton gestations with and without HDP.

More importantly, both studies used a singleton-based birthweight reference to define FGR, which resulted in a very high baseline rate of FGR in the control (no HDP) group (42–50%). Clearly such a high rate is likely to mask smaller changes in the risk of FGR related to HDP. Indeed, in our study, the use of a twin-based reference decreased the rate of FGR in the control (no HDP) group from 20.9% (when a singleton-based reference was used) to 4.7%, thereby making the approximately 5% increase in the rate of FGR attributed to HDP (from 4.7% to 11.8%) more obvious and statistically significant. This increase would have been otherwise masked by the high baseline rate of FGR in the

TABLE 3
Risk of FGR in pregnancies complicated by early-onset HDP in the twin and singleton groups

Definition of FGR	Rate of FGR in women with early-onset HDP [n (%)]	Rate of FGR in women without HDP [n (%)]	Risk of FGR in women with early-onset HDP vs. no HDP[a] [aRR (95%-CI)]
Birthweight <10th percentile			
In singletons (using singleton reference[b])	125/407 (30.7%)	3451/46,951 (7.4%)	**4.57 (3.41–6.17)**
In twins (using singleton reference[b])	15/72 (20.8%)	564/2700 (20.9%)	1.01 (0.89–1.13)
In twins (using twin reference[c])	18/72 (25.0%)	128/2700 (4.7%)	**4.93 (3.18–7.63)**

Significant associations are emphasized in bold font. Denominators reflect the number of singleton and twin fetuses in the early-onset HDP and no-HDP groups.

aRR, adjusted relative risk; *CI*, confidence interval; *early-onset HDP*, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension) requiring delivery at <34 weeks; *FGR*, fetal growth restriction.

[a] Values reflect the results of multivariable log binomial regression analysis and are expressed as adjusted relative risk (95% confidence interval). The dependent variable is FGR (birthweight below the 10th percentile according to the corresponding reference) and the independent variable is early-onset HDP. Models are adjusted for maternal age, nulliparity, and fetal sex. Models for twin neonates were generated using generalized estimating equations to account for the correlation within twin pairs; [b] Using the Canadian singleton reference of Kramer et al.[46]; [c] Using the twin reference of Min et al.[47]

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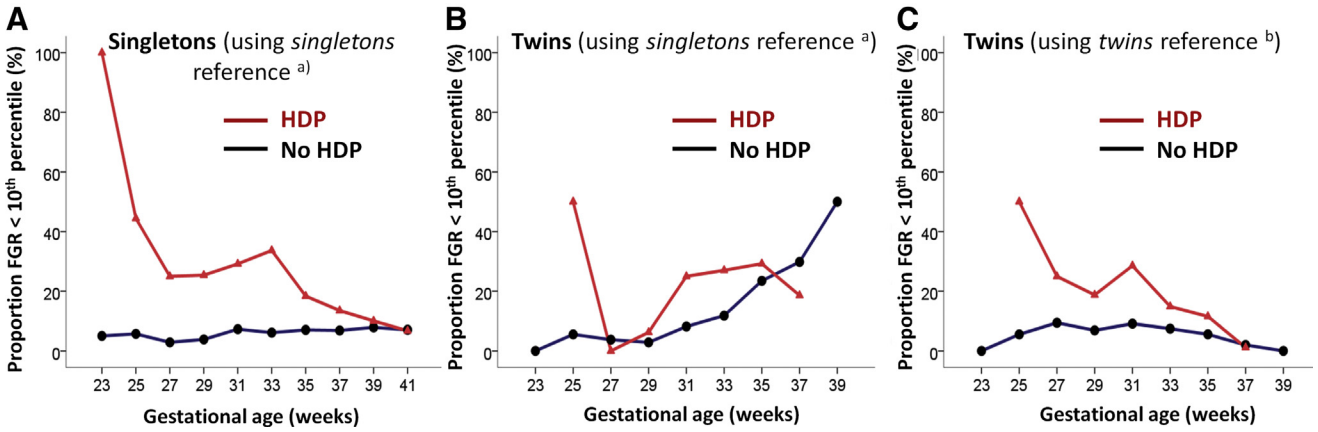
FIGURE 2
Proportion of neonates affected by fetal growth restriction according to gestational age



Proportion of neonates affected by FGR according to gestational age in women with HDP (*red line*) and without HDP (*black line*) is presented for singleton pregnancies using a singleton-based reference[a] **(A)**, for twin pregnancies using a singleton-based reference[a] **(B)**, and for twin pregnancies using a twin-based reference[b] **(C)**.

FGR, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension).

[a] Using the Canadian singleton reference of Kramer et al.[46]
[b] Using the twin reference of Min et al.[47]

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control group when a singleton-based reference is used.

In agreement with our findings, Ferrazzani et al[40] studied 476 women with twins and found that the rate of FGR was significantly higher in women with vs without preeclampsia and that the increase was more obvious when a twin-based reference was used (16.7% vs 10.6%) than when using a singleton-based reference (40.2% vs 31.4%).

We also found that dichorionic twin gestations complicated by FGR are at increased risk of HDP, a finding that was observed only when a twin-based reference was used to diagnose FGR. This finding is in agreement with the study of Wu et al,[38] who reported that in women with twin gestations, the finding of selective FGR (defined as 1 twin fetus with birth weight <10th percentile using a twin-based reference) is associated with an increased risk of preeclampsia (29.0% vs 13.1%).

Our observation that HDP and FGR are associated also in dichorionic twin gestations does not necessarily

TABLE 4
Risk of HDP in pregnancies complicated FGR in the twin and singleton groups

Definition of FGR	Rate of HDP in women with FGR, n (%)	Rate of HDP in women without FGR, n (%)	Risk of HDP in women with FGR vs without FGR,[a] aRR (95% CI)
Singletons with birthweight <10th percentile (using a singleton reference[b])	331/3782 (8.8%)	1661/45,161 (3.7%)	**2.19 (1.95–2.44)**
Twins with only 1 twin with birthweight <10th percentile			
Only 1 twin FGR using a singleton reference[b]	57/397 (14.4%)	100/998 (10.0%)	1.27 (0.94–1.71)
Only 1 twin FGR using a twin reference[c]	32/150 (21.3%)	134/1361 (9.8%)	**2.15 (1.63–3.06)**
Twins with both twins with birthweight <10th percentile			
Both twins FGR using a singleton reference[b]	13/125 (10.4%)	100/998 (10.0%)	1.02 (0.59–1.75)
Both twins FGR using a twin reference[c]	4/9 (44.4%)	134/1361 (9.8%)	**4.18 (2.12–8.23)**

Significant associations are emphasized in bold font. Denominators reflect the number of singleton and twin pregnancies in the FGR and no-FGR groups.

aRR, adjusted relative risk; *CI*, confidence interval; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy (preeclampsia or gestational hypertension).

[a] Values reflect the results of multivariable log binomial regression analysis and are expressed as adjusted relative risk (95% confidence interval). The dependent variable is HDP and the independent variable is FGR (birthweight below the 10th percentile according to the corresponding reference). Models are adjusted for maternal age, nulliparity, and fetal sex; [b] Using the Canadian singleton reference of Kramer et al.[46]; [c] Using the twin reference of Min et al.[47]

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contradict the hypotheses described in the previous text that the pathogenic mechanisms of HDP and FGR in twins may be different from those involved in singletons, involving factors other than abnormal placentation. HDP is associated with several pathophysiological changes including systemic vasoconstriction, which may result in reduced uteroplacental blood flow[24] and may thus be associated with FGR, irrespective of the underlying pathogenetic mechanisms and the presence of primary abnormal placentation.

Strengths and limitations

The main limitations of the current study are its retrospective design and the lack of information on potential confounding variables such as maternal body mass index and assisted reproductive technology. Thus, residual confounding cannot be ruled out.

Another limitation relates to the lack of information on measures such as Doppler findings and growth velocity,[48] which may distinguish fetuses that are truly growth restricted because of a placental insufficiency from those that are constitutionally small for gestational age. However, this limitation is shared by all previous studies addressing this question and reflects the clinical practice in which fetal size (eg, weight below the 10th percentile for gestational age) is often used as a proxy for FGR.

One more limitation relates to the lack of information on neonatal outcomes, although this was not the focus of our research question and is not relevant to the interpretation of the results of the current study.

Finally, the fact that this is a single center study may limit its generalizability to other countries or populations that may have different distribution of birthweight or that may use different criteria for the diagnosis of HDP.

The main strengths of the current study are the large sample size and the use of both a singleton- and a twin-based reference to define FGR. In addition, the inclusion of a positive control group of singletons (with and without HDP) allowed us to directly compare the association of HDP with FGR between twin and singleton gestations and demonstrate that the magnitude of this association in twins is similar to that observed in singletons. Finally, we limited the analysis to dichorionic twins to eliminate confounding related to monochorionic twin pregnancies in which FGR may be more common and may have a different pathogenesis.

Conclusion

In summary, our findings support the hypothesis that HDP and FGR are closely related also in dichorionic twin gestations and that the magnitude of this association is similar to that observed in singletons. In addition, the fact that this association is observed only when FGR is diagnosed using a twin-based birthweight reference (but not when a singleton-based reference is used) suggests that the diagnosis of FGR in twin gestations using a twin-based reference may be more informative and clinically relevant than FGR diagnosed using a singleton-based reference.

These findings have important clinical implications. Women with twins and HDP should be closely monitored for evidence of FGR. Similarly, care providers should be aware that women with a twin gestation complicated by FGR based on a twin-based reference should be followed up closely for signs of HDP and that the risk may be even higher in pregnancies in which both fetuses are growth restricted. Further studies are needed to provide a better understanding of the mechanisms underlying HDP and FGR in twin gestations. ■

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