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Clinical characteristics of fetal and neonatal outcomes in twin pregnancy with preeclampsia in a retrospective case–control study
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Abstract

The aim of our study was to compare the clinical characteristics of fetal and neonatal outcomes in twin pregnancies between women with preeclampsia (PE) and those with normotension in a Chinese population.

There were 143 preeclamptic women and 367 normotensive women with twin pregnancies included in this retrospective case–control study. The baseline characteristics and perinatal outcomes were collected and compared between the groups. Multiple logistic regression and linear regression were used to assess the correlations between PE and the outcomes.

Significant increases were observed in the frequencies of preterm delivery (OR = 2.75, $P < 0.001$), iatrogenic preterm birth (OR = 3.52, $P < 0.001$), and IUGR (OR = 2.94, $P = 0.001$) in the PE group, and the PE group had more than a 2-fold risk of adverse neonatal outcomes. Preeclamptic twin neonates had lower birth weights ($\beta = -147.34$, $P = 0.005$; $\beta = -169.47$, $P = 0.001$). The comparison on the discordance of intertwin weight was not significantly different.

Twin pregnancies with PE are associated with worse perinatal outcomes. The adverse outcomes of preeclamptic twin pregnancies may be associated with lower birth weights rather than the discordance of the intertwin weight, which requires further confirmation. The results may provide helpful references for better clinical assessments, evaluations of prognosis, and a deeper understanding of preeclamptic twin pregnancies.

Abbreviations: EFW = estimated fetal weight, ELBW = extremely low birth weight, IUGR = intrauterine growth restriction, LBW = low birth weight, NICU = neonatal intensive care unit, NRDS = neonatal respiratory distress syndrome, PE = preeclampsia, SGA = small for gestational age, sIUFD = single intrauterine fetal death, VLBW = very low birth weight.

Keywords: birth weight, outcome, preeclampsia (PE), twin pregnancy

1. Introduction

Preeclampsia (PE) is a common and severe form of hypertensive disorder complicating pregnancy (HDCP) and remains a leading direct cause of maternal and neonatal mortality and morbidity.[1]

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The prevalence of PE was approximately 4.0% and 2.88% of all pregnancies worldwide and in mainland China, respectively.[2,3]

Recently, multiple studies have focused on the incidence and risk factors of twin pregnancies with PE,[4–8] but inadequate data exist regarding the clinical characteristics and perinatal outcomes of twin pregnancies with PE.[9–12] It is acknowledged that PE increases the risk of adverse maternal–neonatal outcomes mainly from data of singleton pregnancies.[1,2,13,14] However, twin pregnancies with hypertensive disorders were unexpectedly shown to have better neonatal outcomes than normotensive women in twin pregnancy.[9] Therefore, subjective judgments or deductions could not be made to determine the perinatal outcomes in preeclamptic twin pregnancies, and robust statistical evidence needs to be provided. Meanwhile, a small amount of data on this point has been retrieved in a Chinese population.

The aim of our study was to compare the clinical characteristics of fetal–neonatal outcomes in twin pregnancies between women with PE and those with normotension, and the conclusions of this study may be helpful for better clinical assessments and evaluations of prognosis.

2. Materials and methods

2.1. Subjects

This was a retrospective case–control study that was conducted at the First Affiliated Hospital of Xi'an Jiaotong University,

Shaanxi, China, from January 2008 to March 2015. Women who had a twin pregnancy with a clear confirmation of chorionicity were included; those who had PE were included in the case group, and those who were normotensive were included in the control group.

The diagnosis of PE included the following: severe PE (diastolic blood pressure ≥ 110 mm Hg, systolic blood pressure ≥ 160 mm Hg, proteinuria from none to positive, elevated serum creatinine and transaminase levels, obvious fetal growth restriction (FGR), multiorgan disturbances, such as headache, visual disturbance, upper abdominal pain, oliguria, convulsion, thrombocytopenia, and pulmonary edema) and nonsevere PE (diastolic blood pressure <110 mm Hg, systolic blood pressure <160 mm Hg, proteinuria from none to positive, no multiorgan disturbances or only minimal serum transaminase elevation). Nonsevere PE includes "mild" and "moderate" hypertension, which is not specifically defined. Overt proteinuria may not be a necessary element to characterize the PE syndrome.[15] Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg on at least 2 occasions at a 6-hour interval.

We excluded women with any of following items in the current pregnancy: gestational hypertension, chronic hypertension, or eclampsia; acute internal or surgical diseases; triplet or quadruplet pregnancy; and chorionicity that was unclear. Only cases with a cotwin live birth were included in the analyses for the neonatal outcomes.

The study was approved by the ethics and research committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2015LSL-073), and it conformed to the provisions of the Declaration of Helsinki (as revised in Brazil 2013). A written informed consent was not necessary for this retrospective study, and patient anonymity was preserved.

2.2. Clinical evaluation

The gestational age was calculated using the last menstruation period (LMP) or confirmed by the first-trimester ultrasound. The baseline characteristics and maternal–neonatal outcomes were obtained from the medical records. The determination of twin chorionicity was clinically based on an ultrasound evaluation, including the gestational sac number at early pregnancy, the placental number, the fetal sex, "T" sign or "λ" sign,[16] and it was confirmed by a placenta examination after delivery. Placental anomalies included placental abruption, previa, increta, and adherent. Umbilical cord anomalies included prolapsus, torsion, and knots. Abnormal amniotic fluid referred to at least 1 fetus with polyhydramnios (maximum vertical pocket more than 8 cm) or oligoamnios (maximum vertical pocket was less than 2 cm).[17] The umbilical artery Doppler flow spectrum was recorded from a free floating portion of the umbilical cord during minimal fetal activity and the absence of fetal breathing, and the average pulsatility index (PI) value of the cotwin was used for the final analysis. The values of the amniotic fluid and PI for the analysis were from the last ultrasound before delivery. Intrauterine growth restriction (IUGR) was defined as at least 1 fetus with a birth weight less than the 10th percentile for the gestational age, and the birth weight percentiles for gestational age were determined by the Ananth twin reference curve.[18] Single intrauterine fetal death (sIUFD) referred to the death of 1 twin in the uterine. Discordance of the intertwin birth weight or the estimated fetal weight (EFW) was defined as [(larger baby weight−smaller baby weight)/larger baby weight] (%).[19] The

diagnoses of small for gestational age (SGA), low birth weight (LBW), very low birth weight (VLBW), and extremely low birth weight (ELBW) were each defined according to the William obstetrics.[15]

2.3. Statistical analyses

The data collected from the study subjects were verified and double entered into a data management system. The parameters are presented as the mean ± SD or the median (range) and percentages, as appropriate. The statistical analyses were performed using the Chi-square, Fisher exact, Student t, Mann–Whitney U tests, as appropriate. Multiple logistic regression and linear regression were used to determine the odds ratio (OR) or β and 95% confidence interval (CI) of some of the selected outcomes among the women with or without PE, and the potential confounding factors were included in the analysis. All of the reported P values were 2-tailed, and values <0.05 were considered statistically significant. The statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY).

3. Results

A total of 585 twin pregnancies were retrieved in the hospital information system, and 75 cases were excluded because they did not meet the inclusion criteria or because there were incomplete maternal or neonatal records. As a result, 143 twin pregnancies with PE and 367 twin pregnancies with normotension were included in the final analysis.

The baseline characteristics and maternal–fetal outcomes of the PE and normotension groups in the twin pregnancies are described in Table 1. There were no significances in the baseline characteristics. The total number of preterm deliveries was greater in the twin pregnancies with PE ($P=0.003$) and the iatrogenic type, and those deliveries before 33^{+6} weeks were even more common in this group ($P=0.034$ and $P<0.001$, respectively), and more IUGR occurred in the preeclamptic women ($P<0.001$). They were also more inclined to be hospitalized at an earlier gestational age and deliver earlier ($P=0.010$ and $P=0.005$, respectively), and the total hospitalized duration of the preeclamptic women was also longer ($P<0.001$) (Table 1).

Next, the neonatal outcomes of the cotwin live births between the 2 groups were subsequently compared in Table 2. Cotwin live birth in the PE and normotension groups were 134 (268 neonates, 93.71%) and 341 (682 neonates, 92.91%), respectively; however, there were no significant differences between the 2 groups ($P=0.751$). The larger baby weight, smaller baby weight, and percentile of smaller baby weight were significantly lower in the PE group than the normotension group ($P=0.007$, $P=0.001$, and $P=0.006$, respectively). However, the comparison on the discordance of the intertwin weight was not significant. A series of neonatal complications were more likely to occur in the PE group, such as intracranial hemorrhage ($P=0.043$), neurological complications ($P<0.001$), ischemic myocardial injury ($P<0.001$), and acid-base and electrolyte disturbance ($P=0.020$). Moreover, the number of neonates diagnosed at SGA, LBW, and with an Apgar score 1 minute < 7, were even more in the PE group ($P<0.001$, $P=0.002$, and $P=0.037$, respectively). In addition, more neonates were transferred to the neonatal intensive care unit (NICU) and were hospitalized for longer durations in the PE group ($P<0.001$ for both) (Table 2).

According to the multiple logistic regression adjusted for potential covariates, some of the selected maternal–fetal and

Table 1

The baseline characteristics and maternal–fetal outcomes of preeclampsia and normotension group in twin pregnancy.

Parameters	Twin pregnancy with preeclampsia (n=143)	Twin pregnancy with normotension (n=367)	P
Maternal age, y	29 (17–44)	29 (19–44)	0.600
Gravidity	1 (0–4)	1 (0–6)	0.384
Nulliparous, n%	100 (69.93)	253 (68.94)	0.827
PCOS history, n%	2 (1.40)	9 (2.45)	0.692
Chorionicity, n%			0.095
Monochorionicity	48 (33.57)	96 (26.16)	
Dichorionicity	95 (66.43)	271 (73.84)	
Total preterm delivery, n%	117 (81.82)	252 (68.66)	0.003
Type of preterm delivery, n%			0.034
Spontaneous	34 (29.06)	102 (40.48)	
Iatrogenic	83 (70.94)	150 (59.52)	
Weeks of preterm delivery, n%			<0.001
Before 33^{+6}	72 (61.54)	95 (37.70)	
During 34 to 36^{+6}	45 (38.46)	157 (62.30)	
ICP and/or GDM, n%	20 (13.99)	42 (11.44)	0.430
Anemia, n%	21 (14.68)	42 (11.44)	0.318
Postpartum hemorrhage, n%	6 (4.20)	13 (3.54)	0.726
Placental anomalies, n%	6 (4.20)	12 (3.27)	0.611
Umbilical cord anomalies, n%	5 (3.50)	13 (3.54)	0.980
Umb-PI	0.85±0.17	0.85±0.17	0.760
Abnormal amniotic fluid, n%	13 (9.09)	56 (15.26)	0.067
IUGR, n%	26 (18.18)	25 (6.81)	<0.001
sIUFD, n%	7 (4.89)	14 (3.82)	0.581
Discordance of EFW≥20%, n%	18 (12.59)	40 (10.90)	0.590
Gestational age in admission, wk	34.71 (23.29–40.57)	35.43 (22.43–41.14)	0.010
Gestational age at delivery, wk	35.21 (23.57–40.86)	36.00 (24.23–41.14)	0.005
Expectant duration, d	1 (0–37)	1 (0–23)	0.262
Hospitalized duration, d	9 (3–50)	8 (2–32)	<0.001
Delivery mode, n%			0.725
Cesarean section	102 (71.33)	249 (67.85)	
Induced labor	3 (2.10)	10 (2.72)	
Vaginal delivery	38 (26.57)	108 (29.43)	

EFW = estimated fetal weight, GDM = gestational diabetes mellitus, ICP = intrahepatic cholestasis of pregnancy, IUGR = intrauterine growth restriction, PCOS = polycystic ovary syndrome, sIUFD = single intrauterine fetal death, Umb-PI = umbilical artery pulsatility index.

neonatal outcomes remained statistically significant. There were significant increases in the frequencies of preterm birth (OR = 2.75, 95% CI = 1.69–4.47, P < 0.001), iatrogenic preterm birth (OR = 3.52, 95% CI = 2.73–5.53, P < 0.001), and IUGR (OR = 2.94, 95% CI = 1.56–5.53, P = 0.001) in twin pregnancies with PE. Moreover, the preeclamptic neonates were had more than a 2-fold risk of adverse neonatal outcomes (Table 3).

According to the multiple linear regression adjusted for potential covariates, the larger and smaller baby weights were still significantly lower in the preeclamptic group (β = −147.34, 95% CI = −249.33 to −45.35, P = 0.005; β = −169.47, 95% CI = −267.98 to −70.97, P = 0.001). No significances were observed in the comparisons of the gestational age at delivery and the discordance of the intertwin weight (Table 4).

4. Discussion

4.1. Worse perinatal outcomes in preeclamptic twin pregnancies

Compared with normotensive women with twin pregnancies, there were significant correlations between PE and adverse perinatal outcomes. PE is currently acknowledged as a chronic placental ischemic disease, resulting from inadequate modified spiral arteries. Placental dysfunction and hypoperfusion play an important pathophysiological role and are considered to be

associated with adverse perinatal outcomes, including reduced birth size, IUGR, preterm birth, prenatal loss, and a broad range of complications.[1,20–22] Based on our results, we speculate that the pathophysiological process of PE in twin pregnancies may be similar to that in singleton pregnancies.

However, the relationship between PE and IUGR in twin pregnancies is a point that deserves further discussion. Fox et al[23] proposed that there was no correlation between PE and IUGR in twin pregnancies from a cohort of 578 patients. Women with PE were not more likely to have growth restricted neonates, and women with growth restricted neonates were not more likely to have PE. There was a strong link between PE and reduced fetal growth in singleton pregnancies, according to multiple previous studies as we mentioned above. However, no correlation between these 2 entities in twin pregnancies might reveal different pathological mechanisms of PE and IUGR in this distinctive condition. It is possible that the low birth weight (LBW) in the twin pregnancies is mainly due to the inability of the environment to meet the nutritional needs in multiple pregnancies rather than an ischemic placenta in PE. Meanwhile, risk factors associated with PE or IUGR in singleton pregnancy had inability to predict PE or IUGR in twin pregnancy (aside from obesity and egg donation for PE).[4,23,24]

Interestingly, a retrospective cohort study from Chinese twin pregnancies revealed that PE occurred more frequently in selective IUGR (sIUGR) pregnancies than in normal growth

Table 2

The neonatal outcomes of cotwin live birth in preeclampsia and normotension group.

Parameters	Cotwin live birth with preeclampsia (n=134, 268 neonates)	Cotwin live birth with normotension (n=341, 682 neonates)	P
Larger baby weight, g	2318.3±424.7	2452.1±498.3	0.007
Smaller baby weight, g	1990.6±433.6	2145.0±469.9	0.001
Percentile of larger baby weight, th%	75.5 (2.0–100.0)	79.5 (3.0–100.0)	0.152
Percentile of smaller baby weight, th%	32.0 (0–100.0)	45.0 (0–100.0)	0.006
Discordance of intertwin weight, %	12.2 (0–58.1)	10.1 (0–49.7)	0.086
Neonatal anemia, n%	43 (16.05)	79 (11.58)	0.064
Intracranial hemorrhage, n%	13 (4.85)	16 (2.35)	0.043
Neurological complications, n%	89 (33.21)	126 (18.47)	<0.001
NRDS, n%	41 (15.30)	85 (12.46)	0.246
Ischemic myocardial injury, n%	57 (21.27)	74 (10.85)	<0.001
Acid-base and electrolyte disturbance, n%	79 (29.48)	152 (22.29)	0.020
Structural anomalies, n%	19 (7.09)	31 (4.54)	0.114
Neonatal death, n%	2 (0.75)	1 (0.15)	0.194
SGA, n%	55 (20.52)	71 (10.41)	<0.001
LBW, n%	171 (63.81)	359 (52.64)	0.002
VLBW and ELBW, n%	25 (9.33)	54 (7.92)	0.479
Apgar score 1 min <7, n%	39 (14.55)	67 (9.82)	0.037
Apgar score 5 min <7, n%	15 (5.60)	25 (3.67)	0.182
NICU admission, n%	240 (89.55)	491 (71.99)	<0.001
NICU duration of cotwin, n%	18 (0–67)	14 (0–88)	<0.001

ELBW = extremely low birth weight, LBW = low birth weight, NICU = neonate intensive care unit, NRDS = neonatal respiratory distress syndrome, SGA = small for gestational age, VLBW = very low birth weight.
Structural anomalies were included congenital heart anomalies (atrial/ventricle septal defect, patent ductus arteriosus, tetralogy of fallot), hypospadias, limb deformity.

twin pregnancies, and sIUGR was associated with increased odds of developing severe PE in twin pregnancies.[25] These 2 studies and ours were coming from different perspectives to look into the correlations between PE and IUGR in twin pregnancies. The different definitions of IUGR and the diverse twin growth curve used in the studies may account for these different results. The real pathological correlations between PE and IUGR both in twin and singleton pregnancies should be confirmed by further research.

According to previous studies, PE is one of the risk factors for preterm birth.[26,27] The present study also demonstrated that the occurrence of PE in twin pregnancies was an important risk factor for preterm birth and the iatrogenic type after adjusting for potential covariates. Preeclamptic women were more likely to have a preterm delivery due to medical complications, and the majority of the women delivered at an early gestational week. PE was also found to be one of the most frequent indications for labor induction of iatrogenic late preterm births in the other studies.[28] It was additionally suggested that short-term neonatal outcomes differed by the etiology (spontaneous or iatrogenic) of preterm birth,[29] iatrogenic late preterm birth increased the risk of NICU admission and respiratory disorders in neonates in comparison to the spontaneous type.[28] Although we have observed more iatrogenic preterm births and worse adverse neonatal outcomes in preeclamptic mothers, the correlation between them has not been demonstrated yet. If the iatrogenic preterm birth is confirmed to be associated with adverse neonatal outcomes in preeclamptic twin pregnancies, then more attention should be given to the early detection and intervention of PE to improve the outcomes, and the evaluation of the indication of delivery should be made carefully.

4.2. Previous different results

As suggested above, we found that preeclamptic women with twin pregnancies had worse perinatal outcomes, as we predicted. Surprisingly, Sibai et al[9] reported that women who remained normotensive throughout their pregnancy had a significantly

Table 3

Selected perinatal outcomes in twin pregnancy with preeclampsia compared with normotension group adjusted for potential covariates.

Parameters	Preeclampsia	Normotension	OR	95% CI	P
Preterm birth, n%	117 (81.82)	252 (68.66)	2.75	1.69–4.47	<0.001
Iatrogenic preterm birth, n%	83 (58.04)	150 (40.87)	3.52	2.73–5.53	<0.001
ICP and/or GDM, n%	20 (13.99)	42 (11.44)	1.23	0.68–2.21	0.497
IUGR, n%	26 (18.18)	25 (6.81)	2.94	1.56–5.53	0.001
Intracranial hemorrhage, n%	11 (8.21)	12 (3.52)	2.66	1.12–6.32	0.027
Neurological complications, n%	64 (47.76)	89 (26.10)	2.85	1.85–4.38	<0.001
Ischemic myocardial injury, n%	54 (40.30)	56 (16.42)	3.75	2.36–5.94	<0.001
SGA, n%	27 (20.15)	64 (18.77)	1.01	0.56–1.98	0.839

It was recorded as "adverse outcome" in logistic regression when at least 1 fetus with intracranial hemorrhage (neurological complications, ischemic myocardial injury, or SGA).
The comparisons on preterm delivery, iatrogenic preterm delivery, ICP, GDM, and IUGR were adjusted for maternal age and chorionicity; the comparisons on neonatal complications were adjusted for maternal age, chorionicity, and gestational age at delivery.
CI = confidence interval, GDM = gestational diabetes mellitus, ICP = intrahepatic cholestasis of pregnancy, IUGR = intrauterine growth restriction, OR = odds ratio, SGA = small for gestational age.

Table 4

Neonatal weight outcomes in cotwin live birth with preeclampsia compared with normotension group adjusted for potential covariates.

Parameters	Preeclampsia	Normotension	β	95% CI	P
Gestational age at delivery, wk	35.21 (23.57–40.86)	36.00 (24.23–41.14)	−0.36	−5.01 to 4.29	0.878
Larger baby weight, g	2318.3 ± 424.7	2452.1 ± 498.3	−147.34	−249.33 to −45.35	0.005
Smaller baby weight, g	1990.6 ± 433.6	2145.0 ± 469.9	−169.47	−267.98 to −70.97	0.001
Discordance of intertwin weight, %	12.2 (0–58.1)	10.1 (0–49.7)	1.77	−0.32 to 3.86	0.097

According to multiple linear regression, the comparisons on gestational age at delivery were adjusted for maternal age and chorionicity; the comparisons on weight parameters were adjusted for maternal age, chorionicity, and gestational age at delivery.

CI = confidence interval.

lower gestational age at delivery, a lower birth weight, a higher rate of preterm delivery at both <37 and <35 weeks gestation and a higher rate of perinatal death. In fact, these results were partly from a multicenter randomized trial comparing low-dose aspirin with placebo for the prevention of PE. These women were randomly assigned aspirin or placebo at an early age, which probably had a potential influence on the pathological process and the perinatal outcomes. Moreover, some detailed information, such as the proportions of severe PE or early onset PE could not be obtained from the study, while 82.52% and 33.57% of the women were with severe PE and early onset PE in our study. The constitution of a severe form in the study population is also an influencing factor on the results. However, we thought that what the authors speculated was still reasonable, such that PE may represent a compensatory adaptive mechanism, such as promoting or restoring normal blood perfusion.[30–32] Especially in preeclamptic twin pregnancies, more complex components are involved in its development and outcomes. Placental hypoperfusion is not the only explanation. The discrepant results between Sibai's and our study require further investigation.

4.3. Birth weight of twin pregnancy with PE

After adjusting for confounding factors, we still observed that the birth weight in the PE group was significantly lower, and the comparison of the discordance of the intertwin weight remained insignificant. Unique to multiple pregnancies is the phenomenon of discordant growth. Sparks et al[33] demonstrated that women with hypertension (gestational hypertension and PE) increased the odds ratio of weight discordance ≥20% in the dichorionic twin. However, results from a relevant study were different, indicating that weight discordance was similar between the gestational hypertension and normotension groups in twin pregnancies. In addition, gestational hypertension may play a beneficial role in physiological processes and provided a better placental perfusion in twin pregnancies.[34] According to these results, we thought the physiological mechanism of gestational hypertension might be unclear in twin pregnancies, so we excluded this subgroup in the present study. Finally, we found that, compared with normotensive women, PE was not associated with a higher discordance in the intertwin weight; although, maternal age, chorionicity, and gestational age at delivery were adjusted for in the analysis. Taking into consideration the worse neonatal outcomes in the preeclamptic mothers, we speculated that adverse neonatal outcomes in preeclamptic twin pregnancies were possibly the result of the lower birth weight rather than the weight discordance, which definitely requires further confirmation. Of note, we do not deny that the discordance is associated with a higher perinatal morbidity and mortality in other situations.[35]

The limitation of the present study could be the lack of information on some of the maternal factors, such as the maternal nutritional state, BMI, smoking behavior, and use of drugs. In addition, twin pregnancies in our tertiary care center may have been more likely to suffer from an adverse outcome compared to the average population. Meanwhile, the inability to make comparisons according to chorionicity was limited by a small sample in the monochorionicity group, so it is a challenge for us to obtain a larger population of twin pregnancies specific to chorionicity in the future.

In conclusion, twin pregnancies with PE are associated with worse perinatal outcomes. The adverse outcomes of preeclamptic twin pregnancies may be associated with lower birth weights rather than the discordance of the intertwin weight, which showed no differences between preeclamptic and normotensive women. The results from the present study may provide helpful references for better clinical assessments, evaluations of prognosis, and a deeper understanding in preeclamptic twin pregnancies.

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