Preeclampsia in twin pregnancies: association with selective intrauterine growth restriction

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Abstract

Objective: To identify the association between preeclampsia (PE) and selective intrauterine growth restriction (sIUGR) in twin pregnancies.

Methods: This was a retrospective cohort study of 1004 twin pregnancies from 2008 to 2014. We specifically compared the incidence, clinical characteristics and outcomes of PE between sIUGR and normal-growth twin pregnancies.

Results: PE occurred more frequently in sIUGR pregnancies [29.0% (51/176)] than in normal-growth twin pregnancies [13.1% (99/756), \(p < 0.001\), adjusted odds ratio 3.29]. Among sIUGR, the incidence of PE was significantly higher in dichorionic (DC) pregnancies (37.5%, 30/80) than in monochorionic (MC) pregnancies (21.9%, 21/96). The rates of onset at <32 weeks \((p = 0.045)\) and of severe PE \((p = 0.025)\) were higher in sIUGR pregnancies with PE. The systolic blood pressure was also higher in sIUGR pregnancies with PE (152.6 ± 11.8 mmHg) than in normal-growth pregnancies with PE (148.0 ± 8.2 mmHg) \((p = 0.042)\). Additionally, more sIUGR pregnancies were delivered at 32–36 weeks \((p = 0.001)\), and fewer were delivered at ≥36 weeks \((p < 0.001)\). Moreover, the prevalence of severe neonatal asphyxia was higher in sIUGR pregnancies with PE than in normal-growth pregnancies with PE (8.8% versus 2.5%, \(p = 0.020\)).

Conclusions: sIUGR is associated with increased odds of developing severe PE in twin pregnancies, leading to poorer perinatal outcomes.

Keywords

Preeclampsia, selective intrauterine growth restriction, twin pregnancies

Introduction

Preeclampsia (PE) is a human-pregnancy-specific disease that is thought to complicate 3–5% of pregnancies worldwide [1]. The risk of PE in twin pregnancies is two to threefold higher than that in singleton gestations, with increased maternal-fetal morbidity [2].

In singleton pregnancies, shallow trophoblast invasion and failure of the trophoblast invasion process are believed to be associated with intrauterine growth restriction (IUGR) and PE [3]. In twin pregnancies, the IUGR incidence rate is 15–47%. Selective IUGR (sIUGR), in which only one of the twins experiences IUGR, is a common condition that affects approximately 11–25% of twin pregnancies [4,5]. Besides the placental insufficiency of the smaller twin, other factors such as uneven placental sharing, abnormal umbilical cord insertion (UCI) in the smaller twin or the presence of vascular anastomoses in the placenta may also lead to sIUGR [6,7]. It remains unclear whether the problem of less than half placentas will affect the whole pregnancy causing PE, and the clinical characteristics of PE in sIUGR and normal-growth twin pregnancies have not been compared.

Therefore, the aim of this study was to identify the association between sIUGR and PE in twin pregnancies and to investigate the different clinical characteristics of PE in sIUGR and normal-growth twin pregnancies.

Materials and methods

This retrospective cohort study included 1004 twin pregnancies delivered at ≥20 weeks of gestation at the First Affiliated Hospital of Sun Yat-Sen University from 1 January 2008, to 31 July 2014. After excluding patients with chronic hypertension or major congenital fetal anomalies, 948 patients were included. This study was approved by the institutional review board, and informed consent was not needed in this retrospective study.

PE was characterized as hypertension and proteinuria that often occurred in women who were normotensive before 20 weeks of gestation. Hypertension was diagnosed when two blood pressure readings \(≥140/90\) mmHg were noted 6 h apart. Gestational proteinuria was defined as urinary protein excretion of at least 300 mg per 24 h or 1+ protein or greater on a
Results

There were 948 women with twin pregnancies recruited during the study period. In total, 176 of these pregnancies involved sIUGR. 16 were IUGR of both twins and 756 were normal-growth pregnancies. PE occurred in 29.1% (51/176) of the sIUGR, 25.0% (4/16) of IUGR of both twins and 13.1% (99/756) of the normal-growth twin pregnancies. The rates of PE were significantly higher in sIUGR than in normal-growth twin pregnancies (p<0.001), while it was not different between sIUGR and IUGR of both twins (p=0.737). After adjusting for the characteristics including age, nulliparity, gestational diabetes mellitus (GDM), assisted conception and obesity, the odds of developing PE in an sIUGR twin pregnancy compared with a normal-growth twin pregnancy was 3.29 (95% CI 2.11–5.15). Since the cases of IUGR of both twins were few, we mainly focused on the sIUGR and normal-growth twin pregnancies in the following study.

The maternal characteristics in sIUGR and normal-growth twin pregnancies are reported in Table 1. Most of these characteristics, such as age (p=0.400), nulliparity (p=0.388), GDM (p=0.601), assisted conception (p=0.059) and obesity (p=0.117), exhibited no statistically significant differences between sIUGR and normal-growth twin pregnancies. However, more sIUGR pregnancies than normal-growth pregnancies were MC (sIUGR 54.5% versus normal-growth 20.1%, p<0.001), and abnormal UCI occurred in 27.8% (49/176) of sIUGR and 16.0% (121/756) of normal-growth pregnancies (p<0.001). In addition, among sIUGR pregnancies, the incidence of PE was significant higher in DC pregnancies (37.5%, 30/80) than in MC pregnancies (21.9%, 21/96) (Figure 1).

Next, we compared the clinical characteristics of PE between sIUGR and normal-growth pregnancies (Table 2). The rate of onset at <32 weeks was higher in sIUGR pregnancies with PE (41.2%, 21/51) than in normal-growth pregnancies with PE (25.3%, 25/99) (p=0.045). Moreover, in sIUGR pregnancies with PE, the rate of severe PE was higher (sIUGR PE 43.1% versus normal-growth PE 25.3%, p=0.025). Even though there was no statistically significant difference in the diastolic blood pressure (DBP) (p=0.566), the systolic blood pressure (SBP) was higher in sIUGR pregnancies with PE (152.6±11.8 mmHg) than in normal-growth pregnancies with PE (148.0±8.2 mmHg) (p=0.042). Additionally, there were no statistically significant differences when the data were stratified by urinary protein (p=0.821) or hematocrit (Hct) (p=0.527). We further compared the clinical characteristics of PE between DC sIUGR and MC sIUGR pregnancies (Supplemental Table 1). There was no statistically significant difference in the diastolic blood pressure (DBP) (p=0.566), the systolic blood pressure (SBP) was higher in sIUGR pregnancies with PE (152.6±11.8 mmHg) than in normal-growth pregnancies with PE (148.0±8.2 mmHg) (p=0.042). Additionally, there were no statistically significant differences when the data were stratified by urinary protein (p=0.821) or hematocrit (Hct) (p=0.527). We further compared the clinical characteristics of PE between DC sIUGR and MC sIUGR pregnancies (Supplemental Table 1).
no statistically significant difference in the rate of onset at <32 weeks, the rate of severe PE, the DBP, the SBP, urinary protein or Hct between MC and DC sIUGR pregnancies with PE.

Finally, the outcomes of PE were compared between sIUGR and normal-growth pregnancies (Table 3). Although there were no statistically significant differences, the mean gestational age at delivery for sIUGR pregnancies with PE (33.1 ± 3.2 weeks) was earlier than that for normal-growth pregnancies with PE (34.4 ± 3.4 weeks) (p = 0.069). When we calculated the proportions of sIUGR and normal-growth pregnancies delivered by certain gestational age thresholds, there were no statistically significant differences by <28 weeks (p = 0.495) or 28–32 weeks (p = 0.637). However, more sIUGR pregnancies were delivered at 32–36 weeks (sIUGR 49.0% versus normal-growth 22.2%, p = 0.001), and fewer were delivered at ≥36 weeks (sIUGR 19.6% versus normal-growth 52.5%, p < 0.001). The birth weights of the smaller twins were significantly lower in sIUGR pregnancies compared with normal growth pregnancies (sIUGR 1.40 ± 0.47 kg versus normal-growth 2.00 ± 0.51 kg, p < 0.001), whereas those of the larger twins were not different (sIUGR 2.08 ± 0.56 kg versus normal-growth 2.27 ± 0.49 kg, p = 0.075). Moreover, the Apgar score at 1 and 5 min was compared between the two groups. In sIUGR pregnancies with PE, the proportion with an Apgar score ≤3 at 1 min was higher (sIUGR 8.8% versus normal-growth 2.5%, p = 0.020), and the proportion with an Apgar score ≥8 was lower (sIUGR 76.5% versus normal-growth 86.4%, p = 0.031).

Discussion

In our study, PE occurred more frequently in sIUGR pregnancies than in normal-growth twin pregnancies. In fact, in multivariable analyses, the adjusted odds of developing PE among sIUGR pregnancies was over three times the odds among normal-growth pregnancies.

PE is thought to be a placental disease and is characterized by the increased expression of placental antiangiogenic factors, including soluble fms-like tyrosine kinase-1 (sFLT-1), soluble endoglin (sENG) and hypoxia-inducible factor-1 alpha (HIF-1α), and the decreased expression of angiogenic factors, such as placental growth factor, a vascular endothelial growth factor that causes systemic endothelial dysfunction and is responsible for the maternal syndrome [12,13]. Women with twin pregnancies have sFLT-1 levels that are twice those of singleton pregnancies because of increased placental mass [14]. Previous studies have confirmed that both sFLT-1 and sENG are highly expressed in the placentas of IUGR and IUGR-discordant twins [15,16]. Moreover, abnormal UCI leads to placental hypoxia because of reduced placental perfusion, and local hypoxia encourages the overexpression of HIF-1α in the placenta [17]. In our study, abnormal UCI occurred more frequently in sIUGR pregnancies. We hypothesize that for the reasons stated above, the higher levels of sFLT-1, sENG and HIF-1α likely increased the risk of PE in the PE among sIUGR pregnancies; further investigations are essential to confirm this hypothesis. Moreover, the present study showed that, in sIUGR pregnancies, the odds of development PE was higher in DC twins. That may be account for the different placental characteristics between MC and DC sIUGR.

Table 2. Characteristics of PE in sIUGR and normal-growth twin pregnancies.

|                        | sIUGR pregnancies with PE (n = 51) | Normal-growth pregnancies with PE (n = 99) | p values |
|------------------------|-----------------------------------|------------------------------------------|----------|
| Onset at <32 weeks     | 21 (41.2%) 25 (25.3%)             | 0.045                                    |
| Severe PE              | 22 (43.1%) 25 (25.3%)             | 0.025                                    |
| SBP (mmHg)             | 152.6 ± 11.8 148.0 ± 8.2          | 0.042                                    |
| DBP (mmHg)             | 92.1 ± 8.7 90.9 ± 8.9             | 0.566                                    |
| Urinary protein (g/24 h)| 1.64 ± 1.01 1.55 ± 1.35          | 0.821                                    |
| Hct                    | 0.31 ± 0.05 0.32 ± 0.04           | 0.527                                    |

The data are shown as the mean ± standard deviation or the case number (%). sIUGR, selective intrauterine growth restriction; PE, preeclampsia; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hct, hematocrit.

Table 3. Outcomes of PE in sIUGR and normal-growth twin pregnancies.

|                          | sIUGR pregnancies with PE (n = 51; 102 twins) | Normal-growth pregnancies with PE (n = 99; 198 twins) | p values |
|--------------------------|-----------------------------------------------|-----------------------------------------------------|----------|
| Gestational age at delivery | 33.1 ± 3.2 34.4 ± 3.4 | 0.069                                               |          |
| <28 weeks                | 4 (7.8%) 5 (5.1%) | 0.495                                               |          |
| 28–32 weeks              | 12 (23.5%) 20 (20.2%) | 0.637                                               |          |
| 32–36 weeks              | 25 (49.0%) 22 (22.2%) | 0.001                                               |          |
| ≥36 weeks                | 10 (19.6%) 52 (52.5%) | <0.001                                              |          |
| Birth weight of the bigger twin (kg) | 2.08 ± 0.56 2.27 ± 0.49 | 0.075                                               |          |
| Birth weight of the smaller twin (kg) | 1.40 ± 0.47 2.00 ± 0.51 | <0.001                                              |          |
| Apgar score at 1 min     | 9 (8.8%) 5 (2.5%) | 0.020                                               |          |
| ≤3                       | 15 (14.7%) 22 (11.1%) | 0.362                                               |          |
| ≥8                       | 78 (76.5%) 171 (86.4%) | 0.031                                               |          |
| Apgar score at 5 min     | 5 (4.9%) 3 (1.5%) | 0.126                                               |          |
| ≤3                       | 5 (4.9%) 9 (4.5%) | 0.890                                               |          |
| ≥8                       | 92 (90.2%) 186 (93.9%) | 0.249                                               |          |

The data are shown as the mean ± standard deviation or the case number (%). sIUGR, selective intrauterine growth restriction; PE, preeclampsia.
pregnancies. In MC twins, sIUGR may be associated with different placental sharing [7], whereas in DC twins, sIUGR may be caused by abnormal placentation of the smaller twins [18], which plays a vital role in development of PE.

Furthermore, our study demonstrated that sIUGR was associated with early-onset and severe PE, as the rate of onset at <32 weeks, the rate of severe PE and the SBP were significantly higher in the sIUGR pregnancies than in the normal-growth pregnancies. These findings may suggest that the mechanism of PE development in sIUGR twin pregnancies is different from the mechanism in normal-growth twin pregnancies. Several studies have demonstrated that early-onset PE is associated with abnormal placentation development and that angiogenesis is important in the process of normal placentation [19,20]. As shown above, IUGR and IUIGR-discordant twins have imbalances in factors promoting angiogenesis. We speculate that because of the increased expression of placentantangiogenic factors and the abnormal placental development, PE is more severe and has a much earlier onset in sIUGR pregnancies than in normal-growth pregnancies. PE in normal-growth twin pregnancies may additionally be more directly correlated with an overextended uterus and the number of fetuses, as pregnancies with higher-order multiples have an increasing risk of developing PE [21].

We also found that perinatal outcomes were even poorer for sIUGR pregnancies with PE than for normal-growth pregnancies with PE, as fewer sIUGR pregnancies with PE were delivered at ≥36 weeks and more twins had severe asphyxia (Apgar score at 1 min ≤3). Previous studies have demonstrated that sIUGR pregnancies have less favorable perinatal outcomes [22,23]. As stated above, sIUGR was associated with increased odds of developing early onset and severe PE in twin pregnancies, which lead to early termination of the pregnancies. The smaller gestational week at delivery and the lower birth weight caused the poor outcomes in sIUGR with PE. In view of the results of our study, more attention must be paid to sIUGR than to normal-growth pregnancies with PE.

Fox et al. [24] found no correlation between PE and IUGR in patients with twin pregnancies. The use of different standards to assess IUGR may be the reason why this conclusion was different from ours. These authors specifically used standard tables for singleton pregnancies to define birth weight percentiles for gestational age; the incidence of birth weight <10% was as high as 50.0%, and the incidence of birth weight <5% was 27.5%. However, twins weigh less than single fetuses of the same gestational age do, especially in the third trimester [25]. Although there is no special Chinese twin growth curve, using the Ananth twin reference curve may more closely reflect the actual growth pattern of twins.

One limitation of our study is that the twin pregnancies in our cohort were from only one tertiary hospital. Additionally, several severe cases were sent to our hospital, so the cases could not be randomized. However, this study emphasizes the clinical characteristics of PE in sIUGR twin pregnancies and may provide evidence relevant to cohorts similar to ours.

In conclusion, this study has shown that sIUGR is associated with increased odds of developing PE in twin pregnancies as well as that the clinical manifestations are more severe and that perinatal outcomes are even poorer in sIUGR pregnancies with PE than in normal-growth pregnancies with PE. Moreover, in sIUGR pregnancies, DC twins are more likely to develop PE than MC twins. These findings may inform clinical consultation and management.

Declaration of interest

The authors report no declarations of interest. This work was partially supported by the National Natural Science Foundation of China (No. 81401209) and the Young Teacher Training Project of Sun Yat-sen University (No. 13ykpy18).

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Supplementary material available online

Supplemental Table 1