

# Fetal Growth Restriction as the Initial Finding of Preeclampsia is a Clinical Predictor of Maternal and Neonatal Prognoses: A Single-center Retrospective Study

**Masaya Takahashi**

Juntendo University Urayasu Hospital

**Shintaro Makino** (✉ [shintaro@juntendo.ac.jp](mailto:shintaro@juntendo.ac.jp))

Juntendo University Urayasu Hospital

**Kyoko Oguma**

Juntendo University Urayasu Hospital

**Haruka Imai**

Juntendo University Urayasu Hospital

**Ai Takamizu**

Juntendo University Urayasu Hospital

**Akari Koizumi**

Juntendo University Urayasu Hospital

**Koyo Yoshida**

Juntendo University Urayasu Hospital

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## Research Article

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## Abstract

**Background:** Preeclampsia (PE) is a hypertensive disorder specific to pregnancy, which sometimes causes severe maternal-neonatal complications. The International Society for the Study of Hypertension in Pregnancy revised their criteria for PE in 2018; a PE diagnosis can be established in the absence of proteinuria when other specific symptoms exist, such as other organ dysfunction or uteroplacental dysfunction. Therefore, the initial findings of PE (IFsPE) at the first diagnosis can vary considerably across patients. However, there are no reports on patients with PE based on different IFsPE and their impact on patients' clinical outcomes. Thus, we aimed to investigate the predictors of maternal and neonatal outcomes based on IFsPE according to the new criteria.

**Methods:** This was a retrospective study involving 3729 women who delivered at our hospital between 2015 and 2019. All women were reclassified based on the new criteria. They were divided into three groups based on the IFsPE: *Classification 1 (C-1)*, proteinuria (classical criteria); *Classification 2 (C-2)*, damage to other maternal organs; and *Classification 3 (C-3)*, uteroplacental dysfunction. Maternal and fetal conditions and perinatal outcomes were assessed in the three groups.

**Results:** In total, 104 women with PE were included. Of those, 42 (40.4%), 28 (26.9%), and 34 (32.7%) were assigned to *C-1*, *C-2*, and *C-3* groups, respectively. All women in *C-3* showed fetal growth restriction (FGR). The number of gestational weeks at PE diagnosis and delivery was significantly lower in the *C-3* group (*C-1*, 35.5±3.0 weeks; *C-2*, 35.2±3.6 weeks; *C-3*, 31.6±4.6 weeks,  $P < 0.01$ ; and *C-1*, 36.8±2.8 weeks; *C-2*, 36.3±3.2 weeks; *C-3*, 33.4±4.4 weeks,  $P < 0.01$ , respectively). The rates of preterm delivery at  $< 34$  weeks (odds ratio [OR]=4.58 [1.74-12.10] and OR=2.83 [1.01-7.97]), cesarean delivery (OR=4.35 [1.41-13.45] and OR=5.03 [1.51-16.78]), Apgar scores  $< 7$  at 1 min (OR=6.58 [2.08-20.80] and OR=4.09 [1.26-13.29]), neonatal intensive care unit admission (OR=12.19 [3.62-41.08], OR=7.50 [2.09-26.96]), and composite neonatal complications (OR=6.58 [2.08-20.80] and OR=5.33 [1.52-18.70]) were significantly higher in the *C-3* group than in the *C-1* and *C-2* groups.

**Conclusions:** PE patients with FGR had the most unfavorable prognosis for both maternal and neonatal outcomes.

## Background

Preeclampsia (PE) is a hypertensive disorder that occurs during pregnancy, and the incidence is reported to be 3–8% [1]. It is one of the causes of premature birth, and PE sometimes threatens both maternal and fetal/neonatal life, being responsible for more than 50,000 maternal and 500,000 neonatal deaths worldwide each year [2]. The detailed and exact etiology of PE remains unknown. However, inadequate trophoblast invasion and angiogenesis, resultant inappropriate remodeling of uterine spiral arteries, and increased production of antiangiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), have been identified as crucial contributors [3, 4]. These inappropriate responses can lead to uteroplacental dysfunction and subsequent maternal endothelial dysfunction, which contribute to the development of PE. Uteroplacental dysfunction, which causes placental hypoxic conditions and nutritional deficiency, leads to fetal growth restriction (FGR). Although various studies focusing on treatments used for suppressing PE progression have been conducted [5], the most effective treatment is yet to be identified. Thus, delivery is currently the only treatment for PE.

In recent years, the International Society for the Study of Hypertension in Pregnancy (ISSHP) has revised the definitions of PE and categorized PE into three classes: PE with proteinuria (classical criteria), dysfunction of other maternal organs, and uteroplacental dysfunction [6]. Therefore, a PE diagnosis can be established in the absence of proteinuria when the abovementioned specific findings exist. Therefore, the proportion of non-proteinuric PE cases has increased by approximately 9–15%, compared to that with the classical criteria [7, 8], making treatment more complicated. The authors also showed that the rates of composite maternal and neonatal complications were similar between classical PE and the new PE categories [8]. However, they did not compare those outcomes among patients classified by these new PE categories, and other previous studies have demonstrated significant associations between FGR and poor obstetric outcomes, including maternal and neonatal complications, in patients with PE [9–11]. Thus, it might be inappropriate to provide the same management for all PE patients in the three groups, which may lead to delayed therapeutic intervention in high-risk cases.

The initial findings of PE (IFsPE) at the first diagnosis can vary considerably across patients. Therefore, we hypothesized that if clinical features and maternal/neonatal outcomes could be evaluated and differentiated according to each IFsPE through risk classification, appropriate IFsPE-based management might be proposed. However, there are no reports on PE patients based on different IFsPE and their impact on clinical outcomes. Thus, we aimed to identify the predictors of maternal and neonatal outcomes based on IFsPE according to the new ISSHP criteria by evaluating clinical features and maternal/neonatal outcomes among PE patients with different IFsPE.

## Methods

### Study design and subjects

A retrospective cohort was designed after this study was approved by the ethical committee of Juntendo University Urayasu Hospital (No. 2020–044). The medical records of mothers and neonates were obtained from our electronic medical database. This study included pregnant women who delivered at our teaching hospital between January 2015 and December 2019. Patients with PE were reclassified based on the new ISSHP criteria, and they were divided based on the IFsPE into three groups according to the ISSHP categories: *Classification 1 (C-1)*, proteinuria (classical criteria); *Classification 2 (C-2)*, damage to other maternal organs; and *Classification 3 (C-3)*, uteroplacental dysfunction. As shown in Fig. 1, all patients were diagnosed with PE in the following three situations: (i) IFsPE complicated later by hypertension, (ii) simultaneous onset of both IFsPE and hypertension, and (iii) hypertension complicated later by IFsPE.

### Diagnosis and management of preeclampsia

The new 2018 ISSHP criteria were used to diagnose PE [6], and all women were reclassified based on the new criteria. Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg when measured on at least two occasions. According to the new criteria, PE can be diagnosed in the absence of proteinuria (defined as a protein level > 300 mg/day over 24 hours or a measured urinary protein to creatinine ratio of > 0.3) when specific findings exist, such as maternal organ dysfunction and uteroplacental dysfunction. Maternal organ dysfunction included renal insufficiency, liver involvement with or without involvement of the right upper quadrant or epigastric abdominal pain, neurological complications (altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), and hematological complications (platelet counts < 150,000/ $\mu$ L, disseminated intravascular coagulation, and hemolysis). Uteroplacental dysfunction included FGR, abnormal umbilical artery (UA) Doppler wave forms, and stillbirth. FGR was defined as an estimated fetal body weight of < -1.5 SD. Ultrasound examination and the nonstress test were performed at least once in a week. Blood pressure was evaluated at least three times a day, and blood samples were collected at least once or twice in a week. Rest was prescribed to the patients, and oral antihypertensive drugs, including methyldopa, calcium blockers,  $\alpha$ - and  $\beta$ -blockers, and intravenous calcium blockers, were administered if required. Magnesium sulfate ( $\text{MgSO}_4$ ) was administered to patients with eclampsia or those diagnosed to be at a high risk of eclampsia to prevent seizures.  $\text{MgSO}_4$  (4 g) was administered intravenously for 30 min followed by a dose of 1 g/h, with close monitoring of the serum magnesium level and related side effects. Antenatal betamethasone was administered to mothers for the maturation of fetal lungs before 34 weeks of gestation. Delivery was indicated by the inability to control maternal blood pressure using antihypertensive drugs; placental abruption; eclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; nonreassuring fetal status (NRFS); fetal growth arrest lasting 2 weeks, stillbirth, and 37 weeks of gestation. The attending physician decided the mode of delivery according to obstetric and fetal conditions.

First, to assess the impact of FGR on clinical features and maternal/neonatal outcomes according to the new criteria, we divided the participants into two groups, the PE with FGR and PE without FGR groups, and performed comparisons between the two groups. Second, to investigate the differences in clinical features and maternal/neonatal outcomes among the three groups based on IFsPE (*C-1*, *C-2*, and *C-3*), the following items were evaluated and compared among the three groups: maternal age, pre-pregnancy body mass index (BMI), pregnancy history, the indication of delivery (maternal factors or fetal factors), and the rate of FGR. Maternal outcomes included the gestational age at PE diagnosis, gestational age at delivery, duration from diagnosis to delivery, mode of delivery, NRFS, placental abruption, eclampsia, HELLP syndrome, blood loss, blood transfusion, pleural effusion or ascites, and duration of hospital stay. Composite maternal complications were defined as the presence of one of the following conditions: placental abruption, eclampsia, HELLP syndrome, blood transfusion, and pleural effusion or ascites. Neonatal outcomes included fetal birth weight, Apgar score, umbilical blood analysis (pH,  $\text{O}_2$ ,  $\text{CO}_2$ ,  $\text{HCO}_3$ , base excess [BE], and lactate), and admission to the neonatal intensive care unit (NICU). Composite neonatal complications were defined as the presence of one of the following conditions: stillbirth, neonatal mortality, infant mortality, respiratory distress syndrome (RDS), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and tracheal intubation. Composite neonatal complications were diagnosed by a skilled pediatrician and an ophthalmologist specializing in infants' eyes.

### Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL). The differences between the two groups were evaluated using the Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The differences among the three groups were analyzed using one-way analysis of variance with a multiple comparison test, followed by the *post hoc* Tukey's test for continuous variables and Fisher's exact test for categorical variables. The risks of complications in each group

are presented as crude odds ratios (ORs) with 95% confidence intervals (95% CIs). *P*-values < 0.05 were considered statistically significant. All data are presented as the mean ± SD or n (%).

## Results

Of the 3729 women who delivered at our teaching hospital between January 2015 and December 2019, 158 (4.2%) had PE. After excluding 19 cases of multiple pregnancies, 139 (88.0%) PE cases of singleton pregnancies remained. Further, we excluded 35 cases of superimposed PE. The remaining 104 (74.8%) cases were included in this analysis (Fig. 2).

## Comparison of maternal and neonatal complications between PE patients with FGR and without FGR

Table 1 compares the baseline characteristics between PE patients with and without FGR. Of the 104 patients, 45 (43.3%) and 59 (56.7%) had FGR and did not have FGR, respectively. There was no significant difference between the two groups in maternal age, pre-pregnancy BMI, primiparous rate, and indication of delivery. Maternal pre-pregnancy BMI was significantly lower in PE patients with FGR than in those without FGR (*p* < 0.05).

Table 1  
Maternal characteristics in the two groups based on the presence of fetal growth restriction

	PE with FGR (n = 45)			PE without FGR (n = 59)			P value
Maternal age (years)	35.1	±	5.8	33.6	±	5.1	n.s.
Pre-pregnancy BMI	21.8	±	3.0	23.7	±	4.2	< 0.05
Obesity (BMI > 25 kg/m <sup>2</sup> )	7 (15.6%)			19 (32.2%)			n.s.
Primiparity	30 (66.7%)			41 (69.5%)			n.s.
Indication of delivery							
Maternal factors	29 (64.4%)			47 (79.7%)			n.s.
Fetal factors	16 (35.6%)			12 (20.3%)			
Abbreviations: BMI, body mass index; PE, preeclampsia; FGR, fetal growth restriction; n.s., not significant; SD, standard deviation							
FGR was defined as an estimated fetal body weight of < -1.5 SD							
Data are presented as the mean ± SD or n (%).							
P-values < 0.05 were considered statistically significant.							

Table 2 presents the comparison of maternal outcomes between the two groups. The gestational age at PE diagnosis was significantly lower in PE patients with FGR than in those without FGR (32.1 ± 4.3 weeks vs. 35.7 ± 3.2 weeks, *p* < 0.0001). The rate of early onset PE, defined as PE onset at < 34 weeks of gestation, was significantly higher in PE patients with FGR than in those without FGR (62.2% vs. 28.8%, *p* < 0.001), and the OR was 4.07 (95% CI, 1.78–9.29). The gestational age at delivery was significantly lower in PE patients with FGR than in those without FGR (33.9 ± 4.2 weeks vs. 36.8 ± 2.8 weeks, *p* < 0.0001). In addition, the rates of premature birth at both < 37 and < 34 weeks of gestation were significantly lower in the former group than in the latter group (73.3% vs. 37.4%, *p* < 0.01 and 46.7% vs. 16.9%, *p* < 0.01; respectively), and the corresponding ORs were 3.04 (95% CI, 1.32–7.02) and 4.29 (95% CI, 1.75–10.52), respectively. In contrast, the duration from diagnosis to delivery was significantly shorter in PE patients without FGR than in those with FGR (1.1 ± 1.6 vs. 1.8 ± 1.5 weeks, *p* < 0.05). Regarding the mode of delivery, the rate of cesarean section was significantly higher in PE patients with FGR than in those without FGR (80.0% vs. 57.6%, *p* < 0.05). A significant difference was found in the rate of NRFS between PE patients with FGR and those without FGR (62.2% vs. 35.6%, *p* < 0.01). There were no significant differences in the rates of late-onset PE, instrumental vaginal delivery, placental abruption, eclampsia, HELLP syndrome, blood transfusion, and pleural effusion or ascites. Additionally, no significant difference was found in the amount of blood loss and duration of hospital stay.

Table 2  
Comparison of maternal outcomes according to the presence of fetal growth restriction

	PE with FGR (n = 45)	PE without FGR (n = 59)	P value	OR	95% CI
Gestational age at the diagnosis of PE (weeks)	32.1 ± 4.3	35.7 ± 3.2	< 0.0001	-	-
< 34 weeks	28 (62.2%)	17 (28.8%)	< 0.001	4.07	1.78–9.29
≥ 34 weeks	17 (37.8%)	42 (71.2%)	-	-	-
Gestational age at delivery (weeks)	33.9 ± 4.2	36.8 ± 2.8	< 0.0001	-	-
Premature birth at < 37 weeks	33 (73.3%)	28 (37.4%)	< 0.01	3.04	1.32–7.02
Premature birth at < 34 weeks	21 (46.7%)	10 (16.9%)	< 0.01	4.29	1.75–10.52
Duration from diagnosis to delivery (weeks)	1.8 ± 1.5	1.1 ± 1.6	< 0.05	-	-
Median (range)	1.4 (0-6.6)	0.6 (0-9.3)			
Mode of delivery					
Cesarean section	36 (80.0%)	34 (57.6%)	< 0.05	2.94	1.20–7.19
Instrumental vaginal delivery	3 (6.7%)	12 (20.3%)	-	0.28	0.07–1.06
NRFS	28 (62.2%)	21 (35.6%)	< 0.01	2.98	1.33–6.66
Blood loss (g) Median (range)	493 (99-1300)	635 (165–2060)	n.s.	-	-
Duration of hospital stay	12.6 ± 5.5	12.0 ± 5.8	n.s.	-	-
Composite maternal complications	14 (31.1%)	20 (33.9%)	n.s.	0.88	0.38–2.02
Placental abruption	3 (6.7%)	2 (3.4%)	n.s.	2.04	0.33–12.73
Eclampsia	0 (0.0%)	2 (3.4%)	n.s.	-	-
HELLP syndrome	2 (4.4%)	7 (11.9%)	n.s.	0.35	0.07–1.75
Blood transfusion	6 (13.3%)	7 (11.9%)	n.s.	1.14	0.36–3.67
Pleural effusion or ascites	12 (26.7%)	16 (27.1%)	n.s.	0.98	0.41–2.34
Abbreviations: PE, preeclampsia; NRFS, nonreassuring fetal status; HELLP, hemolysis, elevated liver enzymes, and low platelets; FGR, fetal growth restriction; OR, odds ratio; CI, confidence interval; n.s., not significant; SD, standard deviation					
FGR was defined as an estimated fetal body weight of < -1.5 SD					
Data are presented as the mean ± SD, median with range, n (%), or OR with 95% CI.					
P-values < 0.05 were considered statistically significant.					

Table 3 shows the comparison of neonatal outcomes between the two groups. Birth weight was significantly lower in the PE plus FGR group than in the PE without FGR group (1473 ± 634 g vs. 2415 ± 621 g,  $p < 0.0001$ ). The rates of Apgar scores of < 7 and < 4 at 1 min were significantly higher in the former group than in the latter group (42.2% vs. 11.9%,  $p < 0.001$  and 24.4% vs. 3.4%,  $p < 0.01$ ; respectively); the rate of Apgar scores of < 7 at 5 min was also significantly higher in the former group than in the latter group (13.3% vs. 1.7%,  $p < 0.05$ ). The rates of ROP and tracheal intubation were also significantly higher in the PE plus FGR group than in the PE without FGR group (22.2% vs. 1.7%,  $p < 0.001$  and 31.1% vs. 13.6%,  $p < 0.05$ ; respectively). The rate of composite neonatal complications was significantly higher in the former group than in the latter group (37.8% vs. 13.6%,  $p < 0.001$ ). The rate of admission to the NICU was significantly higher in the PE plus FGR group than in the PE without FGR group (75.6% vs. 44.1%,  $p < 0.01$ ). Only the UA O<sub>2</sub> level was significantly different between the two groups (17.5 ± 4.9 vs. 19.7 ± 5.5,  $p < 0.05$ ). There were no significant differences in the rates of Apgar scores of < 4 at 4 minutes or neonatal complications, such as stillbirth, neonatal mortality, infant mortality, RDS, and PVL. Additionally, no significant differences were found in the other UA values.

Table 3  
Comparison of neonatal outcomes according to the presence of fetal growth restriction

	PE with FGR		PE without FGR		P value	OR	95% CI
	(n = 45)		(n = 59)				
Birth weight (g)	1473	± 634	2415	± 621	< 0.0001	-	-
Apgar score (at 1 min), median (range)	7 (1–9)		8 (2–9)				
< 7	19 (42.2%)		7 (11.9%)		< 0.001	5.43	2.02–14.55
< 4	11 (24.4%)		2 (3.4%)		< 0.01	9.22	1.93–44.12
Apgar score (at 5 min), median (range)	9 (4–10)		9 (6–10)				
< 7	6 (13.3%)		1 (1.7%)		< 0.05	8.92	1.03–77.03
< 4	0 (0.0%)		0 (0.0%)		-	-	-
Umbilical blood analysis							
pH	7.27	± 0.08	7.28	± 0.10	n.s.	-	-
O <sub>2</sub>	17.5	± 4.9	19.7	± 5.5	< 0.05	-	-
CO <sub>2</sub>	54.0	± 10.0	51.0	± 15.4	n.s.	-	-
HCO <sub>3</sub>	23.7	± 2.6	22.9	± 2.8	n.s.	-	-
BE	-4.7	± 5.7	-4.2	± 3.8	n.s.	-	-
Lactate	36.6	± 18.8	34.1	± 15.3	n.s.	-	-
Admission to the NICU	34 (75.6%)		26 (44.1%)		< 0.01	3.92	1.67–9.20
Composite neonatal complications	17 (37.8%)		8 (13.6%)		< 0.001	3.87	1.48–10.09
Stillbirth	1 (2.2%)		0 (0.0%)		-	-	-
Neonatal mortality	1 (2.2%)		0 (0.0%)		-	-	-
Infant mortality	1 (2.2%)		0 (0.0%)		-	-	-
RDS	9 (20.0%)		4 (6.8%)		n.s.	3.44	0.98–12.00
PVL	1 (2.2%)		0 (0.0%)		-	-	-
ROP	10 (22.2%)		1 (1.7%)		< 0.001	16.57	2.03–135.06
Tracheal intubation	14 (31.1%)		8 (13.6%)		< 0.05	2.88	1.08–7.65
Abbreviations: NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; PE, preeclampsia; FGR, fetal growth restriction; OR, odds ratio; CI, confidence interval; n.s., not significant; SD, standard deviation							
FGR was defined as an estimated fetal body weight of < -1.5 SD							
Data are presented as the mean ± SD, median with range, n (%), or OR with 95% CI.							
P-values < 0.05 were considered statistically significant.							

## Comparison of maternal and neonatal complications among C-1, C-2, and C-3

Table 4 compares the baseline characteristics of the three groups (C-1 vs. C-2 vs. C-3). Of the 104 subjects, 42 (40.4%), 28 (26.9%), and 34 (32.7%) were included in the C-1, C-2, and C-3 groups, respectively. There was no significant difference among the three groups in terms of maternal age, pre-pregnancy BMI (including a BMI > 25 kg/m<sup>2</sup>), primiparous rate, and indication of delivery. The number of patients with FGR was 7 (16.7%) in the C-1 group, 4 (14.3%) in the C-2 group, and 34 (100.0%) in the C-3 group, and the rate of FGR was significantly higher in the C-3 group than in the other groups ( $p < 0.0001$ ).

Table 4  
Comparison of maternal characteristics across the three groups based on ISSHP categories

	<b>Classification 1</b>			<b>Classification 2</b>			<b>Classification 3</b>			<b>P value</b>
	<b>(n = 42)</b>			<b>(n = 28)</b>			<b>(n = 34)</b>			
Maternal age (years)	33.8	±	4.9	33.9	±	5.4	35.0	±	6.2	n.s.
Pre-pregnancy BMI	23.4	±	4.4	23.0	±	3.6	22.1	±	3.1	n.s.
Obesity (BMI > 25 kg/m <sup>2</sup> )	13 (31.0%)			7 (25.0%)			6 (17.6%)			n.s.
Primiparity	32 (76.2%)			16 (57.1%)			23 (67.6%)			n.s.
Indication of delivery										
Maternal factors	33 (78.6%)			21 (75.0%)			22 (64.7%)			n.s.
Fetal factors	9 (21.4%)			7 (25.0%)			12 (35.3%)			
FGR	7 (16.7%)			4 (14.3%)			34 (100.0%)			< 0.0001
Abbreviations: BMI, body mass index; FGR, fetal growth restriction; n.s., not significant; SD, standard deviation; ISSHP, International Society for the Study of Hypertension in Pregnancy										
FGR was defined as an estimated fetal body weight of < -1.5 SD										
Data are presented as mean ± SD or n (%).										
P-values < 0.05 were considered as statistically significant.										

Table 5 presents the comparison of maternal outcomes among the three groups. The gestational age at PE diagnosis was significantly lower in the C-3 group than in the other groups (C-1, 35.5 ± 3.0 weeks; C-2, 35.2 ± 3.6 weeks; C-3, 31.6 ± 4.6 weeks; C-1 vs. C-3,  $p < 0.0001$ ; C-2 vs. C-3,  $p < 0.01$ ). The rate of early onset PE was significantly higher in the C-3 group than in the other groups (C-1, 28.6%; C-2, 39.3%; C-3, 64.7%; C-1 vs. C-3,  $p < 0.01$ ; C-2 vs. C-3,  $p < 0.05$ ), and the ORs on comparing the C-3 group with the C-1 and C-2 groups were 4.58 (95% CI, 1.74–12.10) and 2.83 (95% CI, 1.01–7.97), respectively. The gestational age at delivery was significantly lower in the C-3 group than in the other groups (C-1, 36.8 ± 2.8 weeks; C-2, 36.3 ± 3.2 weeks; C-3, 33.4 ± 4.4 weeks; C-1 vs. C-3,  $p < 0.001$ ; C-2 vs. C-3,  $p < 0.01$ ). Moreover, the rates of premature birth, at both < 37 and < 34 weeks of gestation, were significantly different in the C-3 group compared with those in the other groups, as shown in Table 5. However, there was no significant difference in the duration from diagnosis to delivery among the three groups (C-1, 1.3 ± 1.2 weeks; C-2, 1.1 ± 2.0 weeks; C-3, 1.7 ± 1.6 weeks). The temporal relationship of the time from PE diagnosis to delivery is clearly illustrated in Fig. 3. Regarding the mode of delivery, the rate of cesarean section was significantly higher in the C-3 group than in the other groups (C-1, 57.1%; C-2, 53.6%; C-3, 85.3%; C-1 vs. C-3,  $p < 0.05$ ; C-2 vs. C-3,  $p < 0.05$ ). There were no significant differences in the rates of late-onset PE, instrumental vaginal delivery, NRFS, placental abruption, eclampsia, blood transfusion, and pleural effusion or ascites. Additionally, no significant difference was found in the amount of blood loss and duration of hospital stay.

Table 5  
Comparison of maternal outcomes across the three groups based on ISSHP categories

	<i>C-1</i>		<i>C-2</i>		<i>C-3</i>		<i>C-1 vs. C-3</i>		<i>C-2 vs. C-3</i>	
	(n = 42)		(n = 28)		(n = 34)		P value	P value	OR	95% CI
Gestational age at the diagnosis of PE (weeks)	35.5	± 3.0	35.2	± 3.6	31.6	± 4.6	< 0.0001	< 0.01	-	-
< 34 weeks	12	(28.6%)	11	(39.3%)	22	(64.7%)	< 0.01	< 0.05	4.58	1.74–12.10
≥ 34 weeks	30	(71.4%)	17	(60.7%)	12	(35.3%)	n.s.	n.s.	-	-
Gestational age at delivery (weeks)	36.8	± 2.8	36.3	± 3.2	33.4	± 4.4	< 0.001	< 0.01	-	-
Premature birth at < 37 weeks	20	(47.6%)	13	(46.4%)	26	(76.5%)	< 0.05	< 0.05	3.58	1.32–9.69
Premature birth at < 34 weeks	6	(14.3%)	7	(25.0%)	17	(50.0%)	< 0.0001	< 0.0001	6.0	2.01–17.93
Duration from diagnosis to delivery (weeks)	1.3	± 1.2	1.1	± 2.0	1.7	± 1.6	n.s.	n.s.	-	-
Median (range)	7	(0-4.4)	3	(0-9.3)	9.5	(0-6.6)				
Mode of delivery										
Cesarean section	24	(57.1%)	15	(53.6%)	29	(85.3%)	< 0.05	< 0.05	4.35	1.41–13.45
Instrumental vaginal delivery	7	(16.7%)	6	(21.4%)	2	(5.9%)	n.s.	n.s.	0.31	0.06–1.62
NRFS	16	(38.1%)	13	(46.4%)	20	(58.8%)	n.s.	n.s.	2.32	0.92–5.85
Blood loss (g), median (range)	650	(165–1820)	555	(111–2060)	498	(99-1300)	n.s.	n.s.	-	-
Duration of hospital stay	12.6	± 6.2	11.6	± 5.1	12.4	± 5.4	n.s.	n.s.	-	-
Composite maternal complications	18	(42.9%)	11	(39.3%)	13	(38.2%)	n.s.	n.s.	0.83	0.33–2.08
Placental abruption	1	(2.4%)	1	(3.6%)	3	(8.8%)	n.s.	n.s.	3.97	0.39-40.00
Eclampsia	0		2	(7.1%)	0		-	-	-	-
HELLP syndrome	2	(4.8%)	6	(21.4%)	1	(2.9%)	-	-	0.61	0.05–6.98
Blood transfusion	5	(11.9%)	4	(14.3%)	4	(11.8%)	n.s.	n.s.	0.99	0.24-4.00
Pleural effusion or ascites	15	(35.7%)	4	(14.3%)	9	(26.5%)	n.s.	n.s.	0.65	0.24–1.74
Abbreviations: C-1, classification 1; C-2, classification 2; C-3, classification 3; PE, preeclampsia; NRFS, nonreassuring fetal status; HELLP, hemolysis, elevated liver enzymes, and low platelets; OR, odds ratio; CI, confidence interval; n.s., not significant; ISSHP, International Society for the Study of Hypertension in Pregnancy; SD, standard deviation										
Data are presented as the mean ± SD, median with range, n (%), or OR with 95% CI.										
P-values < 0.05 were considered statistically significant										

Table 6 shows the comparison of neonatal outcomes among the three groups. Birth weight was significantly lower in the C-3 group than in the other groups (C-1, 2366 ± 617 g; C-2, 2255 ± 667 g; C-3, 1361 ± 646 g; C-1 vs. C-3,  $p < 0.0001$ ; C-2 vs. C-3,  $p < 0.0001$ ). The rates of Apgar scores of < 7 and < 4 at 1 min, ROP, and tracheal intubation were significantly higher in the C-3 group than in the other groups, as shown in Table 6. The rate of composite neonatal complications was also significantly higher in the C-3 group than in the other groups (C-1, 11.9%; C-2, 14.3%; C-3, 47.1%; C-1 vs. C-3,  $p < 0.001$ ; C-2 vs. C-3,  $p < 0.01$ ). The rate of admission to the NICU was significantly higher in the C-3 group than in the other groups (C-1, 38.1%; C-2, 50.0%; C-3, 88.2%; C-1 vs. C-3,  $p < 0.0001$ ; C-2 vs. C-3,  $p < 0.01$ ). Regarding umbilical blood analysis, the UA O<sub>2</sub> level was significantly lower in the C-3 group than in the C-2 group (C-1, 18.8 ± 5.6; C-2, 20.9 ± 5.1; C-3, 16.9 ± 4.8; C-2 vs. C-3,  $p < 0.01$ ). There were no significant differences in the rates of Apgar scores of < 7 and < 4 at 5 min or neonatal complications, such as stillbirth, neonatal mortality, infant mortality, RDS, and PVL. In addition, no significant differences were found in the other UA values.

Table 6  
Comparison of neonatal outcomes across the three groups based on ISSHP categories

	C-1		C-2		C-3		C-1 vs. C-3	C-2 vs. C-3	C-1 vs. C-3		C-2 vs. C-3	
	(n = 42)		(n = 28)		(n = 34)		P value	P value	OR	95% CI	OR	95% CI
Birth weight (g)	2366	± 617	2255	± 666	1361	± 646	< 0.0001	< 0.0001	-	-	-	-
Apgar score (1 min), Median (range)	8 (2-9)		8 (5-9)		7 (1-9)							
< 7	5 (11.9%)		5 (17.9%)		16 (47.1%)		< 0.001	< 0.05	6.58	2.08-20.80	4.09	1.26-13.29
< 4	3 (7.1%)		0 (0%)		10 (29.4%)		< 0.05	-	5.42	1.35-21.68	-	-
Apgar score (5 min), Median (range)	9 (5-10)		9 (7-10)		8.5 (4-10)							
< 7	2 (4.8%)		0 (0%)		6 (17.6%)		n.s.	-	4.29	0.81-22.80	-	-
< 4	0 (0%)		0 (0%)		0 (0%)		-	-	-	-	-	-
Umbilical blood analysis												
pH	7.28	± 0.10	7.30	± 0.06	7.26	± 0.09	n.s.	n.s.	-	-	-	-
O <sub>2</sub>	18.8	± 5.6	20.9	± 5.0	16.9	± 4.8	n.s.	< 0.01	-	-	-	-
CO <sub>2</sub>	51.6	± 16.2	50.1	± 11.7	55.1	± 10.3	n.s.	n.s.	-	-	-	-
HCO <sub>3</sub>	23.1	± 2.2	22.8	± 3.3	23.8	± 2.6	n.s.	n.s.	-	-	-	-
BE	-4.8	± 5.9	-4.3	± 4.1	-4.0	± 3.4	n.s.	n.s.	-	-	-	-
Lactate	33.0	± 14.1	35.7	± 15.8	37.4	± 20.8	n.s.	n.s.	-	-	-	-
Admission to the NICU	16 (38.1%)		14 (50.0%)		30 (88.2%)		< 0.0001	< 0.01	12.19	3.62-41.08	7.50	2.09-26.96
Composite neonatal complications	5 (11.9%)		4 (14.3%)		16 (47.1%)		< 0.001	< 0.01	6.58	2.08-20.80	5.33	1.52-18.70
Stillbirth	0		0		1 (2.9%)		-	-	-	-	-	-
Neonatal mortality	0		0		1 (2.9%)		-	-	-	-	-	-
Infant mortality	0		0		1 (2.9%)		-	-	-	-	-	-
RDS	4 (9.5%)		1 (3.6%)		8 (23.5%)		n.s.	n.s.	2.92	0.80-10.72	8.31	0.97-71.14
PVL	0		0		1 (2.9%)		-	-	-	-	-	-
ROP	2 (4.8%)		0		9 (26.5%)		< 0.01	-	7.20	1.44-36.08	-	-
Tracheal intubation	5 (11.9%)		4 (14.3%)		13 (38.2%)		< 0.05	< 0.05	4.58	1.43-14.64	3.71	1.05-13.15

Abbreviations: C-1, classification 1; C-2, classification 2; C-3, classification 3; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; PE, preeclampsia; OR, odds ratio; CI, confidence interval; n.s., not significant; SD, standard deviation; ISSHP, International Society for the Study of Hypertension in Pregnancy

Data are presented as the mean  $\pm$  SD, median with range, n (%), or OR with 95% CI.

P-values < 0.05 were considered statistically significant.

## Discussion

This study demonstrated that patients diagnosed with PE in whom the IFsPE was FGR (C-3 group) had significantly higher risks of lower gestational age at PE diagnosis, lower gestational age at delivery, cesarean section, lower Apgar score, admission of the infant to the NICU, and composite neonatal complications than those in the other two groups. These results indicated that patients categorized in the C-3 group showed the most unfavorable prognosis in terms of both maternal and neonatal outcomes, indicating that special attention and more careful management are necessary for PE patients categorized into the C-3 group. Thus, we identified the clinical prognostic factors of PE patients among the three groups, which can be useful for managing the disease and explaining the medical condition to the patients and their families. To the best of our knowledge, this is the first study that compared maternal and neonatal outcomes among the three new ISSHP categories based on IFsPE. Due to the small sample size, we were unable to classify the IFsPE of maternal organ dysfunction (such as renal insufficiency, liver involvement, neurological complications, and hematological complications) in the C-2 group in detail. Therefore, data on additional cases should be accumulated to compare outcomes among more detailed groups and to clarify the differences in prognosis across groups to establish guidelines for IFsPE-based management of PE in the future.

In 2018, the ISSHP revised its definitions of PE [6]. In contrast to the ISSHP criteria, the American College of Obstetricians and Gynecologists guidelines in 2013 did not include uteroplacental dysfunction in the diagnostic criteria of PE because FGR should be managed similarly in patients with or without PE [12]. However, as previous studies have shown, FGR was associated with an increased risk of maternal and neonatal complications in PE patients [9–11]. As uteroplacental dysfunction is a significant etiology of PE, it is acceptable to include it in the diagnostic criteria for PE. In addition, in 2009, Mitani *et al.* showed that about 15% of patients with FGR had proteinuria as a complication, which was diagnosed as PE, suggesting that patients with FGR required close monitoring for PE detection [11]. To address the impact of FGR in PE patients who were reclassified according to the new ISSHP criteria, we performed comparisons between PE patients with FGR and without FGR. Although composite maternal complications were not significantly different, there were significantly higher rates of composite neonatal complications in PE patients with FGR than in those without FGR, consistent with the findings of previous studies [9–11]. Moreover, patients with FGR had significantly higher risks of lower gestational age at PE diagnosis, lower gestational age at delivery, cesarean section, lower Apgar score, and admission of the infant to the NICU. Thus, obstetricians should bear in mind that PE patients with FGR might have a poor obstetric prognosis.

While the exact etiology of PE remains unclear, a two-stage disorder theory for the etiology and pathology of PE has been proposed recently [13, 14]. However, no evidence-based methods of prevention or treatment have been established yet. Therefore, it is clinically important to be aware of the early PE-related symptoms or findings, which widely vary in each patient, and subsequently provide appropriate and early management based on risk classification. Our investigation is the first to focus on the perinatal outcomes of PE patients classified according to the new ISSHP criteria based on IFsPE. We compared maternal and neonatal outcomes among the three groups: C-1, C-2, and C-3. Poor prognosis was observed in the patients in the C-3 group, whose IFsPE included FGR; the rates of both maternal and neonatal complications, including higher risks of lower gestational age at PE diagnosis, lower gestational age at delivery, cesarean section, lower Apgar score, admission of the infant to the NICU, and composite neonatal complications, were higher in the C-3 group than in the other two groups. Thus, special attention should be paid when the patients are diagnosed with PE based on FGR as the IFsPE in the following situations: FGR complicated later by hypertension, simultaneously onset of both FGR and hypertension, and hypertension complicated later by FGR.

As shown in Table 4, most PE patients with FGR were diagnosed with PE based on FGR as the IFsPE. Although FGR is a severe fetal condition with a higher risk of cesarean section, the indications for delivery showed no significant difference among the three groups. The exact reasons for this discrepancy are unclear. However, the production of antiangiogenic factors might increase with worsening uteroplacental circulation, subsequent causing FGR; this would result in worsening maternal endothelial dysfunction. Previous studies have demonstrated that sFlt-1 levels, sEng levels, and the sFlt-1 to placental growth factor (PlGF) ratio (sFlt-1/PlGF) were significantly increased in PE patients with FGR compared to those in patients without FGR, and these results are consistent with our speculation [15, 16]. Further studies are required to clarify the interaction between uteroplacental dysfunction and maternal endothelial dysfunction.

The UA O<sub>2</sub> level was significantly lower in PE patients with FGR than in those without FGR and in PE patients categorized into the C-3 group. Therefore, we speculated that patients with FGR had underlying chronic fetal hypoxia due to uteroplacental dysfunction, which limited the exchange of gas and nutrients and caused the resultant FGR. In recent years, the application of hemoglobin vesicles for the treatment of conditions such as brain ischemia and massive obstetric hemorrhage has been suggested, based on the results of animal models [17–19]. Heng Li *et al.* demonstrated that artificial nano-oxygen carriers can be used to successfully treat placental hypoxia and manage FGR and apoptotic damage in the brain using the PE rat model [20]. Given our results, this noninvasive therapy might have the potential to delay the progression of PE and improve neonatal outcomes. However, this finding had a possible limitation: lower levels of UA O<sub>2</sub> may be the result of fetal conditions such as NRFS and the mode of delivery rather than underlying chronic fetal hypoxia.

The limitations of this study should be acknowledged. This study was a single-center retrospective cohort study with a small sample size. This small sample size might have affected the results of the study. Especially in the C-2 group, various types of IFsPE, such as renal insufficiency, liver involvement, neurological complications, and hematological complications, were included. Therefore, we could not clarify the differences based on detailed IFsPE. Therefore, a study with a large sample size is required to verify the accuracy of our results and the differences in prognosis across the detailed IFsPE groups to establish detailed guidelines for the IFsPE-based management of PE. As our hospital is a perinatal medical center and severe PE patients were likely to be transferred, our results might have some differences compared with those of general hospitals.

The strength of our study was that this was the first study to compare maternal and neonatal outcomes among the three new ISSHP categories based on IFsPE and to show that PE patients presenting with FGR as the IFsPE had a poor prognosis. All data were electronically recorded, and all patients were retrospectively reclassified and diagnosed with PE according to the 2018 ISSHP criteria; thus, there was no selection bias.

## Conclusions

In summary, our study suggested that an unfavorable prognosis was observed in PE patients presenting with FGR as the IFsPE who were classified in the C-3 group, compared with that in other groups, thus indicating that special attention and more careful management are necessary for PE patients categorized into the C-3 group. Moreover, careful and close observation is required in patients presenting with FGR prior to PE diagnosis. Our results are useful in terms of explaining the expected prognosis of PE to patients and their families. Additional studies should be conducted to confirm our findings.

## Abbreviations

BMI Body mass index

FGR Fetal growth restriction

HELLP Hemolysis, elevated liver enzymes, and low platelet

ISSHP International Society for the Study of Hypertension in Pregnancy

NICU Neonatal intensive care unit

OR Odds ratio

RDS Respiratory distress syndrome

ROP Retinopathy of prematurity

UA Umbilical artery

CI Confidence interval

IFsPE Initial findings of PE

NRFS Nonreassuring fetal status

PE Preeclampsia

PIGF Placental growth factor

PVL Periventricular leukomalacia

## Declarations

### Ethics approval and consent to participate

The Ethics Committee of Juntendo University Urayasu Hospital approved this study and the use of an opt-out consent method (Approval No. 2020–044). The requirement for written informed consent was waived by the Ethics Committee of Juntendo University Urayasu Hospital . All methods were performed in accordance with the relevant guidelines and regulations.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the study are available from the corresponding author upon reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

### Author Contributions

MT was the principal investigator and drafted the manuscript with the help of SM. MT

contributed to data collection. MT and SM contributed to data analysis and manuscript revision. KO, HI, AT, AK, and KY contributed to data interpretation and manuscript revision. SM and KY supervised the study. All authors have read and approved the final manuscript.

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Not applicable.

### Authors' information

Department of Obstetrics and Gynecology, Juntendo University Urayasu Hospital, Urayasu City, Chiba, Japan.

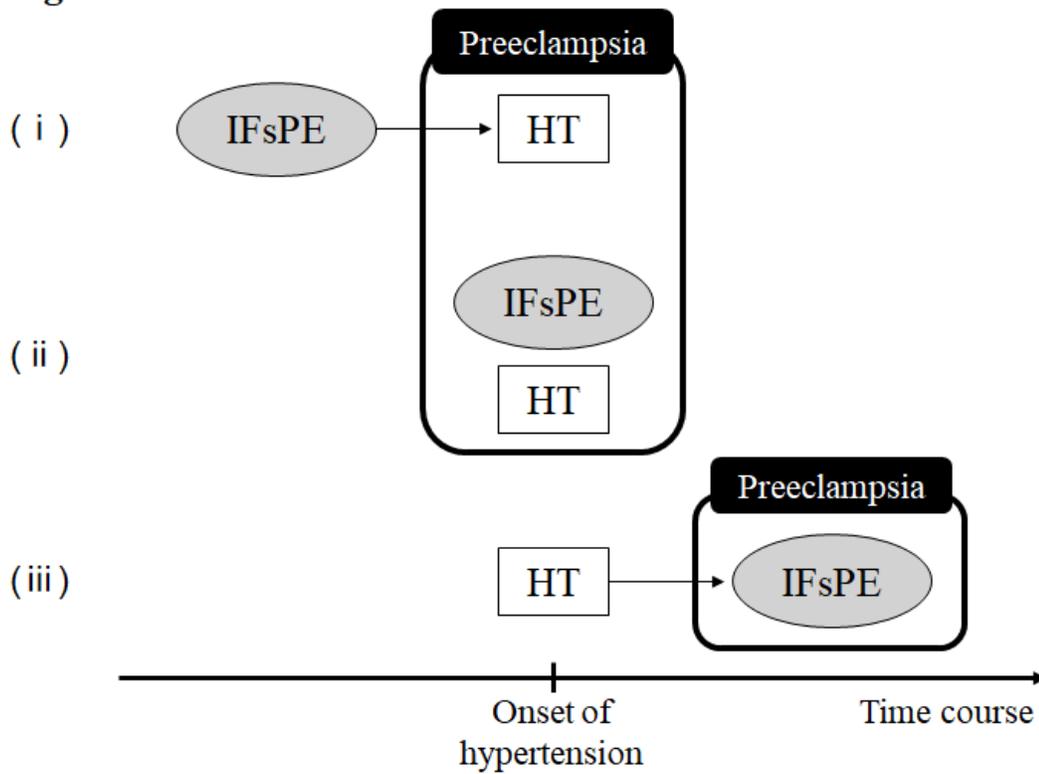
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## Figures

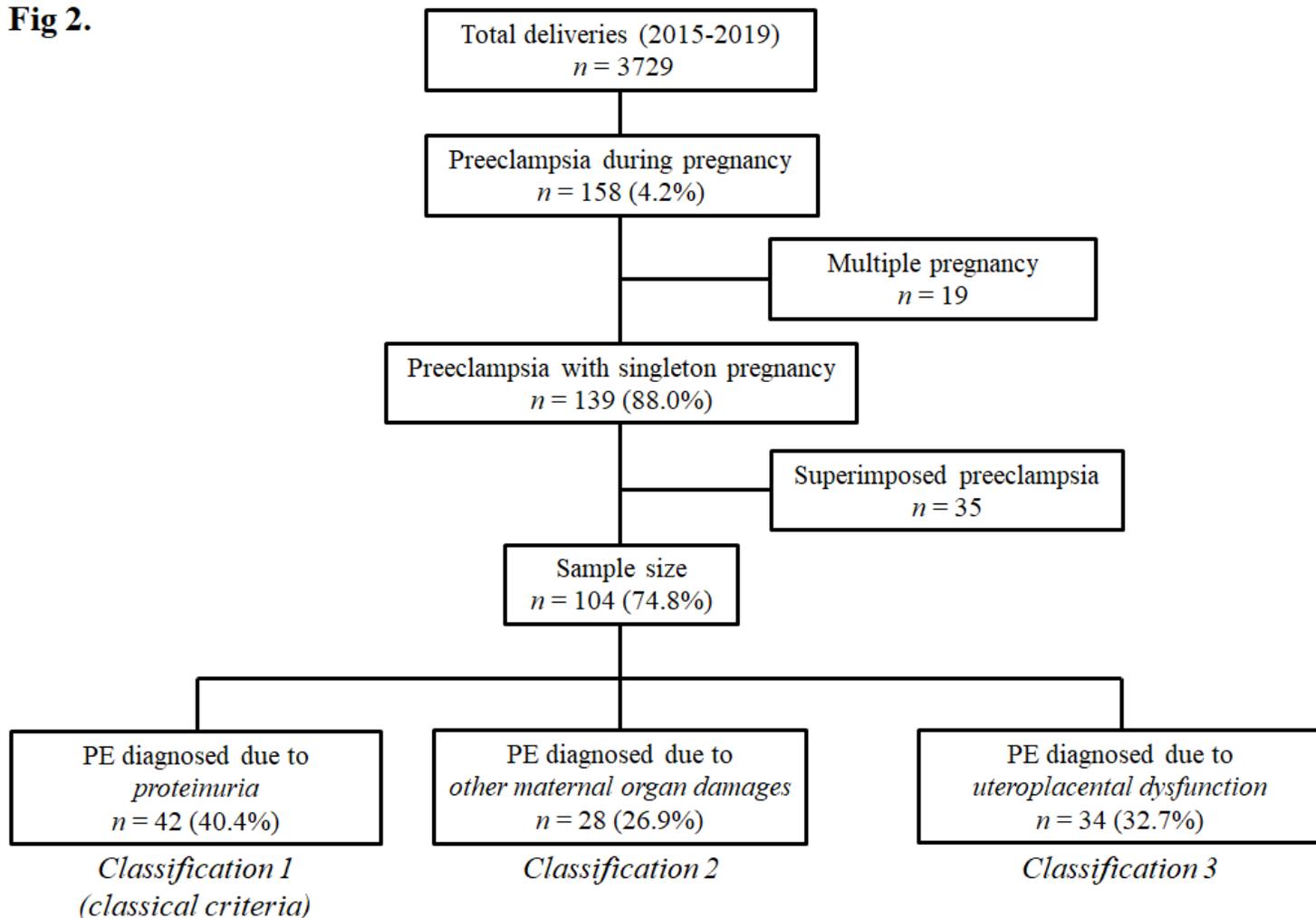
**Fig 1.**



**Figure 1**

Schematic images of time course at the time of preeclampsia diagnosis All patients were diagnosed with PE based on the following three conditions: (i) IFsPE complicated later by hypertension, (ii) simultaneous onset of both IFsPE and hypertension, and (iii) hypertension complicated later by IFsPE. PE, preeclampsia; IFsPE, initial findings of the PE; HT, hypertension

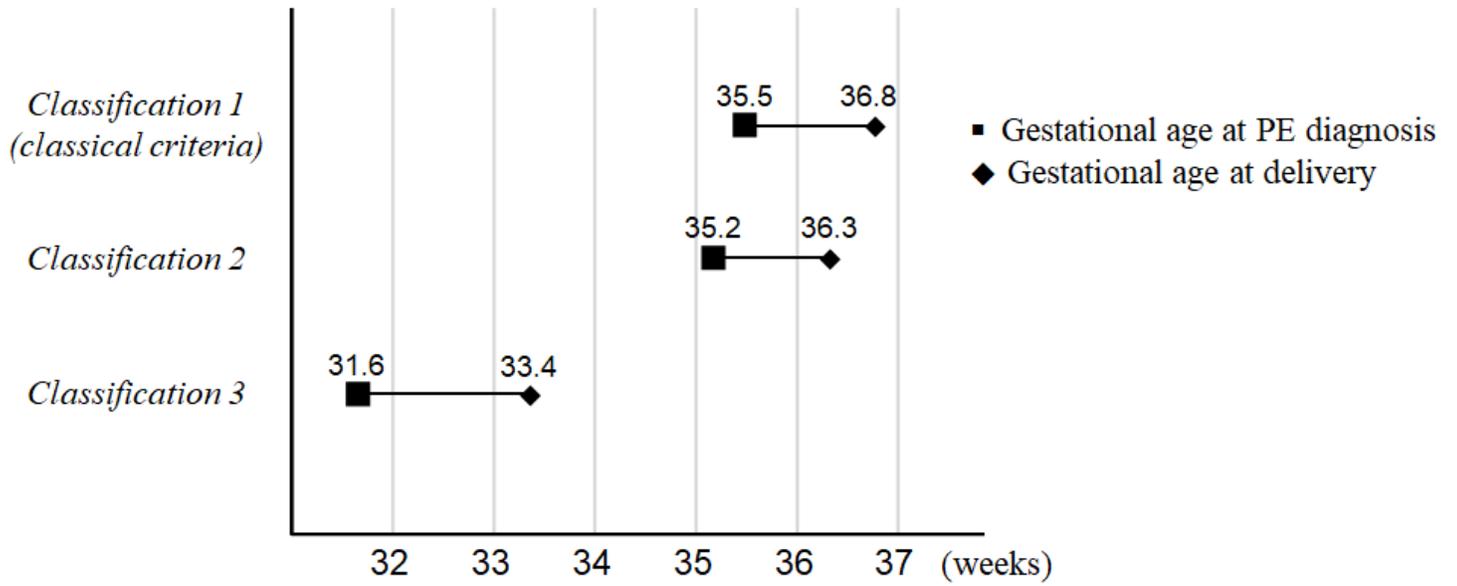
**Fig 2.**



**Figure 2**

Flow diagram of the inclusion of study participants from 2015 to 2019. All women were reclassified based on the ISSHP criteria. They were categorized based on the initial findings of preeclampsia (PE) at the first diagnosis into three groups according to the ISSHP categories: Classification 1 (classical criteria), PE diagnosed based on proteinuria; Classification 2, PE diagnosed based on damage to maternal organs; and Classification 3, PE diagnosed based on uteroplacental dysfunction. ISSHP, International Society for the Study of Hypertension in Pregnancy; PE, preeclampsia.

**Fig 3.**



**Figure 3**

Timing of PE onset and the timing of delivery among the three groups PE, preclampsia