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Differences in the prognosis of preeclampsia according to the initial symptoms: A single-center retrospective report

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1. Introduction

Preeclampsia (PE) is a disease with a combination of hypertension and proteinuria, and the incidence is reported to be 3–5% [1,2]. PE is the cause of 63,000 maternal and fetal deaths globally [3] and one of the primary causes of premature births. The details of the etiology of PE are still unknown; however, a two-stage disorder theory [4] has been proposed, and these details are on the verge of being elucidated. PE onset proceeds in the following order: ① immunogenic maladaptation, ② poor placentation and subsequent impairment of spiral artery remodeling, ③ increased production of antiangiogenic factors (soluble fms-like tyrosine kinase-1 [sFlt-1] and soluble endoglin [sEng]) by the chorionic villi, ④ migration of antiangiogenic factors to the fetal and maternal circulations, accompanied by vascular endothelial damage onset. Eventually, hypertension and proteinuria develop in the mother, while intrauterine growth restriction, fetal dysfunction, etc., develop in the fetus [5]. From the theory on the etiology and disease state of PE, hypertension and proteinuria develop after the disease state is almost complete. Therefore, the clinical symptoms of PE appear after the disease state enters the final stage. Additionally, when likened to a domino effect, the pathogenesis of PE commences with immunogenic maladaptation, followed by poor placentation, and, then, impairment of spiral artery remodeling, which increases production of antiangiogenic factors by the chorionic villi, leading to simultaneous or consecutive onset of multiple factors such as the release of syncytiotrophoblast microparticles and production of inflammatory cytokines. As in a domino effect, the disease state progresses in a complicated manner without the factors affecting each other. Moreover, as dominos do not all fall at the same speed, similarly, the order in which the clinical symptoms that are eventually manifest is presumed to differ according the patient [6].

In fact, there are several ways in which the clinical symptoms appear, namely, cases where hypertension precedes PE (H-PE), cases where proteinuria precedes PE (P-PE), and cases of PE where hypertension and proteinuria develop simultaneously (S-PE). There are few reports on whether the order in which such clinical symptoms appear affect maternal and fetal prognoses.

In PE, severity of hypertension is known to affect maternal and fetal prognoses [7]. Therefore, theoretically, maternal and fetal prognoses are presumed to be poor in the presence of H-PE and S-PE. However, recently, results linking a poor prognosis to the presence of P-PE have been reported [8].

Hypertension, which precedes PE, likely damages the systemic vascular endothelium, whereas proteinuria likely damages the renal vascular endothelium. For that reason, clinically, hypertension preceding PE is considered to worsen readily than proteinuria preceding PE. However, to validate that theory, we have again investigated retrospectively whether the manner in which the clinical symptoms of PE appear causes a difference in both maternal and fetal prognoses.

2. Materials and methods

2.1. Patients

Fig. 1 presents the diagram of this study. The study included 200 (2.26%) of 8838 pregnant women who had PE during pregnancy and delivered from January 2008 to 2016 at this center. Of these, 34 who had multiple pregnancies and 55 with superimposed PE were excluded, and the remaining 111 were the final subjects. The subjects were divided based on the initial symptom into a hypertension preceding PE group (H-PE, n = 48), proteinuria preceding PE group (P-PE, n = 21), and simultaneous onset group (S-PE, n = 42).

The items that were compared between the 3 groups were maternal age, body mass index (BMI) before pregnancy, pregnancy history, gestational age at onset of initial symptoms, gestational age at PE diagnosis, delivery method, level of proteinuria based on 24-h pooled urine at PE diagnosis, duration to improvement of both hypertension and proteinuria postpartum, fetal weight, fetal growth restriction (FGR) status, Apgar score, umbilical cord arterial blood pH, infant status of cerebral palsy, and early neonatal death status.

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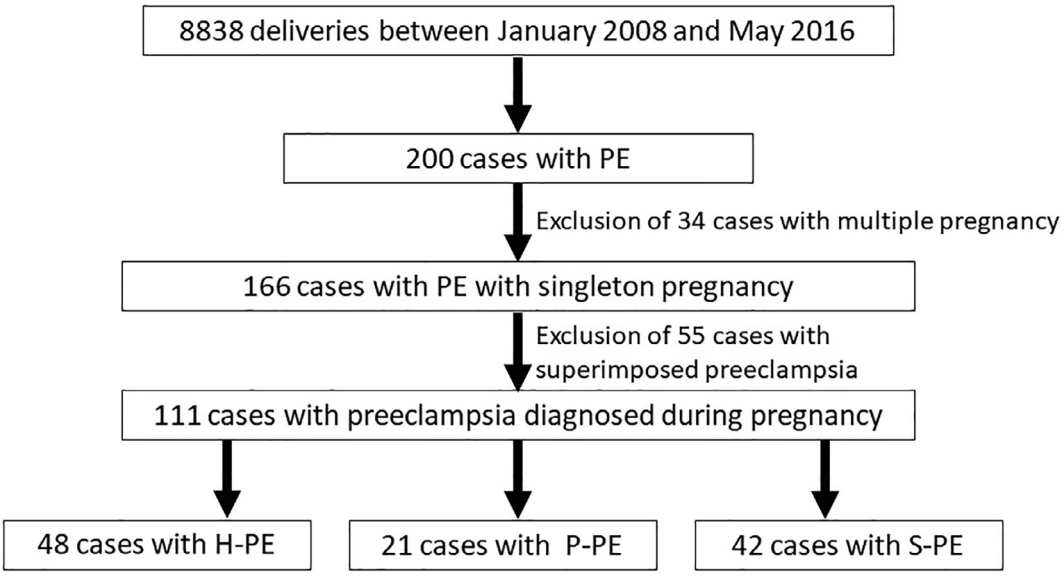

Fig. 1. Diagram of the study. Among 8838 pregnant women who delivered, 111 had PE. Those with multiple pregnancies and superimposed PE were excluded. PE, preeclampsia; H-PE, gestational hypertension preceding preeclampsia; P-PE; proteinuria preceding preeclampsia; S-PE, simultaneous preeclampsia.

2.2. Diagnosis definition

The diagnostic criteria by the International Society for the Study of Hypertension in Pregnancy were used to diagnose PE [9]. Specifically, hypertension was defined as a systolic pressure higher than 140 mmHg or diastolic pressure higher than 90 mmHg when measured at least twice on the same day. Proteinuria was defined as a protein level higher than 300 mg/day in a 24-h pooled urine assay. H-PE was defined as an initial onset of hypertension after 20 weeks of gestation followed by onset of proteinuria more than 2 days later. P-PE was defined as an initial onset of proteinuria after 20 weeks of gestation followed by onset of hypertension more than 2 days later. S-PE was defined as onset of hypertension and proteinuria on the same day or within the following day after 20 weeks of gestation. Moreover, PE was defined as improvement in hypertension and proteinuria by week 12 of the puerperium stage. There was no case in which hypertension or proteinuria persisted even after week 12 of the puerperium stage.

FGR was defined as birth weight < -1.5 SD. For cerebral palsy, the definition set at the Workshop in Bethesda was used. Early neonatal death was defined as death within 4 weeks postpartum.

2.3. Data collection

The items that were compared between the 3 groups were maternal age, BMI before pregnancy, pregnancy history, gestational age at onset of initial symptoms, gestational age at PE diagnosis, gestational age at delivery, premature birth rates less than 37 and 34 weeks of gestation, delivery method, protein level based on 24-h pooled urine assay at PE diagnosis, duration to improvement of both hypertension and proteinuria postpartum, fetal weight, Apgar score, umbilical cord arterial blood pH, infant status of cerebral palsy, and early neonatal death status.

2.4. Ethical statement

This study was conducted after it was approved by the in-house ethics committee of Saitama Medical Center of the Saitama Medical University.

2.5. Statistical analysis

IBM SPSS Statistics 25® was used for the statistical analysis. Comparisons between 2 groups were performed using $\chi 2$ test, *t*-test, and Fisher's exact test, and those between 3 groups were performed using Fisher's exact test and analysis of variance, and P-value < 0.05 indicated statistical significance.

3. Results

Of the 111 subjects, there were 48 in the H-PE group, 21 in the P-PE group, and 42 in the S-PE group.

Table 1 presents the patients' background of the 3 groups. There was no significant difference between the 3 groups regarding maternal age at delivery, status of co-existing obesity, and primiparous rate. Maternal BMI was significantly low in the P-PE group ($p < 0.05$).

Table 2 and Fig. 2 present the comparison between the 3 groups regarding the gestational age at onset of the initial symptoms, gestational age at PE diagnosis, gestational age at delivery, duration from the onset of the initial symptoms to delivery, cesarean section rate, and protein level at PE diagnosis. Gestational age at onset of initial symptoms was significantly lower in the H-PE group (H-PE, 28.9 ± 3.7 weeks; P-PE, 33.3 ± 3.4 weeks; and S-PE, 31.1 ± 3.9 weeks; $p < 0.05$). In the P-PE group, gestational age at PE diagnosis (P-PE, 34.3 ± 3.5 weeks; H-PE, 31.9 ± 3.6 weeks; and S-PE, 31.1 ± 3.9 weeks; $p < 0.05$) and that at delivery (P-PE, 34.3 ± 3.5 weeks; H-PE, 31.9 ± 3.6 weeks; and S-PE, 31.1 ± 3.9 weeks; $p < 0.05$) were significantly greater.

Table 3 presents the premature birth rates at < 37 weeks and < 34 weeks of gestation as the delivery outcomes, birth weight, SD value of the fetal weight, FGR status, Apgar score, umbilical cord arterial

Table 1
Patients' background of the 3 groups. Body mass index > 25 was defined as obesity.

	H-PE(n = 48)	P-PE(n = 21)	S-PE(n = 42)	P value
Maternal age (years)	34.9 ± 4.8	33.7 ± 5.8	34.9 ± 4.6	n.s.
Body Mass Index	22.8 ± 4.3[a]	20.6 ± 3.3[b]	23.9 ± 5.0[a]	< 0.05
Obesity (BMI > 25)	13(27.1%)	3(14.3%)	11(26.2%)	n.s.
Primiparity	34(70.8%)	16(76.2%)	27(64.3%)	n.s.

Table 2
Obstetrical characteristics 1.

	H-PE(n = 48)	P-PE(n = 21)	S-PE(n = 42)	P value
Gestational age at onset (weeks)	28.9 ± 3.7[a]	33.3 ± 3.4[b]	31.1 ± 3.9[b]	< 0.05
Gestational age diagnosed with PE (weeks)	31.9 ± 3.6[a]	34.3 ± 3.5[b]	31.1 ± 3.9[a]	< 0.05
Gestational age at delivery (weeks)	33.0 ± 3.2[a]	34.8 ± 3.9[b]	32.2 ± 4.0[a]	< 0.05
Duration from onset to delivery (days)	28.9 ± 24.6	10.9 ± 8.6	0	< 0.05
Caesarean section	43(89.6%)	17(81.0%)	38(90.5%)	n.s.
Proteinuria (gram/day)	2.1 ± 1.9	1.9 ± 1.9	2.7 ± 3.0	n.s.

blood pH, and duration to improvement of hypertension and proteinuria postpartum. In the P-PE group, premature birth rate at < 37 weeks of gestation was low (P-PE, 61.9%; H-PE, 89.6%; and S-PE, 85.7%; $p < 0.05$). Furthermore, premature birth rate at < 34 weeks of gestation, when the prognosis of premature infants is known to be poor [10], was also low (P-PE, 58.3%; H-PE, 38.1%; and S-PE: 73.8%; $p < 0.05$). In the P-PE group, birth weight was also high (P-PE, 1936 ± 844 g; H-PE, 1541 ± 657 g; and S-PE, 1386 ± 669 g; $p < 0.05$). However, the SD value of the birth weight showed no significant difference. There was also no significant difference in Apgar score and umbilical cord arterial blood pH. In the postpartum follow-up results of the infants, there was 1 case each of cerebral palsy in the H-PE and P-PE groups, and there was 1 case of neonatal death in the P-PE group. However, there was no statistically significant difference.

Fig. 3 is a ROC curve that specifies the gestational age when PE was diagnosed, resulting in premature birth (< 37 weeks of gestation). The cut-off value of the gestational age at the time of PE diagnosis becomes a risk of premature birth at 34.5 weeks (AUC 0.955). Table 4 presents the results of the multivariate analysis regarding the risk factors for premature birth. In a logistic regression analysis based on gestational age at the time of PE diagnosis, being in an H-PE state was a risk factor for premature birth (Odds ratio 13.5, 95% CI: 1.14–160, $p < 0.05$).

The duration to improvement of PE postpartum showed no difference between the 3 groups (H-PE, 41.7 ± 23.2 days; P-PE, 37.9 ± 22.5 days; and S-PE, 38.6 ± 23.7 days; $p = 0.77$).

4. Discussion

There are cases of PE preceded by gestational hypertension (GH), PE preceded by IGP, and that where both symptoms develop simultaneously. However, recent reports revealed that 15–26% of pregnant women with GH and 51% of pregnant women with isolated gestational proteinuria (IGP) have PE. The reports conclude that caution is required in the case of IGP. In this study, PE with GH as the initial symptom developed significantly early compared to PE with IGP as the initial symptom, and moreover, the timing of delivery was also significantly early. This showed that perinatal prognosis is poorer in the former case compared to that in the latter. The gestational age when PE was diagnosed was significantly delayed in the IGP group. However, even in the multivariate analysis where the gestational age when PE was diagnosed was considered as a confounding factor and the effect of gestational age was excluded, it became evident that as a risk of premature birth, GH was an initial symptom and an independent related factor. If the gestational age when PE is diagnosed is early, it is natural to select termination based solely on that. However, the results of this multivariate analysis revealed that the risk of premature birth is not related to gestational age when PE is diagnosed and that the risk was rather high in the H-PE group. Considering the reports that hypertension has a major effect on maternal and fetal prognoses, the results of this study that show that the prognosis is better in the group with IGP compared to the that in other groups are more valid than those in reports on a high risk of onset of PE and early onset of PE and timing of delivery with IGP.

The duration from manifestation of the initial symptom to delivery was significantly shorter in the P-PE than H-PE group (H-PE, 28.9 ± 24.6 days; P-PE, 10.9 ± 8.6 days; $p < 0.05$). The causal factor is the fact that gestational age at onset of PE likely affected the decision on termination. In other words, in P-PE, PE develops at 34.3 ± 3.5 weeks of gestation, which is in the late preterm. Generally, the prognosis of premature infants delivered after 34 weeks of gestation is comparatively good. Therefore, after 34 weeks of gestation, there is no plan to risk prolonging the pregnancy. As such, with P-PE, termination was likely considered more proactively. This resulted in the short duration from the onset of PE to delivery. Even when depressor therapy is performed for early-onset GH, the pregnancy period can be prolonged for only approximately 5–11.6 days. Moreover, this notably affects the timing of onset of hypertension and that of termination. Meanwhile, the timing of onset of proteinuria is also early, and even if it does develop, it does not produce an effect with significance to indicate

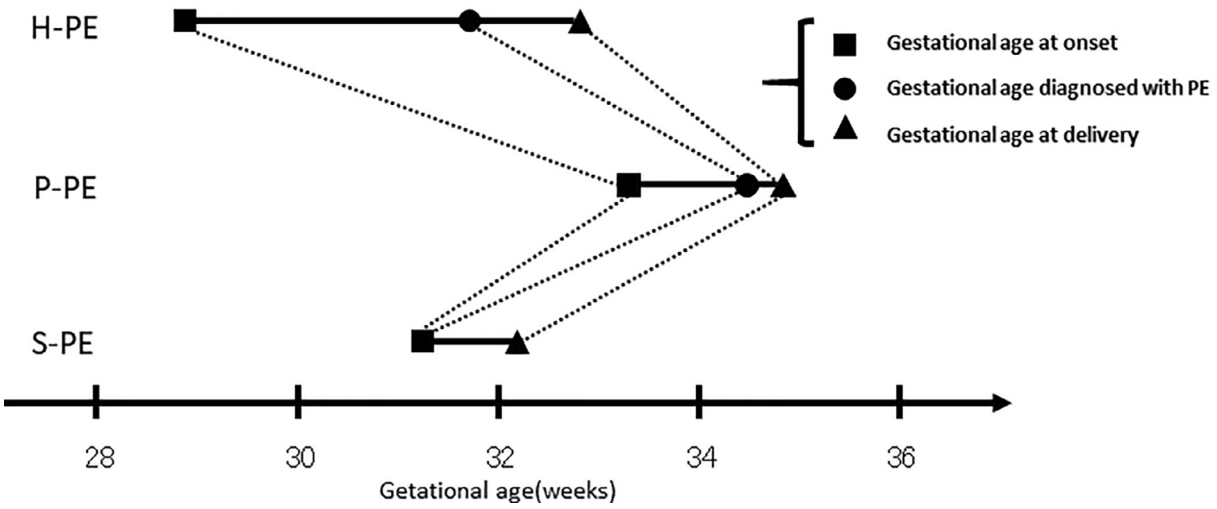

Fig. 2. Respective onsets of H-PE, P-PE, and S-PE and timing of delivery.

Table 3
Obstetrical characteristics 2. (FGR: fetal growth restriction. FGR is defined as estimated fetal weight more than 1.5 SD below the mean gestational age. Apgar: Appearance, pulse, grimace, activity, and respiration. Neonatal death: death within 4 weeks postpartum).

	H-PE(n = 48)	P-PE(n = 21)	S-PE(n = 42)	P value
Premature birth (< 37 weeks)	43(89.6%)[a]	13(61.9%)[b]	36(85.7%)[a]	< 0.05
Premature birth (< 34 weeks)	28(58.3%)[a]	8(38.1%)[b]	31(73.8%)[a]	< 0.05
Birth weight (g)	1541 ± 657[a]	1936 ± 844[b]	1386 ± 669[a]	< 0.05
SD score	−1.61 ± 1.18	−0.93 ± 2.63	−1.79 ± 0.95	n.s.
FGR (< -1.5SD)	28(58.3%)	10(47.6%)	26(61.9%)	n.s.
APGAR score (1 min)	6.89 ± 1.71	7.38 ± 2.04	6.26 ± 2.38	n.s.
APGAR score (5 min)	8.11 ± 1.26	8.33 ± 1.80	8.00 ± 1.61	n.s.
Umbilical artery pH	7.31 ± 0.04	7.31 ± 0.06	7.30 ± 0.07	n.s.
Duration of both hypertension and proteinuria from delivery to the improvement (days)	41.7 ± 23.2	37.9 ± 22.5	38.6 ± 23.7	n.s.

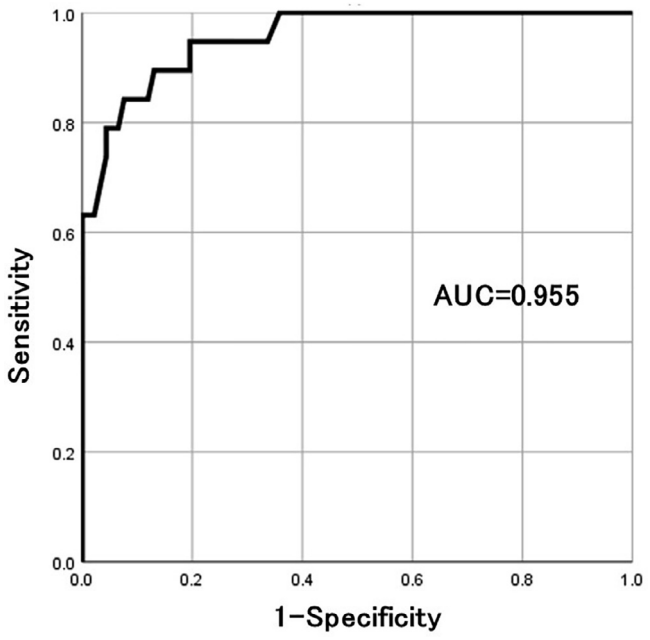

Fig. 3. ROC (Receiver Operating Characteristics) curve that specifies the gestational age when PE was diagnosed, resulting in premature birth (< 37 weeks of gestation). AUC (Area Under The Curve) is 0.955.

termination. These are the major factors responsible for the difference in timing of delivery between the H-PE and P-PE groups. Thus, fetal prematurity due to the difference in timing of delivery likely affects fetal prognosis. All infants delivered by pregnant women who became subjects of this study are undergoing intensive treatment at this center that is equipped with a Neonatal Intensive Care Unit that provides intensive neonatal management. As such, there is the possibility that no statistically significant difference was noted in the neonatal prognosis.

Although there are no reports on the duration of improvement in each puerperal stage of various initial symptoms, our results [11] reporting the duration of puerperal improvement regarding PE and GH showed that neither hypertension nor proteinuria caused a notable difference in the duration of residual PE symptoms. Even in this study where duration of the residual PE symptoms of the respective groups was investigated, there was no significant difference between the 3 groups, and there was no difference in the duration of the residual PE symptoms.

In the two-step disorder theory that was mentioned previously, vascular endothelial damage due to the antiangiogenic factors produced by the chorionic villi precede the onset of PE [5]. However, the difference between PE preceded by hypertension and that preceded by proteinuria could be due to the difference in the site of vascular endothelial damage and time of its development. With regard to the vascular endothelial damage that occurs in the maternal circulation, the factor stipulating whether its action in the early stage is due to hypertension or proteinuria is unknown [12]. Therefore, the reason for the differences in the site and timing of onset of vascular endothelial damage is unknown. The hypothesis is that proteinuria likely develops as a comparatively early symptom of vascular endothelial damage. However, the progress is gradual, while vascular endothelial damage due to hypertension is suggested to be systemic. If PE can be suggested based on the previously mentioned metabolic domino theory, these differences can be easily explained and understood. The fact that the pregnancy outcomes of H-PE and S-PE were poor compared to that of P-PE indicates the possibility that these vascular endothelial damages either occur systemically or in the kidney, causing a difference in the prognoses.

There are recent reports stating that the risk of PE is high in the presence of IGP and the prognosis is also poor. However, this study demonstrated that PE preceded by symptoms that include hypertension (H-PE and S-PE) has a poor perinatal prognosis than PE preceded by IGP.

5. Limitation

False positive results are known to be common in the semi-quantitative analysis of proteinuria by the dipstick test [13]. In this study, 24-h pooled urine assay was performed to determine proteinuria in order to avoid false positive results. It commonly requires in-hospital management. As a simpler method, the pathological proteinuria assay based on the perinatal P/C ratio is useful in the diagnosis [14]. However, there are also negative perspectives [15–17] about it, and caution is therefore required in the interpretation of results. Even at this center, evaluation of proteinuria based on the P/C ratio was recently

Table 4
Results of the multivariate analysis regarding the risk factors for premature birth.

		Univariate analysis			Multivariate analysis		
		Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Gestational age diagnosed with PE < 34.5 (weeks)		56.667	11.6–276.7	< 0.05	136.4	20.9–2943.1	< 0.05
Classification	H-PE	2.457	0.818–7.383	n.s.	10.85	1.43–231.9	< 0.05
	P-PE	0.226	0.077–0.668	< 0.05	2.62	0.318–57.0	n.s.
	S-PE	1.393	0.485–3.996	n.s.	1.0	reference	n.s.

introduced. As recruitment of the subjects of this study commenced in 2008, the proteinuria evaluation was made uniform with the use of 24-h pooled urine samples.

Moreover, the study of Akaishi et al. [8] that was previously mentioned and this study are small scale; therefore, a study with a large sample size is required to evaluate whether the perinatal prognosis of H-PE is good.

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Declaration of interest

None.

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