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Original Article

Comparison of Kidney Function between Gestational Hypertension and Preeclampsia

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Although gestational hypertension (GH) is thought to be different from preeclampsia (PE), in Japan GH and PE are usually treated as the same disease (*i.e.*, pregnancy-induced hypertension). Here we sought to determine whether there are any differences in fetal growth and maternal kidney function between pregnancies with PE and those with GH. We retrospectively analyzed 61 GH patients and 60 PE patients with singleton pregnancies who delivered at Okayama University Hospital (2008-2015). We compared maternal and perinatal outcomes and maternal kidney function parameters between the GH and PE pregnancies. The mean values of maternal age ($p=0.01$), gestational age at delivery ($p<0.0001$), placental weight ($p=0.002$), birth weight and height ($p<0.0001$, $p=0.0001$), and head circumference standard deviation score ($p=0.007$) of newborns of the GH group were significantly higher than those of the PE group. The duration until termination of PE or GH was not significantly correlated with kidney function. The birth weight percentile was significantly correlated with kidney function in PE but not GH. However, GH patients with poor kidney function and small-for-gestational age infants showed perinatal outcomes similar to those of the PE group. Monitoring kidney function is thus important for determining the severity of PE and GH.

Key words: preeclampsia, gestational hypertension, perinatal outcome, kidney function, fetal growth

Pregnancy-induced hypertension (PIH), which is characterized by hypertension and proteinuria, is a multifactor disorder and one of the main causes of perinatal and maternal morbidity and mortality [1]. PIH complicates 3.0-4.6% of Japanese pregnancies [2]. Gestational hypertension (GH) is thought to be different from preeclampsia (PE) in many countries, including the United States and Canada, according to The American Congress of Obstetricians and Gynecologists (http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/ Hypertension-in-Pregnancy; accessed June 1, 2016) and the Journal of Obstetrics and Gynecology Canada (http://sogc.org/wp-content/uploads/2013/01/ui206CPG0803hypertensioncorrection.pdf; accessed June 1, 2016).

However, in Japan GH and PE are usually treated as the same disease (*i.e.*, PIH). GH/PE is classified as a sub-classification of PIH, but GH and PE are treated basically as PIH with superimposed preeclampsia, eclampsia, and management. Methods and guidance specific to PE or GH are not used in Japan. We conducted the present study to determine whether there are any differences in perinatal outcomes, fetal growth, and maternal kidney function between pregnancies with PE and those with GH in order to investigate the

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necessity of different treatments between PE and GH.

Materials and Methods

In this retrospective, cross-sectional study, we retrospectively analyzed the cases of 61 patients with GH and 60 patients with PE who had a singleton pregnancy and delivered at Okayama University Hospital between 2008 and 2015. We compared perinatal outcomes, fetal growth, and maternal kidney function in the GH and PE cases.

GH was defined as the presence of hypertension (blood pressure ≥140/90 mmHg) without proteinuria (we confirmed that there was no proteinuria until delivery) after the 20th week of gestation. Preeclampsia was defined as hypertension (blood pressure ≥140/90 mmHg) and proteinuria (proteinuria ≥300 mg/day) after the 20th week of gestation. The definition of 'severe GH' was blood pressure ≥160/110 mmHg. Cases that involved eclampsia or superimposed PE were excluded from the study. The above-mentioned criteria were issued by the Japan Society for the Study of Hypertension in Pregnancy [3].

We collected data regarding both maternal and perinatal characteristics. The delivery data also included those for artificial termination, membrane rupture, and natural labor pains. We excluded the cesarean section after labor pains and uterus operation from the emergency cesarean section. We identified the birth weight percentile, birth height percentile, and head circumference percentile in each case and compared them with the Japanese standards [4]. 'Small for gestational age (SGA)' was defined as less than the 10th percentile for birth weight. The duration until termination was the length from the onset of PE or GH to delivery.

Blood samples were collected ≤1 week before delivery. Serum uric acid (UA) (Sino-test, Tokyo) and creatinine (Mizuho Medical, Saga, Japan) levels were measured using enzymatic methods [5]. High UA levels were defined as >5.6 mg/dl and normal UA levels as <5.5 mg/dl. The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels (eGFR for Japanese) [6]. We omitted data that were collected >1 week before delivery. The median (range) time that blood samples were collected was 1 day (0-6 days) before delivery for GH and 0 days (0-7 days) before delivery for PE.

We used Microsoft Excel 2010 for Windows 7 for the statistical analysis. Maternal and perinatal outcomes were compared using the Mann-Whitney *U*-test. The statistical significance of complications between the GH and PE groups was determined by the χ^2 test. We performed a Pearson's correlation coefficient test to compare the maternal kidney function with weeks of onset and fetal growth, and to examine the correlations between UA levels, creatinine levels, and eGFR. Values of $p < 0.05$ were considered significant. The study protocol was approved by the Ethics Committee at Okayama University Hospital (1606-516).

Results

The maternal characteristics, kidney function, and perinatal outcomes in the GH and PE groups are summarized in Table 1. The gestational age at diagnosis and at admission in the women with PE were significantly earlier than those in the women with GH. In the GH group, the maternal age was significantly higher ($p = 0.01$), the gestational age at delivery was significantly greater ($p < 0.0001$), the placental weight was significantly heavier ($p < 0.002$), and the birth weight ($p < 0.0001$), birth height ($p = 0.0001$), and head circumference standard deviation score of the newborns were significantly greater ($p < 0.005$) compared to the corresponding values in the PE group. Significantly more patients with PE had high blood pressure than those with GH ($p = 0.0007$).

In the GH group, the maternal weight, body mass index (BMI) before pregnancy, and UA levels were higher than those in the PE group, but these differences were not significant. There were no significant between-group differences in weight gain during pregnancy, the rate of previous PIH, the rate of primipara, the Apgar scores, the pH of the umbilical artery, blood loss, platelets, creatinine levels, eGFR, or maternal complications including diabetes mellitus, collagen disease, and antiphospholipid antibody syndrome. Gestational diabetes mellitus (GDM) was significantly more common among the patients with GH compared to those with PE.

We also analyzed the platelets, antithrombin III levels, D-dimer levels, and hematocrit (in the patients for whom these data were available; Table 1), and no significant differences between the groups were revealed. Previous miscarriage and stillbirth occurred in 11 of 38 (29%) GH patients and 17 of 31 (55%) PE patients, with

Table 1 Maternal and perinatal characteristics and maternal kidney function in the preeclampsia (PE) and gestational hypertension (GH) groups

	GH (n = 61)	PE (n = 60)	*p*
Maternal age (yrs)	34 ± 5.3	32 ± 5.9	0.01
Weight of pre-pregnancy (kg)	62.2 ± 16.0	57.6 ± 15.3	NS
BMI before pregnancy (kg/m^2)	24.6 ± 5.5	23.4 ± 5.8	NS
Gestational weight gain (kg)	8.8 ± 5.7	9.6 ± 5.1	NS
Gestational age at delivery (wks)	37.8 ± 2.1	35.5 ± 3.4	<0.0001
Ratio of PIH in the past for multipara (%)	13	19	NS
Gestational age at diagnosis of GH or PE	35 ± 5.3	33 ± 4.9	0.01
Gestational age at admission	37 ± 2.5	34 ± 4.1	<0.0001
Placental weight (g)	506 ± 132	434 ± 128	0.002
Ratio of primipara (%)	64	73	NS
Infant birth weight (g)	2,657 ± 618	2,105 ± 763	<0.0001
Infant birth weight (primipara) (g)	2,675 ± 590	2,151 ± 770	0.0009
Infant birth weight (multipara) (g)	2,618 ± 691	2,019 ± 765	0.01
Infant birth weight percentile	39.2 ± 31.9	22.7 ± 26.0	0.002
Infant birth height (cm)	48 ± 3.5	44 ± 5.3	0.0001
Infant birth height percentile	55.0 ± 31.6	39.8 ± 30.9	0.008
Head circumference percentile	49.3 ± 29.5	35.9 ± 24.3	0.007
Circumference of the chest/head	0.91 ± 0.06	0.87 ± 0.08	0.03
UmApH	7.29 ± 0.09	7.27 ± 0.08	NS
Apgar score (1 min)	7.6 ± 1.7	7.4 ± 1.7	NS
Apgar score (5 min)	8.7 ± 1.3	8.5 ± 1.4	NS
Ratio of severe blood pressure (%)	36	67	0.0007
Serum albumin (g/ml)	3.0 ± 0.3	2.6 ± 0.4	<0.0001
UA (mg/dl)	5.76 ± 1.66 (n = 50)	6.49 ± 1.95 (n = 53)	NS
Creatinine (mg/dl)	0.63 ± 0.18 (n = 49)	0.68 ± 0.15 (n = 55)	NS
eGFR(ml/min)	97.0 ± 29.1 (n = 49)	88.9 ± 27.0 (n = 56)	NS
DM (types I or II)	4	3	NS
GDM	8	1	0.02
Collagen disease	0	2	NS
APS	7	5	NS

The data are mean ± SD. NS, not significant; BMI, body mass index; UmApH, umbilical artery pH; UA, uric acid; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; GDM, gestational diabetes mellitus; APS, antiphospholipid antibody syndrome.

significant differences between the groups ($p = 0.03$). A previous arrest of fetal growth occurred in 2 of 38 cases of GH and 3 of 31 cases of PE, with no significant differences between the groups ($p = 0.5$).

The rate of use of antihypertensive medicine was 30% in the GH group and 72% in the PE group. The time point of starting antihypertensive medicine was a median (range) of 0 weeks (0-2 weeks) before delivery in the GH group and 1 week (1-12 weeks) before delivery in the PE group. The rate of the use of low-dose aspirin in the first trimester prescribed due to antiphospholipid antibody syndrome was 8.3% in the PE group versus 11.4% in the GH group, with the exception of one GH patient who took medicine for high blood pressure from the 26th gestational week (data not shown).

We analyzed the correlation between maternal kidney function parameters and fetal growth. The correlations between birth weight percentile and maternal kidney function parameters were significant in the PE group (UA: $r = -0.54$ $p < 0.0001$; creatinine: $r = -0.47$, $p = 0.0001$; eGFR: $r = 0.37$, $p = 0.003$), but these were not significant in the GH group (UA: $r = -0.16$, $p = 0.25$; creatinine: $r = -0.01$, $p = 0.92$; eGFR: $r = 0.08$, $p = 0.52$) (Fig. 1). The correlations of maternal kidney function parameters with birth height percentile and head circumference were not significant in either group (data not shown).

We also analyzed the associations between kidney function parameters and mild and severe hypertension in the GH and PE groups. As shown in Table 2, the UA levels were significantly different ($p = 0.03$) between the patients with severe hypertension and those with mild

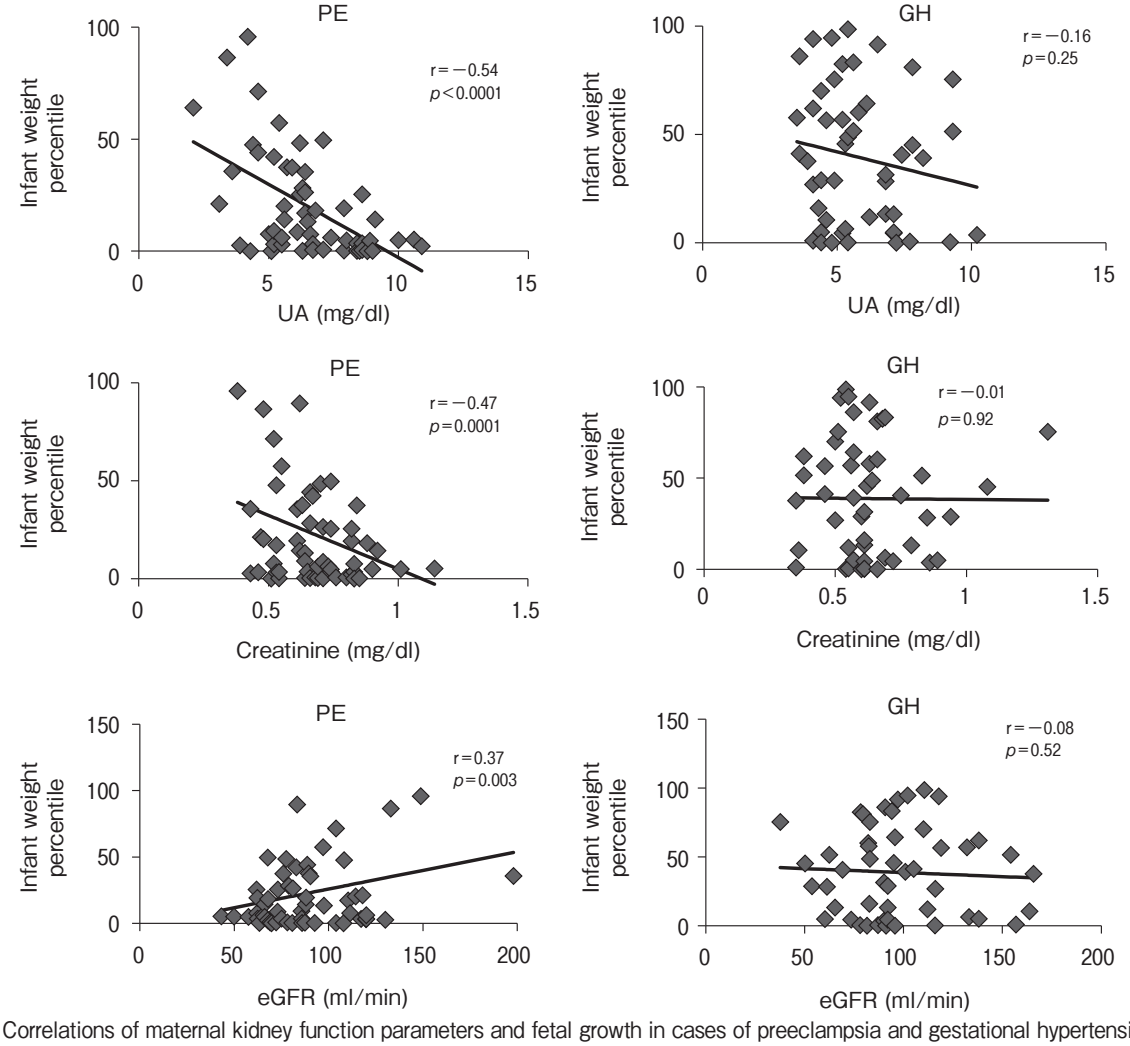

Fig. 1 Correlations of maternal kidney function parameters and fetal growth in cases of preeclampsia and gestational hypertension.

Table 2 Correlations of kidney function parameters with mild and severe hypertension in the gestational hypertension and preeclampsia groups and all patients

		Severe hypertension	Mild hypertension	*p*
		n = 64	n = 57	
PE and GH n = 121	UA (mg/dl)	6.54 ± 1.82	5.76 ± 1.79	0.03
	Creatinine (mg/dl)	0.67 ± 0.18	0.63 ± 0.14	0.20
	eGFR (ml/min)	86.4 ± 26.0	90.9 ± 26.9	0.45
		n = 40	n = 20	
PE n = 60	UA (mg/dl)	6.79 ± 1.83	5.92 ± 2.10	0.12
	Creatinine (mg/dl)	0.69 ± 0.15	0.66 ± 0.16	0.33
	eGFR (ml/min)	84.3 ± 21.0	88.8 ± 24.2	0.51
		n = 24	n = 37	
GH n = 61	UA (mg/dl)	6.10 ± 1.76	5.66 ± 1.59	0.37
	Creatinine (mg/dl)	0.64 ± 0.23	0.62 ± 0.14	0.74
	eGFR (ml/min)	91.9 ± 35.9	92.5 ± 29.3	0.95

PE, preeclampsia; GH, gestational hypertension; UA, uric acid; eGFR, estimated glomerular filtration rate.

hypertension in the complete patient series, but there were no significant differences within the PE or GH groups. There were no significant correlations of blood pressure with creatinine levels or eGFR (Table 2). Our analysis of the association between the duration until termination of PE or GH and maternal kidney function was not significantly (Fig. 2).

We next focused on the GH patients and high UA levels (Table 3). The onset of GH in patients with normal UA levels was significantly earlier than the onset in the GH patients with high UA levels ($p=0.02$). However, the duration until termination in patients with high UA levels was significantly earlier compared to those with normal UA levels ($p=0.04$). Among the patients with GH and high UA levels, 3 patients had hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, 1 had placental abruption, and 4 had non-reassuring fetal status. The rate of HELLP syndrome among the patients with both GH and high UA levels was significantly higher than the rate of patients with GH and normal UA levels. Five other patients with high UA levels had an arrest of fetal development and elevation of blood pressure, and their pregnancies were terminated as soon as possible (Table 3).

We divided the 21 patients with both GH and high UA levels into 2 groups: those with SGA infants and

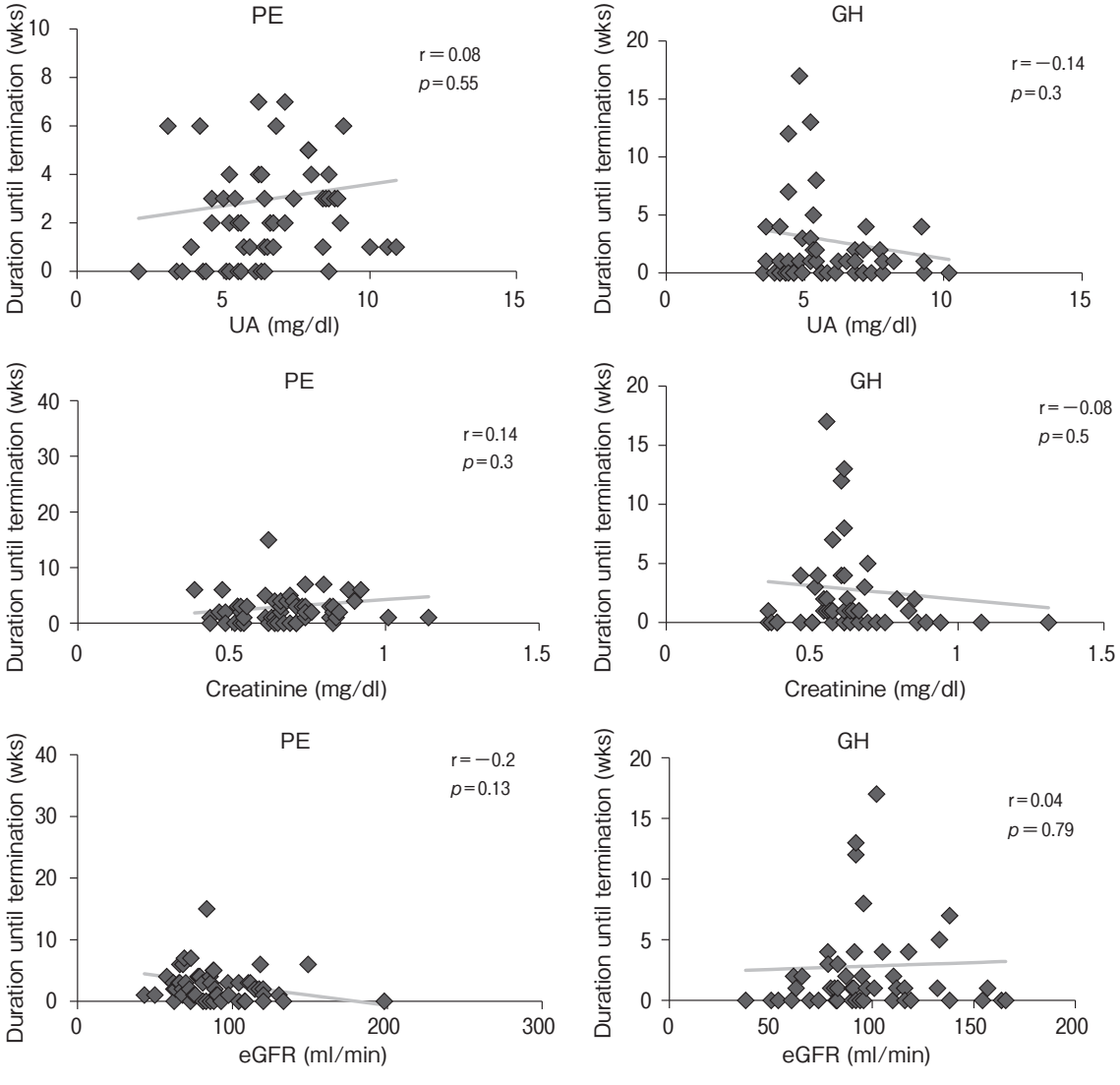

Fig. 2 Association between the duration until termination of preeclampsia or gestational hypertension and maternal kidney function.

those with appropriate-for-gestational age neonates. Between these 2 groups, there were significant differences in the number of gestational weeks at delivery ($p=0.04$), the onset of GH ($p=0.0006$), the duration until termination ($p=0.02$), and placental weight ($p=0.0001$, Table 4). One of the 5 patients with SGA infants had HELLP syndrome, one had placental abruption, and the other 2 patients had non-reassuring fetal status.

Discussion

Our study showed that the mean values of maternal age, gestational age at delivery, placental weight, birth weight, and height of neonates in the cases of PE were significantly greater than those in the cases of GH. Several studies have reported that PE is associated with maternal and perinatal poor outcomes, which is consistent with our present findings. Barton *et al.* reported that gestational age of the infants at delivery, birth weight, incidence of SGA newborns differed significantly in PE with versus those in GH [7]. Other studies reported that the birth weights in PE cases were lower than those of controls, but those in GH cases were not significantly different from the controls [8,9]. In another investigation, the number of gestational weeks and birth weight in PE cases were less than those in GH (not significant), and those in PE and GH cases together were significantly less than those of controls [10]. These studies suggest that there is a marked difference in fetal growth between GH and PE cases.

A pregnancy with PE is terminated at an early gestational age [7-10]. Xiong *et al.* reported that perinatal mortality and fetal growth restriction (FGR) were increased the most in GH cases, followed by PE cases, and then severe PE cases [11]. Our analysis of the cir-

Table 3 Comparison of patients with high uric acid (UA) levels and those with normal uric acid levels in gestational hypertension

	High UA (n = 21)	Normal UA (n = 28)	*p*
Infant birth weight percentile	37.6 ± 30.3	40.7 ± 33.3	0.74
Gestational age at delivery (wks)	38.1 ± 2.5	37.4 ± 2.1	0.23
The onset of GH (wks)	37.2 ± 3.0	34.3 ± 5.0	0.02
Duration until termination(wks)	1.0 ± 1.2	3.1 ± 4.5	0.04
Placenta weight (g)	519 ± 105	486 ± 145	0.37
Ratio of severe hypertension (%)	52	29	0.09
Emergency caesarean section (person)	7 (33%)	7 (25%)	0.16
Placental abruption (person)	1 (5%)	4 (14%)	0.27
HELLP syndrome (person)	3 (14%)	0 (0%)	0.03
NRFS (person)	4 (19%)	5 (18%)	0.91

NRFS, non-reassuring fetal status; UA, uric acid; GH, gestational hypertension.

Table 4 Comparison of patients with gestational hypertension (GH) who had small-for-gestational age (SGA) infants and those who had appropriate-for-gestational age (AGA) infants

		SGA	AGA	*p*
High UA levels		n = 5	n = 16	
	Gestational age at delivery (wks)	35.6 ± 2.5	38.9 ± 1.9	0.04
	Onset of GH (wks)	33.6 ± 2.5	38.3 ± 2.2	0.0006
	Duration until termination (wks)	2.0 ± 2.0	0.6 ± 0.7	0.02
	Placenta weight (g)	386 ± 43.1	561 ± 80.4	0.0001
	Caesarean section (person)	3 (60%)	5 (31%)	0.24
Normal UA levels		n = 2	n = 26	
	Gestational age at delivery (wks)	35.5 ± 3.5	37.5 ± 1.9	0.1
	Onset of GH (wks)	31 ± 8.4	34.5 ± 4.7	0.3
	Duration until termination (wks)	2.0 ± 4.9	3.0 ± 4.5	0.6
	Placenta weight (g)	293 ± 118	500 ± 138	0.05
	Caesarean section (person)	1 (50%)	11 (42%)	0.8

cumferences of the chest/head indicated that newborns born to mothers with PE may have asymmetrical FGR. It is likely that PE leads to asymmetrical FGR based on pathological factors. Because of these maternal and perinatal differences, we conclude that GH is different from PE.

Additionally, our study showed that parameters of kidney function (*i.e.*, UA levels, creatinine levels, and eGFR) were correlated with each other, and that the kidney function of the patients with GH was similar to that of the patients with PE. We divided the GH and PE cases by the difference in proteinuria, but there was no significant difference in the kidney function. Our findings also showed that birth weight was correlated with kidney function only in the cases of PE. However, the kidney function in the PE and GH groups was not correlated with severe hypertension or the duration until termination of PE and GH. Therefore, abnormal kidney function is a high risk of FGR in PE, but not in GH.

Several studies have noted that kidney function plays a major role in hypertensive disorders. An example of this is that UA levels are related to the onset of essential hypertension in children [12]. It has also been reported that UA levels are related to PE. In a study, plasma UA levels predicted fetal death in hypertensive pregnancies [13]. Pramanik *et al.* reported higher UA levels and higher blood pressure in PE during pregnancy compared to normal pregnancy [14].

Other investigations have shown that UA levels were altered at the initial stages of PE [15] and that UA levels were associated with maternal and perinatal outcomes in PE [16]. Additionally, kidney function is correlated with fetal growth. UA and creatinine levels are correlated with fetal growth in normotensive pregnant women [17,18]. Moreover, it was reported that UA levels were predictive of perinatal outcomes but not maternal outcomes in PE [19] and that UA levels were correlated with low birth weight [15].

From a pathological point of view, UA plays a role in inflammation, oxidative stress, and endothelial dysfunction. These situations might affect the development of a small placenta [20], which in turn affects fetal growth. High UA levels in PE may promote inflammation, oxidative stress and endothelial dysfunction, and then the placenta becomes small because of poor vascular remodeling of the placental bed [21]. A small placenta leads to SGA and other perinatal complications [22,23].

In our study, the placenta in the patients with PE was smaller compared to the GH cases. The measurement of kidney function (such as UA levels) might predict FGR in patients with PE or PE in patients with FGR. We found that the UA levels in the patients with PE were higher than those in the patients with GH, but the difference was not significant. Our analysis demonstrated that kidney function was correlated with birth weight only in PE. These findings suggest that a high level of UA is a prognostic factor for FGR in PE.

In our GH patient series, the onset of GH, the duration until termination, and HELLP syndrome in the patients with high UA levels were significantly different from those in the patients with normal UA levels. Although the onset of GH in the patients with high UA levels was significantly later compared to those with normal UA levels, the patients with high UA levels showed a shorter duration until termination, which indicates that their symptoms became worse rapidly. Many of our patients with high UA levels delivered at full term. Therefore, a short period to termination did not influence fetal growth.

Several research groups have suggested that GH with hyperuricemia is a perinatal risk. A case-control study reported that hyperuricemia with GH increased the risks of preterm labor and FGR, and these patients had similar or greater risks than those with PE [24]. Some studies have indicated that HELLP syndrome is associated with the endothelial factor, similar to a small placenta with a high UA level in PE [25,26]. In our study, the patients with both GH and high UA levels with SGA infants showed a significant difference in the number of gestational weeks at delivery, the onset of GH, the duration until termination, and placental weight compared to the patients with GH and high UA levels without SGA infants.

The patients with GH, normal UA levels and SGA infants did not show a significant difference compared with those with GH and normal UA levels without SGA infants. Additionally, the maternal and perinatal outcomes of the patients with GH and high UA levels with SGA infants were extremely high-risk. We consider that these patients could develop PE, or the pathological state may be similar to PE. Schmella *et al.* reported that hyperuricemia is predictive of a high risk of GH, similar to proteinuria [27]. Therefore, we consider that GH is a mixture of former PE and pure GH.

UA affects essential hypertension in children [12]. A brief review showed that there is a pathogenetic role for UA in not only hypertension, but also in cardiovascular and renal disease [28]. The follow-up of UA levels after pregnancy might thus be important for the prediction of cardiovascular or metabolic syndrome in the mother and child later in life.

This study excludes the superimposed preeclampsia and eclampsia at first, but includes the case with maternal complications such as diabetes mellitus. We will investigate the cases of PE and GH associated with no maternal complications in the future. The limitations of this study are (1) the relatively small number of patients, (2) the many patients who showed normal progress did not have all data available, and (3) kidney function was not continuously measured. We need to analyze UA levels continuously during pregnancy to determine when UA levels become high. UA levels increase at approx. 20 weeks of gestation in pregnancies with PE [15]. We believe that UA levels need to be measured at least before pregnancy and after 20 weeks of gestation.

A determination of the predictability of PE and GH is important for clinical treatments, especially for controlling severe hypertensive disorders, termination in the early gestational weeks, and determining maternal and perinatal outcomes. PE cases reached termination at an early point because the onset of PE was early and then proteinuria, kidney function, and maternal and neonatal outcomes are worsen. In contrast, because the onset of GH was late, GH cases reached the point of delivery before the appearance of proteinuria. But in the case such as GH with SGA, the onset was early, these cases were terminated in the early gestational weeks, and maternal and neonatal outcomes turned worse like PE.

Although GH is generally milder than PE, perinatal outcomes are worse if UA levels are high. Patients with GH and high UA levels must be more carefully managed. We believe that kidney function plays an important role in fetal growth and in the severity of PE cases and GH cases that are similar to PE. Cases of GH may actually be PE because of high UA levels, FGR, or in the most severe cases both high UA and FGR. Consequently, monitoring of kidney function by blood tests in PE and GH patients is important.

In conclusion, patients with GH and high UA levels, especially those with SGA infants, have perinatal outcomes similar to those with PE. The monitoring of kidney function is an important examination during pregnancy to determine the severity of GH or PE.

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