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Superimposed Preeclampsia in Women with Chronic Kidney Disease

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Key Words
Preeclampsia · Chronic kidney disease · Perinatal outcome · Renal function · Angiogenesis

Abstract
Aim: To evaluate whether pregnant women with chronic kidney disease (CKD) adapt poorly to increases in renal blood flow. This can exacerbate renal function and impair perinatal outcome, as there is a major interplay between CKD and preeclampsia (PE). ***Methods:*** We analyzed the outcomes of 90 pregnant women with preexisting CKD. The estimated glomerular filtration rate (eGFR) was measured along with the levels of angiogenic factors, soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor, which might act in the pathophysiology of PE. ***Results:*** In pregnancies with CKD, PE and preterm delivery were increased and the increased blood pressure worsened the perinatal outcomes much more than the increased proteinuria. All pregnancies with severe renal insufficiency were delivered preterm because of impaired renal function. The eGFR was correlated significantly with 24-hour creatinine clearance ($r = 0.830$). Significant differences in sFlt-1 and placental growth factor levels were found between severe PE without any complications and severe superimposed PE ($p < 0.05$), and between women with and without declining renal function in superimposed PE ($p < 0.01$). ***Conclusion:*** Pregnancies with CKD have a high risk of obstetrical complications. The eGFR might serve for evaluating renal function during pregnancy. Angiogenic factors might be potential markers for a differential diagnosis between PE and worsening renal function.

Introduction

The mother's healthy adaptation to pregnancy includes a decrease in the systemic vascular resistance and in the mean arterial pressure, despite an increase in cardiac output. At the level of the kidney, this adaptation results in vasodilatation of the collecting system with a small increase in renal size, an increase in renal plasma flow and thus the glomerular filtration rate (GFR), as well as lower plasma osmolality and mild hyponatremia. These renal physiological changes appear to be critical for an optimal pregnancy outcome [1, 2].

Preeclampsia (PE) is a pregnancy-specific and multisystemic disorder characterized by the onset of high blood pressure and proteinuria which develop after 20 weeks of gestation in previously normotensive women or

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which are superimposed on preexisting hypertension or proteinuria. It occurs in about 5% of all pregnancies and results in substantial maternal and neonatal morbidity and mortality [3, 4]. Abnormal vascular growth and impaired endothelial function in the placenta are associated with abnormal pregnancy conditions such as PE and result from the inadequate trophoblastic invasion of maternal spiral arteries during early gestation [5, 6]. Defective placental development can be reflected in the maternal circulation and can be detected as alterations in the concentrations of biological markers, including vascular endothelial growth factor and transforming growth factor-β [5–7]. Consequently, placenta-derived factors are produced that might be partially responsible for PE. The result is a generalized endothelial dysfunction manifested by hypertension, proteinuria and thrombotic microangiopathy. Women with chronic kidney disease (CKD) are less able to make the renal adaptations needed for a healthy pregnancy and reveal endothelial dysfunction with an elevated soluble fms-like tyrosine kinase 1 (sFlt-1) level [8]. Thus, a mild imbalance of angiogenic factors derived from placenta might cause PE in pregnancy associated with CKD.

In this study, we investigated the perinatal outcomes of pregnancies among women with CKD in our hospital and examined whether the estimated glomerular filtration rate (eGFR) was useful for evaluating renal function during pregnancy. We also measured angiogenic factors in pregnancies with CKD to investigate the pathophysiology of superimposed PE in women with CKD.

Patients and Methods

Patients

Ninety pregnant Japanese women with CKD who visited the Department of Obstetrics and Gynecology, Okayama University Hospital, Japan, from 1996 to 2010 were included in this study. According to the definition of the Japan Society of Obstetrics and Gynecology [9], superimposed PE with CKD was defined as new-onset or worsening hypertension and/or proteinuria. This was a persistent blood pressure elevation to levels of 140 mm Hg (systolic) or 90 mm Hg (diastolic) on two occasions several hours apart and/or proteinuria (>300 mg/day). Severe superimposed PE was defined as severe hypertension (systolic blood pressure 160 mm Hg or diastolic blood pressure 110 mm Hg) and/or severe proteinuria (>2,000 mg/day). Baseline demographic information collected from the database included: maternal blood pressure during pregnancy, serum creatinine, urine 24-hour proteinuria, 24-hour creatinine clearance rate (24h-CCR), gestational age (weeks and days) at delivery, newborn percentile and Apgar score. The eGFR was calculated using a formula specific for Japanese women [194 × serum creatinine level $(mg/dl)^{-1.094}$ × age in $years^{-0.287}$ × 0.739] [10]. For an analysis of angiogenic factors, we included 35 women – from the group of the 90 pregnancies with CKD analyzed in this study – who visited Okayama University Hospital from 2007 to 2010, and 35 healthy pregnant women matched for age, gestational age, parity and body mass index with normotensive pregnancies who visited our hospital from 2009 to 2010. All patients gave their informed consent for blood sampling. We added 18 patients with PE who had no preexisting complications and 18 healthy pregnant women matched for age, gestational age, parity and body mass index with normotensive pregnancies, who visited our hospital from 2009 to 2010, to compare superimposed PE with CKD. Immediately after sample collection, serum was separated by centrifugation and stored at –80°C until used. This study was approved by the Institutional Ethical Review Board of Okayama University Hospital (project No. 186, June 21, 2004) and all subjects gave their informed consent.

Enzyme-Linked Immunosorbent Assay for Angiogenic Factors

Serum levels of sFlt-1 and PlGF were determined by enzyme-linked immunosorbent assay following the manufacturer's instructions (R&D Systems, Inc., Minneapolis, Minn., USA). All samples were examined in duplicate and mean values of individual sera were utilized for statistical analysis. Samples for measurement of sFlt-1 were diluted 1/100 prior to the assay. The minimum detectable concentrations in the assays for placental growth factor (PlGF) and sFlt-1 were 7.0 and 5.0 pg/ml, respectively. The intra- and inter-assay coefficients of variation for PlGF were less than 2.8 and 8.9%, and for sFlt-1 they were 3.3 and 7.8%, respectively.

Statistical Analysis

All values were expressed as the mean ± SD. The Kruskal-Wallis test and the Scheffe test following the Shapiro-Wilk test were used for intergroup comparisons of clinical parameters and serum levels of sFlt-1 and PlGF. The associations of 24h-CCR with serum creatinine or eGFR levels were analyzed using Spearman's rank correlation. Statistical analysis was performed using StatView software 5.0 (Abacus Concepts, Berkeley, Calif., USA) and $p < 0.05$ was considered to be statistically significant.

Results

Perinatal Outcomes in Pregnancies with CKD

The cases of 90 pregnant women with CKD, who visited the Department of Obstetrics and Gynecology, Okayama University Hospital, Japan, from 1996 to 2010, are summarized in table 1. The most prevalent disease was chronic glomerulonephritis (77.7%), especially IgA glomerulonephritis (57.8%). The preterm delivery rate was 22.2% and FGR was 20.0%. There were 21 cases of superimposed PE, including 9 severe cases (22.2%). In the superimposed PE patients, the rate of preterm delivery, FGR and abnormal Doppler finding were 71.4, 76.2 and 85.7%, respectively (table 1).

To investigate the effect of blood pressure during pregnancy on perinatal outcomes, the 90 cases were divided

Table 1. Characteristics of pregnancies in women with CKD

	Patients with CKD	Superimposed PE
All pregnancies with CKD	90	21 (9)/90 (23.3%)
Chronic glomerulonephritis	69	17 (6)/69 (24.6%)
IgA glomerulonephritis	52	15 (5)/52 (28.8%)
Mesangial proliferative glomerulonephritis	4	0/4 (0%)
Membranous glomerulonephritis	1	0/1 (0%)
Focal glomerulosclerosis	1	0/1 (0%)
Minimal change	4	1/4 (25.0%)
Others	7	1 (1)/7 (14.3%)
Nephrotic syndrome	4	0/4 (0%)
After renal transplantation	3	(2)/3 (100%)
Chronic renal failure	5	0/5 (0%)
Others	9	1 (1)/9 (11.1%)
Maternal age at delivery, years	29.3 ± 4.3	30.4 ± 3.7
Age at CKD onset, years	20.7 ± 7.5	23.5 ± 9.5
Diabetes or GDM	3/90 (3.3%)	1/21 (4.8%)
Gestational age at delivery, weeks and days	38.1 ± 2.5	37.1 ± 3.0
Preterm delivery	20/90 (22.2%)	15/21 (71.4%)
Cesarean section	24 (rate 26.7%)	10 (rate 45.4%)
Birth weight, g	2,722 ± 681	2,456 ± 653
FGR	18/90 (20.0%)s	16/21 (76.2%)
HELLP syndrome	0/90 (0%)	0/21 (0%)
Maximum blood pressure range, mm Hg	96–132	110–208
Proteinuria, g/day	0–10.4	0–10.4
Abnormal uterine Doppler finding		18/21 (85.7%)

Means ± SD, with severe cases in parentheses. GDM = Gestational diabetes mellitus.

into 3 groups: women with normal blood pressure (<140/90 mm Hg), those with mild hypertension (140–160/90–110 mm Hg) and those with severe hypertension (>160/>110) at delivery. There were no significant differences in mean gestational age or newborn percentile between normotensive and mild hypertension groups, but the average gestational age was significantly earlier and newborn percentile was significantly lower in the severe hypertension group than in both the normotensive and mild hypertension groups. The effect of 24-hour urine proteinuria on perinatal outcomes was also examined. Again, the cases were divided into 3 groups: women with no proteinuria (<300 mg/day), those with mild proteinuria (300–2,000 mg/day) and those with severe proteinuria (>2,000 mg/day) at delivery. There were no significant differences in mean gestational age between groups. The newborn percentile in the severe proteinuria group was significantly lower than in the group with no proteinuria. Moreover, in the group with severe proteinuria, women with hypertension showed an earlier gestational age at delivery and a lower newborn percentile than the normotensive cases, but not significantly (fig. 1).

There were no significant correlations between blood pressure/proteinuria and gestational age/newborn percentiles in our study (data not shown).

eGFR for Evaluating Renal Function during Pregnancy

To examine the usefulness of eGFR for the evaluation of renal function during pregnancy, calculated by the formula for Japanese women, we compared 24h-CCR with serum creatinine and eGFR levels during pregnancy in all patients with CKD. The 24h-CCR was shown to be correlated significantly with eGFR (r = 0.830), and negatively with the serum creatinine level (r = –0.853) (fig. 2a, b).

Perinatal Outcomes in Cases with Renal Function Worsening before Pregnancy

To examine the effect of renal function worsening before pregnancy, 20 women with worsening renal function (24h-CCR <90 ml/min) were evaluated. Mildly worsening cases (24h-CCR 70–90 ml/min; n = 10) and moderately worsening cases (24h-CCR 50–70 ml/min; n = 3)

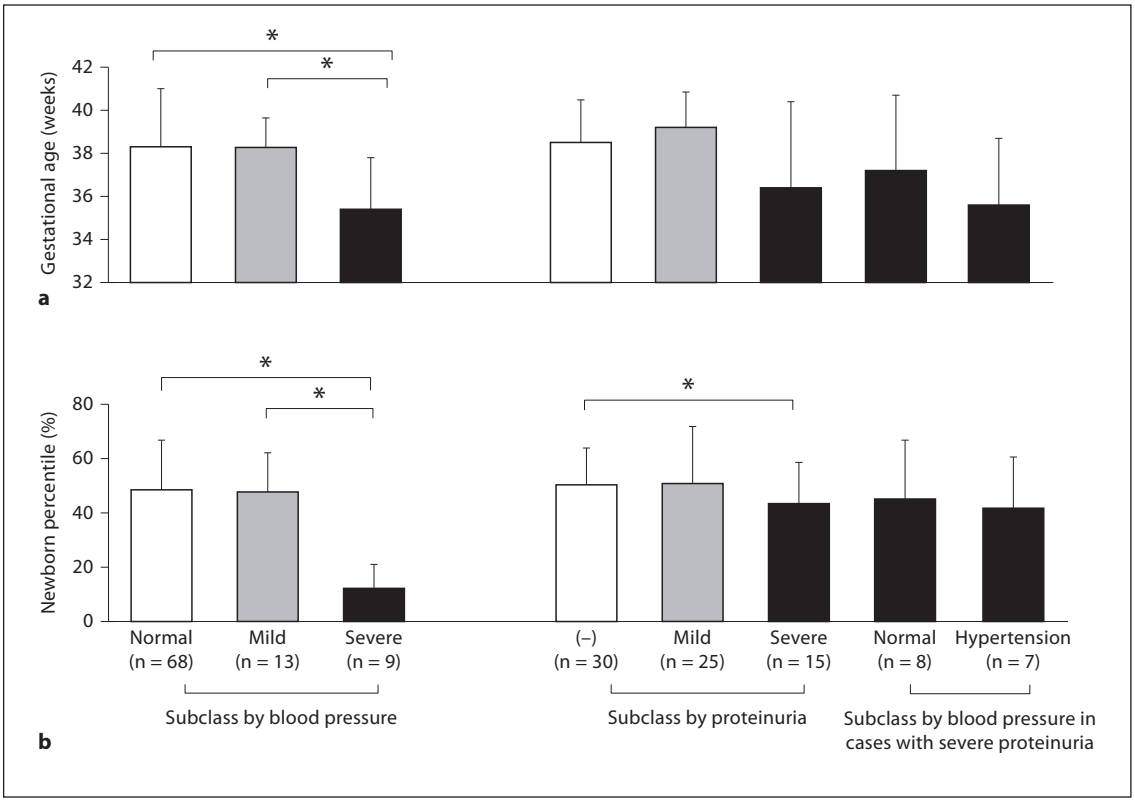

Fig. 1. The effect of blood pressure and proteinuria on perinatal outcomes, gestational age (**a**) and newborn percentile (**b**). Values are shown as the mean ± SD. * $p < 0.05$ compared with normal clinical course.

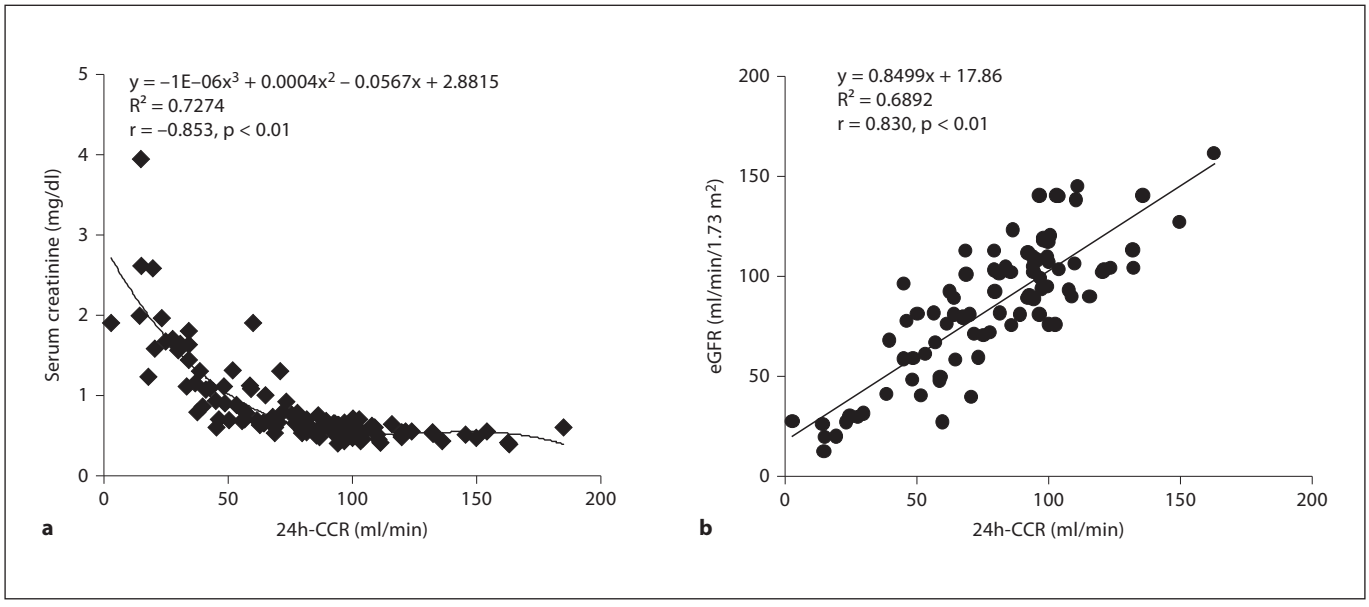

Fig. 2. The significant correlations of 24h-CCR with serum creatinine (**a**) and eGFR (**b**) levels.

Table 2. Perinatal outcomes of cases with renal function worsening before pregnancy

Renal function	Gestational age at delivery, (weeks)	Newborn percentile (%)	AS (1 min)	SGA	NICU
24h-CCR					
Normal (n = 70)	38.2 ± 2.5	49.9 ± 12.8	8.6 ± 1.0	4 (5.6%)	9 (12.9%)
Worsening					
Mild (n = 10)	39.3 ± 1.4	50.3 ± 14.3	8.5 ± 0.5	2 (20.0%)	2 (20.0%)
Moderate (n = 3)	39.5 ± 4.0	52.3 ± 5.9	8.7 ± 0.6	1 (33.3%)	1 (33.3%)
Severe (n = 7)	34.0 ± 2.3*	38.1 ± 4.2*	6.6 ± 2.8*	2 (28.6%)	7 (100.0%)*
eGFR					
Normal (n = 68)	38.1 ± 2.5	48.4 ± 11.4	8.6 ± 1.0	4 (5.9%)	9 (13.2%)
Worsening					
Mild (n = 14)	39.2 ± 1.3	49.3 ± 8.4	8.6 ± 0.5	1 (7.1%)	4 (29.5%)
Moderate (n = 5)	35.6 ± 3.3*	43.8 ± 3.1*	6.8 ± 2.3*	2 (40.0%)	4 (80.0%)*
Severe (n = 3)	36.0 ± 1.0*	44.1 ± 2.8*	8.0 ± 0.0	2 (66.7%)	2 (66.7%)*

AS = Apgar score; NICU = admission to neonatal intensive care unit; SGA = small for gestational age.
* $p < 0.01$ compared with normal.

had normal clinical courses of pregnancy when compared to the cases with normal renal function, but severely worsening cases (24h-CCR <50 ml/min; n = 7) revealed significantly worse perinatal outcomes (table 2). We also examined the perinatal outcomes using eGFR before pregnancy. Mildly worsening cases (eGFR 60–89 ml/min; n = 14) had a normal clinical course of pregnancy compared to the cases with normal renal function, but moderately worsening cases (24h-CCR 30–59 ml/min; n = 5) and severely worsening cases (24h-CCR < 29 ml/min; n = 3) revealed significantly worse perinatal outcomes (table 2).

Serum Concentrations of Angiogenic Factors

To investigate the pathophysiology of superimposed PE on pregnancy in women with CKD, we examined the levels of the angiogenic factors, sFlt-1 and PlGF, and compared them with women with PE with no preexisting complication. Thirty-five women – out of the 90 pregnancies with CKD analyzed in this study – who visited our hospital from 2007 to 2010, and 18 with severe PE and 53 age-, gestational-week-, parity- and BMI-matched healthy women with normotensive pregnancies (who visited our hospital from 2009 to 2010) were recruited. There were significant differences in sFlt-1 and PlGF levels in the women with PE compared to the normal controls. The sFlt-1 levels in pregnancies with superimposed PE were significantly increased and the PlGF levels were significantly decreased when compared to those in women showing severe proteinuria without hypertension or a normal clinical course and the normal controls. There were no significant differences in the levels of angiogenic factors in the group showing severe proteinuria without hypertension, those with a normal clinical course and in the normal controls. Moreover, there were significant differences in sFlt-1 and PlGF levels in pregnancies with superimposed PE associated with chronic glomerulonephritis when stable renal function was compared with declining renal function (table 3).

Discussion

We analyzed the outcomes for 90 pregnant women with preexisting CKD associated without other major complications who were seen at our perinatal center between 1996 and 2010. Among these women, the rates of PE and preterm delivery were increased and the increased blood pressure during pregnancy worsened the perinatal outcomes when compared to the women with increased proteinuria. All pregnant women with severe renal insufficiency were delivered at preterm because of worsening renal function. The eGFR level was shown to be correlated significantly with 24h-CCR during pregnancy. In pregnancies with CKD, the sFlt-1 levels were significantly increased and the PlGF levels decreased in women with superimposed PE when compared to the group with severe proteinuria without hypertension, those with a nor-

mal clinical course and with the normal controls. Moreover, significant differences in sFlt-1 and PlGF levels were found in women with superimposed PE between those with and without declining renal function.

Women with CKD are at a high risk of adverse maternal and fetal outcomes and women with moderate or severe renal dysfunction revealed especially poor perinatal outcomes [4]. In our study, overall preterm delivery rate was 22.2% and all women with severe renal dysfunction before pregnancy (24h-CCR: <50 ml/min) were offered preterm delivery due to worsening renal function or fetal growth restriction. Previous reports demonstrated similar results regarding preterm delivery (overall 20–50% and severe 50–100%) [11]. Twenty-two percent of the pregnant women with CKD developed superimposed PE, suggesting that women with CKD are at high risk, as reported [12, 13]. Also reported previously [11], the high incidence of FGR was also observed overall in pregnant women with CKD (20.0%) and superimposed PE patients (76.2%). Moreover, we examined the effects of abnormal blood pressure and proteinuria on perinatal outcomes. Hypertension had a stronger adverse effect on perinatal outcomes than proteinuria worsening.

The 24h-CCR and serum creatinine levels are generally used to estimate renal function in pregnancy. However, serum creatinine was negatively correlated with 24h-CCR as a polynomial equation, thus the 24h-CCR remains the gold standard for measuring the eGFR in pregnancy even though it requires 24-hour urine collection [1]. The Modification of Diet in Renal Disease (MDRD) formula, which estimates GFR using a combination of serum markers and clinical parameters, has become a standard clinical method to estimate renal function in patients with CKD [1]. However, recent reports demonstrated that current GFR estimation equations including the MDRD and Cockcroft-Gault formulas are not reliable to estimate renal function in pregnancy [14, 15]. In this study, we examined whether the formula for eGFR for Japanese women [10] might also be useful for pregnant women with CKD. The eGFR by this formula was significantly correlated with 24h-CCR during pregnancy even in women with severe renal dysfunction, suggesting that this convenient formula for GFR might indeed be useful. Moreover, women with moderate and severe renal dysfunction before pregnancy measured as eGFR using this formula revealed poor perinatal outcomes compared to women with mild renal dysfunction or normal function. These data were similar to our other results using 24h-CCR in our population and as estimated using the MDRD formula [16].

Table 3. Circulating sFlt-1 and PlGF levels in pregnancies of women with CKD

	Pregnancy without any complications		Pregnancy with CKD		Severe superimposed PE			
	normal control	severe PE	normal control	normal clinical course	severe proteinuria without hypertension	severe superimposed PE	with worsening renal function	without worsening renal function
n	18	18	35	17	8	10	4	6
PlGF, pg/ml	282.4 (203.5–350.2)	110.4 (48.2–150.9)[a]	290.7 (228.4–360.9)[b]	273.1 (219.4-320)[b]	252.5 (200.8–308.3)[b]	132.7 (68.9–188.9)[c]	222.5 (180.2–270.5)	98.2 (54.7–127.2)[d]
sFlt-1, pg/ml	1,587.8 (854.8–2,094.1)	8,244.9 (6,755.9–10,332.8)[a]	1,448.2 (776.8–1,943.8)[b]	1,602.9 (833.8–2,395.3)[b]	2,788.4 (1,321.7–4,143.8)[b]	6,439.2 (5,100.5–7,803.5)[c]	3,220.3 (2,433.6–4,055.7)	9,122.4 (7,955.4–10,355.6)[d]

Median (interquartile range).
[a] $p < 0.01$.
[b] $p < 0.01$ versus normal control.
[c] $p < 0.05$ versus severe PE without any complication.
[d] $p < 0.01$ versus severe superimposed PE with worsening renal function.

Angiogenic factors, such as vascular endothelial growth factor (VEGF) and PlGF are important regulators in the human placenta [17] and decreased concentrations of circulating free VEGF and free PlGF have been noted in women with clinical PE [18–20]. Moreover, recent reports have indicated that the sFlt-1 level is increased in the placenta and serum of women with PE [20–23]. Thus sFlt-1 might act by sequestering free PlGF and free VEGF, thereby preventing interaction between endothelial receptors and these factors on the cell surface and inducing endothelial cell dysfunction. In this study, we observed that the sFlt-1 level was significantly increased and that the PlGF level was decreased in patients with superimposed PE compared to the normal controls, as observed in patients with PE but without preexisting complications. This suggests that angiogenic factors might play an important role in the pathogenesis of PE. Interestingly, there were significant differences in the levels of these factors between the groups with superimposed PE with and without worsening renal function. In addition, women with severe proteinuria without hypertension revealed significantly low sFlt-1 and high PlGF levels compared to those with severe superimposed PE. These data suggest that angiogenic factors might be markers for a differential diagnosis between superimposed PE caused by an imbalance of angiogenic factors and that caused by renal function worsening. Early diagnosis of superimposed PE caused by an imbalance of angiogenic factors might improve clinical outcomes using intensive monitoring and timely intervention such as antihypertensive medications, bed rest, magnesium for seizure prophylaxis, steroids for fetal lung maturity and expedient delivery. Moreover, we also observed that the sFlt-1 level was significantly increased in women with severe proteinuria without hypertension compared to those showing a normal clinical course and to normal controls (there was no significant difference in sFlt-1 levels between these last 2 groups). The sFlt-1 level is significantly higher in patients with CKD associated with impaired renal function and elevated levels of von Willebrand factor, a marker of endothelial dysfunction in nonpregnant women [8]. Further analysis will be required to investigate the potential roles of angiogenic factors in the interaction between PE and CKD.

Our results suggest that pregnant women with renal disease have a high risk of obstetrical complications. The eGFR, which does not require 24-hour urine collection, might be useful for evaluating renal function during pregnancy. Moreover, the angiogenic factors sFlt-1 and PlGF are potential markers for a differential diagnosis between PE and worsening renal function. As this was a small-scale cross-sectional study of Japanese pregnant women with CKD, we also aim to examine a larger sample size in an international study including different races, which should enhance the precision of our findings over a wide area.

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