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Histopathological features of kidney and renal prognosis in patients with preeclampsia

Masanori Sudo [a,*], Kazuhiro Yoshita [a], Yumi Ito [a], Naofumi Imai [a], Noriaki Iino [b], Ichiei Narita [a]

[a] Division of Clinical Nephrology and Rheumatology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan

[b] Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Niigata 949-7302, Japan

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ABSTRACT

Objective: Understanding the long-term prognosis of preeclampsia (PE) is important. Proteinuria and poor renal function persist in some PE patients, but the relationship between their histopathological findings of kidney and renal prognosis is unknown. Our objective was to clarify the relationship between clinicopathological features and renal prognosis in PE patients.

Study design: Retrospective observational study.

Main outcome measures: Seventy patients who had been referred to the Niigata University Hospital between 1977 and 2014 and were diagnosed with PE were classified into unimproved and improved groups. The unimproved group included patients whose serum creatinine level had doubled and/or whose proteinuria had persisted until the end of observation, which included three patients with end-stage kidney disease (ESKD). The improved group included patients whose serum creatinine level did not double and whose proteinuria had disappeared until the last observation. We examined and compared these patients' characteristics, clinical and laboratory findings, and renal histopathological findings from percutaneous kidney biopsies.

Results: There were no significant differences in the clinical backgrounds and clinical findings between the two groups during pregnancy. However, light microscopy findings of their kidney biopsies were able to identify significantly more severe duplications of the capillary loop, interstitial cell infiltration, and interstitial fibrosis in the unimproved group.

Conclusions: Histopathological examination of the kidney may be a valid method for predicting the long-term prognosis of renal function and for histological a risk assessment of poor renal recovery in PE patients.

1. Introduction

Preeclampsia (PE) is characterized by a new onset of hypertension after 20 weeks of gestation accompanied by proteinuria levels greater than 300 mg/day and/or maternal organ dysfunction including uteroplacental circulatory disturbance [1]. PE is a major complication of pregnant woman that affects an estimated 4%–5% of pregnancies [2]. The etiology of PE is not well understood, but previous studies support the possibility that imbalances in angiogenic factors play an important role. Poorly perfused placental tissue releases soluble fms-like tyrosine kinase-1 (sFlt-1) into the maternal circulation, causing endothelial dysfunction [3]. This endothelial cell change sets in motion a cascade of coagulation, vasoconstriction, and intravascular fluid redistribution actions that result in the clinical features of PE. A longitudinal prospective study of PE patients showed a 3.7-fold increased risk for hypertension, a 2.16-fold increased risk for ischemic heart disease, and a 1.81-fold increased risk for stroke after 10–15 years of follow-up [4]. Furthermore, PE increases the risk of future chronic kidney disease (CKD) and the risk of developing end-stage kidney disease (ESKD) within 10 years after pregnancy [5,6]. Although histopathological examination of the kidney has been performed for antepartum or immediate postpartum PE/eclampsia patients to investigate the clinical

Abbreviations: PE, preeclampsia; BMI, body mass index; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HE, hematoxylin–eosin; PAS, periodic acid-Schiff; PAM, periodic acid-methenamine-silver; EM, Elastica-Masson trichrome; RAS, renin-angiotensin system; UP, urinary protein; VEGF, vascular endothelial growth factor.

* Corresponding author at: Division of Clinical Nephrology and Rheumatology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Chuo-ku, Niigata-shi, Niigata 951-8510, Japan.

E-mail address: masanori.s031@gmail.com (M. Sudo).

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features and kidney histopathological findings [7], the correlation between long-term renal prognosis after the delivery and morphological changes of the kidney biopsy specimen is unknown.

It is important to identify the characteristics of the PE patients who eventually develop CKD and ESKD. All subjects in this study were patients who underwent renal biopsy postpartum. This study aimed to examine renal histopathological differences, clinical features during the antepartum and postpartum periods, and long-term prognosis evaluated by the renal function and urinary protein (UP) levels in improved and unimproved PE patients.

2. Methods

This study was a retrospective observational study. From our database, there was an average of 35 ± 6 patients per year who were diagnosed with pregnancy induced hypertension (PIH) and admitted to the Niigata University Hospital during 2006 to 2014. Inferring from this, it was predicted that a total of 1295 PIH patients were admitted to the Niigata University Hospital from 1977 to 2014. On the other hand, there were 6032 female patients who underwent percutaneous kidney biopsy and histopathological examination at the Niigata University Hospital between 1977 and 2014. Among them, 88 patients (6.8% of total PIH) were clinically diagnosed with PE, who showed persistent proteinuria levels of more than 0.3 g/gCr or 0.3 g/day for more than 12 weeks after delivery, and referred to our department for kidney histopathological examination. From the results of percutaneous kidney biopsy, 18 patients were diagnosed with primary glomerulonephritis, and 70 patients (79.5% of total PE patients) were histopathologically diagnosed with PE. Further analyses were carried out with these 70 patients as participants, and they were followed for more than 12 months after their kidney biopsy. The patients had an average age of 29 ± 5 years, and the average observation period was 110 ± 135 months. The patients did not develop diabetes mellitus, glomerulonephritis, or hypertension before pregnancy, and they did not show clinical findings that were suggestive of the development of new glomerular disease within the observation period. They developed PE at 30 ± 6 weeks of gestation, and they showed persistent proteinuria levels of more than 0.3 g/gCr or 0.3 g/day for more than 12 weeks after delivery. They all underwent percutaneous kidney biopsy postpartum because of the need for clinically detailed examination of renal lesions. They were divided into the unimproved (n = 14) and improved groups (n = 56) according to their renal function after this period. The unimproved group included patients whose serum creatinine level had doubled and/or whose proteinuria had persisted until the end of observation, which included three patients with ESKD. The improved group included patients whose serum creatinine level did not double and whose proteinuria had disappeared until the last observation. The patients' characteristics and clinical and laboratory findings were obtained from medical records and were compared between the two groups.

All percutaneous kidney biopsy specimens obtained from these patients were evaluated by light microscopy and immunofluorescence staining. Biopsy specimens (n = 32, including 12 patients in the unimproved group and 22 patients in the improved group) were additionally examined by electron microscopy. The sections undergoing light microscopy examinations were stained with hematoxylin–eosin (HE), periodic acid-Schiff (PAS), periodic acid-methenamine-silver (PAM), PAM-Masson trichrome (PAM-MT), and Elastica-Masson trichrome (EM) stains. Patients with any glomerulonephritis and/or glomerular and tubulointerstitial disease were excluded, as were patients with pathologically diagnosed renal disorders associated with pregnancy. Light microscopy examination of each glomerulus, interstitium, and artery was performed to evaluate the degrees of global sclerosis, segmental sclerosis, duplication of capillary walls, endocapillary hypercellularity, interstitial cell filtration, interstitial fibrosis, arteriolar hyalinosis, and multilayered internal elastic lamina of the interlobular arteries. The glomerular and interstitial lesions were scored as follows: 0 (absent), 1 (<25% of the total glomerular number or cortical area), 2 (25%–50%), 3 (50%–75%), and 4 (greater than75%). Arteriolar hyalinosis was scored as follows: 0 (absent), 1 (mild hyalinosis of at least one arteriole), 2 (moderate hyalinosis of more than one arteriole), and 3 (severe hyalinosis of at least one arteriole). Arteriosclerosis was scored in the most severely affected interlobular artery as follows: 0 (no intimal thickening), 1 (mild intimal thickening), 2 (moderate intimal thickening), and 3 (severe intimal thickening). We also evaluated glomerulomegaly (glomeruli >250 mm in diameter) by measuring the average value of the glomerular area and the diameter from the vascular pole to the urinary pole.

We used *t*-tests, Fisher's exact test, the Mann–Whitney *U* test, and Cramer's V for the statistical comparisons between the two groups. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed with EZR [8], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

3. Results

The patient characteristics are shown in Table 1. All patients had normal blood pressure and urinalysis at the start of their pre-eclamptic pregnancy. Sixty-six patients developed PE after 20 weeks gestation, and four patients developed PE before 20 weeks. The weeks of

Table 1
Patient characteristics: Data are shown as the n (%), mean ± standard deviation, or median (interquartile range). Comparisons between the unimproved and improved groups were performed using Fisher's exact test and *t*-tests, as appropriate. *Statistically significant ($p < 0.05$).

Item	Unimproved group (n = 14)	Improved group (n = 56)	p value
Weeks of pregnancy when developing PE	29 ± 3	30 ± 6	0.352
Days from childbirth to kidney biopsy	31 ± 20	59 ± 67	0.011*
Number of pregnancies	1 (1–1)	1 (1–1)	0.473
Number of early pregnancy terminations for the treatment of PE, n (%)	12 (86%)	34 (61%)	0.116
Months of observation after kidney biopsy, n	56 ± 131	126 ± 134	0.100
Number of cases with a history of PE, n (%)	0 (0%)	2 (4%)	1.000
Number of cases with a history of diabetes mellitus, n (%)	0 (0%)	0 (0%)	NA
Number of cases with a history of the use of antihypertensive drugs, n (%)	9 (64%)	21 (37.5%)	0.129
Number of cases with a history of the use of RAS inhibitor, n (%)	0 (0%)	6 (11%)	0.337
SBP during pregnancy, mmHg	173 ± 19	159 ± 27	0.085
DBP during pregnancy, mmHg	104 ± 19	99 ± 18	0.425
Maximum UP during pregnancy, g/day	10.3 ± 5.2	9.7 ± 9.0	0.773
Serum Cr at last observation, mg/dL	3.0 ± 4.2	0.6 ± 0.1	0.079
UP at last observation, g/day	1.7 ± 1.4	0.1 ± 0.2	0.006*
Number of cases with normal eGFR (eGFR greater than 60 mL/min/1.73 m^3) at last observation, n (%)	8 (57%)	41 (73%)	0.011*
Number of cases with normal UP at last observation, n (%)	0 (0%)	43 (77%)	<0.001*
Number of CKD cases at last observation, n (%)	5 (36%)	0 (0%)	<0.001*

Abbreviations: DM, diabetes mellitus; RAS, renin-angiotensin system; SBP, systolic blood pressure; DBP, diastolic blood pressure; UP, urinary protein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

pregnancy at which PE developed did not differ significantly between the groups. There were significantly fewer days from delivery to percutaneous kidney biopsy, and more UP at last observation in the unimproved group than in the improved group. There was no significant difference between the two groups for the number of terminations, observation period after renal biopsy, past history of PE, past history of diabetes, drug history of renin-angiotensin system (RAS) inhibitors and other antihypertensive agents such as calcium antagonists and diuretics, maximum systolic and diastolic blood pressure during pregnancy, the maximum amount of UP during pregnancy, and serum creatinine measured at last observation. UP at last observation was higher in the unimproved group, and significantly more cases with normal eGFR and normal UP at last observation were found in the improved group. Especially, the number of patients of CKD onset (cases with eGFR of less than 60 mL/min/1.73 m^3 and who were positive for UP) at the time of the final observation was significantly different between 0 cases in the improvement group and 5 cases in the unimprovement group (Table 1). Additionally, there were no significant differences in age, blood pressure, body mass index (BMI), complete blood counts, biochemical findings, and urinary findings between the two groups at the time of percutaneous kidney biopsy (Table 2).

When comparing the histopathological findings between the two groups, no crescent formations or vasculitis were evident in any specimens via light microscopy. Additionally, all specimens did not show any specific findings in immunofluorescence staining examination. In the light microscopy examination, there was no significant difference in the number of evaluated glomeruli, in the percentages of global sclerosis and segmental sclerosis, and in endocapillary hypercellularity and arteriolar hyalinosis. However, the severities of duplications of the capillary wall, interstitial cell infiltration, and interstitial fibrosis were significantly higher in the unimproved group than in the improved group. There were no significant differences in the mean glomerular area or diameter between the two groups (Table 3). Fig. 1 shows typical histopathological findings of PE patient whose renal function declined until the introduction of hemodialysis. Severe duplications of the capillary loop, glomerulomegaly, segmental sclerosis, interstitial cell infiltration, and interstitial fibrosis were observed, which were typical findings in unimproved group patients.

When comparing the electron microscopy findings between the two groups, the unimproved group included significantly more patients who underwent electron microscopy examinations than the improvement group. All specimens did not contain electron dense deposits and mesangial interposition. There were no significant differences in endothelial cell detachment, proliferation, and swelling and loss of foot processes (Table 4).

The calculations of Cramer's V values between the two groups and each category of light and electron microscopy findings, endocapillary duplication, and interstitial fibrosis identified moderate associations with unimproved group. Interstitial cell infiltration, arteriolar hyalinosis, arteriosclerosis, endothelial detachment, and endothelial swelling were weakly associated with renal dysfunction (Table 5).

Table 2
Clinical and laboratory findings at the time of percutaneous kidney biopsy: Data are shown as the mean ± standard deviation. Comparisons between the unimproved and improved groups were performed using the *t* test.

Parameter	Unimproved group (n = 14)	Improved group (n = 56)	p value
Age, years	28 ± 5	29 ± 5	0.559
SBP, mmHg	134 ± 31	126 ± 21	0.267
DBP, mmHg	86 ± 19	79 ± 13	0.085
BMI, kg/m^2	22 ± 2	22 ± 3	0.935
Hb, g/dL	11.1 ± 1.3	11.4 ± 2.1	0.702
Ht, %	34 ± 9	35 ± 4	0.509
Plt, 10^4/μL	26 ± 10	31 ± 9	0.127
BUN, mg/dL	19 ± 11	13 ± 3	0.079
Cr, mg/dL	0.9 ± 0.5	0.7 ± 0.3	0.370
UA, mg/dL	6.0 ± 2.5	5.6 ± 1.6	0.607
UP, g/day	3.4 ± 2.3	2.0 ± 2.9	0.081
U-RBC, /hpf	6 ± 10	4 ± 6	0.615
Ccr, mL/min	83 ± 42	99 ± 31	0.139

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Hb, hemoglobin; Ht, hematocrit; Plt, platelet count; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; UP, urinary protein; U-RBC, urine sediment red blood cells; Ccr, 24-h creatinine clearance.

Table 3
Light microscopic findings of each glomerular, interstitial, and arterial lesion in percutaneous kidney biopsy specimens and measurement of the diameter and area of each glomeruli: Data are shown as the median (interquartile range) or mean ± standard deviation. Comparisons between the unimproved and improved groups were performed using the Mann–Whitney *U* test and *t*-tests, as appropriate. *Statistically significant ($p < 0.05$).

Parameter	Unimproved group (n = 14)	Improved group (n = 56)	p value
Number of evaluated glomeruli	9.0 (6.25–15.00)	12.0 (7.00–18.25)	0.559
Global sclerosis (%)	11 ± 26	2 ± 9	0.254
Segmental sclerosis (%)	7 ± 12	2 ± 6	0.179
Endocapillary duplication	2.5 (2.00–3.00)	1.0 (1.00–2.00)	0.024*
Endocapillary hypercellularity	0.0 (0.00–0.00)	0.0 (0.00–0.00)	0.061
Interstitial cell infiltration	0.0 (0.00–0.75)	0.0 (0.00–0.00)	0.026*
Interstitial fibrosis	0.5 (0.00–1.00)	0.0 (0.00–0.00)	0.023*
Arteriolar hyalinosis	0.0 (0.00–0.00)	0.0 (0.00–0.25)	0.151
Arteriosclerosis	0.0 (0.00–0.75)	0.0 (0.00–0.00)	0.503
Number of evaluated glomeruli	7 (4.25–10.75)	7 (4.75–12.00)	0.825
Average glomerular area, μm^2	15960 ± 5790	15928 ± 3661	0.984
Average glomerular diameter, μm	167 ± 25	163 ± 18	0.486

4. Discussion

Abnormal placentation and the development of maternal syndrome are considered as the pathogenesis of PE. Genetic abnormalities, maternal risk factors such as diabetes or hypertension, and immunological imbalance may cause placental dysfunction, which leads to the release of antiangiogenic factors such as sFLT-1, soluble endoglin (sENG), and other inflammatory mediators that induce systemic vascular dysfunction, capillary leakage, and vasospasm [9].

Glomerular endotheliosis is a characteristic finding of kidney in PE patients, and these lesions are mediated by soluble vascular endothelial growth factor receptor that deprives glomerular endothelial cells of the vascular endothelial growth factor, leading to cellular injury and disruption of the filtration apparatus with subsequent proteinuria [10–12]. A recent study showed that glomerular endotheliosis was found even in women with normal pregnancies and non-proteinuric gestational hypertension and in patients with PE, which suggests that PE may reflect the extreme condition of glomerular hypertensive stress in the normal pregnancy process [13].

In this study, we clarified the histological differences between the unimproved and the improved groups in PE patients. Although no differences in clinical or laboratory information were observed between the two groups, the severities of glomerular capillary wall duplication, interstitial cell infiltration, and interstitial fibrosis were significantly greater in the unimproved group than in the improved group. In the unimproved group, chronic lesions such as glomerular capillary wall duplication and interstitial fibrosis had already formed when kidney biopsies were taken, and vascular endothelial damage may have persisted for a longer time period. These findings may be related to persistent proteinuria and decreased renal function because the participants in our study did not develop other glomerular disorders.

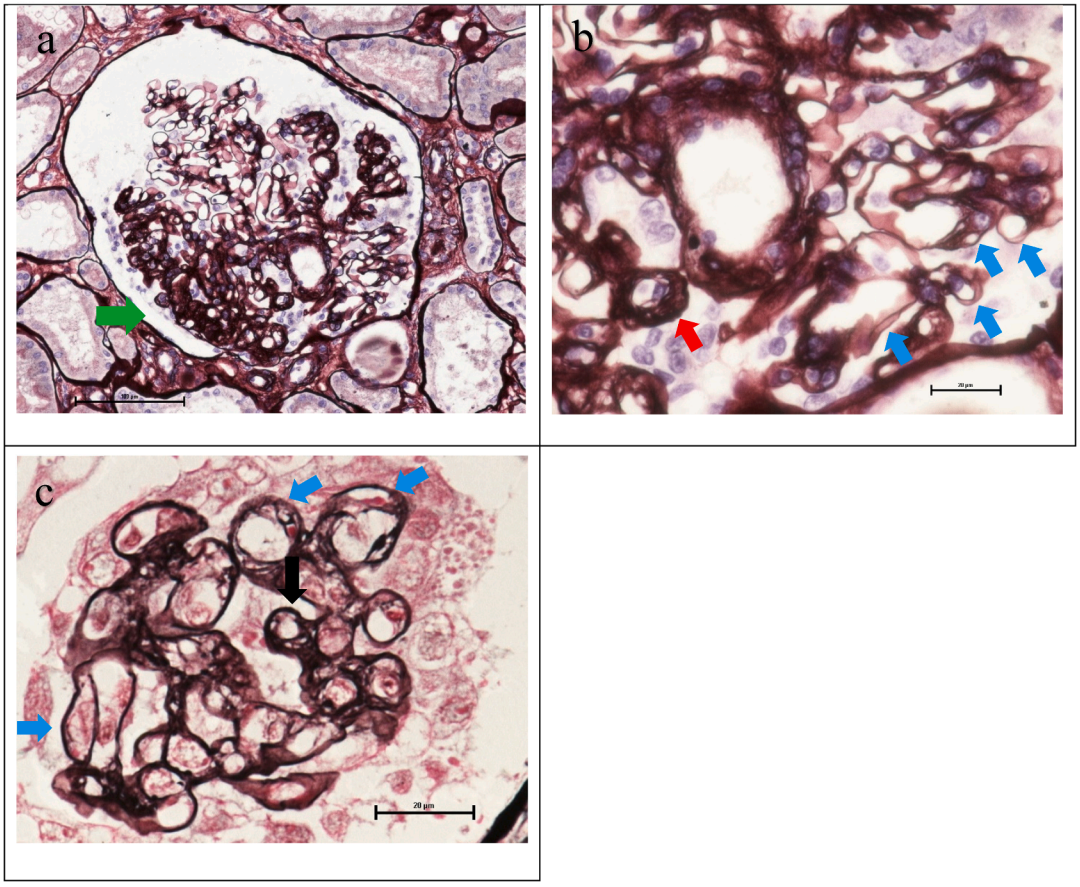

Fig. 1. Light microscopy findings in percutaneous kidney biopsy specimens: Focal segmental glomerulosclerosis lesion (black arrow) was observed (a). Both lesions of duplication of capillary walls (blue arrow) and mesangial interposition (red arrow) were observed (b). Clear lesions of duplication of capillary walls (blue arrow) were observed in specimens of a different patient (c). (a and b; periodic acid-methenamine-silver stain, c; Periodic acid-methenamine-silver and Masson Trichrome stains). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Electron microscopy findings of each glomerular lesion in percutaneous kidney biopsy specimens: Data are shown as the n (%) or median (interquartile range). Comparisons between the unimproved and improved groups were performed using Fisher's exact or Mann–Whitney *U* test, as appropriate. *Statistically significant ($p < 0.05$).

Parameter	Unimproved group (n = 14)	Improved group (n = 56)	p value
Number of evaluated cases	12 (86%)	22 (39%)	0.002*
Endothelial detachment	2.0 (1.75–4.00)	2.0 (1.00–3.75)	0.361
Endothelial proliferation	0.0 (0.00–0.00)	0.0 (0.00–0.00)	0.499
Endothelial swelling	2.5 (1.75–4.00)	2.0 (1.00–3.50)	0.223
Loss of foot process	1.0 (0.00–1.00)	1.0 (0.00–1.75)	0.374

Table 5
Cramer's V between renal function and each histopathological finding: Cramer's V was calculated in tables with rows and columns in a 2 × 4 formation. Cramer's V was used as a post-test to determine the strengths of association after the Chi-square test determined significance.

Parameter	Cramer's V
Endocapillary duplication	0.32
Interstitial fibrosis	0.33
Interstitial cell infiltration	0.21
Arteriolar hyalinosis	0.13
Arteriosclerosis	0.12
Endothelial detachment	0.23
Endothelial swelling	0.27

Glomerular basement membrane duplication means glomerular endothelial injury, which can play an important role in causing renal impairment and renal prognosis in diabetic nephropathy [14], thrombotic microangiopathies such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura [15], or acute antibody-mediated rejection [16]. Interstitial fibrosis and tubular atrophy without any specific etiology (IF/TA) is also related to poor renal prognosis, such as IgA nephropathy [17] and nephrosclerosis [18]. The results of our study indicate that IF/TA may be associated with renal prognosis in PE as well.

Patients with PE may require more careful clinical observation and intervention to avoid possible risk factors of endothelial damage such as smoking or obesity, particularly if glomerular basement membrane duplication or interstitial fibrosis in the kidney tissue is recognized in the kidney biopsy. This study showed that the severe histopathological damage to the glomerular basement membrane and interstitium of the kidney may affect long-term renal prognosis in patients with PE. Although clinical severity did not differ significantly between the unimproved and improved groups, there were significant differences in the pathological findings. There was no significant difference in glomerulomegaly between the two groups, but this may be biologically plausible because other biochemical changes in addition to hypertensive stress are involved in the pathogenesis of PE. Several previous studies have shown that excess circulating antiangiogenic substances such as

sFlt1, together with decreased placental growth factor and vascular endothelial growth factor (VEGF) signaling, play an important role in the pathogenesis of PE [19,20]. Other studies provided experimental evidence that anti-VEGF antibodies produce proteinuria, hypertension, and loss of glomerular endothelial fenestrae [21,22]. Additionally, there was no significant difference in the electron microscopy examination between the two groups, but we performed this examination particularly for those patients who showed poor kidney function, so sampling bias may have led to this observation. A previous study examined precise glomerular endothelial expansion by electron microscopy [23,24]; electron microscopic examination may also be useful for evaluating kidney biopsy specimens from patients with PE. The duplication of glomerular capillary walls and interstitial fibrosis are considered to be chronic lesions. However, there was no significant difference in the number of weeks of pregnancy when PE was developed between the two groups. This result implies that abnormal vascular responsiveness and oxidative stress may persist for longer period in the unimproved group than in the improved group, which reflects a similar pathophysiology previously indicated by studies in mice [25]. Since endothelial cell damage often disappears relatively early after childbirth, clinical laboratory findings do not detect a significant association with prognosis, and the degree of chronic pathological changes formed early in PE is prognostic for renal disease.

Several limitations of this study should be acknowledged. First, the selected participants in this study are only a small part of all patients with PE. In addition, there were fewer patients in the unimproved group, so it is unlikely that the results of this study will be applicable to all patients with PE because of the possibility of selection bias. There were patients with PE who were treated with RAS inhibitors during the observation period. Hence, there was a possibility that patients with PE with residual lesions could be less accurately evaluated due to the effects of treatment during the observation period. It is possible that the type 2 error might have occurred in this study. For more precise examination, getting together patients with PE who underwent percutaneous kidney biopsy may be necessary.

In conclusion, histopathological examination of the kidney may be a suitable and effective method for predicting the prognosis of renal function in PE patients. Although percutaneous renal biopsy is an invasive and patient-intensive examination, histological assessment may assess the risk of poor renal recovery of PE patients. The clinical indices after delivery were similar; there were significant differences in histological findings, which suggest that renal prognosis may be estimated from these findings. This study implies that more severe histopathological kidney injury predicts poor renal prognosis, and it may be possible to manage treatment including hypertension while predicting the future clinical course of PE patients. In cases where renal dysfunction and proteinuria persist longer after delivery, chronic lesions may have formed in the renal tissue, and measures based on the prevention of CKD and cardiovascular disease progression are necessary.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Compliance with ethical standards

This study protocol was approved by the Ethical Review Board of Niigata University (Approval number: 2019-0179). We obtained the patients' permission and agreement for this study by opt-out bio-repository. Ethical consideration in this research followed the Declaration of Helsinki.

Author declarations

Masanori Sudo wrote the initial draft of the manuscript. The other co-authors assisted in the preparation of the manuscript. All authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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