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Short Communication

Renal Diseases Associated with Preeclampsia in Postmenopausal Women

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Abstract

Preeclampsia is a disorder that occurs during pregnancy and is characterized by hypertension and proteinuria. Consequently there is an association of preeclampsia with renal disease. However, it remains unknown what association lies between preeclampsia and de novo renal diseases in postmenopausal women.

Methods: The electronic medical record was searched between April 1995 and March 2011 for renal biopsied patients with postmenopause. Information during pregnancy was obtained using the maternal health record book, which is issued from the patients' district health office for every pregnant woman. The kidney biopsy diagnoses of glomerular diseases were basically made in accordance with the criteria given in the World Health Organization monographs of kidney disease.

Results: Of the 37 women in the preeclampsia group, there were 10 with nephrosclerosis and 8 with focal segmental glomerular sclerosis. In the non-preeclampsia group of 96, 11 had nephrosclerosis and 1 with focal glomerular sclerosis. On that basis, there were more of the 2 kidney disorders in the preeclampsia than the non-preeclampsia group with significance ($P<0.05$ and $P<0.01$ respectively).

However, the prevalence of IgA nephropathy was not different between the two groups (10 vs. 20). At the time of renal biopsy, there were no differences in the levels of blood pressure, urinary excretion of protein and estimated glomerular filtration rate (eGFR).

Conclusion: Renal diseases diagnosed after menopause are strongly influenced by a past history of preeclampsia. Further it cannot be denied that this might contribute to cardiovascular diseases in postmenopausal women.

ABBREVIATIONS

CVD: cardiovascular disease; CKD: chronic kidney disease; FSGS: Focal Segmental Glomerular Sclerosis; eGFR: estimated glomerular filtration rate.

INTRODUCTION

Preeclampsia has been reported to be associated with the development of cardiovascular disease (CVD) [1,2] and with renal disease [3,4] in later life. Sibai et al. [5] reported that women with recurrent severe preeclampsia in the early third trimester had the highest risk for remote development of hypertension. In contrast, those with only normotensive pregnancies are at lowest risk. Besides, a long-term elevation of blood pressure produces renal damage while damage in the kidney elevates blood pressure [6]. Further, our previous data showed that in postmenopausal women with a past history of preeclampsia blood pressure easily began to elevate [7]. The renal pathology of preeclampsia has been widely investigated and a specific glomerular pattern has been reported [8-10]. Although these data are available, there are few reports discussing an association between preeclampsia and the development of chronic kidney disease (CKD) in later life [11]. To explore the effects of preeclampsia on kidney disease found in postmenopausal women, characteristics of renal biopsy proven renal disease in women with and without a past history of preeclampsia were compared.

MATERIALS AND METHODS

Patient selection

A retrospective cohort study was conducted using the electronic medical record between April 1995 and March 2011 in the Kidney Disease Center, Saitama Medical University. From a total of 1,586 kidney biopsies performed during this period,

biopsy specimens were selected according to gender (female) and post menopause (between 45 and 60 years). Patients diagnosed as diabetes mellitus and acute kidney injury was excluded. Using their maternity health record book, the presence of preeclampsia was determined. Preeclampsia was defined as BP>140/90 mmHg with proteinuria by a dipstick test after 20 weeks of gestation. Eclampsia was defined as a seizure either antenatally, in labor or within 24 hrs of delivery in a woman with raised BP after 20 weeks of gestation. Eclampsia and HELP syndrome were excluded from this study.

Other information including neonatal birth weight, gestational week, and delivery method were also obtained from the maternal health record book, which is issued from the patients' district health office to every pregnant woman.

This study was approved by the institute's ethics committee, and all patients provided written informed consent at the time of biopsy. The decision for renal biopsy was made by the physician. Usually, decision of renal biopsy was made when patients were suspected having renal disease judged by urinary examinations, the levels of eGFR, and ultrasonographic examination.

Renal biopsy was carried out during hospitalization. During hospitalization, basic data including use of drugs, physical examination and laboratory data were collected. A single kidney biopsy section from each patient was stained with Hematoxylin & Eosin (HE), Periodic acid Schiff (PAS), Periodic acid silver-methenamine (PAM), and Masson Trichrome.

Diagnosis of kidney biopsy

The kidney biopsy diagnoses of glomerular diseases were made in accordance with the criteria given in the World Health Organization monographs of kidney disease [12].

1) Nephrosclerosis thickened and hyalinized vessel walls, hyaline deposition in arterioles, fibroelastic hyperplasia in lobular / arcuate arteries and tubular atrophy, interstitial fibrosis and periglomerular fibrosis [13 14].

2) Focal Segmental Glomerular Sclerosis (FSGS)

i) NOS: At least one glomerulus with segmental increase in matrix obliterating the capillary lumina. There may be segmental glomerular basement membrane collapse without podocyte hyperplasia.

ii) Perihilar variant: Perihilar sclerosis and hyalinosis involving 50% of segmentally sclerotic glomeruli.

iii) Cellular variant: At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis.

iv) Tip variant: At least one segmental lesion involving the tip domain (Outer 25% of tuft next to origin of proximal tubule). The tubular pole must be identified in the defining lesion. The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck.

v) Collapsing variant: At least one glomerulus with segmental or global collapse.

3) IgA nephropathy is defined as a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA.

4) Membranous glomerulonephritis is defined by the presence of sub epithelial immune deposits.

5) Minimal changes is defined as light microscopy shows no or minimal glomerular abnormality.

6) Necrotizing glomerulonephritis is defined after modification of the 2012 Chapel Hill Consensus Conference [15].

eGFR was calculated using a modified three-variable equation for eGFR in Japanese patients: $eGFR=194 \times age^{-0.287} \times sCr^{-1.094}$ (x0.739, if female), where sCr=serum creatinine [16].

STATISTICAL ANALYSIS

Statistical analyses were performed using JMP software, version 9 (JMP, A Business Unit of SAS, Cary, NC USA). Values are given as the mean ± SD. Statistical analysis was performed using Student's *t* test for comparing means of unpaired variables (or Mann-Whitney tests when applicable). A p value of 0.05 was considered significant.

RESULTS AND DISCUSSION

Renal diseases diagnosed by renal biopsy in women with and without a past history of preeclampsia are shown in (Table 1). The proportions of renal diseases detected by renal biopsy differed significantly between the two groups. In the preeclamptic group, the prevalences of nephrosclerosis and FSGS were higher ($P<0.05$ and $P<0.01$ respectively) and those of minimal changes and membranous nephropathy were lower ($P<0.05$). IgA nephropathy was distributed equally in both groups.

The baseline characteristics relating with pregnancy and delivery are summarized in (Table 2A), and hemodynamic variables and laboratory findings at birth are shown in (Table 2B). Among these variables, gestation months and birth weight of new born were significantly lower in the preeclamptic group than in the non preeclamptic group ($P<0.05$). The age at birth, levels of systolic and diastolic BP were significantly higher in the preeclamptic group ($P<0.05$). The average levels of urinary excretion of protein and eGFR were similar in the two groups at the time of renal biopsy (Table 2B). In (Tables 3A) and (Tables 3B), the basal values at delivery and at renal biopsy of IgA nephropathy in women with and without a past history of preeclampsia are compared.

Table 1: Prevalence of renal diseases in women with and without a past history of preeclampsia.

	Past History (+) N=37	Past History (-) N=96	p value
IgA nephropathy	10 (27)	20 (21)	
Nephrosclerosis	10 (27)	11 (11)	0.05
Minimal changes	2 (5)	15 (16)	0.05
Membranous nephropathy	2 (5)	12 (13)	0.05
Focal glomerular sclerosis	8 (22)	1 (1)	0.01
Necrotizing nephropathy	0	6 (6)	
Systemic Lupus nephritis	0	2 (2)	
Others	5 (14)	29 (30)	

Table 2: Characteristics of basal values at birth (A) and at biopsy (B) in women with or without a past history of preeclampsia.

A	Past History (+) N=37	Past History (-) N=96	p value
Age at first pregnancy (year)	34±8	28±1	0.05
Gestation month (month)	8.2±1.1	11.6±0.3	0.05
Weight of new born (g)	2450±350	3100±80	0.05
Systolic blood pressure (mm Hg)	160±6	112±6	0.05
Diastolic blood pressure (mm Hg)	98±9	63±4	0.05
Proteinuria more than 2+	100%	11/96 (11%)	Not significant
B	**Past History (+) N=37**	**Past History (-) N=96**	**p value**
Age (year)	49±3.0	48.5±1.5	Not significant
Systolic blood pressure (mm Hg)	160±6	112±6	0.05
Diastolic blood pressure (mm Hg)	98±9	63±4	0.05
eGFR (mL/min/1.73m^2)	74.2±17.6	78.3±14.4	Not significant
Proteinuria (mg/day)	1.2±0.2	1.1±0.2	Not significant

Values expressed as mean ±SD.

Table 3: Characteristics of basal values at birth (A) and at biopsy (B) in women with or without a past history of preeclampsia in IgA.

A	Past History (+) N=10	Past History (-) N=20
Age(years)	29±7	28±1
Systolic/Diastolic Blood Pressure (mm Hg)	153±7/97±6	112±6/66±5 (at term)
Proteinuria	3+	7 patients 2+ 2 patients 1+ Others negative
New born child (g)	2365±492	2884±217
B	**Past History (+) N=10**	**Past History (-) N=20**
Age(years)	46±4	49±7
Systolic /Diastoli Blood Pressure (mm Hg)	136±2/78±4	121±6/67±5
eGFR (mL/min/1.73m^2)	68.2±19.5	73.3±15.9
Proteinuria (mg/day)	1.4±0.5	1.0±1.6
Age(years)	46±4	49±7

Values expressed as mean ±SD

During pregnancy, all patients with preeclampsia had severe proteinuria and 9 patients without preeclampsia had mild proteinuria. At the time of renal biopsy, there were no differences in variables between the two groups. (Table 4A) shows hemodynamic variables and laboratory findings at birth between preeclamptic and non eclamptic women with nephrosclerosis.

At the time of birth, the levels of systolic and diastolic blood pressure were significantly higher and birth weight of new born were significantly lower in the preeclamptic group compared with those of the non preeclamptic group (P<0.05). However, at the time of biopsy, there were no differences in systolic and diastolic BP, urinary excretion of protein and eGFR between the two groups (Table 4B). Lastly, only one patient who had no past history of preeclampsia was found to have FSGS compared with 8 patients who had a past history of preeclampsia. The morphological variants were as follows: 5 collapsing variants and 2 NOS and 1 perihilar variant. Further, variables at the time of birth and biopsy were not different from those of the total population (Data are not shown).

Discussion

The present study has demonstrated that kidney diseases in postmenopausal women are influenced by a past history of preeclampsia. It has been reported that preeclampsia is more common in women with an underlying kidney disease [Pollak, 1960 #2776]. Moreover, it has been suggested that preeclampsia itself increases the risk of kidney disease later in life [3]. The renal pathology of preeclampsia has been widely investigated, and its peculiar glomerular pattern is considered as a specific finding [8,10,17]. However, there have been few reports discussing the remote effects of preeclampsia on the kidney.

In a few postpartum renal biopsies, the typical lesions of preeclamptic nephropathy in conjunction with FSGS have been described [18-20]. Nochy et al. [17] suggested that FSGS might develop during preeclampsia and disappear in postpartum.

Glomerular hypertrophy may be a physiological response to glomerular hyper filtration during the course of pregnancy. Superimposed systemic hypertension in this setting of glomerular hypertrophy and hyper filtration seems to be necessary for the development of FSGS, as the group with FSGS had the most severe hypertension as well as the largest glomeruli.

In conjunction with continuous elevation of blood pressure,

Table 4: Characteristics of basal values at birth (A) and at biopsy (B) in women with or without a past history of preeclampsia in Nephrosclerosis.

A	Past History (+) N=10	Past History (-)N=11	p value
Age(years)	33±4	31±6	Not significant
Systolic/Diastolic Blood Pressure (mm Hg)	160±8/95±4	114±6/62±5	0.05
Proteinuria	3+	negative	Not significant
New born child (g)	2304±590	3166±880	0.05

B	Past History (+) N=10	Past History (-) N=11
Age(years)	46±4	52±7
Systolic/Diastolic Blood Pressure (mm Hg)	138±2/83±11	140±3/88±15
eGFR (mL/min/1.73m^2)	68.2±19.5	73.3±15.9
Proteinuria (mg/day)	0.6±0.5	0.3±0.5

Values expressed as mean ±SD

which is not usually recognized, the lesions of FSGS remained after delivery or gradually progressed in women with a past history of preeclampsia.

Gaber & Sargo (1987) [21] proposed that this focal segmental sclerosis appears to be of ischemic nature, induced by the ongoing indolent hypertensive process, perhaps compounded further by the renal hemodynamic alterations that occur during pregnancy. The form of segmental sclerosis that we described in relation to preeclampsia superimposed on nephrosclerosis does not demonstrate the ultra structural or the immunologic criteria of primary FSGS. Moreover, they [21] proposed that FSGS is not a feature of pure preeclampsia, but rather an indicator of underlying nephrosclerosis.

It has been reported that half of the participating women with a history of preeclampsia were hypertensive at 10 years after delivery compared with one-third who were hypertensive at a 5-year evaluation [22].

Hill [23] has recently reviewed nephrosclerosis as consisting of two different processes leading to glomerulosclerosis, and the combination of the two begins to explain why global correlations between hypertension and morphologic lesions are destined to remain poor. Arterial stiffening with increased pulse pressure down as far as the afferent arteriolar level likely plays an important role in the progression of glomerular lesions. Loss of renal auto regulation with glomerular hypertrophy, hyper filtration, and focal segmental glomerulosclerosis is now recognized to contribute significantly to nephrosclerosis, particularly in the black population. Ischemic glomerulosclerosis, however, may ultimately be the most important lesion, with consequent hypoxia in the parenchyma beyond, leading to tubular atrophy and interstitial fibrosis.

In the present study, these two morphological renal lesions were found more frequently in women with a past history of preeclampsia suggesting that renal damage is induced during pregnancy and that these alterations persisting with hypertension may appear as nephrosclerosis in later life.

IgA nephropathy is the most common form of GN in Japan and the effects of IgA nephropathy on the course of renal diseases after delivery have been a matter of dispute [24-30].

Considering the nature of IgA nephropathy, it is conceivable that these findings might be reasonable. In the present study, seven of 20 patients without preeclampsia were found to have mild proteinuria during pregnancy, probably indicating that subclinical renal disease might be accelerated by cessation of menstruation. If the levels of renal dysfunction are very mild, it is true that pregnancy does not affect the long-term outcome [31]. However, if renal dysfunction is moderately impaired, the long-term outcome is not promising. Moreover, there are very few data of long-term follow up of more than 20 years, which might be different from the prognosis of less than 10 years.

STUDY LIMITATIONS

First, this study was conducted in a single center and the results may be less applicable in general to other settings. However, renal biopsy would be recommended when CKD in postmenopausal women with a past history of preeclampsia are presented.

Second, the number of participating patients was small and greater numbers of such patients are required to unequivocally confirm our current findings.

This study was a retrospective and not a prospective one. No precise data during the pregnancy were obtained and the data were dependent only on the patients' health record. Also, more than 90% participants were introduced for the purpose of renal biopsy, indicating no information after delivery and at the time of renal biopsy.

Lastly, all patients in this study were postmenopausal women. This might influence the renal damage observed, since menopause has been associated with an increased risk of CVD, atherosclerosis, osteoporosis, change in body composition and increased inflammatory conditions [32]. In addition, our previous study reported that a larger proportion of women who became hypertensive in post menopause had a past history of preeclampsia [7]. After withdrawal of menstruation, risk of CVD is well known to be increased. Among the risk factors, hypertension is recognized as the leading cause of CVD. Besides, hypertension promotes kidney diseases and is closely associated with progression of kidney disease itself. Further it is also possible that a subclinical GN could be present before pregnancy and accelerated by preeclampsia as GN often has a long asymptomatic period. With these facts in mind, it cannot be

denied that combined effects may have contributed to the renal damage in the present study.

CONCLUSION

In conclusion, this is the first demonstration to compare renal diseases with and without a past history of preeclampsia.

First, two distinct diseases, FSGS and nephrosclerosis, may be strongly associated with a past history of preeclampsia. Second, evaluation for renal diseases should be included in postmenopausal subjects with a past history of preeclampsia. However, further studies are needed, because the underlying mechanisms for the remote effects of preeclampsia on renal diseases are complex and probably multifactorial.

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