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Effect of preeclampsia and its severity on maternal serum NGAL and KIM-1 levels during pregnancy and the post-pregnancy period

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ABSTRACT

Objective: The purpose of this trial was to appraise the effects of preeclampsia and its intensity on maternal serum neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) levels during pregnancy and the post-pregnancy period.
Study design: Firstly pregnant participants (n = 156) were separated into three groups, as control, mild, and severe preeclampsia. Secondly women in post-pregnancy period (n = 368) were separated into three groups according to history of pregnancy, as healthy control, mild, and severe preeclampsia. These women were identified through the hospital data system and contacted by telephone to participate in the study.
Results: Our study comprised 147 patients, 77 of whom were pregnant and 70 of whom were in their post-pregnancy period after the exclusion criteria had been applied. In terms of maternal serum NGAL levels, there is a significant increase in the severe preeclampsia group compared with that in the mild preeclampsia and normal pregnancy groups ($p < 0.001$). During the post-pregnancy period, the maternal serum NGAL levels were found significantly higher in the severe preeclampsia group than in the mild preeclampsia group and non-hypertension control group ($p < 0.001$). Maternal serum KIM-1 levels were found as significantly higher in the severe and mild preeclampsia groups than in the non-hypertension pregnancy group ($p = 0.004$). During the post-pregnancy period, maternal serum KIM-1 levels were found as similar among all post pregnant groups ($p = 0.792$).
Conclusions: Our results indicated that as the severity of preeclampsia increases, kidney damage as assessed using NGAL levels continues for a long period of time, even during the post-pregnancy period.

Introduction

Preeclampsia, which launches in the placenta at first and then affects all mother body and her baby, is a pregnancy disorder and is seen at about 5% frequency in the world [1]. One of the most important morbidity and mortality factors in terms of mother and her baby is the preeclampsia, in spite of the advances in modern medicine [2]. It remains unknown how preeclampsia occurs, but asymptomatic clinical signs may lead to the deterioration of several organs [3]. Edema, ischemia, endothelial dysfunction, and vasospasm, which affect all organs, are consistent with preeclampsia [3].

Neutrophil gelatinase-associated lipocalin (NGAL; is also known as lipocalin-2), which is found in human neutrophil granules, is a 25-kDa glycoprotein [4] that is also expressed in other human tissues, such as the liver, kidney, colon, and breast, and its production is significantly increased during inflammation or neoplasia during which epithelial cells are severely damaged [5,6]. NGAL is increased in kidney diseases. There is an important relationship between renal function and serum and urine NGAL levels [7]. Kidney injury molecule-1 (KIM-1) can attach to epithelial cells using their immunoglobulin-like domain, ectodomain mucin, and type-1 trans-membrane glycoprotein [8]. Small amounts of KIM-1 are secreted from healthy renal tissue, making them difficult to accurately measure; however, this secretion increases after renal damage [9,10].

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Although the effect of preeclampsia on kidney tubules is clear, there is no clear information on whether that effect is reversible or permanent during the postpartum period. Both serum NGAL and KIM-1 levels are important markers for the presence of kidney damage. The purpose of this trial was to appraise the effects of preeclampsia and its intensity on maternal serum NGAL and KIM-1 levels during pregnancy and the post-pregnancy period.

Materials and methods

The present trial was made at Erciyes University School of Medicine, Department of Obstetrics, according to the Declaration of Helsinki. In addition, the present study has an approval from the Ethics Committee of Erciyes University (123/2019). Only pregnant women who signed the consent form were included in the study.

Study population and inclusion and exclusion criteria

A total of 524 participants were evaluated. Firstly pregnant participants (n = 156) were separated into three groups, as control, mild, and severe preeclampsia. Secondly women in post-pregnancy period (n = 368) were separated into three groups according to history of pregnancy, as healthy control, mild, and severe preeclampsia. These women were identified through the hospital data system and contacted by telephone to participate in the study. Chronic systemic diseases, collagen vascular disease, chronic hypertension, all types of diabetes mellitus, multiple pregnancies, and fetal or chromosomal anomaly were accepted as the exclusion criteria of this research. Those not showing signs of the factors for exclusion from the study were considered healthy and were included in the study. During routine visits to the clinic, the healthy pregnant women were designated as the control group. The patients with preeclampsia without history of high blood pressure were incorporated to this study after being hospitalized.

We wanted to choose the participants in the post-pregnancy period from pregnant women who do not have pregnancy again after pregnancy complicated by preeclampsia and who do not have a disease or drug use that may affect their kidney health in this period. The reason for this is that these situations may add additional adverse problems on the kidney and the effect of preeclampsia on the kidney in the post-pregnancy period cannot be clearly demonstrated. Hence, we retrospectively scanned the pregnant women complicated with preeclampsia through the hospital data system. In this analysis, the information of a total of 368 pregnant women was reached and the pregnant women who became pregnant again after pregnancy complicated by preeclampsia, had a disease or drug use that could affect the kidney health, and met other exclusion criteria were excluded from the study. After this final analysis, 70 participants who met the criteria and volunteered to participate in the study were selected in a way that their maternal demographic characteristics were similar and were classified in the group of women in the post-pregnancy period in line with the power analysis.

Preeclampsia was identified in these women considering to those criteria, systolic blood pressure (SBP) $\geq$ 140 mmHg and diastolic blood pressure (DBP) $\geq$ 90 mmHg, surveyed at two times within six hours interval after 20th gestational weeks, and a proteinuria level > 0.3 g/24 h or a spot urine protein creatinine ratio > 300 mg/mmol [11]. If the pregnant woman with preeclampsia had at least one or more those risk factors such as headache, visual or cerebral disturbance, elevated liver enzymes, thrombocytopenia, dispne due to pulmonary edema, progressive renal failure, sistolic blood pressure $\geq$ 160 mmHg and/or diastolic blood pressure $\geq$ 110 mmHg, those patients were classified as

Table 1
Comparison of maternal and neonatal characteristics among all groups.

Characteristic	Normal pregnancy group (n = 25)	Mild preeclampsia group(n = 26)	Severe preeclampsia group (n = 26)	P-value	Control group in post-pregnancy period (n = 24)	Mild preeclampsia group in post-pregnancy period (n = 24)	Severe preeclampsia group in post-pregnancy period (n = 22)	P-value
Maternal age (year)	27.3 ± 5.0	30.4 ± 4.8	28.1 ± 5.7	0.099	29.9 ± 4.5	30.2 ± 4.8	30.0 ± 8.4	0.773
Parity	1.0 ± 0.9	1.3 ± 1.2	1.3 ± 1.1	0.587	1.7 ± 1.6	1.2 ± 1.1	1.7 ± 1.3	0.627
Duration of pregnancy at blood draw (weeks)	34.6 ± 2.8	33.0 ± 2.6	32.6 ± 2.8	0.06	–	–	–	–
Time after the delivery (month)	–	–	–	–	18.4 ± 9.1	18.9 ± 10.1	19.3 ± 10	0.862
BMI (kg/m^2)	29.4 ± 5.8	32.8 ± 5.8	31.1 ± 5.4	0.108	24.4 ± 5.8	25.4 ± 5.1	26.0 ± 5.0	0.621
Ethnicity (Caucasian)	23 (92 %)	26 (100 %)	26 (100 %)	0.350	24 (100 %)	24 (100 %)	22 (100 %)	0.960
SBP at the time of diagnosis (mm/Hg)	109 ± 14^A	152 ± 11^B	179 ± 18^C	<**0.001**	–	–	–	–
DBP at the time of diagnosis (mm/Hg)	65 ± 11^D	96 ± 14^E	129 ± 14^F	<**0.001**	–	–	–	–
Protein excretion in 24-h urine (mg)	–	682.0 ± 685.4	3216.8 ± 4216.6	<**0.001***	–	–	–	–
Gestational age at delivery (week)	38.7 ± 1.1^G	36.7 ± 1.2^H	33.6 ± 2.7^I	<**0.001**	38.2 ± 1.7^M	36.2 ± 2.2^N	33.0 ± 2.8^O	<**0.001**
Male newborns	13 (52 %)	13 (50 %)	12 (46 %)	0.210	12 (50 %)	11 (46 %)	12 (54 %)	0.180
Fetal weight (g)	3195.7 ± 315.1^J	2910.0 ± 787.4^K	1873.6 ± 774.7^L	<**0.001**	3015.9 ± 701.9^P	2690.9 ± 669.9^Q	1680.0 ± 667.1^R	<**0.001**

Notes: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CS, caesarian section; *, values were compared using the Mann Whitney U test. All comparisons were made using Tukey Post Hoc Test. Values are presented as the mean ± standard deviation, or n (%).
^{A} vs ^{B} -significant, ^{B} vs ^{C} -significant, ^{A} vs ^{C} -significant;
^{D} vs ^{E} -significant, ^{E} vs ^{F} -significant, ^{D} vs ^{F} -significant;
^{G} vs ^{H} -significant, ^{H} vs ^{I} -significant, ^{G} vs ^{I} -significant;
^{J} vs ^{K} -significant, ^{K} vs ^{L} -significant, ^{J} vs ^{L} -significant;
^{M} vs ^{N} -significant, ^{N} vs ^{O} -significant, ^{M} vs ^{O} -significant;
^{P} vs ^{Q} -significant, ^{Q} vs ^{R} -significant, ^{P} vs ^{R} -significant.

severe preeclampsia [11]. The gestational age of participants was identified in accordance with the initial day of the last menstrual period and was certified by ultrasonically calculating the early pregnancy week's crown-rump length.

Biochemical analysis

For analyzing the maternal serum NGAL and KIM-1 levels, 4 mL venous blood was collected and placed in a separate biochemistry tube. The specimens were centrifuged at 1000 rpm at 4 °C for 600 s. The supernatant from each sample was then transferred in to a clear 1.5-mL Eppendorf tube and stored at −80 °C for enzyme-linked immunosorbentassay (ELISA). The serum NGAL and KIM-1 levels were calculated using the sandwich Human NGAL ELISA Kit (catalog number, EK 0853) and Human KIM-1 ELISA Kit (catalog number, EK 0883).

Participants' specimens were removed from –80 °C and thawed at 37 °C then processed at room temperature. Specimens (10 μl/well) were added to the 384-well plate. Additionally, all specimens, each plate contained a calibration curve formed multiple analyte concentrations and control specimens. Calibration curves were prepared gravimetrically in plasma from healthy donors. For the specimens were obliged to be diluted to fit within the calibration curve, the calibrators were composed in a CD8 assay buffer (10 mmol/l Tris-HCl (pH 8.0), 150 mmol/l NaCl, 1 mmol/l MgCl 2, 0.1 mmol/l ZnCl 2, 10 ml/l polyvinyl alcohol (MW 9,000–10,000), 10 g/l bovine serum albumin, and 1 g/l NaN 3), which was also used for specimen dilution. The plates were read through a fluorometer. Calibration curves were eight points tested at multiple locations on the assay plate. The calibration curve was computed using a five-parameter logistic fit and specimen concentration was identified. The intra-assay accuracy was usually <5% and the inter-assay accuracy 10 % [12].

Statistical and power analyses

A pilot study examining the maternal serum NGAL levels from the severe preeclampsia (n = 10) and the healthy control (n = 10) during pregnancy was calculated to estimate a suitable sample size. The NGAL levels in the maternal serum were 97.0 ± 23.6 ng/mL in the severe preeclampsia group and 78.5 ± 27.9 ng/mL in the control group. With an alpha = 0.05, power (1-<beta>) = 0.8 and a group ratio = 1:1, the Cohen's D effect size was 0.715 suggesting 24 participants per group would be sufficient. Allowing for a 10 % drop-out rate, 26 patients per group were identified for a total of 156 patients.

All study statistics were done with SPSS ver. 22 (IBM Corp., Armonk, NY, USA). The values are presented as the mean ± standard deviation or n (%). P value <0.05 was considered statistically significant. To test the assumption of homogeneity of variance, the Levene's test was used. The Kruskal Wallis-H Test was performed for determining the normality of the data. The one way analysis of variance (Tukey's post-hoc test; ANOVA) compares normal pregnancy, mild and severe preeclampsia groups during pregnancy, and separately compare three groups during post-pregnancy.

Results

Our study comprised 147 patients, 77 of whom were pregnant and 70 of whom were in their post-pregnancy period after the exclusion criteria had been applied. Maternal and neonatal characteristics among all groups are compared and illustrated in Table 1. Maternal age, parity, duration of pregnancy at blood draw, ethnicity, and males born were similar among the all study groups. SBP and DBP during diagnosis, protein excretion in 24 h urine (mg), gestational age at birth, and fetal weight were significantly different among all pregnancy groups (all $p < 0.001$); however, only gestational age at birth, and fetal weight were significantly different among all post-pregnancy groups (all $p < 0.001$)

Maternal biochemical parameters including NGAL and KIM-1 levels were compared among all groups and were illustrated in Table 2 for the pregnancy groups and were illustrated in Table 3 for the post-pregnancy groups. In pregnancy groups, maternal serum blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels were statistically importantly higher in the severe preeclampsia group than in the mild preeclampsia group and control group ($p = 0.027$, $p = 0.015$, $p = 0.027$, $p = 0.040$, respectively). In post-pregnancy period we found that maternal serum BUN, creatinine, AST, ALT and LDH levels were statistically importantly higher in the severe preeclampsia group than in the mild preeclampsia group and non-hypertensive control group ($p < 0.001$, $p < 0.001$, $p = 0.007$, $p = 0.001$, $p = 0.005$, respectively).

Time after delivery was 18.4 ± 9.1 months in the control group in post-pregnancy period, 18.9 ± 10.1 months in the mild preeclampsia group in post-pregnancy period, and 19.3 ± 10 months in the severe preeclampsia group in post-pregnancy period ($p = 0.862$). Maternal serum NGAL levels were 76.5 ± 28.9 ng/mL in the normal pregnancy group, 76.0 ± 24.4 ng/mL in the mild preeclampsia group, and 109.0 ± 23.6 ng/mL in the severe

Table 2
Comparison of maternal biochemical parameters, NGAL, and KIM-1 levels among the pregnancy groups groups.

Characteristic	Normal pregnancy group (n = 25)	Mild preeclampsia group (n = 26)	Severe preeclampsia group (n = 26)	P-value
Serum NGAL (ng/mL)	76.5 ± 28.9^{A}	76.0 ± 24.4^{B}	109.0 ± 23.6^{C}	<0.001
Serum KIM-1 (ng/mL)	0.46 ± 0.11^{D}	0.73 ± 0.42^{E}	0.81 ± 0.40^{F}	0.004
Serum Na (mmol/L)	139.4 ± 1.7	138.6 ± 1.8	137.4 ± 2.6	0.075
Serum K (mmol/L)	4.17 ± 0.30	4.31 ± 0.33	4.36 ± 0.33	0.096
Serum BUN (mg/dl.)	6.68 ± 2.21^{G}	8.47 ± 2.75^{H}	12.76 ± 8.30^{I}	**0.027**
Serum creatinine (mg/dl)	0.52 ± 0.10^{J}	0.56 ± 0.18^{K}	0.68 ± 0.26^{L}	**0.015**
Serum AST (u/L)	17.16 ± 5.09	18.47 ± 5.72	53.88 ± 105.91	0.059
Serum ALT (u/L)	11.20 ± 4.77^{M}	15.81 ± 12.48^{N}	48.96 ± 91.40^{O}	**0.027**
LDH (u/L)	228.17 ± 81.80^{P}	244.27 ± 123.27^{Q}	318.96 ± 77.42^{R}	**0.040**

Notes: NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; Na, sodium; K, potassium, BUN,blood urea nitrogen;AST, aspartat aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; All comparisons were made using Tukey Post Hoc Test. Values are presented as the mean ± standard deviation.
^{A} vs ^{B} -not significant, ^{B} vs ^{C} -significant, ^{A} vs ^{C} -significant;
^{D} vs ^{E} -significant, ^{E} vs ^{F} -not significant, ^{D} vs ^{F} -significant;
^{G} vs ^{H} -not significant, ^{H} vs ^{I} -not significant, ^{G} vs ^{I} -significant;
^{J} vs ^{K} -not significant, ^{K} vs ^{L} -not significant, ^{J} vs ^{L} -significant;
^{M} vs ^{N} -not significant, ^{N} vs ^{O} -not significant, ^{M} vs ^{O} -significant;
^{P} vs ^{Q} -not significant, ^{Q} vs ^{R} -not significant, ^{P} vs ^{R} -significant.

Table 3
Comparison of maternal biochemical parameters, NGAL, and KIM-1 levels among the post-pregnancy groups.

Characteristic	Control group in post-pregnancy period (n = 24)	Mild preeclampsia group in post-pregnancy period (n = 24)	Severe preeclampsia group in post-pregnancy period (n = 22)	P-value
Serum NGAL (ng/mL)	76.6 ± 32.4[A]	80.4 ± 27.4[B]	113.21 ± 33.9[C]	<**0.001**
Serum KIM-1 (ng/mL)	0.50 ± 0.19	0.52 ± 0.33	0.56 ± 0.39	0.792
Serum Na (mmol/L)	138.2 ± 2.7	137.4 ± 2.7	136.2 ± 4.6	0.783
Serum K (mmol/L)	4.42 ± 0.33	4.48 ± 0.45	4.60 ± 0.75	0.880
Serum BUN (mg/dl.)	5.95 ± 1.50[D]	9.54 ± 3.87[E]	12.1 ± 3.85[F]	<**0.001**
Serum creatinine (mg/dl)	0.49 ± 0.11[G]	0.63 ± 0.19[H]	0.74 ± 0.13[I]	<**0.001**
Serum AST (u/L)	20.42 ± 8.67[J]	20.67 ± 8.36[K]	85.18 ± 111.67[L]	**0.007**
Serum ALT (u/L)	13.77 ± 8.58[M]	16.46 ± 14.93[N]	64.24 ± 78.20[O]	**0.001**
LDH (u/L)	238.71 ± 104.56[P]	303.50 ± 95.54[Q]	353.33 ± 98.05[R]	**0.005**

Notes: NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; Na, sodium; K, potassium, BUN,blood urea nitrogen;AST, aspartat aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; All comparisons were made using Tukey Post Hoc Test. Values are presented as the mean ± standard deviation.
[A] vs [B] -not significant, [B] vs [C] -significant, [A] vs [C] –significant;
[D] vs [E] -significant, [E] vs [F] -significant, [D] vs [F] –significant;
[G] vs [H] -significant, [H] vs [I] -significant, [G] vs [I] –significant;
[J] vs [K] –not significant, [K] vs [L] -significant, [J] vs [L] –significant;
[M] vs [N] -not significant, [N] vs [O] -significant, [M] vs [O] –significant;
[P] vs [Q] -not significant, [Q] vs [R] -not significant, [P] vs [R] –significant;

preeclampsia group—a significant increase in the severe preeclampsia group over that in the mild preeclampsia group and non-hypertension pregnancy group ($p < 0.001$). During the post-pregnancy period, maternal serum NGAL levels were 76.6 ± 32.4 ng/mL in the control group, 80.4 ± 27.4 ng/mL in the mild preeclampsia group, and 113.21 ± 33.9 ng/mL in the severe preeclampsia group —a significant increase in the severe preeclampsia group in post-pregnancy period compared with that in the mild preeclampsia group and non-hypertension pregnancy group in post-pregnancy period ($p < 0.001$). Maternal serum KIM-1 levels were found to be significantly higher in the mild and severe preeclampsia groups than in the control group ($p < 0.004$). Maternal serum KIM-1 levels were similar among the post-pregnancy groups.

Discussion

Preeclampsia causes renal damage and proteinuria; however, the damage to specific areas of the nephron remains unclear. Severe preeclampsia can cause the glomerular barrier to become nonfunctional, increasing glomerular endotheliosis and podocytes loss, determine by marked albuminuria [13–15]. In addition, inflammation and damage to the proximal tubule contributes to the pathogenesis of several other renal diseases [16,17]. An assessment of urinary proteins when preeclampsia is diagnosed must refer to both the model of glomerular and non-glomerular damage because the tubule-interstitium (>90 % of renal volume) can be affected independent of glomerular disease [18]. Our results showed that pregnant women with severe preeclampsia had higher serum NGAL and KIM-1, BUN, creatinine, ALT and LDH levels than pregnant women with mild preeclampsia or non-hypertension. Our results agree with those of several other studies that have demonstrated this same increase in terms of serum NGAL and KIM-1 levels for pregnant women with preeclampsia [19–26]. The renal dysfunction resulting from preeclampsia is well known; however, the effects of preeclampsia on the kidneys during the post-pregnancy period remain unclear. The potential repercussions on the organs from preeclampsia contain acute kidney dysfunction, which occurs during pregnancy and does not solve during the post-pregnancy period, a reduction of the trigger point for acute kidney disorder given renal insult during postpartum, and an increased sensitivity to later chronic renal disorders.

In this trial, we found that increased maternal serum KIM-1 levels were reduced until about 19 months after birth in those with severe and mild preeclampsia, and similar among all post-pregnancy period groups. Surprisingly, we found that patients having history of severe preeclampsia in post-pregnancy period even up to 19 months had higher serum NGAL levels and also higher serum BUN, creatinine, AST, ALT and LDH levels than patients having history of mild preeclampsia or non-hypertension in post-pregnancy period. By evaluating the pathophysiology of NGAL and KIM-1, we can explain our study results that KIM-1 is specific for proximal renal tubules, where acute toxic and ischemic renal injury occur and its release increases [9,10]; however, NGAL is also expressed in other human tissues, such as those of the liver, kidney, breast, and colon, and its production is significantly increased during inflammation or neoplasia, where severe epithelial damage occurs [5,6]. NGAL levels rose in pregnant women with severe preeclampsia and remained higher during the post-pregnancy period because of placental hypoxia and ischemia, which led to systemic excessive oxidative stress caused by ignificantly decreased in post-pregnancy samples from both groups. Other studies of manifest kidney disorder after hypertensive disease during pregnancy have mainly focused on chronic renal disorder, especially end-stage renal disorder; therefore, some did not find a relationship between previous hypertensive disease and later chronic renal disorder [27,28]. Other studies have reported strong associations among these outcomes [29–33]. Vikse et al. [29] have found that a history of preeclampsia in women who had two pregnancies increased the risk of end-stage renal disorder by three- to six folds, connected to whether or not a woman had preeclampsia in the first pregnancy, and/or second pregnancy. Wang et al. [30] have shown that women with a history of hypertensive disease during pregnancy have nine times the risk of chronic renal disorder and twelve times the risk of end-stage renal disorder than those without these disorders. In line with this study results, adjustment for hypertension and other co-morbidities has reduced the estimated results; however, these hypertensive disorders have been linked to a two to three-fold increase in the risk of renal disorder later in life. Similarly, Wu et al. [31] have found that a history of hypertensive disease during pregnancy is related to a tenfold increase in the risk of end-stage kidney disorder. Preeclampsia, especially that early in the pregnancy, is also strongly related to several chronic kidney diseases later in life

[32]. Finally, Ayansina et al. [33] have found that preeclampsia is related to a two fold increase in the risk of chronic kidney disorder later in life.

Conclusion

Our results indicated that as the severity of preeclampsia increases, the kidney damage done by the condition during pregnancy remains during the post-pregnancy period and later.

Study limitations

There were both limitations and strengths to our study. Although the sample size was determined by conducting a power analysis, the small size of the sample used in our study was considered to be a limitation. Absence of urinary KIM-1 and NGAL levels can be another limitation of study. It would have been better to fo the post-pregnancy period for a longer period of time to determine the recovery time of kidney damage.

One aim of the study was to determine whether there were lingering effects of preeclampsia in the post-pregnancy women but using separate groups of women pregnancy and post-pregnancy introduces much inter-individual variation between the pre and post groups. A much stronger design would be to recruit the three groups during pregnancy then to re-contact these women 6–12 months after delivery of their child; however, we wanted to show the effect of preeclampsia in a longer period of time, and especially for this purpose, we wanted to show it with the participants who do not have pregnancy again after pregnancy complicated by preeclampsia and were not complicated by a disease affecting the kidney. For a longer and broader study, we could not guarantee that pregnant women in the preeclampsia group would not conceive again and would not be complicated by a disease affecting the krmine the recovery time of kidney damage.

One aim of the study was to determine whether there were lingering effects of preeclampsia in the post-pregnancy women but using separate groups of women pregnancy and post-pregnancy introduces much inter-individual variation between the pre and post groups. A much stronger design would be to recruit the three groups during pregnancy then to re-contact these women 6–12 months after delivery of their child; however, we wanted to show the effect of preeclampsia in a longer period of time, and especially for this purpose, we wanted to show it with the participants who do not have pregnancy again after pregnancy complicated by preeclampsia and were not complicated by a disease affecting the kidney. For a longer and broader study, we could not guarantee that pregnant women in the preeclampsia group would not conceive again and would not be complicated by a disease affecting the kidney.

We believe that the strengths of our study were that unlike those in similar studies, our groups were evaluated according to the severity of preeclampsia. In addition, those post-pregnancy women were examined until 19 months. Those who remained after exclusion criteria were evaluated. Finally, the collected blood was studied to determine NGAL and KIM1 levels, which prevented bias.

Data availability

The data from our study are available and can be accessed from the corresponding author on request.

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Declaration of Competing Interest

All authors declare that they have no conflicts of interest associated with the study or its results.

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