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Preeclampsia and the 10-year Risk of Incident Chronic Kidney Disease

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Abstract

Background: Although preeclampsia (PE), as an endothelial disorder can lead to renal dysfunction during pregnancy, results of studies focusing on the potential long term potential effects of preeclampsia on renal function are insufficient and those available are controversial. This study investigated the incidence rate and risk of chronic kidney disease (CKD) among women with prior history of PE compared with healthy-controls in a long-term population-based study.

Methods: This was a prospective population-based cohort study. Subjects were 1851 eligible women, aged 20–50 years, with at least one pregnancy (177 women with prior-PE and 1674 non-PE controls) selected from among the Tehran-Lipid and Glucose-Study-participants. A pooled-logistic-regression-model and Cox's-proportional-hazards-models were utilized to estimate the risk of CKD in women of both PE and without PE groups, after further adjustment for confounders.

Results: Median and interquartile ranges for follow-up durations of the PE and non-PE groups were 7.78 (5.19-10.40) and 7.32 (4.73-11.00) years, respectively. Total cumulative incidence rates of CKD at the median follow-up time of each group was 35/100000 (95% CI: 25/100000, 50/100000) and 36/100000 (95% CI: 32/100000, 39/100000) in PE and non-PE women respectively. (P-value= 0.90). Based on pooled-logistic-regression-analysis, OR of CKD progression (adjusted for age, BMI, SBP and DBP) for the PE group did not differ, compared to their non-PE counterparts. (OR: 1.04; P-value= 0.80; 95% CI: 0.77, 1.40). Compared to non-PE women, women with prior PE did not have higher hazard ratios of developing CKD in the unadjusted model (unadjusted HR 1.1; 95% CI, 0.83–1.69; P = 0.35), results which remained unchanged after adjustment for age, BMI, baseline SBP and DBP.

Conclusion: Preeclampsia was not found to be a risk factor for CKD. More studies using a prospective cohort design with long term follow-ups are needed to investigate the relationship between preeclamsia and CKD.

Keywords: preeclampsia, chronic kidney disease, prospective population- based study, Tehran-Lipid and Glucose-Study (TLGS).

Introduction

Preeclampsia (PE) is a multisystem disorder affecting 3%–10% of all pregnant women with simultaneous increased rates of obesity, advanced maternal age and nulliparity [1, 2]. This disorder constitutes as a major cause of maternal morbidity and mortality worldwide.

The exact underlying etiology and pathogenesis of PE remains unknown, although it has been shown that genetic, immunological and environmental factors are associated with the endothelial dysfunction of PE [3]. Moreover, the imbalance of proangiogenic and anti-angiogenic proteins and disturbances in the renin–angiotensin aldosterone system, common mechanisms in chronic kidney disease, may play an important role in PE [4, 5]. Endothelial dysfunction in PE can also affect kidney function; it is well documented that PE is strongly associated with acute kidney dysfunction, viz. glomerular endotheliosis [6]. Kidney dysfunction, reflected by either decreased glomerular filtration rate (GFR) or albuminuria that usually recovers within six weeks of birth [7], unless there is glomerular scarring [8]. Nonetheless, some women may experience persistently decreased kidney function long after their complicated pregnancy with PE [9].

Relatively little is known about its long term effects on the kidney function later in life and data available reveal conflicting results. While some studies report kidney dysfunction can be resolved in most women with a history of PE [10-13], it has been shown that some women with PE may experience decreased glomerular filtration rate (GFR) and/or persistent proteinuria and/or

increased risk of CKD after PE [9, 14-18], discrepancies which may be partly explained by differences in ethnicities, study design, definition of kidney function and limited follow-up durations after pregnancy.

Considering the data available on the history of PE of the Tehran-Lipid and Glucose-Study (TLGS) participants enabled us to compare the incidence of CKD events among women with a prior history of PE compared with healthy controls in a long-term population-based study.

Methods

The Medical Ethics Committee of the Research Institute for Endocrine Sciences approved the research protocol. Written informed consent was obtained from all participants before the initiation of the study. (Ethic code: IR.SBMU.ENDOCRINE.REC.1398074)

Study population

This was a prospective cohort study with a 15-year follow-up conducted among 1851 women aged 20-50 years diagnosed with and without PE after the index pregnancy. The study participants were recruited from the Tehran Lipid and Glucose Study (TLGS). An ongoing study, initiated in 1998 to investigate the prevalence and risk factors of non-communicable diseases, in particular, cardiovascular risk factors. Briefly, in the TLGS, a total of 15,005 individuals, aged ≥ 3 years, were followed within 3-years intervals to collect data on demographic, anthropometric, reproductive and metabolic characteristics, general physical examinations, and laboratory measurements. Details of the procedures of TLGS have been published previously [19]. All participants were visited at the outpatient clinic of TLGS between February 1999 and August 2001. At initiation of our study, TLGS completed five phases with 3-year intervals (phase 1: 1999-2001, phase 2: 2002-2005, phase 3: 2005- 2008, phase 4: 2008- 2011 and phase 5: 2011- 2014). Therefore, current data were available for five phases including baseline and four follow-ups.

At the beginning of this study, all women, aged 20-50 years with at least one pregnancy were assessed (n= 3901), of whom 499 women had a history of PE during their pregnancies and 3402 did not. All women who were present at the baseline of the study and had at least one follow-up visit were included. Excluded were women with CKD (n= 203), hypertension (HTN) (n= 1265), CKD plus HTN (n= 224), and those without at least one follow up visit (n= 358). Finally, a total of 1851 women were recruited to participate in this study (Figure 1).

Measurements

All clinical, anthropometric, and biochemical parameters were measured by trained interviewers at baseline and follow-up visits; detailed descriptions of the measurements in TLGS have been published elsewhere [20, 21]. In brief, Body mass index (BMI) was calculated using the formula [weight in kilograms (kg) divided by height squared (m^2)]. Waist circumference (WC) was measured with an unstretched tape measure at the level of the umbilicus, without any pressure to the body surface. Hip circumference (HC) was measured at the level of the anterior superior iliac spine without any pressure to body surface. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice on the right arm in a seated position using a standard mercury sphygmomanometer after 15 mines of rest and the mean of these measurements was recorded. Blood samples were taken from participants after 12 h of overnight fasting and all blood analyses were performed at the TLGS research laboratory on the day of blood collection. Triglyceride (TG) levels were assayed using glycerol phosphate. Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. Levels of high-density lipoprotein cholesterol (HDL-C) were measured after precipitation of the apolipoprotein B (apo B)-containing lipoproteins with phosphotungstic acid; we used a modified Friedewald to calculate LDL-C. All metabolic analyses were performed using related kits (Pars Azmon Inc.,

Tehran, Iran) and a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Intra-assay and inter-assay coefficients of variations for TG, TC, HDL-C, and LDL-C were less than 2.1, 1.9, 3, and 3%, respectively. Serum creatinine (cr) levels were assayed by kinetic colorimetric Jaffe; sensitivity of the assay was 0.2 mg/dL (range, 18–1330 µmol/L (0.2–15 mg/dL). Reference intervals based on the manufacturer's recommendation was 53–97 µmol/L (0.6–1.1 mg/dL) in men. Intra-assay and inter-assay CVs < 3.1% in both baseline and follow-up phases. All biochemical assays were performed using commercial kits (Pars Azmoon Inc., Tehran, Iran) using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Assay performance was monitored after every 25 tests using lyophilized serum controls in normal and pathologic ranges and all samples were analyzed only when the internal quality control met the standard acceptable criteria [20, 21].

Term definitions

Data on history of PE were collected using a validated self-reporting questionnaire. According to the national guideline, the international standard criteria were used for the diagnosis of PE, i.e. the onset of a BP level ≥ 140/ 90 mm Hg along with proteinuria > 0.3 g/24 h after 20 weeks' gestation (22).

HTN was diagnosed based on the JNC-VI criteria (23), as a mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90 mm Hg, or the current use of anti-hypertensive medicine (24, 25).

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73m^2 (26). In this study, GFR was estimated using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease (MDRD) study as follows: GFR = 186 ×

(SCr) -1.154 × (Age) -0.203, in which eGFR (estimated GFR) is expressed as mL/min per 1.73 m^2 and serum creatinine (Scr) is expressed as mg/dL. Incident CKD was an eGFR of < 60 mL/min per 1.73 m^2 occurring at any time during the follow-up period [20, 26, 27].

Diabetes was defined as fasting plasma glucose (FPG) of ≥7.0 mmol/L or 2-hpost-challenge plasma glucose (2 h-PCPG) ≥11.1mmol/L or taking anti-diabetic medication in all phases of study

Statistical analyses

All continuous variables were assessed for normality using the one-sample Kolmogorov–Smirnoff test, and are expressed as mean (standard deviation), if variables had a normal distribution, or median with inter-quartile range (IQ25-75) for variables with skewed distribution. The characteristics of participants at baseline were compared between the PE and non-PE groups using two independent-sample t-tests or the equivalent nonparametric Mann-Whitney U test. Categorical variables, expressed as percentages, were compared using the Pearson's test. To analyze the person-time incidence rate of CKD the following description was used: the number of new events of the condition (cases) in the study time divided by the sum of person-time (person * year) at risk in the study participants. Initially, all variables were included in the univariate model. Next, the variables found to be significant in the univariate model were further included in the multivariate model. Adjustment for diabetes and dyslipidemia did not have any effect on the magnitude of the estimates. Pooled logistic regression was used to assess (1) the association between the dichotomous outcome variable (PE) and time-dependent covariates as the data was interval censored and time to CKD was not known, and (2) to calculate odds ratios (OR). This model treats every interval as a mini follow-up study, pools the observations of all intervals together into one pooled sample and does a logistic regression on the pooled dataset. In addition, the multivariable analysis was repeated using the time-dependent Cox proportional hazard regression assuming the

CKD event occurs is in the mid-time between visits. Kaplan-Meier plots and log-rank tests were employed as the univariate test for between-group differences in survival from CKD. Cox's proportional hazard model was used to calculate the hazard ratio between groups. Both these models were adjusted for age, BMI, SBP, DBP and smoking. Statistical analysis was performed using the software package STATA (version 14; STATA Inc., College station, TX, USA). Significance level was set at $p < 0.05$, with a confidence interval (CI) of 95%.

Results

Characteristics of the study subjects

During 15 years of follow-up, 1851 eligible participants including 177 women with PE and 1674 without PE were recruited; median and interquartile range for the follow-up years of PE and non-PE groups were 7.78 (5.19-10.40) and 7.32 (4.73-11.00) years, respectively. Baseline characteristics of the subjects are presented in Table 1.

Compared to non-PE controls, women with prior PE were more likely to be younger, [31.1 (7.4) versus 33.7 (7.5) years ($P < 0.001$)], and had significantly higher WC [86.5 (11.7) vs. 83.9 (10.7) cm, $P = 0.002$], BMI [(27.5 (4.6) vs. 26.5 (4.2) kg/m^2, $P = 0.003$], WHR [(0.8 (0.07) vs. 0.8 (0.07), $P < 0.02$] as well as SBP (108.1 (9.4) mmHg vs. 105.3 (9.2) mmHg), and DBP (71.3 (5.8) mmHg vs. 69.6 (6.2) mmHg) levels. Moreover, there was no statistically significant difference in the proportion of current smoking between women with and without prior PE. Based on the table 1 the prevalence of DM was the same for both groups at baseline (p-value=0.2). Neither was the mean of FBS and BS significantly different in both groups at baseline.

The total cumulative incidence rate of CKD at the median follow-up time was 35/100000 (95% CI: 25/100000, 50/100000) and 36/100000 (95% CI: 32/100000, 39/100000) in PE and non-PE women, respectively (P-value =0.90).

Pooled logistic regression and survival analysis

According to the pooled logistic regression analysis, OR of CKD progression (adjusted for age, BMI, SBP and DBP) in the PE group was not significantly different compared to the non-PE one (OR: 1.04; P-value= 0.80; 95% CI: 0.77, 1.40) (Table 2). In addition, the interaction of age and PE status (not statistically significant) showed that the relationship between PE, and CKD progression, was not age dependent (table 2).

The Kaplan-Meier plot, (Figure 2) illustrated the time for development of CKD for women in the PE and non-PE groups. The Kaplan-Meier plot for women with PE was not significantly different from that of non-PE women (P-value=0.35). Compared to non-PE women, women with prior PE did not have higher risk of developing CKD in the unadjusted model (unadjusted HR 1.1; 95% CI, 0.83–1.69; P = 0.35), even after multiple adjustments for potential confounders related to CKD, including age, BMI and baseline SBP (multiple- adjusted HR 1.2; 95% CI, 0.84–1.7 P = 0.31) (Table 2).

Pooled logistic and cox regression models for 4 subgroups of women including those with history of PE at: baseline (n=112), 1st follow up (n=43), 2nd follow up (n=22), and women without history of PE (n=1674) revealed no difference in incidence of CKD among these four sub-groups (supplementary table 1).

Discussion

This long-term, prospective and population-based study evaluated the incidence rate and risk of CKD among women with and without the prior history of PE. Without HTN, progression to CKD after the median follow-up time of 12 years was comparable between women with and without prior PE even after adjustment for potential confounders (age, BMI and blood pressure).

The underlying pathophysiology of preeclampsia is yet only partly understood. Impaired placentation at the early stage of gestations, as well as endothelial dysfunction, could play an important role in an affected pregnancy. It is well documented that kidney function alters during preeclamptic pregnancy; both renal blood flow and GFR decrease in preeclampsia, but absolute levels may remain above the non-pregnant range. It has been shown that renal lesions and glomerular deposits of various hemostatic factors can disappear within weeks after delivery [10]. In addition, data shows that decreased levels of GFR resolve a decade after preeclampsia that is comparable in women with and without a history of PE [9, 28]. However, microalbuminuria in women with prior PE is more likely to persist over the years, compared to controls of similar ages [28], which may be associated with developing of cardiovascular disease (CVD) and HTN in these women [29, 30]. Furthermore, CVD and HTN are comorbidities that may also accelerate the developing of subsequent CKD in these women.

Results of studies focusing on CKD among women with the history of PE are controversial. In agreement with our findings, Paauw et al. (2018) in a well-designed long term longitudinal study with a median follow-up of 11 years, assessed kidney dysfunction including CKD and end-stage renal disease (ESRD) following the pregnancy hypertensive disorder; during follow-up, none of the women developed ESRD. In addition, hypertensive pregnancy disorder did not increase the incidence of CKD (HR, 1.04; 95% CI, 0.79-1.37; P=0.8) [13]. In another population-based study, Sandvik et al. (2013) using data from the Medical Birth Registry in Norway reported that preeclampsia was not associated with higher rates of microalbuminuria or increased urinary albumin excretion, i.e. Median urinary ACR: 0.53 mg/mmol and 0.50 mg/mmol for women with and without prior preeclampsia respectively, P=0.54 (31). In addition, a meta-analysis (2019) conducted on kidney disease after preeclampsia, of seven studies reported that 31 percent of

women with history of PE after a mean follow-up of 7 years, had microalbuminuria, which was much higher than the 7% observed in women without the condition. However, there was no significant difference in the GFR, estimated using urinary creatinine clearance (mean difference, -0.04 mL/s [95% CI, -0.12 to 0.04] [9].

Other studies have focused mostly on end-stage renal disease. Vikse et al. (2008) demonstrated that prior preeclampsia could significantly increase the risk of end-stage renal disease 3-6 fold, depending on whether a woman had had pre-eclampsia in the first, second or both pregnancies [32]. A recent study by Kristensen et al (2019) evaluated associations between PE and later risk of kidney disease in a national register-based prospective study [18], in which more than one million women were followed for an average 18.6 years/woman; their results showed that compared with women without previous PE, those with a history of it were more likely to develop chronic renal conditions: HR 3.93, 95% CI: 2.90-5.33, for early preterm PE who delivered <34 weeks, 2.81 (2.1-3.71) for late preterm PE who delivered 34-36 weeks and 2.27 (2.02-2.55) for term PE who delivered ≥37 weeks. However, the definition of CKD in this study differed to our study. They included hypertensive kidney disease, most glomerular disease diagnoses, chronic tubulointerstitial nephritis, and renal failure. Since maternal age and BMI are suspected of mediating the associations between PE and CKD, the effect of age and BMI in our model was adjusted, whereas they were not adjusted in that study.

The main strengths of our study are its methodology as a long term prospective population-based study with a large sample size. Low levels of loss to follow-up are other strengths of this study, which helped us to estimate the study outcome with a high precision. However, our study was limited by a number of factors that should be considered when interpreting the results. Preeclampsia diagnosis was self-reported in this study, which may induce recall bias, affecting the

results; using the valid questionnaire that included proxy variables and checking the summary report of hospitalization for those with uncertain situation may reduce such bias (35, 36). In addition, it was reported that the self-reported history of hypertensive pregnancy disorders has a sensitivity of 72–80% and specificity of 96–99% (33, 34). Moreover, recurrent PE and severity of PE were not assessed, which might have influenced the severity of endothelial dysfunction after pregnancy. Furthermore, as in most epidemiologic studies, the CKD definition was based on creatinine measurements which may vary day-to-day (15.5–19.6%) and were not repeated within three months to confirm a chronic reduction in GFR. In addition, we lacked data on proteinuria or microalbuminuria (causing underestimation of CKD incidence) that could have given us more accurate results; however, eGFR as a measure of kidney function is closely linked to proteinuria (37, 38). Some epidemiologic studies use serum creatinine for definition of the CKD, a non-expensive and simple method, easily applied for large population measurements (39). Also, despite controlling for various confounders in our analysis, residual confounding due to unknown or unmeasured confounders such as socioeconomic factors and family history of CKD cannot be excluded. Last but not least, since this study was performed only on Iranian women, the findings cannot be generalized to other population with different covariate distributions.

Conclusion

Women with the history of PE showed no higher risk of subsequent chronic kidney disease over 15 years of follow up, a finding independent of the women's age, BMI, SBP, and DBP. Further comprehensive prospective studies with a precise definition of the severity of PE and kidney disease and longer adequate follow-ups are needed to confirm the study's findings.

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Disclosure Statement

None of the authors have reported conflicts of interest.

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Table 1. Baseline characteristics of the women with and without history of preeclampsia

Variables	PE (N=177)	Non-PE (N=1674)	P- value[d]
Age [a] (years)	31.11 (7.45)	33.73 (7.54)	< 0.001
Parity [a]	0.97 (0.15)	1.00 (0.08)	0.14
BMI [a] (kg/m^2)	27.5 (4.60)	26.50 (4.23)	0.003
WC [a] (cm)	86.58 (11.77)	83.91 (10.70)	0.002
HC [a] (cm)	104.28 (9.24)	102.80 (8.35)	0.03
Waist to hip ratio [a]	0.83 (0.07)	0.81 (0.07)	0.02
SBP [a] (mmHg)	108.12 (9.46)	105.40 (9.21)	< 0.001
DBP [a] (mmHg)	71.34 (5.81)	69.60 (6.23)	< 0.001
TG [b] (mmol/L)	1.31 (0.87-1.88)	1.23 (0.88-1.81)	0.56
TC [a] (mmol/L)	5.00 (1.07)	4.97 (1.04)	0.77
LDL-C [a] (mmol/L)	3.20 (0.93)	3.13 (0.88)	0.40
HDL-C [a] (mmol/L)	1.13 (0.28)	1.16 (0.29)	0.08
Prevalence of DM[c]	8 (4.5)	50 (3)	0.2
FBS[a] (mmol/L)	5±1.3	5±1.1	0.7
2 h-PCPG [a] (mmol/L)	6±2.4	5.9±1.9	0.4
Current Smoking [c]	10 (5.6%)	72 (4.3%)	0.44

[a] values are presented as mean (SD).
[b] presented as median (interquartile range).
[c] data shown as number (percentage).
[d] Significant differences (P-value<0.05), analyzed using independent t-test for superscripts [a], Mann-Whitney U test for superscripts [b] , and Pearson's χ^2 test for superscripts [c].

PE= preeclampsia; Non-PE= Non Preeclampsia; BMI= body mass index; WC= waist circumference; HC= hip circumference; SBP= systolic blood pressure; DBP= diastolic blood pressure; TG= triglycerides; TC= total cholesterol; LDL-C= Low-density lipoprotein cholesterol; HDL-C= high-density lipoprotein cholesterol; HTN= hypertension; FPG= fasting plasma glucose; 2 h-PCPG= 2-hpost-challenge plasma glucose

Table 2. Pooled logistic regression and the cox regression model for CKD among women with and without preeclampsia.

		Variables	**Odds Ratio**	**95% Confidence interval**	**P-value**
Pooled logistic regression analysis	Unadjusted	PE	0.82	(0.63 , 1.07)	0.14
	Multiple adjusted	PE	0.61	(0.14,2.62)	0.51
		Age (year)	1.07	(1.05, 1.08)	<0.001
		Age * PE	1.01	(0.97, 1.05)	0.47
		PE	1.04	(0.77, 1.40)	0.80
		Time			
		Follow-up 1	Reference		
		Follow-up 2	2.37	(0.87, 1.43)	<0.001
		Follow-up 3	2.82	(1.13, 1.81)	<0.001
		Follow-up 4	3.05	(1.15, 1.96)	<0.001
		Age (year)	1.07	(1.05, 1.08)	<0.001
		BMI (kg/m2)	0.99	(0.97, 1.01)	0.35
		SBP (mmHg)	1.00	(0.99, 1.01)	0.39
		DBP (mmHg)	1.00	(0.99, 1.02)	0.68
		Smoking	1.34	(0.93, 1.93)	0.12
		Variables	**Hazard Ratio**	**95% Confidence interval**	**P-value**
Cox regression analysis	Unadjusted	PE	0.78	(0.57, 1.07)	0.13
	Multiple adjusted	PE	0.88	(0.63, 1.23)	0.45
		Age (year)	1.05	(1.04, 1.07)	<0.001
		BMI (kg/m2)	1.00	(0.97, 1.01)	0.67
		SBP (mmHg)	1.02	(0.97, 1.04)	0.15
		DBP (mmHg)	1.01	(0.98, 1.03)	0.51
		Smoking	1.28	(0.89, 1.85)	0.2

PE= preeclampsia, BMI= body mass index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure

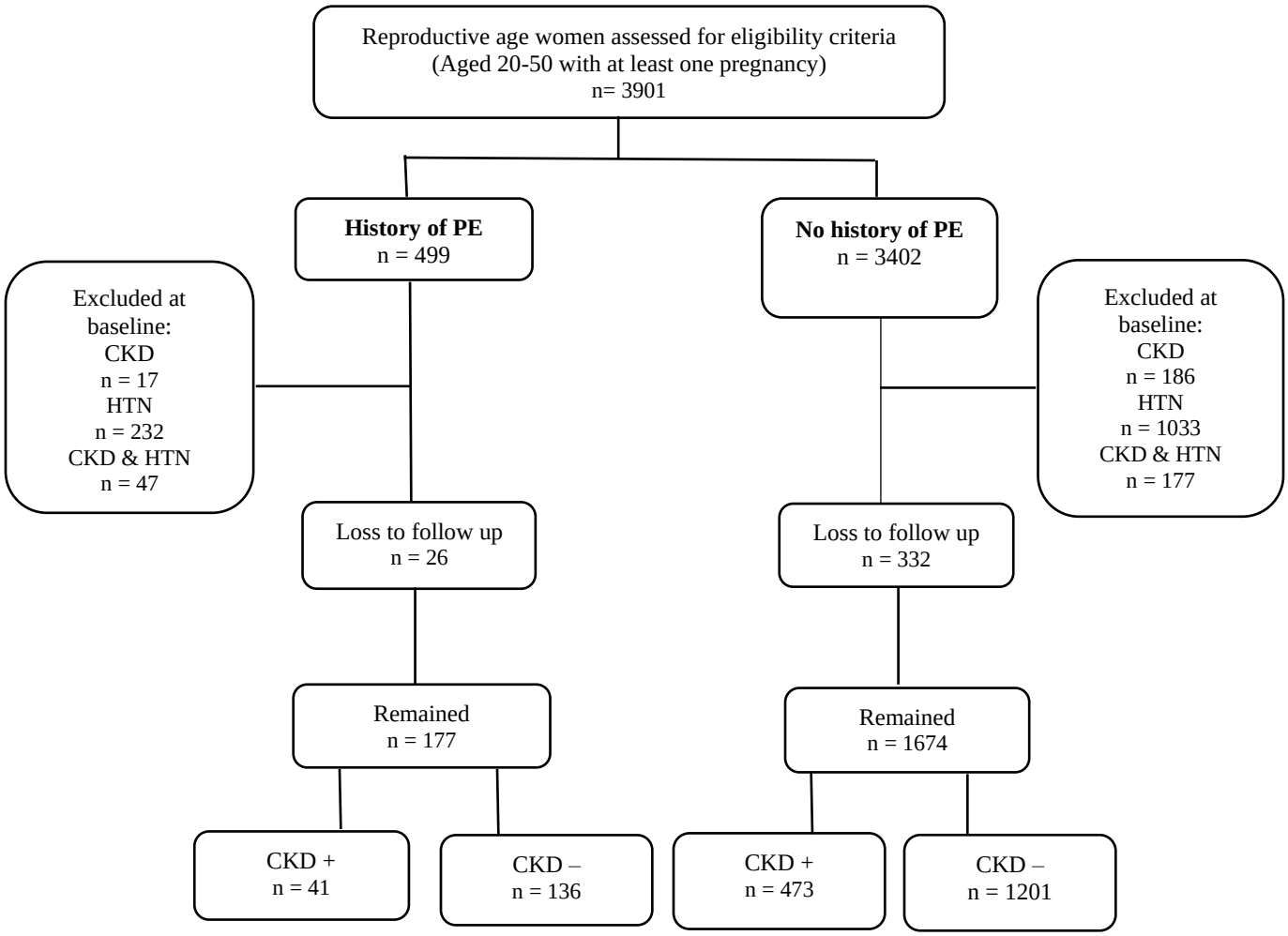

Figure 1. Study flowchart.

PE: preeclampsia, CKD: chronic kidney disease, HTN: hypertension

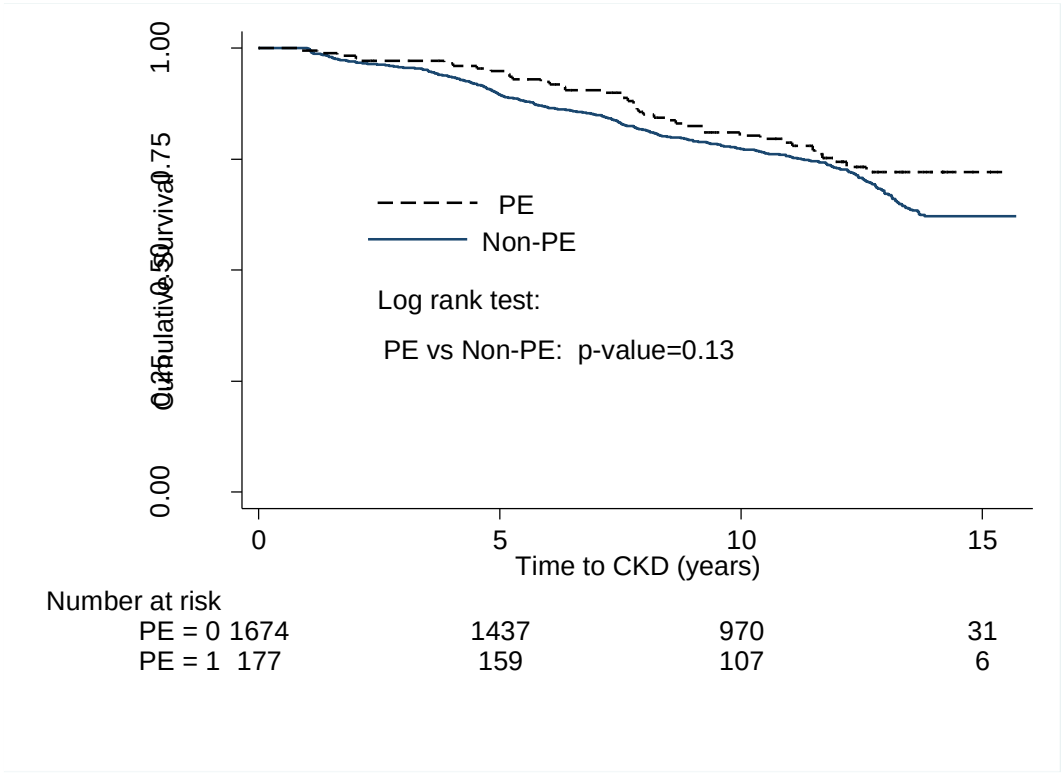

Figure 2. Kaplan-Meier survival estimate plot showing survival (time to CKD) curves for PE and non-PE groups.

PE: preeclampsia

Supplementary file:

Supplementary table 1: Pooled logistic and cox regression models for 4 subgroups of women including those with history of PE at: baseline (n=112), 1st follow up (n=43), 2nd follow up (n=22), and women without history of PE (n=1674)

		Variables	**Odds Ratio**	**95% Confidence interval**	**P-value**
Pooled logistic regression analysis	Unadjusted	1	0.96	(0.70 , 1.32)	0.**82**
		2	0.72	(0.42, 1.21)	**0.21**
		3	0.82	(0.77, 1.10)	**0.6**
		4	REF		
	Multiple adjusted	1	1.12	(0.79 , 1.60)	0.**67**
		2	1.10	(0.61, 1.94)	**0.32**
		3	1.11	(0.86, 1.97)	**0.43**
		4	REF		
		Time			
		Follow-up 1	Reference		
		Follow-up 2	2.36	(1.75, 3.17)	<0.001
		Follow-up 3	2.81	(2.11, 3.75)	<0.001
		Follow-up 4	3.07	(2.27, 4.13)	<0.001
		Age (year)	1.06	(1.05, 1.08)	<0.001
		BMI (kg/m2)	0.99	(0.97, 1.01)	0.35
		SBP (mmHg)	1.00	(0.99, 1.01)	0.3**8**
		DBP (mmHg)	1.00	(0.99, 1.02)	0.**51**
		Smoking	1.35	(0.93, 1.93)	0.1**1**
		Variables	**Hazard Ratio**	**95% Confidence interval**	**P-value**
Cox regression analysis	Unadjusted	1	0.88	(0.60 , 1.30)	0.**53**
		2	0.65	(0.34, 1.27)	**0.21**
		3	0.75	(0.48, 1.23)	**0.24**
		4	REF		
	Multiple adjusted	1	0.92	(0.62 , 1.36)	0.**67**
		2	0.91	(0.50, 1.84)	**0.80**
		3	0.83	(0.43, 1.69)	**0.46**
		4	REF		
		Age (year)	1.05	(1.04, 1.07)	<0.001
		BMI (kg/m2)	1.00	(0.97, 1.01)	0.**72**
		SBP (mmHg)	1.00	(0.98, 1.01)	0.**49**
		DBP (mmHg)	1.00	(0.98, 1.01	0.**64**
		Smoking	1.29	(0.89, 1.86)	0.**18**

PE= preeclampsia, BMI= body mass index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure

Preeclampsia and the 10-year Risk of Incident Chronic Kidney Disease

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Abstract

Background: Although preeclampsia (PE), as an endothelial disorder can lead to renal dysfunction during pregnancy, results of studies focusing on the potential long term potential effects of preeclampsia on renal function are insufficient and those available are controversial. This study investigated the incidence rate and risk of chronic kidney disease (CKD) among women with prior history of PE compared with healthy-controls in a long-term population-based study.

Methods: This was a prospective population-based cohort study. Subjects were 1851 eligible women, aged 20–50 years, with at least one pregnancy (177 women with prior-PE and 1674 non-PE controls) selected from among the Tehran-Lipid and Glucose-Study-participants. A pooled-logistic-regression-model and Cox's-proportional-hazards-models were utilized to estimate the risk of CKD in women of both PE and without PE groups, after further adjustment for confounders.

Results: Median and interquartile ranges for follow-up durations of the PE and non-PE groups were 7.78 (5.19-10.40) and 7.32 (4.73-11.00) years, respectively. Total cumulative incidence rates of CKD at the median follow-up time of each group was 35/100000 (95% CI: 25/100000, 50/100000) and 36/100000 (95% CI: 32/100000, 39/100000) in PE and non-PE women respectively. (P-value= 0.90). Based on pooled-logistic-regression-analysis, OR of CKD progression (adjusted for age, BMI, SBP and DBP) for the PE group did not differ, compared to their non-PE counterparts. (OR: 1.04; P-value= 0.80; 95% CI: 0.77, 1.40). Compared to non-PE women, women with prior PE did not have higher hazard ratios of developing CKD in the unadjusted model (unadjusted HR 1.1; 95% CI, 0.83–1.69; P = 0.35), results which remained unchanged after adjustment for age, BMI, baseline SBP and DBP.

Conclusion: Preeclampsia was not found to be a risk factor for CKD. More studies using a prospective cohort design with long term follow-ups are needed to investigate the relationship between preeclamsia and CKD.

Keywords: preeclampsia, chronic kidney disease, prospective population- based study, Tehran-Lipid and Glucose-Study (TLGS).

Introduction

Preeclampsia (PE) is a multisystem disorder affecting 3%–10% of all pregnant women with simultaneous increased rates of obesity, advanced maternal age and nulliparity [1, 2]. This disorder constitutes as a major cause of maternal morbidity and mortality worldwide.

The exact underlying etiology and pathogenesis of PE remains unknown, although it has been shown that genetic, immunological and environmental factors are associated with the endothelial dysfunction of PE [3]. Moreover, the imbalance of proangiogenic and anti-angiogenic proteins and disturbances in the renin–angiotensin aldosterone system, common mechanisms in chronic kidney disease, may play an important role in PE [4, 5]. Endothelial dysfunction in PE can also affect kidney function; it is well documented that PE is strongly associated with acute kidney dysfunction, viz. glomerular endotheliosis [6]. Kidney dysfunction, reflected by either decreased glomerular filtration rate (GFR) or albuminuria that usually recovers within six weeks of birth [7], unless there is glomerular scarring [8]. Nonetheless, some women may experience persistently decreased kidney function long after their complicated pregnancy with PE [9].

Relatively little is known about its long term effects on the kidney function later in life and data available reveal conflicting results. While some studies report kidney dysfunction can be resolved in most women with a history of PE [10-13], it has been shown that some women with PE may experience decreased glomerular filtration rate (GFR) and/or persistent proteinuria and/or

increased risk of CKD after PE [9, 14-18], discrepancies which may be partly explained by differences in ethnicities, study design, definition of kidney function and limited follow-up durations after pregnancy.

Considering the data available on the history of PE of the Tehran-Lipid and Glucose-Study (TLGS) participants enabled us to compare the incidence of CKD events among women with a prior history of PE compared with healthy controls in a long-term population-based study.

Methods

The Medical Ethics Committee of the Research Institute for Endocrine Sciences approved the research protocol. Written informed consent was obtained from all participants before the initiation of the study. (Ethic code: IR.SBMU.ENDOCRINE.REC.1398074)

Study population

This was a prospective cohort study with a 15-year follow-up conducted among 1851 women aged 20-50 years diagnosed with and without PE after the index pregnancy. The study participants were recruited from the Tehran Lipid and Glucose Study (TLGS). An ongoing study, initiated in 1998 to investigate the prevalence and risk factors of non-communicable diseases, in particular, cardiovascular risk factors. Briefly, in the TLGS, a total of 15,005 individuals, aged ≥ 3 years, were followed within 3-years intervals to collect data on demographic, anthropometric, reproductive and metabolic characteristics, general physical examinations, and laboratory measurements. Details of the procedures of TLGS have been published previously [19]. All participants were visited at the outpatient clinic of TLGS between February 1999 and August 2001. At initiation of our study, TLGS completed five phases with 3-year intervals (phase 1: 1999-2001, phase 2: 2002-2005, phase 3: 2005- 2008, phase 4: 2008- 2011 and phase 5: 2011- 2014). Therefore, current data were available for five phases including baseline and four follow-ups.

At the beginning of this study, all women, aged 20-50 years with at least one pregnancy were assessed (n= 3901), of whom 499 women had a history of PE during their pregnancies and 3402 did not. All women who were present at the baseline of the study and had at least one follow-up visit were included. Excluded were women with CKD (n= 203), hypertension (HTN) (n= 1265), CKD plus HTN (n= 224), and those without at least one follow up visit (n= 358). Finally, a total of 1851 women were recruited to participate in this study (Figure 1).

Measurements

All clinical, anthropometric, and biochemical parameters were measured by trained interviewers at baseline and follow-up visits; detailed descriptions of the measurements in TLGS have been published elsewhere [20, 21]. In brief, Body mass index (BMI) was calculated using the formula [weight in kilograms (kg) divided by height squared (m^2)]. Waist circumference (WC) was measured with an unstretched tape measure at the level of the umbilicus, without any pressure to the body surface. Hip circumference (HC) was measured at the level of the anterior superior iliac spine without any pressure to body surface. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice on the right arm in a seated position using a standard mercury sphygmomanometer after 15 mines of rest and the mean of these measurements was recorded. Blood samples were taken from participants after 12 h of overnight fasting and all blood analyses were performed at the TLGS research laboratory on the day of blood collection. Triglyceride (TG) levels were assayed using glycerol phosphate. Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. Levels of high-density lipoprotein cholesterol (HDL-C) were measured after precipitation of the apolipoprotein B (apo B)-containing lipoproteins with phosphotungstic acid; we used a modified Friedewald to calculate LDL-C. All metabolic analyses were performed using related kits (Pars Azmon Inc.,

Tehran, Iran) and a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Intra-assay and inter-assay coefficients of variations for TG, TC, HDL-C, and LDL-C were less than 2.1, 1.9, 3, and 3%, respectively. Serum creatinine (cr) levels were assayed by kinetic colorimetric Jaffe; sensitivity of the assay was 0.2 mg/dL (range, 18–1330 µmol/L (0.2–15 mg/dL). Reference intervals based on the manufacturer's recommendation was 53–97 µmol/L (0.6–1.1 mg/dL) in men. Intra-assay and inter-assay CVs < 3.1% in both baseline and follow-up phases. All biochemical assays were performed using commercial kits (Pars Azmoon Inc., Tehran, Iran) using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Assay performance was monitored after every 25 tests using lyophilized serum controls in normal and pathologic ranges and all samples were analyzed only when the internal quality control met the standard acceptable criteria [20, 21].

Term definitions

Data on history of PE were collected using a validated self-reporting questionnaire. According to the national guideline, the international standard criteria were used for the diagnosis of PE, i.e. the onset of a BP level ≥ 140/ 90 mm Hg along with proteinuria > 0.3 g/24 h after 20 weeks' gestation (22).

HTN was diagnosed based on the JNC-VI criteria (23), as a mean systolic blood pressure ≥ 140 mm Hg, mean diastolic blood pressure ≥ 90 mm Hg, or the current use of anti-hypertensive medicine (24, 25).

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73m^2 (26). In this study, GFR was estimated using the abbreviated prediction equation, provided by the Modification of Diet in Renal Disease (MDRD) study as follows: GFR = 186 ×

(SCr) -1.154 × (Age) -0.203, in which eGFR (estimated GFR) is expressed as mL/min per 1.73 m^2 and serum creatinine (Scr) is expressed as mg/dL. Incident CKD was an eGFR of < 60 mL/min per 1.73 m^2 occurring at any time during the follow-up period [20, 26, 27].

Diabetes was defined as fasting plasma glucose (FPG) of ≥7.0 mmol/L or 2-hpost-challenge plasma glucose (2 h-PCPG) ≥11.1mmol/L or taking anti-diabetic medication in all phases of study

Statistical analyses

All continuous variables were assessed for normality using the one-sample Kolmogorov–Smirnoff test, and are expressed as mean (standard deviation), if variables had a normal distribution, or median with inter-quartile range (IQ25-75) for variables with skewed distribution. The characteristics of participants at baseline were compared between the PE and non-PE groups using two independent-sample t-tests or the equivalent nonparametric Mann-Whitney U test. Categorical variables, expressed as percentages, were compared using the Pearson's test. To analyze the person-time incidence rate of CKD the following description was used: the number of new events of the condition (cases) in the study time divided by the sum of person-time (person * year) at risk in the study participants. Initially, all variables were included in the univariate model. Next, the variables found to be significant in the univariate model were further included in the multivariate model. Adjustment for diabetes and dyslipidemia did not have any effect on the magnitude of the estimates. Pooled logistic regression was used to assess (1) the association between the dichotomous outcome variable (PE) and time-dependent covariates as the data was interval censored and time to CKD was not known, and (2) to calculate odds ratios (OR). This model treats every interval as a mini follow-up study, pools the observations of all intervals together into one pooled sample and does a logistic regression on the pooled dataset. In addition, the multivariable analysis was repeated using the time-dependent Cox proportional hazard regression assuming the

CKD event occurs is in the mid-time between visits. Kaplan-Meier plots and log-rank tests were employed as the univariate test for between-group differences in survival from CKD. Cox's proportional hazard model was used to calculate the hazard ratio between groups. Both these models were adjusted for age, BMI, SBP, DBP and smoking. Statistical analysis was performed using the software package STATA (version 14; STATA Inc., College station, TX, USA). Significance level was set at $p < 0.05$, with a confidence interval (CI) of 95%.

Results

Characteristics of the study subjects

During 15 years of follow-up, 1851 eligible participants including 177 women with PE and 1674 without PE were recruited; median and interquartile range for the follow-up years of PE and non-PE groups were 7.78 (5.19-10.40) and 7.32 (4.73-11.00) years, respectively. Baseline characteristics of the subjects are presented in Table 1.

Compared to non-PE controls, women with prior PE were more likely to be younger, [31.1 (7.4) versus 33.7 (7.5) years ($P < 0.001$)], and had significantly higher WC [86.5 (11.7) vs. 83.9 (10.7) cm, $P = 0.002$], BMI [(27.5 (4.6) vs. 26.5 (4.2) kg/m^2, $P = 0.003$], WHR [(0.8 (0.07) vs. 0.8 (0.07), $P < 0.02$] as well as SBP (108.1 (9.4) mmHg vs. 105.3 (9.2) mmHg), and DBP (71.3 (5.8) mmHg vs. 69.6 (6.2) mmHg) levels. Moreover, there was no statistically significant difference in the proportion of current smoking between women with and without prior PE. Based on the table 1 the prevalence of DM was the same for both groups at baseline (p-value=0.2). Neither was the mean of FBS and BS significantly different in both groups at baseline.

The total cumulative incidence rate of CKD at the median follow-up time was 35/100000 (95% CI: 25/100000, 50/100000) and 36/100000 (95% CI: 32/100000, 39/100000) in PE and non-PE women, respectively (P-value =0.90).

Pooled logistic regression and survival analysis

According to the pooled logistic regression analysis, OR of CKD progression (adjusted for age, BMI, SBP and DBP) in the PE group was not significantly different compared to the non-PE one (OR: 1.04; P-value= 0.80; 95% CI: 0.77, 1.40) (Table 2). In addition, the interaction of age and PE status (not statistically significant) showed that the relationship between PE, and CKD progression, was not age dependent (table 2).

The Kaplan-Meier plot, (Figure 2) illustrated the time for development of CKD for women in the PE and non-PE groups. The Kaplan-Meier plot for women with PE was not significantly different from that of non-PE women (P-value=0.35). Compared to non-PE women, women with prior PE did not have higher risk of developing CKD in the unadjusted model (unadjusted HR 1.1; 95% CI, 0.83–1.69; P = 0.35), even after multiple adjustments for potential confounders related to CKD, including age, BMI and baseline SBP (multiple- adjusted HR 1.2; 95% CI, 0.84–1.7 P = 0.31) (Table 2).

Pooled logistic and cox regression models for 4 subgroups of women including those with history of PE at: baseline (n=112), 1st follow up (n=43), 2nd follow up (n=22), and women without history of PE (n=1674) revealed no difference in incidence of CKD among these four sub-groups (supplementary table 1).

Discussion

This long-term, prospective and population-based study evaluated the incidence rate and risk of CKD among women with and without the prior history of PE. Without HTN, progression to CKD after the median follow-up time of 12 years was comparable between women with and without prior PE even after adjustment for potential confounders (age, BMI and blood pressure).

The underlying pathophysiology of preeclampsia is yet only partly understood. Impaired placentation at the early stage of gestations, as well as endothelial dysfunction, could play an important role in an affected pregnancy. It is well documented that kidney function alters during preeclamptic pregnancy; both renal blood flow and GFR decrease in preeclampsia, but absolute levels may remain above the non-pregnant range. It has been shown that renal lesions and glomerular deposits of various hemostatic factors can disappear within weeks after delivery [10]. In addition, data shows that decreased levels of GFR resolve a decade after preeclampsia that is comparable in women with and without a history of PE [9, 28]. However, microalbuminuria in women with prior PE is more likely to persist over the years, compared to controls of similar ages [28], which may be associated with developing of cardiovascular disease (CVD) and HTN in these women [29, 30]. Furthermore, CVD and HTN are comorbidities that may also accelerate the developing of subsequent CKD in these women.

Results of studies focusing on CKD among women with the history of PE are controversial. In agreement with our findings, Paauw et al. (2018) in a well-designed long term longitudinal study with a median follow-up of 11 years, assessed kidney dysfunction including CKD and end-stage renal disease (ESRD) following the pregnancy hypertensive disorder; during follow-up, none of the women developed ESRD. In addition, hypertensive pregnancy disorder did not increase the incidence of CKD (HR, 1.04; 95% CI, 0.79-1.37; P=0.8) [13]. In another population-based study, Sandvik et al. (2013) using data from the Medical Birth Registry in Norway reported that preeclampsia was not associated with higher rates of microalbuminuria or increased urinary albumin excretion, i.e. Median urinary ACR: 0.53 mg/mmol and 0.50 mg/mmol for women with and without prior preeclampsia respectively, P=0.54 (31). In addition, a meta-analysis (2019) conducted on kidney disease after preeclampsia, of seven studies reported that 31 percent of

women with history of PE after a mean follow-up of 7 years, had microalbuminuria, which was much higher than the 7% observed in women without the condition. However, there was no significant difference in the GFR, estimated using urinary creatinine clearance (mean difference, -0.04 mL/s [95% CI, -0.12 to 0.04] [9].

Other studies have focused mostly on end-stage renal disease. Vikse et al. (2008) demonstrated that prior preeclampsia could significantly increase the risk of end-stage renal disease 3-6 fold, depending on whether a woman had had pre-eclampsia in the first, second or both pregnancies [32]. A recent study by Kristensen et al (2019) evaluated associations between PE and later risk of kidney disease in a national register-based prospective study [18], in which more than one million women were followed for an average 18.6 years/woman; their results showed that compared with women without previous PE, those with a history of it were more likely to develop chronic renal conditions: HR 3.93, 95% CI: 2.90-5.33, for early preterm PE who delivered <34 weeks, 2.81 (2.1-3.71) for late preterm PE who delivered 34-36 weeks and 2.27 (2.02-2.55) for term PE who delivered ≥37 weeks. However, the definition of CKD in this study differed to our study. They included hypertensive kidney disease, most glomerular disease diagnoses, chronic tubulointerstitial nephritis, and renal failure. Since maternal age and BMI are suspected of mediating the associations between PE and CKD, the effect of age and BMI in our model was adjusted, whereas they were not adjusted in that study.

The main strengths of our study are its methodology as a long term prospective population-based study with a large sample size. Low levels of loss to follow-up are other strengths of this study, which helped us to estimate the study outcome with a high precision. However, our study was limited by a number of factors that should be considered when interpreting the results. Preeclampsia diagnosis was self-reported in this study, which may induce recall bias, affecting the

results; using the valid questionnaire that included proxy variables and checking the summary report of hospitalization for those with uncertain situation may reduce such bias (35, 36). In addition, it was reported that the self-reported history of hypertensive pregnancy disorders has a sensitivity of 72–80% and specificity of 96–99% (33, 34). Moreover, recurrent PE and severity of PE were not assessed, which might have influenced the severity of endothelial dysfunction after pregnancy. Furthermore, as in most epidemiologic studies, the CKD definition was based on creatinine measurements which may vary day-to-day (15.5–19.6%) and were not repeated within three months to confirm a chronic reduction in GFR. In addition, we lacked data on proteinuria or microalbuminuria (causing underestimation of CKD incidence) that could have given us more accurate results; however, eGFR as a measure of kidney function is closely linked to proteinuria (37, 38). Some epidemiologic studies use serum creatinine for definition of the CKD, a non-expensive and simple method, easily applied for large population measurements (39). Also, despite controlling for various confounders in our analysis, residual confounding due to unknown or unmeasured confounders such as socioeconomic factors and family history of CKD cannot be excluded. Last but not least, since this study was performed only on Iranian women, the findings cannot be generalized to other population with different covariate distributions.

Conclusion

Women with the history of PE showed no higher risk of subsequent chronic kidney disease over 15 years of follow up, a finding independent of the women's age, BMI, SBP, and DBP. Further comprehensive prospective studies with a precise definition of the severity of PE and kidney disease and longer adequate follow-ups are needed to confirm the study's findings.

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Disclosure Statement

None of the authors have reported conflicts of interest.

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