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Original Investigation

Preeclampsia and ESRD: The Role of Shared Risk Factors

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Background: Several registry-based studies, using diagnostic codes, have suggested that preeclampsia is a risk factor for end-stage renal disease (ESRD). However, because the 2 diseases share risk factors, the true nature of their association remains uncertain. Our goals were to conduct a population-based study to determine the magnitude of the association between preeclampsia and ESRD and evaluate the role of shared risk factors.

Study Design: Population-based nested case-control study.

Setting & Participants: The US Renal Data System was used to identify women with ESRD from a cohort of 34,581 women who gave birth in 1976 to 2010 in Olmsted County, MN. 44 cases of ESRD were identified and each one was matched to 2 controls based on year of birth (±1 year), age at first pregnancy (±2 years), and parity (±1 or ≥4).

Predictor: Preeclamptic pregnancy, confirmed by medical record review.

Outcome: ESRD.

Measurements: Prepregnancy serum creatinine and urine protein measurements were recorded. Comorbid conditions existing prior to pregnancy were abstracted from medical records and included kidney disease, obesity, diabetes, and hypertension.

Results: There was evidence of kidney disease prior to the first pregnancy in 9 of 44 (21%) cases and 1 of 88 (<1%) controls. Per chart review, 8 of 44 (18%) cases versus 4 of 88 (5%) controls had preeclamptic pregnancies (unadjusted OR, 4.0; 95% CI, 1.21-13.28). Results were similar after independent adjustment for race, education, diabetes, and hypertension prior to pregnancy. However, the association was attenuated and no longer significant after adjustment for obesity (OR, 3.25; 95% CI, 0.93-11.37).

Limitations: The limited number of ESRD cases and missing data for prepregnancy kidney function.

Conclusions: Our findings confirm that there is a sizable association between preeclampsia and ESRD; however, obesity is a previously unexplored confounder. Pre-existing kidney disease was common, but not consistently coded or diagnosed.

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INDEX WORDS: Preeclampsia; hypertension; pregnancy; hypertensive pregnancy disorders; toxemia; risk factor; end-stage renal disease (ESRD); obesity.

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Hypertension complicates ~8% of pregnancies and leads to significant maternal morbidity and mortality.[1] Certain long-term effects of hypertensive pregnancies on maternal health have been recognized, particularly the increased risk for cardiovascular disease.[2-5] Several large registry-based studies also have demonstrated associations between hypertensive pregnancy disorders and the development of advanced kidney disease, including end-stage renal disease (ESRD).[6-8]

The studies reporting that hypertensive pregnancy disorders are risk factors for ESRD had adequate sample sizes to study ESRD, a rare outcome with an incidence rate of 357 per million in the US population.[9] However, these studies had several important limitations. First, *International Classification of Diseases* codes, rather than a review of the complete medical records using accepted clinical criteria, were used to identify hypertensive pregnancy disorders and relevant comorbid conditions. Second, the frequencies of kidney disease and obesity prior to pregnancy, both significant risk factors for preeclampsia and ESRD, and therefore potential confounders, could not be determined.[10-12]

We performed a population-based nested case-control study to determine the magnitude of the association between preeclampsia and ESRD using the

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complete medical records of cases and controls to identify and confirm preeclampsia and the US Renal Data System (USRDS) to identify ESRD cases. We also studied how comorbid conditions, including decreased kidney function, obesity, hypertension, and diabetes mellitus (DM), prior to pregnancy may be confounding the association between preeclampsia and ESRD.

METHODS

Study Setting

We identified a cohort of women who had live or still births during 1976 to 2010 while residing in Olmsted County, MN, using the unique population-based records-linkage system of the Rochester Epidemiology Project (REP). The REP captures health care information for virtually all individuals who have been residents of Olmsted County from 1966 to the present day.[13-16] All research protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards (numbers 12-001892 and 044-OMC-12, respectively). Informed consent was waived for this study, but only patients who had authorized access to their medical records for research, ~98% of the Olmsted County population, were considered in this analysis.[15,16]

ESRD Case Identification and Matched Controls

The definition of ESRD was the need for dialysis (vintage > 3 months) or kidney transplantation. We identified cases from the USRDS, the national data system that has an archive of information about ESRD in the United States going back to 1978. We sent all available patient identifiers for the cohort of women to the USRDS to perform the linkage. The USRDS provided the dates of initiation of dialysis therapy or transplantation, the causes of ESRD, and the comorbid conditions that were recorded by the treating physicians at the time of initiation of renal replacement therapy (Centers for Medicare & Medicaid Services 2728 forms). Women were excluded if they had ESRD prior to or during any pregnancy.

For each confirmed ESRD case, 2 women without ESRD (controls) were randomly selected from among all women who had been in contact with a medical care provider of the REP within 3 years of the case's ESRD date. Cases and controls were individually matched for year of birth (±1 year), age at first pregnancy (±2 years), and parity (±1 pregnancy or ≥4 pregnancies). The 2-to-1 matching was used to increase statistical power.

Data Collection

We reviewed the complete medical records of the cases and controls for each delivery, including prenatal visits and hospital charts. Blood pressure (BP) readings, urine protein measurements, all available laboratory values, patient demographics, and comorbid conditions were abstracted by 2 reviewers (A.G.K. and Promilla Perrattur) and entered into a database. The 2 reviewers had to have 100% agreement in BP and urine protein measurements in 5 charts before data abstraction was allowed to proceed.

Exposure of Interest

The exposure of interest was a preeclamptic pregnancy, including preeclampsia, preeclampsia superimposed on chronic hypertension, and/or eclampsia in any pregnancy. All hypertensive pregnancy disorders, including gestational hypertension, preeclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and eclampsia, were defined by the research team using criteria that are consistent with current clinical practice (Table S1, available as online supplementary material).[17] An electronic diagnostic algorithm was developed for the diagnoses of hypertensive pregnancy disorders using the data abstracted from medical records. This approach was validated by comparing the diagnoses of hypertensive pregnancy disorders obtained using the algorithm to the gold standard, that is, diagnoses made by the blinded review of 75 charts (25 with preeclampsia) by 3 maternal-fetal medicine experts (V.D.G., unpublished data). Sensitivity for the diagnosis of preeclampsia by algorithm was 100% (95% confidence interval [CI], 83%-100%) and specificity was 100% (95% CI, 91%–100%).

Briefly, a diagnosis of preeclampsia required new-onset sustained hypertension (systolic BP > 140 or diastolic BP > 90 mm Hg) and/or the use of an antihypertensive medication after 20 weeks' gestation, in combination with new or worsening proteinuria and/or other features indicative of severe disease (elevated liver enzymes, thrombocytopenia, or acute kidney injury). A diagnosis of preeclampsia superimposed on chronic hypertension required worsening of BP after 20 weeks of gestation or the addition of another antihypertensive medication, in addition to the previously mentioned criteria for preeclampsia. Finally, a diagnosis of eclampsia required evidence of seizures.

Comorbid Conditions and Risk Factors for Kidney Disease

Obesity was defined as a body mass index > 30 kg/m^2 at the first prenatal visit before 20 weeks' gestation in any pregnancy. DM was defined as having a physician-documented diagnosis of DM, a fasting blood glucose level ≥ 126 mg/dL on 2 separate occasions, or positive oral glucose tolerance test results. Gestational DM was not routinely screened for during the majority of the study period and was not included in the diagnosis of DM. The diagnosis of chronic hypertension unrelated to pregnancy required a physician diagnosis, 2 outpatient systolic BPs > 140 mm Hg or diastolic BPs > 90 mm Hg within 1 year, or use of an antihypertensive medication on 2 separate outpatient visits. The diagnoses of DM and hypertension were drawn from the USRDS files for women who had moved out of Olmsted County, MN, after their pregnancies.

Prepregnancy serum creatinine and proteinuria values were used to identify pre-existing kidney disease. Serum creatinine values from prior to 2006 were standardized via a previously validated equation.[18] We defined pre-existing kidney disease based on either estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation[19] or proteinuria. Proteinuria was defined as protein excretion ≥1+ on dipstick, protein excretion > 300 mg/24 h, a protein-creatinine ratio > 0.3 g/g Cr, or a protein-osmolality ratio > 0.3.[20] We considered undetectable to trace protein on dipstick as normal. Abnormal protein values (≥1+) were only taken from dipsticks without evidence of a urinary tract infection or nonglomerular hematuria, and 2 abnormal values prior to pregnancy were required to make the diagnosis of pre-existing kidney disease.

Statistical Analysis

Consistent with the matched case-control study design, conditional logistic regression modeling was used to compare characteristics of cases and controls and evaluate the association between exposure status (preeclamptic pregnancy) and case-control status. Additional models were fit adjusting independently for the prespecified confounders of interest, including prepregnancy diagnoses of hypertension, DM, and obesity (defined as a body mass index > 30 kg/m^2 prior to 20 weeks at any first prenatal visit). We also adjusted for characteristics found to be significantly different between cases and controls prior to their first pregnancies (race and education). Each variable had a separate category for missing values. All P values were 2 sided, and $P < 0.05$ was considered

statistically significant. Statistical analyses were performed using the SAS version 9.3 software package (SAS Institute Inc).

RESULTS

ESRD Case Identification

We identified 34,581 women with live or stillbirths in 1976 to 2010 in Olmsted County, MN (Fig 1). After linkage with the USRDS, we identified 48 potential cases, but 5 women were excluded because they had ESRD prior to or during any pregnancy. One additional woman received a kidney transplant after the linkage was performed and therefore was only found in the REP database. This resulted in a total of 44 confirmed cases. Median time from the last pregnancy to the onset of ESRD was 17.7 (interquartile range [IQR], 10.9-24.2) years, and median age at diagnosis of ESRD was 45.5 (IQR, 40-53) years.

Patient and Pregnancy Characteristics

Clinical characteristics of the 44 cases and 88 matched controls are listed in Table 1. Age at first birth (either live or stillbirth) and parity were comparable by design. The majority of pregnancies in both cases (64%) and controls (80%) were delivered at term (Table S2). Cases were significantly more likely to be nonwhite, less educated, and obese, and to have DM and hypertension.

Pre-existing Kidney Disease

We identified pre-existing kidney disease in 9 cases and 1 control based on our definitions of reduced eGFR and/or proteinuria (Table 1), but only 5 (50%) of these women had diagnostic codes for kidney disease in the REP database prior to their first pregnancies. Kidney disease was attributed to autosomal dominant polycystic kidney disease (n = 4), glomerulonephritis (n = 3), and diabetic nephropathy (n = 2) in the 9 cases and autosomal recessive polycystic kidney disease in the 1 control.

A baseline serum creatinine value prior to the first pregnancy was available for 20 cases and 32 controls. The median range of serum creatinine levels was 0.65 (IQR, 0.28-0.75) mg/dL in cases and 0.72 (IQR, 0.55-0.75) mg/dL in controls. One case had an eGFR < 60 mL/min/1.73 m^2, and 92% of cases and controls had eGFRs > 90 mL/min/1.73 m^2. Baseline urine protein measurements were available for 30 cases and 64 controls. Among the cases, 23 had normal urine dipstick findings, 6 had protein excretion $\geq 1+$ on urine dipstick, and 2 had 24-hour urine collections with protein excretion $>1{,}000$ mg/24 h. Among controls, 60 had normal urine dipstick findings, 3 had normal protein-osmolality ratios, and 1 had an elevated protein-osmolality ratio.

Hypertensive Pregnancy Disorders

Among the 132 women (44 cases and 88 controls), there were 292 total pregnancies that lasted more than 20 weeks and had sufficient information to evaluate for hypertensive pregnancy disorders (Table 2). The median number of measurements from prenatal visits was 11 (IQR, 9-13) for BP and 9 (IQR, 6-11) for urine dipsticks.

Using the diagnostic algorithm for hypertensive pregnancy disorders (Table S1), 18% of cases and 5% of controls had at least one preeclamptic pregnancy (Table 2). The frequency of ever having a pregnancy complicated by chronic hypertension was more common in cases (7%) than in controls (0%). However, the frequency of women with at least one pregnancy affected by gestational hypertension was similar in cases and controls (5% vs 6%). Two cases

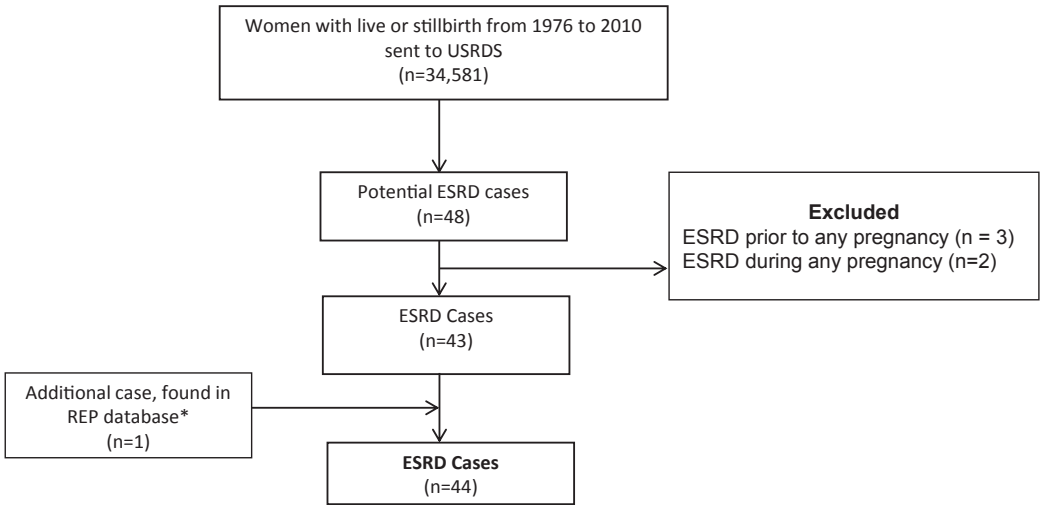

Figure 1. Identification of women with end-stage renal disease (ESRD) via linkage. *One case was not identified by US Renal Data System (USRDS) linkage, but was identified by the Rochester Epidemiology Project (REP). This woman received a kidney transplant after the linkage with the USRDS was performed.

Table 1. Characteristics in Cases and Controls

Characteristic	Cases (n = 44)	Controls (n = 88)	P[a]
Age at first live or still birth, y	22 [20-25]	22 [20-26]	0.2
Year of first live or still birth			0.08
1950-1969	7 (16)	11 (13)	
1970-1989	31 (71)	61 (69)	
1990-2010	6 (14)	16 (18)	
Race			0.003
Nonwhite	7 (16)	1 (1)	
White	37 (84)	87 (99)	
Ethnicity			0.2
Not Hispanic	39 (89)	84 (96)	
Hispanic	2 (5)	1 (1)	
Unknown	3 (7)	3 (3)	
Highest education level			0.002
<HS graduate	9 (21)	3 (3)	
HS graduate or adult diploma	15 (34)	31 (35)	
Some college	16 (36)	31 (35)	
≥College graduate	4 (9)	16 (18)	
Unknown	0 (0)	7 (8)	
Gravidity	2.0 [2.0-3.5]	2.5 [2.0-3.0]	0.7
Parity	2.0 [1.0-3.0]	2.0 [2.0-3.0]	0.4
Pre-existing kidney disease[b]			<0.001
No	24 (55)	77 (88)	
Yes	9 (21)	1 (1)	
Unknown	11 (25)	10 (11)	
Obesity[c] at any first prenatal visit			0.02
No	27 (61)	72 (82)	
Yes	12 (27)	12 (14)	
Unknown	5 (11)	4 (5)	
History of HTN	39 (89)	34 (39)	<0.001[d]
No	5 (11)	54 (61)	
Before first pregnancy	7 (16)	6 (7)	
Before last pregnancy	2 (5)	1 (1)	
After last pregnancy	30 (68)	27 (31)	
History of diabetes	21 (48)	10 (11)	<0.001[d]
No	23 (52)	78 (89)	
Before first pregnancy	7 (16)	0 (0)	
Before last pregnancy	1 (2)	0 (0)	
After last pregnancy	13 (30)	10 (11)	

Note: Values for categorical variables are given as number (percentage); for continuous variables, as median [interquartile range].

Abbreviations: HS, high school; HTN, hypertension.

[a]Exact *P* value derived from the score statistic from fitting a separate conditional logistic regression model to assess each characteristic.

[b]Defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 and/or proteinuria prior to first pregnancy.

[c]Obesity defined as a body mass index > 30 kg/m^2.

[d]*P* value for the association between case/control status and presence/absence of any history.

and 1 control had 2 or more pregnancies complicated by a hypertensive pregnancy disorder. The frequency of women with exclusively normotensive pregnancies was 71% in cases and 90% in controls (Table 2).

Preeclamptic Pregnancy

A history of preeclamptic pregnancy occurred more frequently in cases compared with controls (unadjusted odds ratio [OR], 4.0; 95% CI, 1.21-13.28; Table 3). The OR remained significant after independent adjustments for race (OR, 4.85; 95% CI, 1.37-17.11), higher education (some college or greater vs high school graduate or less: OR, 5.29; 95% CI, 1.34-20.91), DM (OR, 7.00; 95% CI, 1.45-33.7), and hypertension (OR, 3.68; 95% CI, 1.09-12.47). However, the association was attenuated and no longer statistically significant after adjusting for obesity (OR, 3.25; 95% CI, 0.93-11.37). Similar results were observed when using a broader definition of exposure to include any hypertensive pregnancy disorder, including gestational and chronic hypertension (unadjusted OR, 3.34; 95% CI, 1.32-8.47). Table 4 shows the causes of ESRD among women with and without a hypertensive pregnancy disorder.

Agreement With Diagnostic Codes

We searched the REP electronic indexes from 1 year prior to the first pregnancy to 1 year after the last pregnancy of all women to identify a set of codes that could be related to a hypertensive pregnancy disorder (Table S3). We then searched all 292 pregnancies for any of the aforementioned codes and compared the code-based diagnoses with the algorithm-based diagnoses. The sensitivity of using diagnostic codes for any type of hypertensive pregnancy disorder was only 61.5% (95% CI, 40.7%-79.1%), whereas specificity was 98.1% (95% CI, 95.4%-99.3%). Using codes specifically for preeclampsia, sensitivity was reduced further to 42.9% (95% CI, 18.8%-70.4%), and specificity increased to 99.3% (95% CI, 97.2%-99.9%).

DISCUSSION

In the present study, the odds of having ESRD were 4 times greater in women with a history of preeclamptic pregnancy compared to those without, after matching for age and parity. This association remained significant after independent adjustments for race, education, DM, and hypertension prior to a woman's first pregnancy. However, the association was attenuated and no longer significant after adjusting for obesity, suggesting that obesity is a confounder that has not been explored previously. We also found that 20% of women who developed ESRD had laboratory evidence of decreased kidney function prior to their first pregnancies. Although our statistical

Table 2. Frequency of Hypertensive Pregnancy Disorders in Cases and Controls

Hypertensive Pregnancy Disorder	Per Woman[a]		Per Pregnancy[b]	
	Cases (n = 44)	Controls (n = 88)	Cases (n = 132)	Controls (n = 269)
Normotensive pregnancy	31 (71)	79 (90)	65 (49.2)	201 (74.7)
Gestational HTN	2 (5)	5 (6)	3 (2.3)	6 (2.2)
Chronic HTN	3 (7)	0 (0)	3 (2.3)	0 (0)
Preeclamptic pregnancy	8 (18)	4 (5)	10 (7.6)	4 (1.5)
Probable	2 (5)	3 (3)	3 (2.3)	3 (1.1)
Definite	5 (11)	1 (1)	4 (3.0)	1 (<1)
Superimposed on chronic HTN	1 (2)	0 (0)	3 (2.3)	0 (0)
Probable/definite eclampsia	0 (0)	0 (0)	0 (0)	0 (0)
Pregnancies with unknown exposure[c]				
Insufficient pregnancy data	0 (0)	0 (0)	29 (22.0)[d]	16 (6.0)
Pregnancy <20 wk	0 (0)	0 (0)	22 (16.7)	42 (15.6)

Note: Values are given as number (percentage).

Abbreviation: HTN, hypertension.

[a]All women classified according to most severely affected pregnancy or as normotensive if no pregnancy was complicated by a hypertensive pregnancy disorder.

[b]There were 401 pregnancies in the 44 cases (n = 132) and 88 controls (n = 269), but only 292 with sufficient information to evaluate for a hypertensive pregnancy disorder.

[c]Pregnancies with unknown exposure included those with insufficient data (occurred outside of Olmsted County, MN) and pregnancies less than 20 weeks, including spontaneous and therapeutic abortions. All women had to have at least 1 pregnancy lasting longer than 20 weeks in Olmsted County, MN, to be included in the cohort.

[d]Includes 11 pregnancies from 2 different cases that occurred outside of Olmsted County, MN.

power was limited, our ability to review the entire medical record allowed us to explore additional confounders that may play a role in the association between preeclampsia and ESRD.

Previous studies investigating the association of hypertensive pregnancy disorders with subsequent ESRD have shown variable magnitudes of risk. In a study involving a population of 570,433 women who gave birth in Norway in 1967 to 2004, a history of preeclampsia was associated with an almost 5-fold increased risk for ESRD (relative risk, 4.7; 95% CI, 3.6-6.1).[6] The diagnosis of preeclampsia was determined using *International Classification of Diseases* codes from the Medical Birth Registry, and women with codes for hypertension, kidney disease, rheumatic disease, or DM before the pregnancy were

Table 3. Case-Control Analyses for Odds of ESRD after Preeclamptic Pregnancy

	OR (95% CI)	*P*[a]
Unadjusted	4.00 (1.21-13.28)	0.02
Adjusted for		
Race	4.85 (1.37-17.11)	0.01
Higher education[b]	5.29 (1.34-20.91)	0.02
HTN	3.68 (1.09-12.47)	0.04
Diabetes	7.00 (1.45-33.70)	0.02
Obesity[c]	3.25 (0.93-11.37)	0.07

Note: Analyses of 44 cases (8 [18%] affected) and 88 controls (4 [5%] affected). Preeclamptic pregnancy includes preeclampsia (definite or probable), preeclampsia superimposed on chronic HTN, and eclampsia.

Abbreviations: CI, confidence interval; HTN, hypertension; OR, odds ratio.

[a]*P* values were derived using conditional logistic regression modeling.

[b]Includes some college, college graduate, or more compared with less than high school, high school graduate, or adult diploma. Missing values were coded as "missing" and included in model.

[c]Missing values were coded as missing for obesity status and included in model.

Table 4. Primary Cause of ESRD by Most Severe Hypertensive Pregnancy Disorder

Primary Cause	All Normotensive (n = 31)	Preeclampsia[a] (n = 8)	Chronic or Gestational HTN (n = 5)
Diabetes mellitus	11 (36)	3 (38)	2 (40)
Polycystic kidney disease	2 (7)	3 (38)	1 (20)
HTN	0 (0)	0 (0)	1 (20)
Acute tubular necrosis	2 (7)	0 (0)	0 (0)
Glomerulonephritis	8 (26)	1 (13)	0 (0)
Chronic obstruction	1 (3)	0 (0)	1 (20)
Unknown cause	4 (13)	1 (13)	0 (0)
Other	3 (10)	0 (0)	0 (0)

Note: Values are given as number (percentage). For women who had more than 1 hypertensive pregnancy disorder, only the most severe was considered in this analysis. Chronic and gestational HTN were combined into 1 category.

Abbreviations: ESRD, end-stage renal disease; HTN, hypertension.

[a]Includes preeclampsia (definite or probable), preeclampsia superimposed on chronic HTN, and eclampsia.

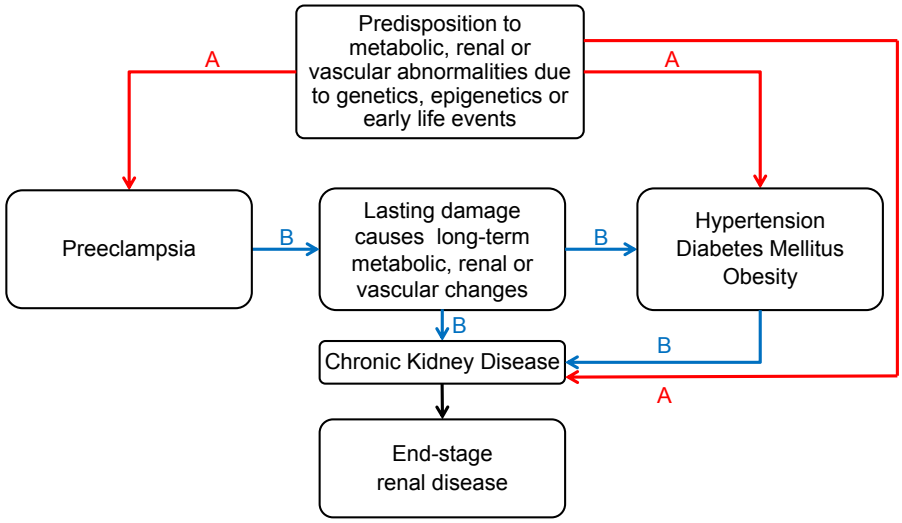

Figure 2. Possible explanations for the association between preeclampsia and end-stage renal disease (ESRD). The pathway shown in red (A) depicts the effects of confounding variables. The observed association between preeclampsia and ESRD may be confounded by a common predisposition, shared risk factors, or shared disease processes. The pathway shown in blue (B) represents how preeclampsia may contribute to ESRD via metabolic and vascular changes. These changes may lead directly to chronic kidney disease or via intervening variables such as hypertension. Both explanations may be true and the association may be partly due to confounding effects and partly causal. The relative contributions of the 2 pathways may vary among women. In either case, recognition of the association has clinical implications.

excluded. Another study from Taiwan that used insurance claims data from 1998 to 2009 showed a significantly increased risk for ESRD after hypertensive pregnancy (hazard ratio [HR], 12.4; 95% CI, 8.54-18.0).[7] Women with preeclampsia or eclampsia had a higher risk for ESRD than those with only gestational hypertension. Risk in the Taiwanese women was considerably lower after adjusting for hypertension and DM before the pregnancy (HR, 2.72; 95% CI, 1.76-4.22), demonstrating that prepregnancy diseases confound the association of preeclampsia and ESRD and need to be accounted for when considering any potential causal relationship.

An important limitation of prior studies was that administrative codes were used to diagnose hypertensive pregnancy disorders and comorbid conditions. We found that half the women with laboratory evidence of prepregnancy kidney dysfunction had no diagnostic codes for kidney disease prior to their pregnancies. This is consistent with a seminal study by Fisher et al[21] in which investigators performed kidney biopsies for research purposes in 176 women with hypertensive pregnancies within the first week postpartum. Primary kidney disease was present in 20% of biopsies, often unsuspected by providers.[21] A study by Vikse et al[22] found that women with a history of preeclampsia who had low-birth-weight infants had increased risk for having a kidney biopsy later in life. Biopsies in this national cohort revealed a wide variety of renal pathology, from glomerular to tubulointerstitial disease, further emphasizing a possible role of unrecognized kidney disease at the time of preeclamptic pregnancies.[22] The authors raise the point that subclinical kidney disease may be present prior to pregnancy, thereby increasing the risk for preeclampsia, but acknowledged that they did not have access to prepregnancy measures of kidney function.

Another limitation of previous studies is that there was no adjustment for obesity at the time of pregnancy because obesity is often poorly coded in the medical records.[10] Obesity, defined as body mass index $> 30\ kg/m^2$, is associated with a 2- to 3-fold increased risk for preeclampsia and 3.5-fold increased risk for ESRD.[12,23] Therefore, obesity may be a significant confounder between preeclampsia and ESRD, as our data would support. However, even after adjustment for obesity, the OR was compatible with a more than 3-fold increased risk.

The mechanisms that underlie the association between preeclampsia and future ESRD are poorly understood. Preeclampsia is a heterogeneous disorder in which both maternal and placental factors lead to endothelial dysfunction, which manifests in the kidney as glomerular endotheliosis and proteinuria.[24,25] Given its heterogeneity, it is possible that the relationship between preeclampsia and ESRD is mediated by different mechanisms in different women. First, conditions such as obesity or kidney disease prior to pregnancy may be significant confounders, leading to preeclampsia and ESRD at different times of a woman's life. Second, it is plausible that kidney damage that occurs at the time of preeclamptic pregnancies may have an independent effect on kidney function later in life. There is a growing body of

evidence suggesting that podocyturia, the urinary loss of viable podocytes, may disrupt the glomerular filtration barrier and lead to proteinuria in preeclampsia.[26] Although this injury is thought to be transient,[27] some evidence suggests that moderately increased albuminuria is present for up to 20 years after the hypertensive pregnancy.[28-30] Podocyturia may be sustained in the postpartum period in some women with preeclampsia, which could reflect ongoing kidney damage or even systemic endothelial dysfunction.[31,32] Third, women with preeclampsia are at increased risk for hypertension and may develop hypertension earlier than women with normotensive pregnancies, suggesting that hypertension may be an important mediating factor on the causal pathway from preeclampsia to ESRD.[2,4,5,33-35] Figure 2 shows a schema demonstrating how underlying risk factors may affect the risk for preeclampsia, as well as the future risk for ESRD. It is unknown to what extent preeclampsia increases the risk for ESRD independent of shared risk factors.

This study has several strengths. It is the first study to evaluate the association between preeclampsia and ESRD using extensive review of the entire medical record to confirm the accuracy of clinical information. Our review of the medical records allowed us to accurately identify comorbid conditions that may contribute to ESRD and identify pre-existing kidney disease in a subset of women. Use of an electronic algorithm prevented bias in the determination of preeclampsia and other hypertensive pregnancy disorders. Last, we used the USRDS to identify ESRD cases.

The main limitation of our study is that although we studied a significant number (n = 34,581) of women, the number of cases was small, reflecting the low incidence of advanced kidney disease in general and in women in particular.[36] We thus had limited power to study the associations of interest. We did not have prepregnancy serum creatinine or urine protein measurements for all women, limiting our ability to incorporate these data into our models. Last, because the population of Olmsted County, MN, is predominantly white, this might limit generalizability. Of note, there were significantly more nonwhite cases than controls; however, adjusting for race did not affect the significance of our results.

Despite these limitations, our study provides strong evidence of a positive association between having a history of preeclampsia and the subsequent development of ESRD in a population-based study in which both exposures and outcomes were confirmed using clinical criteria. The presented results extend our understanding of this association by clearly identifying a subset of preeclamptic women who develop ESRD in the setting of: (1) kidney disease that predated their pregnancies, which might not have been coded or remained undiagnosed in prior studies; and (2) shared risk factors. However, our study was not adequately powered to assess the role of preeclampsia as an independent risk factor for future ESRD. This study adds to the growing body of evidence that preeclampsia is associated with the future risk for kidney disease while simultaneously raising questions for future studies that aim to address the potential causal pathways.[6,7,29,30] Preeclampsia may identify women early in life who are at future risk for kidney disease. The optimal follow-up for women with preeclampsia remains unclear; at a minimum, women with preeclampsia should be counseled about the risk for future disease and encouraged to implement lifestyle modifications.

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Contributions: Research idea: AGK, VDG; study design: AGK, DCS, MMM, ALW, WW, VDG; data acquisition: SA, AGK, DCS; data analysis/interpretation: AGK, MMM, WAR, ALW, LEV, VMM, TLW, VDG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. VDG takes responsibility that this study has been reported honestly, accurately and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Diagnostic algorithms for hypertensive pregnancy disorders.

Table S2: Pregnancy outcomes.

Table S3: Diagnostic codes identified for cases and controls from all REP-affiliated providers.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.07.034) is available at www.ajkd.org

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