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LONG-TERM RISK OF CHRONIC AND END-STAGE KIDNEY DISEASE AFTER PREECLAMPSIA: SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Preeclampsia (PE) is a pregnancy-related syndrome, and its diagnosis has evolved to consider factors like hypertension and kidney involvement, with serum creatinine gaining importance. Despite the traditional view of PE as transient and reversible kidney disease, recent studies link it to long-term risks, including cardiovascular and renal diseases. The systematic review, "Long-Term Risk of Chronic and End-Stage Kidney Disease After Preeclampsia," aims to gather updated information from recent studies, focusing on ESRD, CKD, and kidney-related morbidity after PE. The goal is to inform the formulation of effective long-term control and prevention strategies for CKD associated with a history of preeclampsia.

Method: The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

Result: This systematic review investigated final 16 articles. After looking at the titles and summaries, we found 8 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included five papers in our final analysis. These papers included a nation-wide cohort, nationwide register based cohort study, observational cohort study, population-based nested case-control study, and longitudinal cohort study.

Conclusion: Our study reveals a significant long-term impact of preeclampsia on kidney health, with a 5-fold higher risk of end-stage kidney disease (ESKD) for affected women. Ongoing clinical monitoring and further research are crucial to identify high-risk individuals, understand underlying mechanisms, and establish optimal follow-up and intervention strategies.

Keyword: *Chronic kidney disease, end-stage kidney disease, pre-eclampsia*

INTRODUCTION

Preeclampsia (PE) is a syndrome associated with pregnancy, varying in severity and defined by factors like hypertension, fetal growth, and kidney involvement. While proteinuria was traditionally considered crucial for diagnosis, it is no longer deemed essential. Instead, an increase in serum creatinine is now considered an alternative diagnostic element, emphasizing the role of the kidney in this syndrome. PE has been described as a transient reversible kidney disease resolving after delivery, with kidney derangements typically reversing within 1 to 3 months, although exceptions exist, and the link between PE and chronic kidney disease (CKD) is not fully understood.[1,2]

Estimates of PE prevalence range from 3% to 5%, decreasing to 1% to 2% in "low-risk pregnancies" and rising to over 10% when including related disorders. The definition of superimposed PE, where the syndrome develops in the presence of preexisting hypertension or kidney disease, adds complexity. The debate on whether PE is a single disease, a syndrome, or a spectrum of alterations remains open. Molecular approaches, such as the analysis of proangiogenic and anti-angiogenic factors, may provide insights into its pathogenesis.[3,4]

Contrary to the previous perception of PE as transitory, it is now associated with various cardiovascular and renal diseases, posing risks in subsequent pregnancies. Studies indicate an increased risk of cardiovascular and metabolic diseases in individuals with a history of PE, but the extent, timing, and control strategies are unclear, lacking large prospective cohort studies.[3] Similarly, the risk of CKD (including end-stage renal disease [ESRD]) may manifest in the long term, with a low global prevalence that may not justify specific follow-up programs. A 2010 systematic review focused on kidney disease, revealing an association between microalbuminuria and a previous PE episode. However, recent studies are accumulating information on hard outcomes, such as ESRD.[5] Given this context, the present systematic review aims to gather updated information from recent large observational and cohort studies, focusing on the long-term occurrence of ESRD, CKD, and kidney-related morbidity after PE episodes. This review serves as a guide for formulating long-term control and CKD prevention strategies.

The purpose of this systematic review, titled "Long-Term Risk of Chronic and End-Stage Kidney Disease After Preeclampsia," is to compile updated information from recent large observational and cohort studies. The focus is on investigating the prolonged occurrence of end-stage renal disease (ESRD), chronic kidney disease (CKD), and morbidity related to the kidneys following episodes of preeclampsia (PE). By undertaking this comprehensive review, the aim is to provide valuable insights that can guide the development of long-term control and prevention strategies for CKD associated with a history of preeclampsia.

METHODS

Protocol

The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

Criteria for Eligibility

For inclusion in the study, published articles had to meet particular requirements. They had to be research papers written in English, focusing long-term risk of chronic and end-stage kidney disease after preeclampsia. The studies had to meet the following criteria: articles need to have been published after 2016 but within the applicable timeframe for this systematic review. Articles falling into categories like editorials, lacking a DOI, review articles that were already published, or duplicating previously published journal papers were excluded from the assessment.

Search Strategy

We conducted a comprehensive literature search using PubMed, Wiley Journal Database, and ScienceDirect focusing on studies published from 2016 to 2024. The search terms employed were as follows "long-term"[All Fields] AND ("risk"[MeSH Terms] OR "risk"[All Fields] OR "risk of"[All Fields]) AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("end"[All Fields] AND "stage"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "end stage kidney disease"[All Fields]) AND "after"[All Fields] AND ("pre eclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "preeclampsia"[All Fields]). Moreover, we performed cross-referencing of relevant articles to reveal additional research. The evaluation of study quality, methodology, interventions, and results was undertaken independently by the researchers, resolving any differences through discussion and agreement. Furthermore, both researchers collected and compared discoveries from all studies, considering the potential for conducting a meta-analysis if deemed feasible.

Inclusion and exclusion criteria

Inclusion criteria for the studies were as follows: (1) original research that assesses long-term risk of chronic and end-stage kidney disease after preeclampsia; (2) Randomized Controlled Trials (RCTs) or observational studies (cohort or case-control studies); (3) availability of relevant data. Exclusion criteria were as follows: (1) ongoing studies or studies without available data; (2) duplicate publications. In cases of duplicate publications, the most recent article was chosen; (3) Non-English language studies were excluded.

Data Retrieval

The authors conducted a thorough examination of relevant studies, specifically selecting those that met precise inclusion criteria. They focused on original, unpublished papers in English to ensure a refined and high-quality selection. The analysis covered essential information, such as study particulars, authors, publication dates, locations, and research methodologies, aligning with the study's objectives.

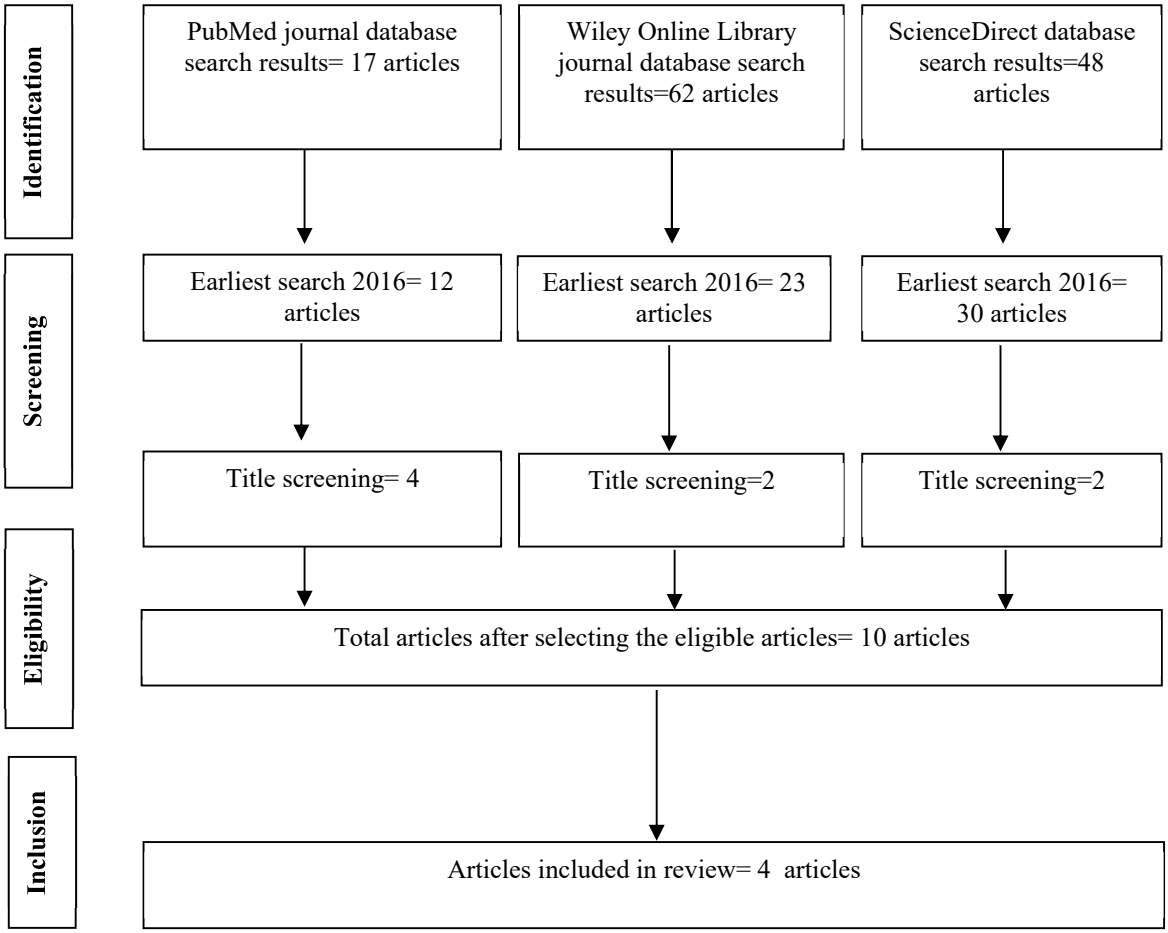

Figure 1. Article search flowchart

RESULT

This systematic review investigated final 16 articles. After looking at the titles and summaries, we found 8 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included five papers in our final analysis. These papers included a nation-wide cohort, nationwide register based cohort study, observational cohort study, population-based nested case-control study, and longitudinal cohort study.

Khashan AS, , et al. 2019.[8]	Sweden	Nation-wide cohort.	The cohort consisted of 1,366,441 healthy women who had 2,665,320 singleton live births in Sweden between 1982 and 2012.	At the first pregnancy, women's mean (SD) age and BMI were 27.8 (5.13) and 23.4 (4.03), respectively, 15.2% were smokers, and 80.7% were native Swedish. The overall median (interquartile range [IQR]) follow-up was 7.4 years (3.2–17.4) and 16.4 years (10.3–22.0) among women with ESKD diagnosis. During the study period, 67,273 (4.9%) women having 74,648 (2.8% of allpregnancies) singleton live births had preeclampsia, and 410 women developed ESKD with an incidence rate of 1.85 per 100,000 person-years. There was an association between preeclampsia and ESKD in the unadjusted analysis (hazard ratio [HR] = 4.99, 95% confidence interval [CI] 3.93–6.33; p < 0.001), which remained in the extensively adjusted (HR = 4.96, 95% CI 3.89–6.32, p < 0.001) models. Women who had preterm preeclampsia (adjusted HR = 9.19; 95% CI 5.16–15.61, p < 0.001) and women who had preeclampsia in 2 pregnancies (adjusted HR = 7.13, 95% CI 3.12–16.31, p < 0.001) had the highest risk of ESKD compared with women with no preeclampsia.
Kristensen et al., 2019.[9]	Denmark	Nationwide register based cohort study.	All women with at least one pregnancy lasting at least 20 weeks between 1978 and 2015.	Compared with women with no previous pre-eclampsia, those with a history of pre-eclampsia were more likely to develop chronic renal conditions: hazard ratio 3.93 (95% confidence interval 2.90 to 5.33, for early preterm pre-eclampsia (delivery <34 weeks); 2.81 (2.13 to 3.71) for late preterm preeclampsia (delivery 34-36 weeks); 2.27 (2.02 to 2.55) for term pre-eclampsia (delivery ≥37 weeks). In particular, strong associations were observed for chronic kidney disease, hypertensive kidney disease, and glomerular/proteinuric disease. Adjustment for cardiovascular disease and hypertension only partially attenuated the observed associations. Stratifying the analyses on time since pregnancy showed that associations between pre-eclampsia and chronic kidney disease and glomerular/proteinuric disease were much stronger within five years of the latest pregnancy (hazard ratio 6.11 (3.84 to 9.72) and 4.77 (3.88 to 5.86), respectively) than five years or longer after the latest pregnancy (2.06 (1.69 to 2.50) and 1.50 (1.19 to 1.88).
Goetz et al., 2021.[10]	Germany	Observational cohort study	The cohort consisted of 193,152 women with 257,481 singleton live births.	The cohort consisted of 193,152 women with 257,481 singleton live births. Mean observation time was 5.44 years. In total, there were 16,948 preterm deliveries (6.58%) and 14,448 births with at least one prior diagnosis of preeclampsia (5.61%). With a mean age of 30.51 years, 1,821 women developed any form of CKD. Compared to women with no risk exposure, women with a history of at least one preterm delivery (HR = 1.789) and women with a history of at least one preeclampsia (HR = 1.784) had an increased risk for any subsequent CKD. The highest risk for CKD was found for women with a joint exposure of preterm delivery and preeclampsia (HR = 5.227). These effects were the same in magnitude only for the outcome of mild to moderate CKD, but strongly increased for the outcome of severe CKD (HR = 11.90). Preterm delivery and preeclampsia were identified as independent risk factors for all CKD stages.
Kattah et al., 2016.[11]		Population-based nested case-control study.	34,581 women who gave birth in 1976 to 2010 in Olmsted County, MN.	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).
Li et al., 2023.[12]	China	Longitudinal cohort study.	103 pregnant CKD patients with	This longitudinal cohort study including 103 pregnant CKD patients with preeclampsia and 103 matched CKD patients without preeclampsia with minimum follow-up of 1 year, the

	preeclampsia and 103 matched CKD patients without preeclampsia with minimum follow-up of 1 year.	association between preeclampsia and long-term kidney function decline or ESRD among CKD patients were analyzed. Compared with CKD patients without preeclampsia, the eGFR declined more significantly in patients with preeclampsia [98.43 (79.48, 116.47) to 81.32 (41.20, 102.97) mL/min/1.73 m2 vs. 100.00 (74.86, 120.04) to 89.45 (63.69, 105.60) mL/min/1.73 m2; P=0.041]. Multivariable analysis showed that increased Scr levels (HR=3.02, 95% CI: 1.53–5.94, P=0.001), higher CKD stage (HR=2.76, 95% CI: 1.46–5.22, P=0.002), proteinuria

The study cohort comprised 1,366,441 women (2,665,320 singleton live births) with no history of chronic kidney disease (CKD), cardiovascular disease (CVD), hypertension, or diabetes before their first pregnancy. Over the study period, 4.9% of women (67,273/1,366,441) received at least one diagnosis of preeclampsia. Among them, 410 women were diagnosed with end-stage kidney disease (ESKD). The overall median (interquartile range [IQR]) follow-up was 7.4 years (3.2–17.4), increasing to 16.4 years (10.3–22.0) for women with ESKD. Women with preeclampsia tended to be older on average and had a higher BMI.[8]

The incidence rate of ESKD per 100,000 person-years was 1.85 (95% CI 1.66–2.05) among women without preeclampsia and 12.35 (95% CI 9.61–15.88) among those with preeclampsia. Crude analysis showed a significant association between preeclampsia and the risk of ESKD (HR = 4.99, 95% CI 3.93–6.33, $p < 0.001$), which persisted in the adjusted model (HR = 4.96, 95% CI 3.89–6.32, $p < 0.001$). Restricting the analysis to women with their first birth from 1991 onwards supported the same conclusion, with a higher HR (HR = 6.88; 95% CI 4.77–9.92, $p < 0.001$).[8]

Women with preeclampsia in two pregnancies had over a sevenfold increased risk of ESKD (HR = 7.13; 95% CI 3.12–16.31, $p < 0.001$), while those with preeclampsia in one pregnancy had a more than fourfold increased risk (HR = 4.43; 95% CI 2.92–6.70, $p < 0.001$). The association was over fourfold for term preeclampsia (HR = 4.67; 95% CI 3.60–6.04, $p < 0.001$) and almost ninefold for preterm preeclampsia (HR = 8.76; 95% CI 4.91–15.61, $p < 0.001$). Preeclampsia without small-for-gestational-age (SGA) had an almost fivefold association (HR = 4.89; 95% CI 3.77–6.34, $p < 0.001$), whereas preeclampsia with SGA showed a slightly larger HR (HR = 5.71; 95% CI 3.28–9.96, $p < 0.001$).[8]

No significant interaction was found between preeclampsia and maternal age, BMI, or smoking at the first pregnancy. Of the 410 women with ESKD, diagnoses included glomerulonephritis (23.5%), interstitial nephritis (4.9%), diabetic nephropathy (12.5%), nephrosclerosis due to hypertension (3.9%), autosomal dominant polycystic kidney disease (ADPKD) (19.3%), other specified renal diseases (27.3%), and unknown renal disease (8.8%). Excluding women who developed ESKD due to ADPKD slightly reduced the association (HR = 4.50; 95% CI 3.37–5.93; $p < 0.001$).[8]

The association between preeclampsia and ESKD due to diabetic nephropathy was ninefold (HR = 9.60; 95% CI 5.27–17.51, $p < 0.001$), due to interstitial nephritis was tenfold (HR = 10.54; 95% CI 4.09–27.13, $p < 0.001$), threefold for glomerulonephritis (HR = 3.44; 95% CI 1.93–6.11, $p < 0.001$), and threefold for other causes (HR = 3.29; 95% CI 2.08–5.21, $p < 0.001$). However, these results should be interpreted cautiously due to the small number of events in specific models, preventing the calculation of the association with hypertension. The population attributable fraction associated with preeclampsia was 0.14, indicating that exposure to preeclampsia accounted for 14% of all ESKD in the studied population.[8]

The research cohort encompassed 1,072,330 women with a total of 2,046,984 pregnancies resulting in live birth or stillbirth throughout the study period. These women were monitored over 19,994,470 person-years, averaging 18.6 years per woman. Over the follow-up period, 14,816 women developed kidney disease, with 7,320 cases of acute renal disorders (3.6/100,000 person-years), 3,901 cases of chronic renal disorders (1.9/100,000 person-years), 1,470 cases of other specified renal disorders (0.7/100,000 person-years), and 2,125 cases of unspecified renal disorders (1.1/100,000 person-years). Among them, 1,062 (7.2%) had a history of pre-eclampsia. A total of 55,503 women (5.2%) were lost to follow-up, primarily due to relocation abroad (n=26,835) or death (n=28,161).[9]

Our findings revealed modest associations between pre-eclampsia occurring later in pregnancy (late preterm and term) and subsequent acute renal disorders. However, no statistical support was found for an association with early preterm pre-eclampsia.Notably, instances of acute renal disorders were scarce among women delivering preterm, especially those with concurrent pre-eclampsia, resulting in wide confidence intervals for estimates related to early preterm pre-eclampsia.[9]

In contrast, women with a history of pre-eclampsia had at least double the risk of later chronic renal disorders overall, compared to women who delivered at the same gestational age without pre-eclampsia. The association magnitudes were more pronounced for earlier gestational ages at delivery ($P<0.001$), with the risk of any chronic renal disorder nearly quadrupling for women with a history of early preterm pre-eclampsia. A similar pattern was observed for three of the four subtypes of chronic renal disorder, with only the pattern for glomerular and proteinuric disease being statistically significant ($P<0.001$). Chronic tubulointerstitial nephritis diagnoses were infrequent, making it challenging to draw conclusions about this particular

type of chronic renal disorder. Patterns of association for other and unspecified kidney diseases resembled those observed for chronic renal disorders, while hazard ratios for unspecified tubulointerstitial nephritis more closely mirrored estimates for acute renal disorders.[9]

When examining the impact of time since the latest pregnancy on our results, pre-eclampsia exhibited a particularly strong association with the risk of chronic kidney disease and glomerular and proteinuric disease within five years of the latest pregnancy (hazard ratio 6.11 (95% confidence interval 3.84 to 9.72) and 4.77 (3.88 to 5.86), respectively). Subsequently, the strength of these associations diminished (chronic kidney disease, P for difference<0.001; glomerular and proteinuric disease, P for difference<0.001). However, even five years or more after the latest pregnancy, women with a history of pre-eclampsia still faced risks of chronic kidney disease and glomerular and proteinuric disease that were 100% and 50% higher than those observed in women with no history of pre-eclampsia (hazard ratio 2.06 (1.69 to 2.50) and 1.50 (1.19 to 1.88), respectively). In contrast, hazard ratios for acute renal disorders and other subtypes of chronic renal disorder seemed more stable over time. Adjusting for diabetes and autoimmune/inflammatory disease diagnosed during follow-up had minimal impact on our estimates. Conversely, adjusting for post-pregnancy cardiovascular disease and hypertension led to a 20-30% decrease in the strength of the observed associations.[9]

The study included 193,152 women with 257,481 singleton live births. The average maternal age at delivery was 30.68 years (SD 5.27 years), with an average interpregnancy interval of 2.76 years (SD 1.25 years). Among the pregnancies, there were 16,948 preterm deliveries (6.58%) and 14,448 pregnancies (5.61%) with a preeclampsia diagnosis. A total of 1,821 women (0.71%) were diagnosed with any chronic kidney disease (CKD), with 1,577 having CKD stages 1–3 (0.61%), and 190 (0.07%) developing severe CKD, including end-stage kidney disease (ESKD). The mean age at any CKD diagnosis was 30.51 years (SD = 5.60 years), with no significant difference according to CKD severity.[10]

The study categorized participants into four strata based on the presence of two binary prior risk exposures: i) 228,214 had neither preterm delivery nor preeclampsia exposure, ii) 12,319 had no preterm delivery but at least one preeclampsia exposure, iii) 14,819 had at least one preterm delivery but no preeclampsia exposure, and iv) 2,129 had joint exposure to preterm delivery and preeclampsia. In comparison to women without risk exposure, those with a history of preterm delivery had a significantly increased CKD risk (HR 1.789, 95% CI [1.531; 2.091]). Similarly, women with a history of preeclampsia during any pregnancy exhibited an increased risk of subsequent CKD (HR 1.784, 95% CI [1.516; 2.098]), regardless of CKD severity. The highest risk increase was observed in women with combined exposure to preeclampsia and preterm delivery, with a more than fivefold risk for subsequent CKD (HR 5.227, 95% CI [4.201; 6.504]).[10]

The effects were consistent in magnitude for mild to moderate CKD; however, for severe CKD, the estimated hazard ratios exceeded those of prior models. Women with a history of at least one preeclampsia alone had almost a threefold risk for subsequent severe CKD compared to those without any risk exposure (HR 2.971, 95% CI [1.874; 4.711]). Similarly, the risk was significantly increased for a history of preterm delivery (HR 4.705, 95% CI [3.259; 6.794]), with almost a fivefold higher risk compared to women without any risk exposure. Women with combined exposure had the highest risk, nearly 12 times that of those without any exposure. The confidence intervals in this model were wider, and maternal age, diabetes, and obesity did not reach statistical significance.[10]

We identified 34,581 women with live or stillbirths in Olmsted County, MN, spanning the years 1976 to 2010. After merging with the United States Renal Data System (USRDS), we initially identified 48 potential cases, but 5 women were excluded due to pre-existing end-stage renal disease (ESRD) before or during any pregnancy. Additionally, one woman underwent a kidney transplant after the linkage, appearing only in the REP database. This led to a total of 44 confirmed cases. The median time from the last pregnancy to the onset of ESRD was 17.7 years (interquartile range [IQR], 10.9-24.2), and the median age at the diagnosis of ESRD was 45.5 years (IQR, 40-53). [11]

Age at first birth (live or stillbirth) and parity were intentionally comparable. Most pregnancies for both cases (64%) and controls (80%) were delivered at term. Cases were notably more likely to be nonwhite, have lower education levels, be obese, and have a history of diabetes mellitus (DM) and hypertension. [11]

Pre-existing kidney disease was identified in 9 cases and 1 control based on reduced estimated glomerular filtration rate (eGFR) and/or proteinuria definitions. However, only 5 (50%) of these women had diagnostic codes for kidney disease in the REP database before their first pregnancies. Kidney disease causes included autosomal dominant polycystic kidney disease (n = 4), glomerulonephritis (n = 3), and diabetic nephropathy (n = 2) among the cases and autosomal recessive polycystic kidney disease in the control. [11]

Baseline serum creatinine values before the first pregnancy were available for 20 cases and 32 controls. Median serum creatinine levels were 0.65 (IQR, 0.28-0.75) mg/dL in cases and 0.72 (IQR, 0.55-0.75) mg/dL in controls. Only one case had an eGFR < 60 mL/min/1.73 m2, and 92% of cases and controls had eGFRs > 90 mL/min/1.73 m2. Baseline urine protein measurements were available for 30 cases and 64 controls. Among cases, 23 had normal urine dipstick findings, 6 had protein excretion >11 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. [11]

Among the 132 women (44 cases and 88 controls), there were 292 pregnancies lasting more than 20 weeks with sufficient information to evaluate hypertensive pregnancy disorders. The median number of measurements from prenatal visits was 11 (IQR, 9-13) for blood pressure (BP) and 9 (IQR, 6-11) for urine dipsticks. Using the diagnostic algorithm for hypertensive pregnancy disorders, 18% of cases and 5% of controls experienced at least one preeclamptic pregnancy. The frequency of chronic hypertension during pregnancy 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 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. [11]

Cases had a significantly higher occurrence of a history of preeclamptic pregnancy compared with controls (unadjusted odds ratio [OR], 4.0; 95% CI, 1.21-13.28). This 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). [11]

To assess the agreement with diagnostic codes, we conducted a search of the REP electronic indexes for codes related to a hypertensive pregnancy disorder within 1 year prior to the first pregnancy to 1 year after the last pregnancy for all women. We then compared the code-based diagnoses with algorithm-based diagnoses for all 292 pregnancies. The sensitivity of using diagnostic codes for any hypertensive pregnancy disorder was 61.5% (95% CI, 40.7%-79.1%), with a specificity of 98.1% (95% CI, 95.4%-99.3%). Using codes specifically for preeclampsia reduced sensitivity further to 42.9% (95% CI, 18.8%-70.4%), while specificity increased to 99.3% (95% CI, 97.2%-99.9%).[11]

From January 2009 to May 2022, a total of 602 patients diagnosed with CKD were included in the database. Among them, 117 patients (19.44%) developed superimposed preeclampsia, and 103 of these were followed up for a minimum of 1 year. The control group comprised 103 matched patients. Consequently, the study involved 206 CKD patients, with a median maternal age of 32.00 (29.00, 34.00) years at the baseline visit. The median postpartum follow-up time was 5.00 (3.00, 9.00) years. At baseline, 108 (52.43%) CKD patients were in stage 1, 67 (32.52%) were in stage 2, and 31 (15.05%) were in stage 3-4. Thirty percent of patients had chronic hypertension, and 35.44% received low-dose aspirin (LDA) therapy during pregnancy. The baseline clinical information for the two groups was comparable. Notably, 40.78% of patients presented with early-onset preeclampsia, while 59.22% presented with late-onset preeclampsia.[12]

Adverse pregnancy and renal outcomes among pregnant CKD women included a mean gestational age at birth of 35.00 weeks and a median neonatal birth weight of 2614.93 g. Compared to CKD patients without preeclampsia, those with preeclampsia had significantly higher incidences of perinatal mortality, preterm birth, and very low birth weight (VLBW) ($P<0.01$).[12]

Throughout the follow-up period, 42.72% of CKD patients with preeclampsia and 19.42% of CKD patients without preeclampsia experienced an eGFR decline >30% or developed ESRD. Additionally, 27.18% of CKD patients with preeclampsia and 17.77% of those without preeclampsia had an eGFR decline >50% or developed ESRD. Notably, in stage 1-2 CKD patients or stage 3-4 CKD patients, the incidence of progression of renal function decline or ESRD was significantly higher in the preeclampsia group than in the non-preeclampsia group, particularly in those with early-onset preeclampsia ($P<0.01$). To better assess the impact of preeclampsia on renal function in CKD patients, the study population was classified into six subgroups, considering CKD stage and preeclampsia status. Among CKD patients with preeclampsia, one stage 1 CKD patient, three stage 2 CKD patients, two stage 3a CKD patients, two stage 3b CKD patients, and one stage 4 CKD patient progressed to ESRD at a median of 5 years after delivery. One of these nine patients underwent kidney transplantation. In the group without preeclampsia, two stage 3a CKD patients and one stage 4 CKD patient progressed to ESRD.[12]

Examining changes in eGFR and Scr levels during pregnancy and the follow-up period, it was observed that, compared with CKD patients without preeclampsia, those with preeclampsia experienced a more significant decline in eGFR (98.43 (79.48, 116.47) to 81.32 (41.20, 102.97) mL/min/1.73 m2 vs. 100.00 (74.86, 120.04) to 89.45 (63.69, 105.60) mL/min/1.73 m2; $P=0.041$). A significant decrease in eGFR [93.63 (59.18, 114.94) to 68.71 (28.62, 90.35) mL/min/1.73 m2; $P<0.05$] and an increase in Scr level [81.95 (56.48, 106.00) to 112.95 (74.72, 182.33) μmol/L; $P<0.05$] were noted in CKD patients with early-onset preeclampsia. Similarly, CKD patients with late-onset preeclampsia exhibited a decrease in eGFR [100.00 (84.94, 118.00) to 84.06 (47.13, 106.05) mL/min/1.73 m2; $P<0.05$] and an increase in Scr level [68.00 (54.85, 84.75) to 81.00 (69.00, 117.00) μmol/L; $P<0.05$]. In CKD patients without preeclampsia, a decrease in eGFR [100.00 (74.86, 120.04) to 89.45 (63.69, 105.60) mL/min/1.73 m2, $P<0.05$] and an increase in Scr level [66.80 (55.80, 85.00) to 74.00 (63.90, 98.05) μmol/L; $P<0.05$] were also noted, albeit less pronounced than in CKD patients with preeclampsia.[12]

For a comprehensive understanding of the impact of preeclampsia on long-term renal function in CKD patients, univariable Cox regression was employed to assess the relationship between each risk factor and adverse renal outcomes. This analysis revealed that hemoglobin levels (HR=0.98, 95% CI: 0.96–0.99, P=0.029), serum albumin levels (HR=0.95, 95% CI: 0.91–0.99, P=0.016), Scr levels (HR=4.83, 95% CI: 2.68–8.69, P<0.01), CKD stage (HR=4.91, 95% CI: 2.90–8.31, P<0.01), proteinuria ≥1.00 g/24h (HR=4.22, 95% CI: 2.13–8.35, P<0.001), early-onset preeclampsia (HR=3.44, 95% CI: 1.89–6.27, P<0.01), and late-onset preeclampsia (HR=1.87, 95% CI: 1.02–3.46, P<0.05) were associated with an eGFR decline >30% or ESRD. Variables with P<0.05 in the univariable analysis and well-established risk factors like age, BMI, and MAP were included in the multivariable models, even if they did not reach statistical significance in the univariate analysis. Multivariable analysis demonstrated that increased Scr levels (HR=3.02, 95% CI: 1.53–5.94, P=0.001), higher CKD stage (HR=2.76, 95% CI: 1.46–5.22, P=0.002), proteinuria ≥1.00 g/24h (HR=2.70, 95% CI: 1.39–5.25, P=0.003), early-onset preeclampsia (HR=2.82, 95% CI: 1.48–5.39, P<0.01), and late-onset preeclampsia (HR=2.51, 95% CI: 1.28–4.93, P<0.05) were risk factors for an eGFR decline >30% or ESRD. Additionally, increased Scr levels, higher proteinuria levels, and preeclampsia were associated with an eGFR decline >50% or ESRD. The risk of renal function decline was higher in patients with preeclampsia, especially early-onset preeclampsia. [12]

DISCUSSION

In an extensive nationwide cohort study, spanning up to 30 years post-first pregnancy in healthy women, indicates that those with preeclampsia face an almost fivefold elevated risk of developing end-stage kidney disease (ESKD). This association remains independent of various potential confounding factors, including pre-existing conditions like chronic kidney disease (CKD), cardiovascular disease (CVD), diabetes, and hypertension. The highest ESKD risk is observed in women with preterm preeclampsia, those experiencing preeclampsia and small-for-gestational-age (SGA) in the same pregnancy, and those with preeclampsia in two pregnancies, particularly associated with diabetic nephropathy.

Preeclampsia is estimated to contribute to 14% of ESKD cases in parous women, assuming a causal relationship. Restricting analysis to women with their first delivery from 1991 onwards yields a higher hazard ratio (HR). The risk of ESKD appears elevated within the first 5 and 10 years after preeclampsia, possibly due to missed ESKD diagnoses between 1982 and 1990. These findings align with a Norwegian study, though differences in cohort size prevent direct HR comparison. Two Taiwanese studies reported varied ESKD risks associated with hypertensive disorders in pregnancy, while a United States Renal Data System study and a Canada Institute for Health Information study also support the link between preeclampsia and ESKD.

The underlying pathophysiological mechanisms connecting preeclampsia and ESKD are not entirely clear, but shared risk factors and endothelial dysfunction likely play a role. Preeclampsia's association with a 9-fold increased risk of ESKD from diabetic nephropathy raises questions about shared genetic factors influencing susceptibility to lifestyle diseases. Women with a history of preeclampsia show an increased incidence of microalbuminuria, a potential marker for renal disease. The meta-analysis indicates persistent renal disturbances after preeclampsia, potentially contributing to an elevated risk of developing CKD. Changes in renal haemodynamics postpartum, particularly hyperfiltration, may serve as early signs of renal abnormalities, linking preeclampsia to progressive renal damage and declining glomerular filtration rate.

This study revealed robust, statistically significant connections between pre-eclampsia and subsequent chronic kidney disease, hypertensive kidney disease, and glomerular and proteinuric diseases. Notably, earlier onset of pre-eclampsia showed stronger associations. The heightened risks for glomerular and proteinuric diseases, as well as chronic kidney disease, were particularly pronounced in the five years post-pregnancy. Adjustments for hypertension and cardiovascular disease during follow-up partially mitigated, but didn't eliminate, observed links to chronic renal disorders, implying partial mediation by these factors. Conversely, adjustments for diabetes and autoimmune and inflammatory conditions had minimal impact on estimates.

The nationwide cohort, spanning 38 years, minimized selection bias, empowering us to explore onset timing, post-pregnancy duration, and specific kidney disease subtypes. Rigorous definitions in national registers reduced recall bias. Utilizing Cox regression accommodated variable follow-up and time-dependent covariates.

While pre-eclampsia diagnoses in the National Patient Register exhibit high specificity (>99%), moderate sensitivity (69%) might lead to underestimation of affected cases. Changes in pre-eclampsia definitions over time and underreporting of mild renal impairment might influence findings. The study's focus on ICD-8 and ICD-10 codes, requiring proteinuria for pre-eclampsia diagnosis, likely minimizes heterogeneity.

Changes in chronic kidney disease staging and acute kidney injury criteria could impact classification, but overall definitions remained consistent, preserving study integrity. Cardiovascular disease, hypertension, and diabetes, common in pre-eclampsia, partially explained links to chronic renal disorders. The study lacks pre-pregnancy body mass index data, potentially affecting obesity-related confounding. Some residual confounding and limited generalizability to non-white populations may exist.

The findings align with prior studies linking pre-eclampsia to chronic kidney disease, but add nuances. The study identifies elevated risks for glomerular and proteinuric diseases, especially within five years post-pregnancy. While modest associations exist between pre-eclampsia and later acute renal disorders, particularly in later onset cases, the study acknowledges limitations in data precision and potential for shared susceptibility. Detection bias and monitoring practices may contribute to observed associations, but measures were taken to minimize this effect.

In patients with chronic kidney disease (CKD), pregnancy itself poses a challenge to renal function, often exacerbating decline, especially in advanced stages with higher protein levels and chronic hypertension. However, the impact of superimposed preeclampsia on renal function decline in CKD patients remains understudied. Our findings reveal that preeclampsia accelerates renal function decline, particularly in patients with stage 3-4 CKD and more prominently in early-onset cases.

Preeclampsia, an idiopathic pregnancy disorder, induces systemic vascular endothelial cell activation, leading to multiorgan damage, including the kidneys. While most kidney damage related to preeclampsia is reversible after delivery, our study suggests that superimposed preeclampsia intensifies the deterioration of renal function, affecting both stage 1-2 and stage 3-4 CKD patients. Early-onset preeclampsia exhibits more pronounced renal damage than late-onset cases.

Prophylactic measures to prevent preeclampsia, especially early-onset cases, are crucial for improving pregnancy outcomes and long-term renal prognosis in CKD patients. Although Low-Dose Aspirin (LDA) might delay preeclampsia onset, our study emphasizes its potential benefits, particularly in preventing early-onset cases and mitigating kidney function decline. However, precise screening for CKD patients who would benefit from LDA therapy, considering factors like proteinuria levels, is essential. Notably, managing proteinuria aggressively post-delivery in CKD patients with superimposed preeclampsia might slow down renal function decline, a strategy requiring further investigation beyond conventional obstetric practices.

CONCLUSION

In summary, our study reveals a substantial long-term impact of preeclampsia on kidney health. Women who experienced preeclampsia during pregnancy face a 5-fold higher risk of end-stage kidney disease (ESKD) compared to those without this complication. Despite the relatively low overall risk of ESKD, further exploration of screening and preventive strategies for women with adverse pregnancy outcomes is crucial. Additionally, our findings stress the necessity for ongoing clinical monitoring of women with a history of pre-eclampsia in the immediate post-pregnancy years. Early detection of chronic renal disorders in this group enables timely intervention, potentially preventing the onset of chronic kidney disease. However, continued research is essential to identify high-risk individuals, understand underlying mechanisms, and establish optimal follow-up and intervention strategies.

Our study also highlights the heightened risk of maternal chronic kidney disease (CKD) associated with preterm delivery, especially in conjunction with preeclampsia. Current maternity care falls short in addressing this concern, emphasizing the need for the development and implementation of preventive strategies. Further research is critical to investigate the effectiveness and timing of systematic renal follow-up, potentially integrating it into existing primary care prevention programs. Additionally, our study contributes to the expanding evidence linking preeclampsia to future kidney disease risk, suggesting it as an early indicator of women at risk later in life. Although the optimal follow-up for women with preeclampsia remains uncertain, considering lifestyle modifications and encouraging additional research to uncover potential causal pathways is crucial.

Finally, our study underscores the association between preeclampsia and an increased risk of long-term kidney function decline or ESKD, particularly in CKD patients with early-onset preeclampsia. This emphasizes the need for comprehensive monitoring and management strategies for CKD patients with a history of preeclampsia, aiming to mitigate adverse renal outcomes.

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