# Association between preterm delivery and the risk of maternal renal disease: A systematic review and meta-analysis

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Received March 27, 2024; Accepted June 18, 2024

DOI: 10.3892/etm.2024.12667

**Abstract.** The present systematic review and meta-analysis aimed to generate high-quality evidence on the association between preterm delivery (PTD) and subsequent risk of renal disease in the mother. A literature search was conducted on PubMed, Embase, CENTRAL and Scopus until the 15th of May 2023 for studies reporting an adjusted association between PTD and the risk of maternal renal disease. A total of seven studies were eligible. The pooled analysis found that women with PTD had a statistically significant increased risk of chronic kidney disease in the long term [hazard ratio (HR): 1.82 95% confidence interval (CI): 1.38, 2.40; $I^2$=85%]. Similarly, the meta-analysis also found a statistically significant increased risk of end-stage renal disease (ESRD) amongst women with PTD as compared with those without PTD (HR: 2.22 95% CI: 1.95, 2.53; $I^2$=0%). Overall, the pooled analysis showed a significantly higher incidence of renal disorders with PTD (HR: 1.98; 95% CI: 1.57, 2.50; $I^2$=88%). The results were unchanged on sensitivity analysis. Women with PTD could be at increased risk of future chronic kidney disease and ESRD. The small number of studies and retrospective nature of data are important limitations. Further studies are needed to supplement the available evidence.

## Introduction

Preterm delivery (PTD) is commonly defined as live birth occurring before the completion of 37 weeks of pregnancy. Worldwide, ~15 million newborns are delivered preterm every year with a global PTD rate of 11% (1). Most of the cases occur spontaneously, while ~30% are performed for medical causes such as pre-eclampsia or eclampsia and fetal growth restriction (2). While the underlying cause of PTD is not fully clear, it has been suggested that infection, inflammation and vascular diseases may have a role in its pathophysiology (3).

PTD constitutes a major cause of perinatal and childhood mortality causing 18% of deaths in children and 35% deaths in neonates (1). Additionally, PTD is a well-recognized risk factor for several maternal complications later in life. Research has shown that PTD increases the risk of cardiovascular disorders at 3 years post-partum by alteration of systolic blood pressure and lipid levels (4). A different study has found an increase in systolic and diastolic blood pressure up to 20 years post-partum in women with PTD vs. those delivering at term (5). Amongst other diseases, the risk of type-2 diabetes mellitus and hypercholesterolemia is also increased in the first 10 years after PTD (6).

Diabetes and hypertension in turn are important risk factors for chronic kidney disease (CKD) in adults. Indeed, CKD is a major global health concern and is the 16th most common cause of mortality around the world (7). Up to 16% of the global population is affected by CKD with mortality rates as high as 60% in end-stage renal disease (ESRD) (8). Owing to the high morbidity and mortality of CKD and ESRD, there have been efforts to identify and control risk factors that lead to the development of the disease.

Previously, there have been several studies linking PTD to the long-term risk of maternal CKD (9-11). Since chronic hypertension and hypertensive disorders of pregnancy have both been linked with the risk of CKD (7,12), and there is a close association between PTD and hypertensive disorders (5), it is plausible that PTD could be a risk factor for CKD later in life. In this context, a detailed literature search was conducted to systematically analyze and a quantitative analysis was also conducted to examine the association between PTD and the risk of maternal CKD.

## Materials and methods

*Literature source and search strategy*. The protocol of the review was registered and then published on PROSPERO (registration no. CRD42023422085; https://www.crd.york.ac.uk/prospero/). PRISMA guidelines were followed (13). Studies for the present review were searched in the electronic databases of PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/landing?status=grey), CENTRAL (https://www.cochranelibrary.com/central) and Scopus (https://www.scopus.com/home.uri). Gray literature

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*Key words:* chronic kidney disease, pregnancy, complications, maternal

was searched on Google Scholar (https://scholar.google.com/). Two reviewers performed the search separately which was completed on 15th May 2023. The databases were examined with key words consisting of 'chronic kidney disease', 'renal disease', 'dialysis', 'pregnancy', 'maternal', 'complications', 'preterm birth' and 'preterm delivery' in different combinations. Details of the search are further provided in Table SI. All search results were congregated and deduplicated electronically. The titles and abstracts of all articles were screened to identify relevant studies. Non-relevant articles were excluded and the remaining underwent full-text analysis. The reviewers carefully screened these studies based on the following criteria for further inclusion. Any disagreements were solved by consensus. The reference lists of the included studies were also examined for any other missed articles.

*Inclusion criteria*. Studies conducted on a population of pregnant women were included. The exposure was PTD. The comparative group was pregnant women without PTD. The outcome variable was CKD in the mother. Studies were to report adjusted effect size with 95% confidence intervals (CI) of the association between PTD and risk of maternal CKD. Both case-control and cohort studies were eligible provided they were published in peer-reviewed journals.

Studies reporting outcomes for the offspring, studies not reporting adjusted data and studies using the same database with the same study period were excluded. Additionally, review articles, case reports and non-English language studies were not considered.

*Extracted data and outcomes*. The studies underwent data extraction using a pre-formatted table. Two reviewers independently retrieved data on the author's name, year of publication, the database for the study, location, study type, sample size, inclusion criteria, the definition of PTD, type of renal disorder and its method of identification, percentage of women with PTD and renal disorder in the study, confounders adjusted and follow-up period. Study details were then cross-matched and any discrepancies were resolved in discussion with the third author.

*Risk of bias analysis*. Two reviewers judged the quality of the study based on Newcastle Ottawa Scale (NOS) (14). The NOS has three domains: Representativeness of the study cohort, comparability and measurement of outcomes. Points are given based on the preformatted questions. The final score of a study can range from 0-9.

*Statistical analysis*. Review Manager (RevMan; v.5.3; The Cochrane Collaboration) was employed for combining data from included studies. The pooled association between PTD and the risk of maternal CKD was presented as a hazard ratio (HR) with 95% CIs in the form of a forest plot. The meta-analysis was conducted in a random-effects model. Since the studies presented data on CKD or ESRD in the maternal population, subgroup analyses were conducted for all CKD and ESRD.

Funnel plots were generated using RevMan to judge publication bias. The $I^2$ statistic was the tool to determine inter-study heterogeneity. $I^2$<50% indicated low and >50% indicated substantial heterogeneity. A sensitivity analysis was performed to check for outliers in the analysis. One study at a time was removed from the meta-analysis and the results were regenerated. The results of the sensitivity analysis were presented in tabular form.

## Results

*Search results*. The outcomes of every step of the search strategy are presented in a flowchart form (Fig. 1). The initial search yielded 16,618 articles. Amongst these, 9,982 duplicate studies were eliminated. The remaining 6,636 records were screened for primary eligibility. The reviewers selected 26 for full-text review. Of these, a total of 7 reviews (9-11,15-18) made it to the final review while the rest were not eligible.

*Details of included studies*. Data from the studies are revealed in Table I. While the publication years of the studies were from 2010 to 2021, the cohorts included in them dated back up to 1967. Three of the studies were from Scandinavia, while the remaining were from Israel, Canada, Germany and Iran. All were cohort studies retrospectively examining their respective databases. The two Norwegian and one Iranian study consisted of a limited sample size with <3,500 participants. The remaining studies were with large sample sizes ranging from 99,338 to 1,943,716 participants. PTD was defined as birth after <37 of gestation across most studies. In addition, women with baseline CKD were excluded from all studies. In total, 3 studies examined the risk of ESRD, 3 different studies were on CKD while 1 study reported the association between PTD and both CKD and ESRD. Renal disorders were identified by clinical evaluation of estimated glomerular filtration rate (eGFR) in only 1 study. The other studies identified renal disease by using international classification of disease (ICD) codes, hospitalization episodes for renal disease, or by the treatment modality (dialysis/renal transplantation). The confounders adjusted for the association varied across the studies. The follow-up duration ranged from 5.4 years to up to 37 years. As per the author's judgment, the studies were of moderate quality receiving a NOS score of 7 or 8.

*Meta-analysis*. The meta-analysis of the association between PTD and maternal renal disease is shown in Fig. 2. Pooled analysis of 4 studies found that women with PTD had a statistically significant increased risk of CKD in the long term (HR: 1.82; 95% CI: 1.38, 2.40; $I^2$=85%). Similarly, the meta-analysis also revealed a statistically significant increased risk of ESRD amongst women with PTD as compared with those without PTD (HR: 2.22; 95% CI: 1.95, 2.53; $I^2$=0%). Overall, the pooled analysis demonstrated a significantly higher incidence of renal disorders with PTD (HR: 1.98; 95% CI: 1.57, 2.50; $I^2$=88%). There was no gross asymmetry on the funnel plot indicating no publication bias (Fig. 3).

To examine if any study had a major effect on the outcomes, a sensitivity analysis was performed (Table II). On the exclusion of studies from the meta-analysis of CKD or ESRD, there was no change in the significance of the results.

## Discussion

Pregnancy has been often considered as a metabolic stress test for females which uncovers any intrinsic vascular disease and

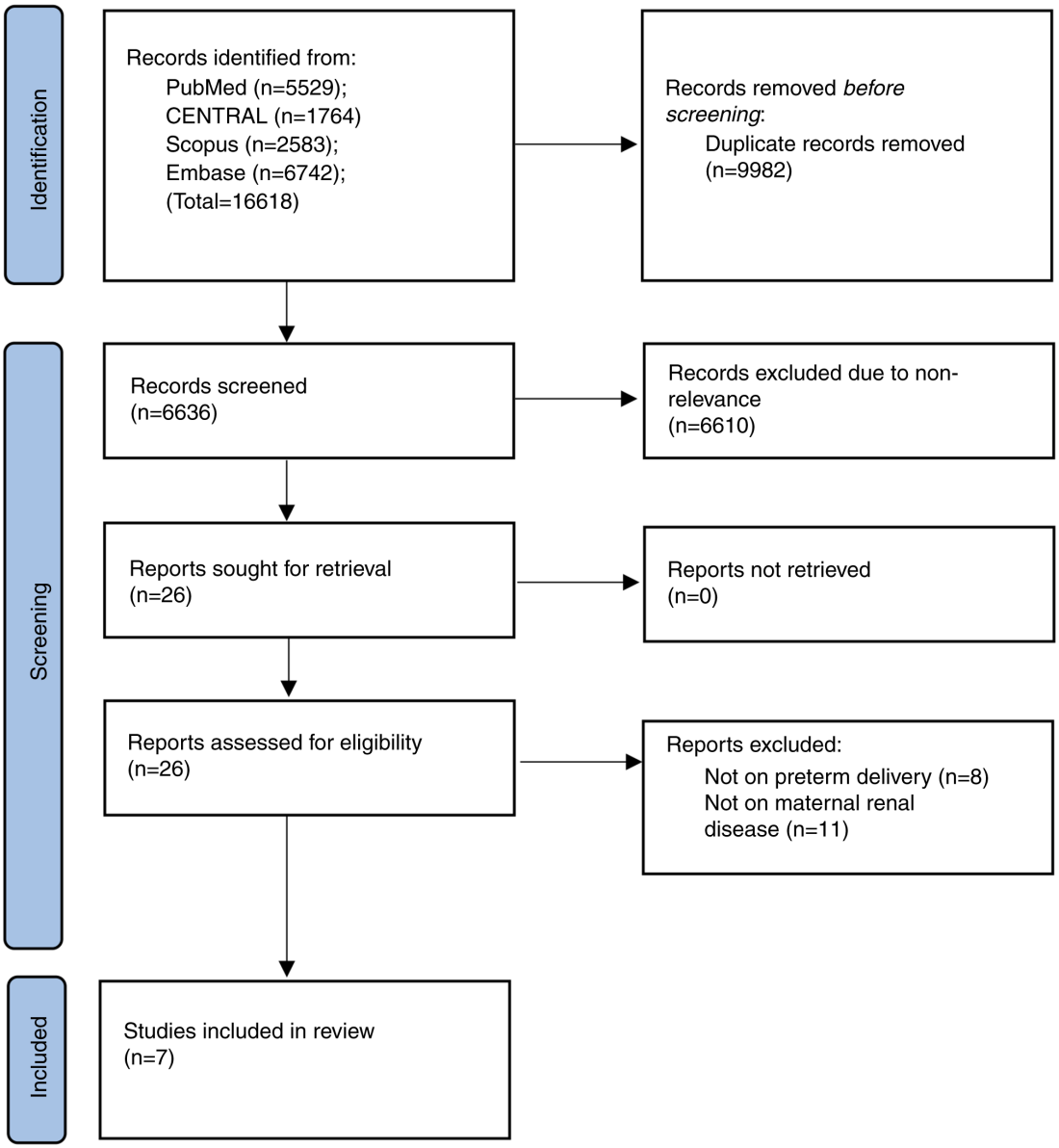


Figure 1. Study flow chart.

endothelial anomalies (19). Indeed, several pregnancy-related complications including gestational diabetes, hypertensive disorders of pregnancy and intra-uterine growth restriction have been linked with adverse long-term maternal cardiovascular disorders (20). Nevertheless, little is known about the relationship between adverse pregnancy outcomes and the future risk of CKD in females. Barrett *et al* (21) in a systematic review and meta-analysis showed that gestational diabetes and pre-eclampsia are both associated with increased risk of CKD and ESRD. The same review also examined the relationship between PTD and the risk of ESRD but could include just 3 studies in the meta-analysis. In the present study, the authors undertook an updated literature search and included several new studies to assess whether PTD is an independent risk factor for maternal CKD and ESRD.

The results of the current review revealed that women with PTD have an increased risk of renal disorders later in life as compared with those delivering at term. It was noted that PTD increases the risk of CKD by 82% and the risk of ESRD is increased by an alarming 122%. The results were more or less consistent across all included studies with only minor differences in the risk estimates in their respective populations. On the singular exclusion of one study at a time, the results still demonstrated a consistently increased risk of CKD and ESRD in the mother. While the results concurred with the prior review of Barett *et al* (21), it has important differences. The previous studies were solely on ESRD and included only 3 studies. In the present study, the authors included 4 additional studies and conducted separate analyses for both CKD and ESRD thereby providing the most recent and comprehensive evidence on the research question.

Despite several studies showing a positive association between PTD and CKD/ESRD, the underlying pathological mechanism is not clearly understood. As both PTD and CKD have multiple risk factors, the higher risk of CKD with PTD may be mediated by several shared mechanisms. Catov *et al* (22) identified that PTD increases the risk of metabolic syndrome later in life independent of other pregnancy

Table I. Details of included studies.

| First author, year | Location | Database | Study type | Sample size | Inclusion criteria | Definition of preterm birth | Preterm birth (%) | Identification of renal disorder | Renal disorder (%) | Confounders adjusted | Follow-up | NOS score | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sandvik *et al*, 2010 | Norway | Medical Birth Registry & Norwegian Renal Registry (1967-1994) | RC | 1,481 | Women with single pregnancies with preexisting diabetes | <37 weeks | 25.1 | ESRD; identified as undergoing dialysis or renal transplantation | 3.2 | Year of birth, age, marital status, stillbirth, congenital malformations of offspring, caesarean section in first pregnancy | Up to 37 years | 7 | (18) |
| Vikse *et al*, 2010 | Norway | Medical Birth Registry & Norwegian kidney biopsy registry (1988-2005) | RC | 582 | Not specified | <37 weeks | 9.5 | ESRD; identified as undergoing dialysis or renal transplantation | 13 | Maternal age, eGFR, proteinuria, diastolic blood pressure, duration of renal disease, interstitial fibrosis and inflammation | Up to 16 years | 8 | (10) |
| Pariente *et al*, 2017 | Israel | Soroka University Medical Center (1988-2012) | RC | 99,338 | All women with pregnancies | <37 weeks | 16.4 | CKD; identified by hospitalization episode | 0.13 | Preeclampsia diabetes mellitus and indicated preterm delivery | Mean 11.2 years | 7 | (9) |
| Dai *et al*, 2018 | Canada | Canadian Institute for Health Information (1993-2002) | RC | 1,598,043 | All women with pregnancies | NR | 6.3 | ESRD; identified by hospitalization episode | 0.03 | Maternal age, region, time period, obesity, preterm delivery, intrauterine death, fetal distress, placental disorders/abruption, oligohydramnios, prolonged pregnancy, postpartum haemorrhage, deep vein thrombosis, cardiac disease, blood transfusion, caesarean delivery | Median 15 years | 8 | (11) |
| Barrett *et al*, 2020 | Sweden | Swedish Medical Birth Register & Swedish Renal Register (1973-2012) | RC | 1,943,716 | All women with singleton pregnancies | <37 weeks | 8.4 | CKD & ESRD; identified by ICD codes | CKD: 0.92<br>ESRD: 0.06 | Maternal age, year of delivery, country of origin, education level, body mass index, smoking during pregnancy, gestational diabetes, preeclampsia, parity, and inter-pregnancy interval | Median 20.6 years | 8 | (17) |
| Goetz *et al*, 2021 | Germany | AOK Baden-Wuerttemberg insurance database (2010-2017) | RC | 193,152 | All women with singleton pregnancies | <37 weeks | 6.6 | CKD; identified by ICD codes | 0.71 | Maternal age, diabetes, or gestational diabetes as well as obesity and dyslipidemia | Mean 5.4 years | 8 | (16) |

Table I. Continued.

| First author, year | Location | Database | Study type | Sample size | Inclusion criteria | Definition of preterm birth | Preterm birth (%) | Identification of renal disorder | Renal disorder (%) | Confounders adjusted | Follow-up | NOS score | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Naz *et al*, 2021 | Iran | Tehran Lipid and Glucose Study | RC | 3,035 | All women with at least one pregnancy | <37 weeks | 6.9 | CKD; identified by eGFR | 36.5 | Smoking, parity, age at first delivery, body mass index, educational level, preeclampsia, and gestational diabetes mellitus | Median 16 years | 7 | (15) |

RC, retrospective cohort; NOS, Newcastle Ottawa scale; ESRD, end-stage renal disease; CKD, chronic kidney disease; ICD, international classification of diseases; eGFR, estimated glomerular filtration rate.

Table II. Sensitivity analysis.

A, CKD

| Excluded study, author(s), year | HR (95% CI) | (Refs.) |
|---|---|---|
| Pariente *et al*, 2017 | 1.61 (1.26-2.06) | (9) |
| Barrett *et al*, 2020 | 2.13 (1.54-2.94) | (17) |
| Naz *et al*, 2021 | 1.77 (1.33-2.35) | (15) |
| Goetz *et al*, 2021 | 2.01 (1.15-3.51) | (16) |

B, ESRD

| Excluded study, author(s), year | HR (95% CI) | (Refs.) |
|---|---|---|
| Sandvik *et al*, 2010 | 2.26 (1.98-2.58) | (18) |
| Vikse *et al*, 2010 | 1.96 (1.53-2.49) | (10) |
| Dai *et al*, 2018 | 1.92 (1.50-2.45) | (11) |
| Barrett *et al*, 2020 | 1.93 (1.51-2.45) | (17) |

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease.

complications and pre-pregnancy metabolic status. Metabolic syndrome is a known independent risk factor for CKD which is primarily mediated via insulin resistance and excess free-fatty acid production (23). Secondly, a systemic proinflammatory profile has been associated with an increased risk of PTD (24). C-reactive protein, a pro-inflammatory marker is found in increased quantities in mothers with PTD and the same marker is an independent predictor of CKD (25,26). Metabolic diseases such as diabetes, hypertension and obesity; all of which are associated with a pro-inflammatory phase are known to increase the risk of PTD (27). In addition, placental dysfunction is an important component of these metabolic diseases which increases the risk of PTD (16). It leads to increased release of proinflammatory and antiangiogenic cytokines which hasten endothelial dysfunction and systemic atherosclerosis; all of which result in end-organ dysfunction. Taking into account such common pathophysiological mechanisms it is tenable that PTD is a result of the baseline subclinical predisposition to future CKD in women with a shared risk profile (17). Moreover, the role of reactive oxygen species, which are overproduced at the end of the pregnancy and during labor, is important (28). Oxidative stress can cause endothelial dysfunction and microvascular damage, leading to kidney injury, interstitial fibrosis and proteinuria (29).

One of the most important confounders in the association between PTD and CKD or ESRD can be pre-eclampsia which is a strong risk factor for the latter (12). PTD is frequently performed as an iatrogenic procedure for pre-eclampsia and intrauterine growth restriction and these factors could lead single-handedly to CKD. Therefore, the next valid question is if the risk of CKD increases in both spontaneous and iatrogenic PTD. Nevertheless, limited literature exists to answer this. Barrett *et al* (17) have revealed that the risk of CKD or ESRD is increased in both spontaneous and iatrogenic PTD with the risk being stronger with the latter. In addition, the risk

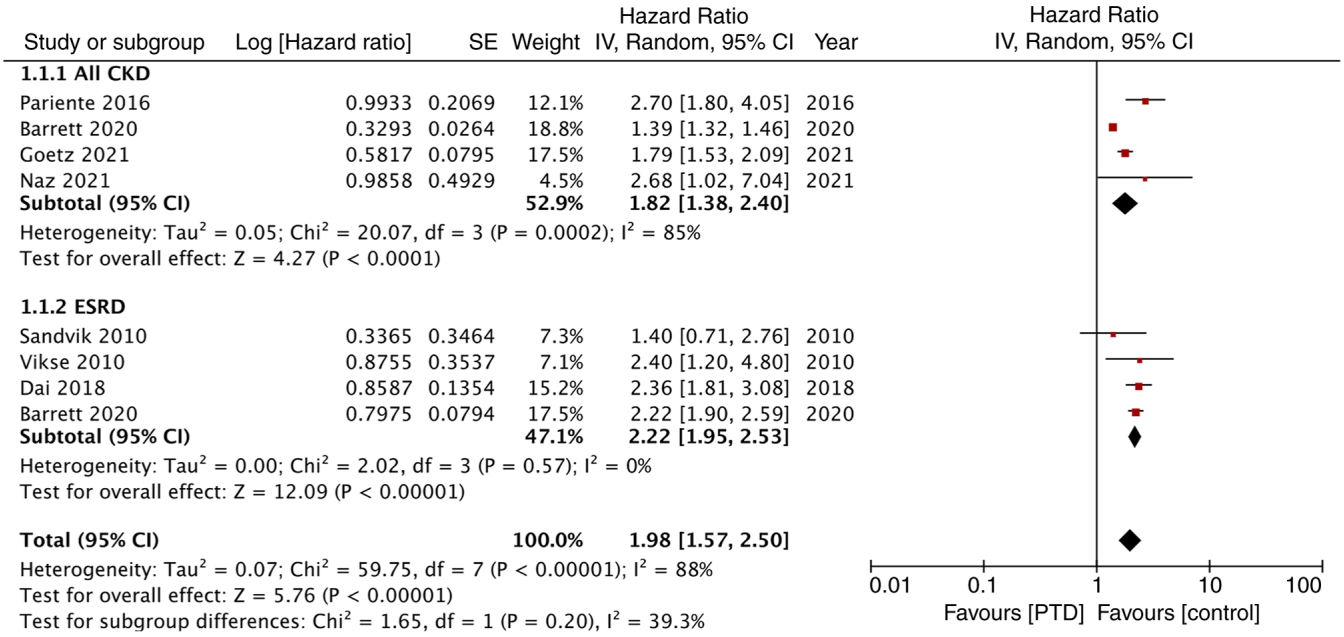


Figure 2. Meta-analysis of the association between PTD and maternal CKD or ESRD. PTD, preterm delivery; CKD, chronic kidney disease; ESRD, end-stage renal disease; CI, confidence interval; IV, inverse variance; SE, standard error; df, degrees of freedom.

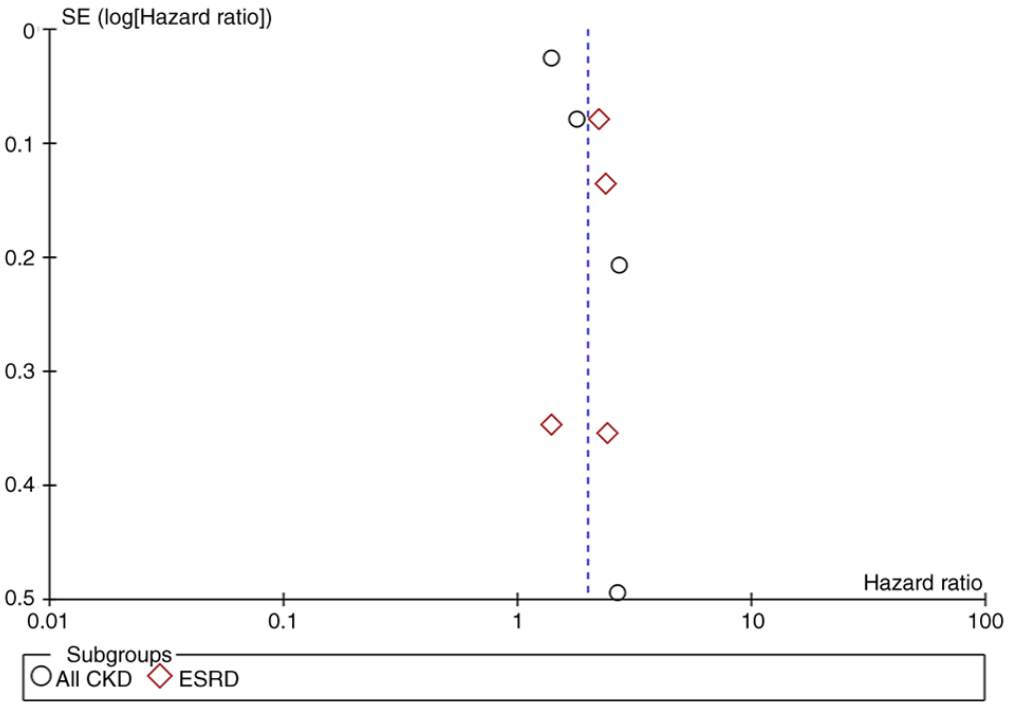


Figure 3. Funnel plot to assess publication bias. CKD, chronic kidney disease; ESRD, end-stage renal disease; SE, standard error.

was still increased based on different gestational ages and even with very/extreme PTD. Similar results were demonstrated by Pariente *et al* (9) who reported significantly increased risk in both spontaneous and induced PTD.

There are limitations to the present meta-analysis. Foremost, the retrospective and database-derived nature of the data is prone to selection bias and data-entry errors. Secondly, the high heterogeneity of the meta-analysis of CKD is a cause of concern, and hence results may be cautiously interpreted. The scarce number of studies in the meta-analysis also prevented any detailed subgroup analysis and meta-regression. Thirdly, only one study estimated the outcome by actual measurements of eGFR. The remaining studies used ICD codes or identified patients with renal hospitalization episodes. The latter may be an important source of bias affecting the credibility of results. Furthermore, there was no assessment of the stage of CKD in the included studies and a separate analysis was possible only for stage 5 CKD (ESRD). The distribution of CKD severity and

its progression in PTD females remains unclear. Furthermore, the adjusted confounders were not the same across studies. Some studies included important factors like pre-eclampsia and gestational diabetes while others did not. Several other unknown variables could have been missed and hence the current measure should not be considered fool-proof. Lastly, the data were derived from a very limited geographical location and hence its generalizability is questionable.

Despite these limitations, the present study provided the best possible evidence on the link between PTD, CKD and ESRD in females. A detailed and comprehensive search was undertaken of multiple databases involving two independent reviewers. Only adjusted measures were used to avoid baseline confounding. A separate analysis was conducted for CKD and ESRD with sensitivity analysis to check for outliners.

The current findings have important clinical implications. The prevalence of CKD is significantly increasing with stage 3 and higher disease being prevalent in 12% of the global female population (30). Given the results of the review, the women's obstetric history should be an important component during the assessment of CKD. Female patients with PTD should be counseled and closely monitored for future risk of CKD to prevent deterioration to ESRD. Additionally, further robust studies which take into account the limitations of the current literature are needed to enhance the quality of evidence and to identify risk-reducing interventions.

Women with PTD could be at increased risk of future CKD and ESRD. The limited number of studies and retrospective nature of data are important limitations. Further studies are needed to supplement the available evidence.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

WW conceived and designed the study. YC, XZ, QZ and QS collected the data and performed the literature search. QZ and QS conducted the meta-analysis. WW was involved in the writing of the manuscript. All authors have read and approved the final manuscript. YC and XZ confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

Not applicable.

**Patients consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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