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Review Article

Association between intrauterine device use and preeclampsia risk: a meta-analysis of observational studies

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Abstract: Background: Preeclampsia, whose causes remain unknown, is a multifaceted syndrome suffered by pregnant women world-wide. Objectives: This study is to quantitatively analyze the association between exposure to intrauterine devices (IUDs) and risks of developing preeclampsia during pregnancy. Search strategy: Literature search was performed on Pubmed, Medline, EMBASE and COHRANE Library. Both mesh terms and free terms were used. Reference lists were also reviewed. Section criteria: Primary studies that described preeclampsia as one of the outcomes of interest between women exposed (IUD was used during or before pregnancy) and unexposed (no IUD use) to IUDs were included. Data collection and analysis: The summary risk ratios (RRs) were estimated using a fixed effect model. Risk of bias was assessed with the Newcastle-Ottawa Scale (NOS) System. Main results: Two retrospective cohort studies (n = 153780) and one case-control study (n = 13900) were included. The summary RR for previous use of IUDs (*in situ* or early removal) *vs* no use of IUDs was 0.74 (95% CI, 0.61-0.90). No statistically significant difference was found between pregnancy with an IUD *in situ* and IUD early removal (RR = 0.74, 95% CI, 0.37-1.47). Conclusions: Any use (either before or during pregnancy) of IUDs may contribute to the reduced risk of preeclampsia.

Keywords: Intrauterine device (IUD), preeclampsia, meta-analysis

Introduction

Preeclampsia, which is a multifaceted syndrome uniquely found in human, occurs after 20 weeks of gestation [1]. Hypertension and proteinuria are common criteria to confirm a diagnosis of preeclampsia [2]. On average, one out of twenty gravidas worldwide is suffering from preeclampsia every year [2]. It accounts for up to 18% maternal deaths [3] and is a leading cause of fetal loss [4], premature labor [5] and many other maternal and fetal adverse complications [6-8]. Despite that the exact causes of preeclampsia remain unknown [1], recent studies have pointed out that the risk factors may include genetic factors [9], nulliparity, multi-pregnancy [10], and classic cardiovascular risk factors [11]. Finding effective measures for management and prevention of preeclampsia remains a clinical challenge.

Intrauterine devices (IUDs) are widely used among women of reproductive age to prevent unintended pregnancy [12-14]. The adverse complications of exposure to IUDs have been intensively studied [5, 8, 15]. Many published literatures showed that use of IUDs, especially pregnancy with an IUD in situ, was related to adverse pregnancy outcomes, such as ectopic pregnancy, miscarriage [15, 16] and preterm delivery [7, 8, 16]. However, a recent published case-control study based on large population indicated that the use of IUDs, either before pregnancy or in situ, might contribute to the reduced risk of preeclampsia [17]. The conclusion was significant to the prevention of preeclampsia, however, to date, there are no large-sample randomized controlled trials (RCTs) published on this issue to support it. In order to obtain a quantitative analysis of the association between exposure to IUDs and the risk of

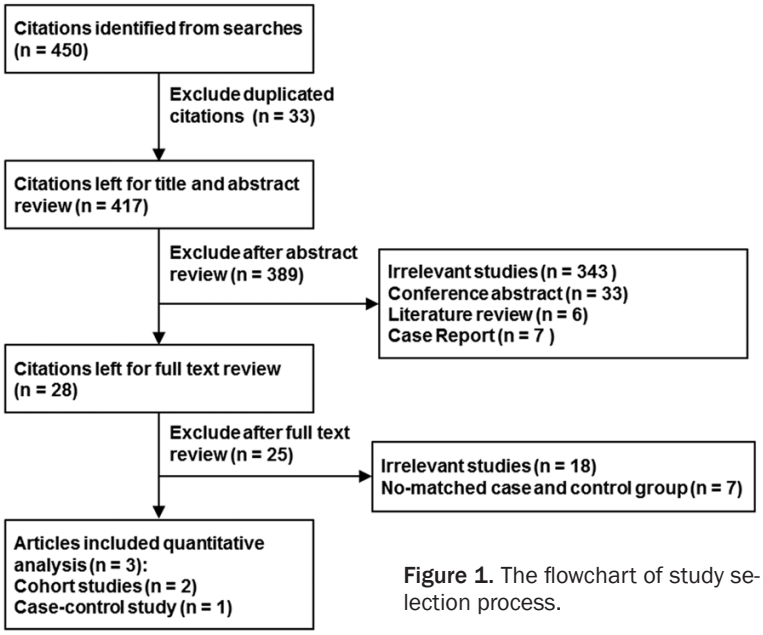

Figure 1. The flowchart of study selection process.

developing preeclampsia during pregnancy, we performed a meta analysis of all observational studies available.

Materials and methods

Search strategy

The literature search was independently conducted by both authors on biomedical databases including Pubmed, Medline, EMBASE and COHRANE Library. The following MESH terms were used: *pre-eclampsia* and *intrauterine devices*. To capture the articles that may have been ignored using the MESH terms, we further used the combinations of some free terms: *intrauterine device*, *intrauterine contraceptive device*, *IUD*, *pre-eclampsia*, and *preeclampsia* in the search. Furthermore, we reviewed the reference list of each article in order to find the studies that may not have been included in the previous literature searches. All literatures taken into consideration were published in English between 1965 and June 2015.

Study selection

Two authors (Huaying Li and Jing Zhang) reviewed the studies for inclusion independently and disagreement was resolved by consulting a third reviewer. At last, consensus was reached between the authors. Inclusion criteria: observational studies, including retrospective cohort study and case-control study, were included in our analysis. Primary studies that described preeclampsia as one of the outcomes of interest among women exposed (IUD use or early removal) and unexposed (no IUD use) to IUDs were included. Finally, three observational studies (two retrospective cohort studies and one case-control study) met the inclusion criteria and were included in this meta-analysis. We assessed the quality of the observational studies with the Newcastle-Ottawa Scale (NOS) System [18] and assigned a quality score to each study.

Outcome measures

The primary outcome of interest was preeclampsia. According to the ACOG Committee on Practice Bulletin, preeclampsia was defined as blood pressure ≥ 140 mmHg systolic blood pressure or ≥ 90 mmHg diastolic blood pressure after 20 weeks of gestation accompanied by urinary protein excretion ≥ 300 mg/d [2].

Data extraction

Two authors (Huaying Li, Jing Zhang) carried out the data extraction independently using a standardized data collection form. Discrepancy was solved by involving a third reviewer. Consensus was reached for all the extractions. For each of the three studies, the study design, cases and controls, and confounding factors were collected. Note that in case-control study, the case group was patients diagnosed with preeclampsia and the control group was patients without preeclampsia. We converted it into two groups, i.e. patients exposed to IUD *versus* unexposed to IUD, so that the effect size could be summarized.

Statistical analysis

The summary effect size was measured using risk ratios (RRs) and the corresponding 95% confidence intervals (CIs). We employed both funnel plots and Egger's test to assess the pub-

Table 1. Main Characteristics of the studies included in this meta-analysis

Study	Characteristics
SE Parker *et al.* 2015 [17]	
Type of study	Case-control Study
Time span	1993~2010
Country	UK
Device	Not mentioned
Participants	[a]Pregnancy with an IUD *in situ* (n = 51); [b]IUD early removal (n = 519); [c]no IUD use (n = 13330); total (n = 13849)
Inclusion criteria	Singleton pregnancies resulting in a live or stillbirth of at least 20 weeks of gestation; deliveries with at least 15 months of recorded medical history prior to the delivery date
Exclusion criteria	Gestational hypertension and unspecified hypertension during pregnancy; pre-existing chronic hypertension requiring treatment with an antihypertensive;
Interventions	
All	Intrauterine device use (IUD use was defined as any IUD receipt prior to the index pregnancy without an intervening pregnancy). The timing of removal was categorized as *in situ*, < 12 months, and ≥ 12 months.
Case	Pregnancies affected by pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzyme levels, and low platelet levels)
Control	No history of preeclampsia prior to the index date in the Clinical Practice Research Datalink (CPRD), UK.
Outcomes of interest	Preeclampsia
Adjustment	BMI, smoker, prior delivery, induced abortion, fertility problems, pre-existing diabetes
Sun Kwon Kim *et al.* 2010 [22]	
Type of study	Retrospective cohort study
Time span	1997~2007
Country	Chile
Device	Copper T 380A IUD
Participants	[a]Pregnancy with an IUD *in situ* (n = 196); [d]pregnancy without an IUD (n = 12,101); total (n = 12,297)
Inclusion criteria	Singleton pregnancies and parous women;
Exclusion criteria	Patients post-IUD removal during early pregnancy (n = 12)
Interventions	
Case	Copper T 380A IUD *in situ* during pregnancy
Control	No IUD during pregnancy
Outcomes of interest	Preterm birth; late spontaneous abortion (> 12 weeks); fetal death; preeclampsia; SGA; vaginal bleeding; clinical chorioamnionitis; placental abruption; placenta previa; cesarean delivery; fetal congenital malformation
Adjustment	BMI, smoker, age, parity, gestational age at delivery, underlying medical condition
Hadas Ganer *et al.* 2009 [6]	
Type of study	Retrospective cohort study
Time span	1988~2007
Country	Israel
Device	Copper devices
Participants	[a]Pregnancy with an IUD *in situ* (n = 98); [b]IUD early removal (n = 194); [c]no IUD use (n = 141191); total (n = 141483)
Inclusion criteria	Pregnancies of women with an IUD, after IUD removal at the beginning of the pregnancy, and without IUD; all pregnancies of at least 22 weeks of gestation were included.
Exclusion criteria	Nulligravid deliveries; deliveries of women with no prenatal care and multiple gestations
Interventions	
Case	Women with an IUD, after IUD removal at the beginning of the pregnancy
Control	Women without an IUD

Outcomes of interest	Fertility treatments; hypertensive disorders (defined as mild-to-severe preeclampsia or chronic hypertension); gestational or pregestational diabetes mellitus; intrauterine growth restriction (IUGR); malpresentation; premature rupture of membranes (PROM); labor induction; placental abruption, placenta previa; meconium-stained amniotic fluid; mode of delivery, Apgar score at 1 and 5 points, birthweight; congenital malformations; tubal ligation; perinatal mortality; chorioamnionitis
Adjustment	No statement

[a]*Pregnancy with IUD in situ*: pregnancy in the presence of an IUD. [b]*IUD early removal:* the IUD was removed before the pregnancy or before the first trimester of the pregnancy. [c]*No IUD use*: no IUD use before or during the pregnancy. [d]*Pregnancy without an IUD*: no IUD use or early IUD removal.

Table 2. Quality assessment of the observational cohort studies by the Newcastle-Ottawa Scale system

Study	Selection				Comparability	Outcome			Total Scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	
Hadas Ganer et al. 2009 [6]	★	★	★	★	★★	★	★	★	9
Sun Kwon Kim et al. 2010 [22]	★	★			★★	★	★		6

Note: The maximum number of stars (★) is 2 for comparability and 1 for the other categories. Rating sheets with no stars are left blank.

Table 3. Quality assessment of the observational case-control study by the Newcastle-Ottawa Scale system

Study	Selection				Comparability	Exposure			Total Scores
	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
SE Parker et al. 2015 [17]	★	★	★		★	★★	★	★	8

Note: The maximum number of stars (★) is 2 for comparability and 1 for the other categories. Rating sheets with no stars are left blank.

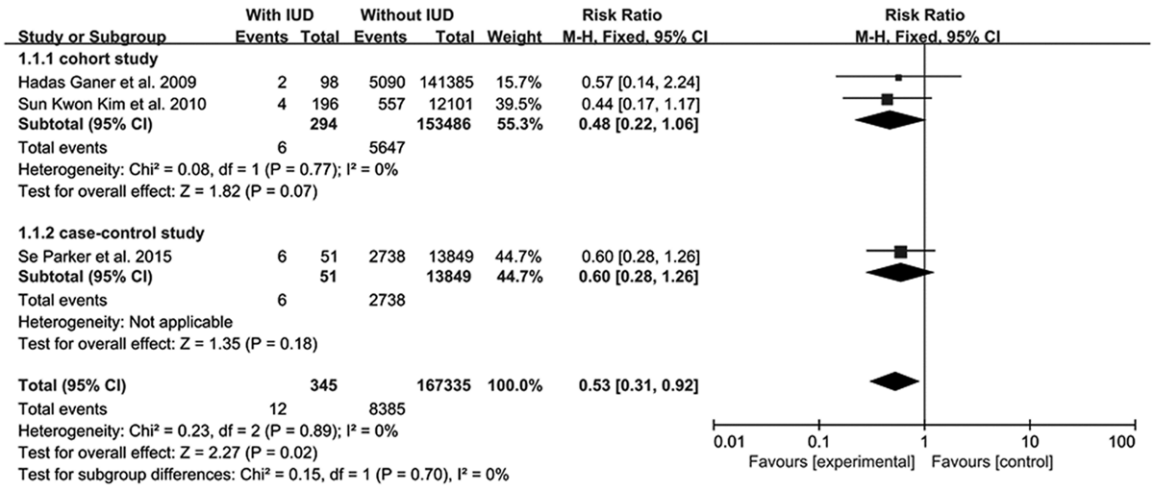

Figure 2. The summary RRs of preeclampsia for pregnancy with an IUD *vs* pregnancy without an IUD (never use or early removal). The summary RRs for the risk of preeclampsia was 0.53 (95% CI, 0.31-0.92) with no heterogeneity (I^2 = 0, df = 2). RRs of subgroup analysis were 0.48 (95% CI, 0.22-1.06, *P* = 0.07) for the cohort studies and 0.6 (95% CI, 0.28-1.26, *P* = 0.18) for the case-control study.

lication bias, and the results suggested that no obvious publication bias was detected (*P* > 0.05 for Egger's test).

Chi Square (χ^2) test was employed to assess the heterogeneity among studies and *P* < 0.1 was considered to be heterogeneous. According to Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [19], the heterogeneity was acceptable in cases of I^2 < 50. To have a thorough understanding of the association between exposure to IUDs and the risk of preeclampsia, meta-analysis was respectively performed on four groups, i.e. pregnancy with an IUD *vs* pregnancy without an IUD, any IUD use *vs* no IUD use, IUD *in situ vs* IUD early removal, and IUD early removal *vs* no IUD use. No heterogeneity was found within each group (I^2 = 0), thus fix-effect model was applied to summarize the effect size. Furthermore, to address the potential bias caused by study type (case-control or retrospective cohort), study-specific subgroup analysis was carried out. All the statistical analysis was performed using Review Manager Software (version 5.3; The Nordic Cochrane Centre, København, Denmark) and R software (version 3.21).

Results

Studies selection

A total of 450 citations were retrieved from the databases. After removing the duplicate ones, 417 citations were left for title and abstract review. Then, 389 citations were excluded, including 343 irrelevant studies, 33 conference abstracts, 6 literature reviews and 7 case reports. Because IUD was also an abbreviation for intrauterine death, such studies were considered as irrelevant. After full-text review of the remaining 28 articles, 18 were excluded for irrelevance with our objective and 7 were excluded for non-matched case-control groups. Finally, three observational studies that met our inclusion criteria were included in this meta-analysis. The study selection process was shown in **Figure 1** and the characteristics of the included studies were summarized in **Table 1**. The quality assessment of the studies included was shown in **Tables 2** and **3**.

Pregnancy with an IUD vs pregnancy without an IUD

To determine the risk of developing pre-eclampsia between pregnancies with and without IUDs, patients in this subset were extracted for meta-analysis. **Figure 2** and **Table 4** showed the summary RRs for pregnancy with an IUD *vs* pregnancy without an IUD (no IUD use or early removal of IUD) from all included studies. The summary RRs for the risk of preeclampsia was 0.53 (95% CI, 0.31-0.92), and no heterogeneity was detected (I^2 = 0, df = 2). The result was statistically significant (*P* = 0.03), suggesting that compared to pregnancy without an IUD, pregnancy with an IUD could reduce the risk of

Table 4. Summary RRs and corresponding 95% CI for the exposure to IUD and risk of preeclampsia

Variables	Cases/Control	Risk Ratio [95% CI]	I^2 for heterogeneity	*P* value
Pregnancy with IUD *vs* without IUD				
All studies	345/167335	0.53 [0.31, 0.92]	0	0.02
Cohort studies	294/153486	0.48 [0.22, 1.06]	0	0.07
Case-control Studies	51/13849	0.60 [0.28, 1.26]	Not applicable	0.18
Any IUDs use *vs* No IUD use				
All studies	862/154521	0.74 [0.61, 0.90]	0	0.002
Cohort studies	292/141191	0.86 [0.45, 1.63]	Not applicable	0.64
Case-control Studies	570/13330	0.73 [0.60, 0.89]	Not applicable	0.002
IUD *in situ vs* IUD early removal				
All studies	149/713	0.74 [0.37, 1.47]	0	0.39
Cohort studies	51/519	0.79 [0.36, 1.73]	Not applicable	0.56
Case-control Studies	98/194	0.57 [0.12, 2.67]	Not applicable	0.47
IUD early removal *vs* No IUD use				
All studies	713/154521	0.76 [0.62, 0.93]	0	0.007
Cohort studies	194/141191	1.00 [0.48, 2.08]	Not applicable	1.00
Case-control Studies	519/13330	0.74 [0.60, 0.92]	Not applicable	0.005

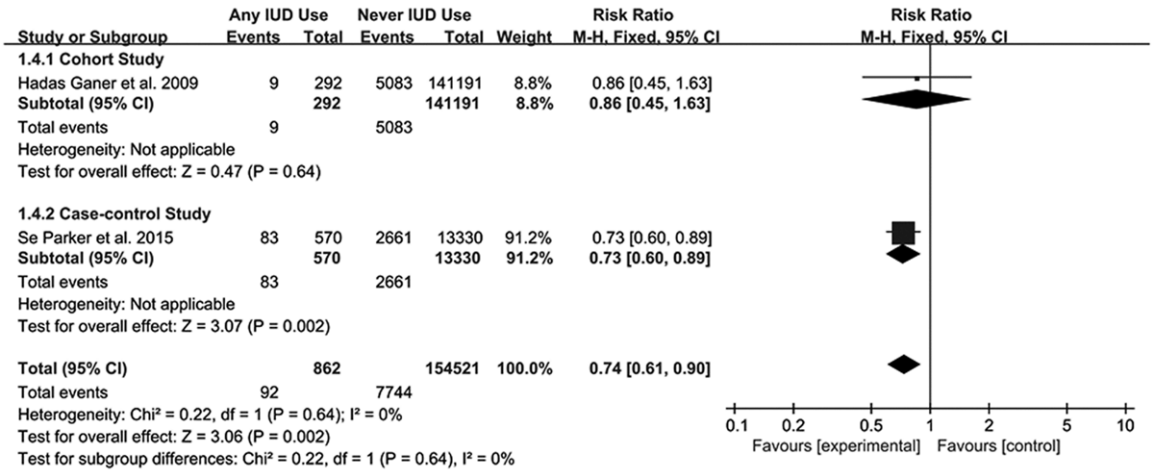

Figure 3. The summary RRs of preeclampsia for any IUD use (in situ or early removal) *vs* no IUD use. The summary RRs for the risk of preeclampsia was 0.74 (95% CI, 0.61-0.90) with no heterogeneity (I^2 = 0, df = 1). The summary RRs of subgroup analysis were 0.86 (95% CI, 0.45-1.63, *P* = 0.64) for the cohort studies and 0.73 (95% CI, 0.60-0.89, *P* = .002) for the case-control study.

preeclampsia by 47%. The summary RRs were 0.48 (95% CI, 0.22-1.06, *P* = 0.07) for the cohort studies and 0.6 (95% CI, 0.28-1.26, *P* = 0.18) for the case-control study, both of which were statistically insignificant. This indicates that pregnancy with an IUD *in situ* has dramatically reduced the risk of developing preeclampsia.

Any IUD use vs no IUD use

The risk of pre-eclampisa between gravidas who had ever used IUD (either before pregnancy or during pregnancy) and those who had never used IUDs was further analyzed. **Figure 3** and **Table 4** showed the summary RRs for any IUD use *vs* no IUD use from all included studies. The summary RRs for the risk of preeclampsia was 0.74 (95% CI, 0.61-0.90), and no heterogeneity was detected (I^2 = 0, df = 1). The result was statistically significant (*P* = .002), suggesting that compared to no IUD use, any use of IUD could reduce the risk of preeclampsia by 26%. The summary RRs were 0.86 (95% CI, 0.45-1.63, *P* = 0.64) for the cohort studies and 0.73

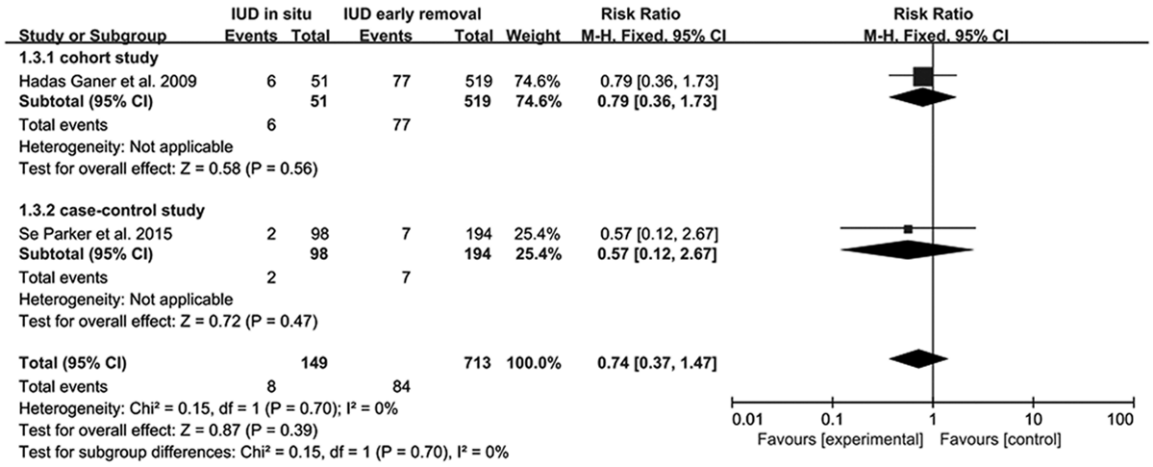

Figure 4. The summary RRs of preeclampsia for IUD in situ *vs* IUD early removal. The summary RR for all studies was 0.74 (95% CI, 0.37-1.47, *P* = 0.39) with no heterogeneity (I^2 = 0, df = 1). The RRs of subgroup analysis were 0.79 (95% CI, 0.36-1.73) for cohort study and 0.57 (95% CI, 0.12-2.67) for case-control study.

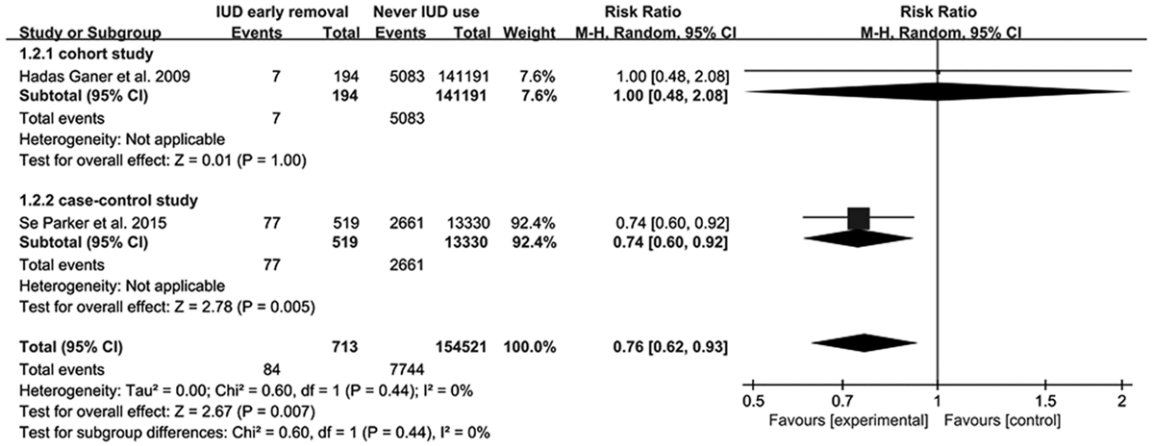

Figure 5. The summary RRs of preeclampsia for IUD early removal *vs* no IUD use. The summary RR for all studies was 0.76 (95% CI, 0.62-0.93) with no heterogeneity (I^2 = 0, df = 1) detected. The RR for the cohort study was 1.00 (95% CI, 0.48-2.08) and the RR for the case-control study was 0.74 (95% CI, 0.60-0.92).

(95% CI, 0.60-0.89, *P* = .002) for the case-control study. This indicates that the risk of developing preeclampsia is much lower for gravidas who have ever used IUDs.

IUD in situ vs IUD early removal

To further determine the effect of IUD use, the subset of patients who conceived with an IUD and who had IUDs removed early before pregnancy were analyzed. **Figure 4** and **Table 4** showed the summary RRs for IUD *in situ vs* IUD early removal. The summary RR for all studies was 0.74 (95% CI, 0.37-1.47, *P* = 0.39) with no heterogeneity (I^2 = 0, df = 1) detected. The RRs were 0.79 (95% CI, 0.36-1.73) for cohort study and 0.57 (95% CI, 0.12-2.67) for case-control study. The result was statistically insignificant (*P* = 0.39), indicating that there was no statistical difference between IUD *in situ* and IUD early removal.

IUD early removal and no IUD use

To determine if IUDs early removal could reduce the risk of developing preeclampsia, analysis between patients who had IUD early removed and who had never used an IUD was performed. **Figure 5** and **Table 4** showed the summary RRs for IUD early removal and never IUD use. The

summary RR for all studies was 0.76 (95% CI, 0.62-0.93) with no heterogeneity (I^2 = 0, df = 1) detected. The result was statistically significant (P = 0.007), indicating that comparing to no IUD use, early IUD removal could reduce the risk of preeclampsia by 24%. The RR for the cohort study was 1.00 (95% CI, 0.48-2.08), and no difference was found between IUD early removal and no IUD use. The RR for the case-control study was 0.74 (95% CI, 0.60-0.92) with statistically significant difference (P = 0.005) between IUD early removal and no IUD use. This suggests that IUD use before pregnancy is also able to reduce the risk of developing preeclampsia.

Discussion

Main findings

The main finding of this meta-analysis was that any use of IUDs (either pregnancy in the presence of an IUD or early removal of IUD) could reduce the risk of preeclampsia by 26%, while no statistically significant difference was found between IUD *in situ* and IUD early removal in the risk of developing preeclampsia. Comparing to conceiving with an IUD, pregnant women without an IUD suffer more risks. The analysis also indicates that early IUD removal can reduce the risk of preeclampsia comparing with no IUD use.

Strengths and limitations

Preeclampsia is a common obstetrical complication worldwide, of which the causes remain unknown [1]. In this study, we quantified the risk of preeclampsia between women exposed and unexposed to IUDs for the first time. The results indicate that exposure to IUDs might be a protection against preeclampsia.

This meta-analysis was based on large population observational studies. The quality of the inclusions was high according to the NOS system. No statistical heterogeneity was detected among the studies. All these strengths make the conclusions relatively convincing. And, our findings may provide potential guidelines for clinical practice.

However, the study also has some limitations inherited from the observational studies. First, although the funnel plot and Egge's test showed no publication bias, there remained possibility that only positive results were published. Second, pregnancy in the presence of IUD was rare [20, 21] and we only collected the published data from three regions, which made the generality of the conclusion limited. Third, the use of different types of IUDs and time of use may alter the environment of uterine [22, 23], which may in turn affect the morbidity of preeclampsia. We did not take them into consideration due to a lack of data. SE Parker *et al.* [17] suggested that the time interval of IUD removal before pregnancy was inversely associated with the risk of preeclampsia, however, their conclusion required further evidences in clinic.

It has been proved in animal models that placenta hypoxia and endothelial dysfunction in early pregnancy are possible risk factors for preeclampsia [24, 25]. The mechanism underlying the effect of exposure to IUDs on the risk of preeclampsia may be the decreased risk of placenta hypoxia caused by vasorelaxation. Evidences are as follows. First, in the placenta of patients diagnosed with preeclampsia, the circulating levels of two important indicators, i.e. sFlt-1 and PlGF, are different (increased sFlt-1 level and decreased PlGF level) [1, 26]. PlGF is released by placenta and functions as a vasorelaxation factor [27]. It is a homolog of vascular endothelial growth factor (VSGF) [28, 29]. However, sFlt-1 is an inhibitor of VSGF. IUDs, no matter copper-containing or hormone-releasing, would alter the endometrium cytokine profile [17]. Thus, exposure to IUDs may decrease the level of sFlt-1 and raise PlGF level. Second, prostaglandins have a vasodilatory effect as well [30]. It is able to increase the blood perfusions. Endometrium would release prostaglandins locally in the presence of a copper devices [20, 31]. Last but not least, the presence of IUD would cause some endometrial damages, whereas such injury may be helpful for placentation [32]. Evidences showed that decidual injury would increase the potential of trophoblastic cell invasions to maternal spiral arteries [26], which can remodel the arteries, provide the embryo with adequate vascular supply, and thus enable the fetus to access the oxygen and nutrients from the mother [33]. If such process is not complete, preeclampsia may occur [32].

However, insertion of IUD into the uterine may cause local mechanical damages [34, 35] and

increase the risk of infections [36]. Many literatures indicated that IUD use was associated with several adverse pregnancy outcomes [6, 15, 37]. The WHO protocol also suggested that IUDs should be removed in cases that they were visible and could be removed easily [38]. However, another study found no differences between the pregnancy outcomes among patients with an IUD *in situ* and those with IUD removed at early trimester [39]. It remains open to discussion whether or not to remove the IUD in cases of conceiving with an IUD.

Conclusions

To the best of our knowledge, this is the first study that quantifies the association between women exposure to IUDs and their risks of developing preeclampsia. The results based on the observational studies indicated that exposure to IUDs could reduce the risk of preeclampsia. However, larger-sample-size RCTs are required to support this conclusion. Despite some limitations, this study offers some useful insights for clinical practice and clues for researches on nosetiology of preeclampsia. Future work could focus on determining the association between timing of IUD removal, IUD type and the risk of preeclampsia, so as to prevent preeclampsia as well as avoid adverse pregnancy outcomes with IUD use.

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Disclosure of conflict of interest

None.

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