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Effectiveness, Efficacy, and Safety of Folate Supplementation for Preeclampsia: A Comprehensive Systematic Review and Meta-analysis Studies

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ABSTRACT

Background: Preeclampsia poses severe maternal and perinatal risks. Although folic acid may reduce homocysteine levels, its effectiveness in lowering preeclampsia risk remains debated and inconclusive. This systematic review and meta-analysis aim to evaluate the efficacy, effectiveness, and safety of folate supplementation for preeclampsia based on literatures of the last 10 years.

Method: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines using the PICO framework. Rigorous screening, data extraction, risk of bias assessment, and statistical analysis were performed to evaluate the effectiveness, efficacy, and safety of folate supplementation for preeclampsia.

Results: A total of 89 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane). After three rounds of screening, five articles directly relevant to the meta-analysis were selected for full-text reading and analysis. The results showed that the effectiveness of folate supplementation for preeclampsia is not statistically significant with overall size effects of RR = 0.81 (95% CI: 0.59, 1.13)

Conclusion: The meta-analysis indicates that folic acid supplementation alone does not significantly reduce pre-eclampsia risk.

Keywords: pre-eclampsia, folic acid, gestational hypertension, pregnancy

INTRODUCTION

Preeclampsia is one of the most significant complications during pregnancy, leading to a range of maternal and perinatal complications, including increased morbidity and mortality.[1] Despite advances in maternal care, the prevalence of preeclampsia continues to rise, particularly in developed countries, where lifestyle factors such as delayed childbearing, obesity, and insulin resistance contribute to its increased incidence. Additionally, inadequate prenatal care in developing countries exacerbates the burden of this condition, further highlighting the global challenge posed by preeclampsia.[2,3]

Women with preeclampsia face higher risks of placental abruption, chronic hypertension, cardiovascular diseases, and adverse fetal outcomes like preterm birth and intrauterine growth restriction. The global incidence of preeclampsia is approximately 4.6%, varying by region.[4] Gestational hypertension, another hypertensive disorder, involves new-onset hypertension after 20 weeks without the proteinuria seen in preeclampsia. It is suggested that preeclampsia and gestational hypertension may have different biological pathways and impact maternal and fetal health differently.[5,6]

The precise etiological factors of preeclampsia remain elusive. However, current understanding points to two critical processes: abnormal placentation and the subsequent development of maternal–placental syndrome, which is linked to an excess of antiangiogenic factors. These insights into the placental origins of preeclampsia have been instrumental in shaping the management strategies for this complex condition, although significant questions about its etiology, pathogenesis, and therapeutic management persist.[6,7]

Folate, a vital B vitamin, is crucial for human growth and development, especially during pregnancy, due to its role in nucleic acid synthesis, DNA methylation, cell division, and embryogenesis.[8,9] Adequate folate intake before and during pregnancy is essential for placentation, fetal development, and preventing neural tube defects. Due to difficulties in achieving sufficient dietary folate, supplementation is recommended pre-conceptionally and during the first trimester.[3,10]

Research into potential preventative and treatment options for preeclampsia has been extensive. Among the various factors explored, abnormalities in folic acid metabolism and elevated homocysteine levels have been identified as contributors to hypertensive disorders in pregnancy, including preeclampsia. Folate, a vital nutrient during pregnancy, has been shown in multiple studies to reduce elevated blood homocysteine levels, suggesting a potential role in mitigating the risk of preeclampsia.[11–13]

The relationship between folic acid supplementation and a decreased risk of preeclampsia is still debated despite evidence that folate reduces homocysteine levels. Studies have yielded inconsistent conclusions regarding the optimal dosage and efficacy of folic acid in preventing preeclampsia, although lower folate levels have been linked to its development. Previous meta-analysis suggested a protective role for folic acid, but more research is needed to confirm its efficacy and safety in preeclampsia prevention.[14]

This systematic review and meta-analysis aim to evaluate the efficacy, effectiveness, and safety of folate supplementation as a preventative strategy for preeclampsia based on literatures of the last 10 years.

METHODS

This systematic review meta-analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. This study used the PICO (Population, Intervention, Comparator, and Outcomes) framework, comprising of Population: Pregnant women; Intervention: Folic acid supplementation (varying doses); Comparison: Placebo or no folic acid supplementation; and Outcome: Incidence of preeclampsia.

Eligibility Criteria

For the meta-analysis on efficacy, effectiveness, and safety of folate supplementation as a preventative strategy for preeclampsia, the eligibility criteria included several key aspects. Inclusion criteria focused on studies involving pregnant women, particularly those at varying risk levels for preeclampsia, such as those with advanced maternal age, obesity, hypertension, or a history of

preeclampsia. The intervention considered was folate supplementation, whether alone or combined with other interventions, across different dosages, especially when started in the first trimester and continued through pregnancy. Eligible studies needed to include a control group receiving either a placebo, no supplementation, or standard prenatal care. The primary outcome of interest was the incidence of preeclampsia, while secondary outcomes included maternal and fetal complications such as gestational hypertension, preterm birth, low birth weight, and neonatal Apgar scores. Study designs considered were randomized controlled trials (RCTs), cohort studies, case-control studies, as well as meta-analyses and systematic reviews. Only peer-reviewed studies published in English were included.

Exclusion criteria omitted studies involving non-pregnant women or those with unrelated pre-existing conditions that could confound results. Research focusing on folate supplementation for other purposes or studies where folate's effects could not be isolated were excluded. Additionally, studies that did not report on preeclampsia incidence or relevant maternal and fetal outcomes were excluded, as were those that focused solely on biochemical markers without clinical outcomes. Case reports, editorials, opinion pieces, non-randomized studies with significant flaws, and non-peer-reviewed articles or studies published in languages other than English were also excluded.

Data Sources and Search Strategy

Authors utilized various data sources and search strategies, including the Medical Subject Headings (MeSH) database. A comprehensive search was conducted across PubMed, SagePub, Nature, and Cochrane to identify relevant studies. Keywords included in this study are pre-eclampsia, folic acid, gestasional hypertension, pregnancy. Boolean operators were employed to combine these terms effectively. Filters were applied to limit results to human studies published in English.

The Boolean MeSH keywords inputted on databases for this study are: ("pre eclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR ("pre"[All Fields] AND "eclampsia"[All Fields]) OR "pre eclampsia"[All Fields]) AND ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic

acid"[All Fields]) AND ("gestasional"[All Fields] AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])

Study Selection

An initial screening of titles and abstracts is then conducted to exclude studies that clearly do not meet the inclusion criteria. This stage is performed independently by two or more reviewers to minimize bias and ensure objectivity. Studies that pass this preliminary screening are retrieved in full text for a more detailed assessment. During the full-text review, the reviewers carefully evaluate the studies against the inclusion and exclusion criteria. Any discrepancies between reviewers are resolved through discussion or by consulting a third reviewer to reach a consensus, ensuring that only the most relevant and high-quality studies are selected.

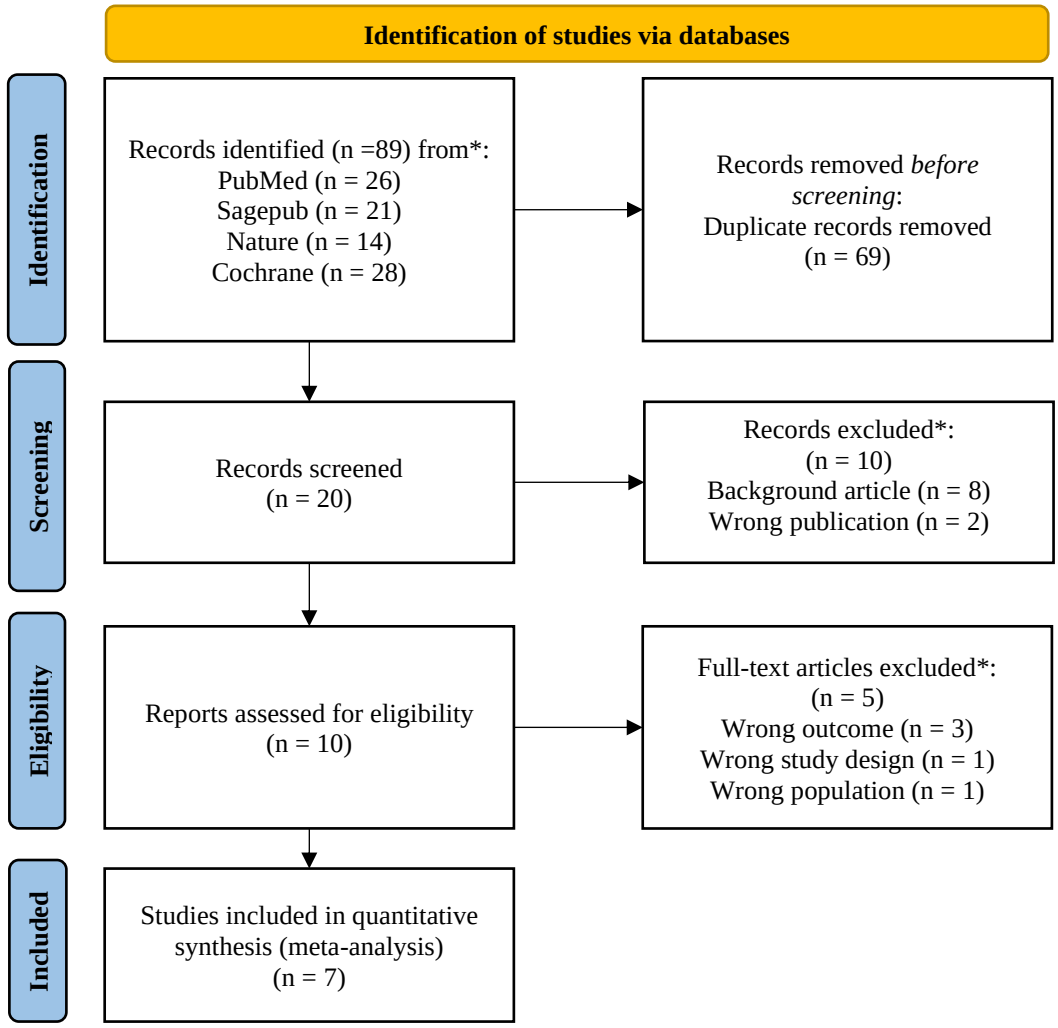

Figure 1. Search strategy and selection of studies for the meta-analysis.

Data Extraction

Data extraction was performed in duplicate from full-text versions of eligible studies by authors. Information regarding the effectiveness, efficacy, and safety of folate supplementation for preeclampsia was extracted at various time intervals. Data presented in tabular format were the primary source for extraction.

Risk of Bias

The risk of bias in each trial was assessed across six domains using the RevMan 5.4 tool (Cochrane, UK). These domains included sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting, and other potential sources of bias. Trials were categorized as having high, low, or

unclear bias in each domain, with detailed justifications provided for each determination.

Data Synthesis and Analysis

The core of the data synthesis for this meta-analysis involved statistical analysis, with the primary outcome measure being the risk ratio (RR) used to evaluate the effectiveness of folate supplementation. Data analysis was performed using Review Manager Software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). This software facilitated the calculation of pooled effect sizes to assess the impact of folate supplementation on preeclampsia. To account for variability among the studies, we employed random-effects models, given the heterogeneity among study results. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test to determine the extent of variation across studies.

The results were visually represented in forest plots, which displayed the risk ratios (RR) and their confidence intervals for each individual study. These plots also summarized the overall pooled effect, providing a comprehensive view of the efficacy and safety of folate supplementation in preventing preeclampsia. The risk ratio indicates the extent to which the risk of preeclampsia is altered in the intervention group (those receiving folate supplementation) compared to the control group (those not receiving supplementation).

RESULT

A total of 89 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane). After three rounds of screening, 20 articles directly relevant to the systematic review were selected for full-text reading and analysis. This meta-analysis synthesizes data from five studies the effectiveness, efficacy, and safety of folate supplementation for preeclampsia. The characteristics of the studies are showed in Table 1 and 2.

Table 1. Characteristics of studies included in the systematic review

No.	Author	Origin	Study Design	Sample Size	Result
1.	Corsi, et al.[15] (2022)	Multicenter	Randomized controlled trial	428 pregnant women	Out of 2,464 participants randomized, 462 had confirmed twin pregnancies. After excluding withdrawals and those without primary outcome data, 428 women were analyzed. The crude analysis showed a significantly higher rate of preeclampsia in the folic acid group compared to the placebo group (17.2% vs. 9.9%, relative risk [RR] 1.75, 95% CI 1.06–2.88, p = .029). However, multivariable analyses attenuated this effect, rendering it not statistically significant (RR 1.58, 95% CI 0.95–2.63, p = .079).
2.	Kim, et al.[16] (2014)	South Korea	Retrospective case control study	215 pregnant women	The results showed that maternal blood concentration of folic acid significantly increased following supplementation, while homocysteine levels decreased. Furthermore, the rates of both preeclampsia and small for gestational age (SGA) were lower in the folic acid supplementation group compared to the control group. Specifically, the odds ratio (OR) for preeclampsia was 0.27 (95% confidence interval [CI], 0.09–0.76), and for SGA, it was 0.42 (95% CI, 0.18–0.99). However, no significant associations were found between folic acid supplementation and other pregnancy outcomes.

3.	Vanderlelie, et al.[17] (2014)	Australia	Prospective cohort study	719 pregnant women	he HD group had significantly higher plasma levels of homocysteine and FA. This group also experienced reductions in severe gestational hypertension, early onset pre-eclampsia, severe pre-eclampsia, and low Apgar scores at 5 minutes. Additionally, the incidence of pre-eclampsia was lower in the HD group, particularly when compliance exceeded 50%.
4.	Wang, et al.[18] (2015)	China	Retrospective case control	10,041 pregnant women	The findings indicated that compared to non-users, women who used folic acid supplements had a reduced risk of preeclampsia, with an odds ratio (OR) of 0.61 and a 95% confidence interval (CI) of 0.43–0.87. Additionally, a significant dose-response relationship was observed for the duration of folic acid supplementation during pregnancy only, suggesting a potential protective effect. The reduced risk associated with folic acid supplementation was consistent across different subtypes of preeclampsia, including mild or severe, and early- or late-onset. However, statistically significant associations were only observed for mild (OR = 0.50, 95% CI: 0.30–0.81) and late-onset (OR = 0.60, 95% CI: 0.42–0.86) preeclampsia. Furthermore, higher dietary folate intake during pregnancy was also associated with a reduced risk of preeclampsia, particularly for severe preeclampsia (OR = 0.52,

					95% CI: 0.31–0.87 for the highest quartile of dietary folate intake compared with the lowest).
5.	Wen, et al.[19] (2016)	Canada	Prospective cohort study	7,669 women	In the results, it was found that a total of 7,669 participants were included in the final analysis, with 95% of them taking folic acid supplementation in the early second trimester. The rate of preeclampsia (PE) was observed to be lower in the supplementation group compared to the non-supplementation group. This difference was found to be statistically significant, particularly among high-risk women. Additionally, similar patterns of associations were observed when analyzing data based on red blood cell (RBC) and serum folate levels, as well as in the dose-response analysis.
6.	Wen, et al.[20] (2018)	China	Randomized clinical trial	1144 pregnant women	Pre-eclampsia occurred in 14.8% of women in the folic acid group (169 out of 1144) compared to 13.5% in the placebo group (156 out of 1157), with a relative risk of 1.10 (95% CI: 0.90 to 1.34; P=0.37). There were no significant differences between the groups for any other adverse maternal or neonatal outcomes.
7.	Zheng, et al.[21] (2020)	China	Randomized clinical trial	1,576 pregnant women	Participants were divided into two groups: the low-dose (LD) group receiving 0.4 mg of FA daily and the high-dose (HD) group receiving 4 mg of FA daily, starting from the first three months of pregnancy until delivery. The HD

					group exhibited significantly higher plasma homocysteine and FA levels compared to the LD group. Notably, severe gestational hypertension, early onset pre-eclampsia, severe pre-eclampsia, and low Apgar scores at 5 minutes were reduced in the HD group. Moreover, the incidence of pre-eclampsia was decreased in the HD group with compliance exceeding 50%.

Table 2. Characteristics of studies included in the meta-analysis

No.	Author	Country	Study Design	Total Sample	Folate Supplementation Timing	Experimental		Control		Risk Ratio RE, 95% CI
						Events	Total	Events	Total	
1.	Corsi, et al.[15] (2022)	Multicenter	Randomized controlled trial	428 pregnant women	Prenatal	42	215	23	213	1.81 [1.13, 2.90]
2.	Kim, et al.[16] (2014)	South Korea	Retrospective secondary analysis	215 pregnant women	Prenatal	6	134	12	81	0.30 [0.12, 0.77]
3.	Vanderlelie, et al.[17] (2014)	Australia	Cohort study	719 pregnant women	First trimester	13	1195	31	1066	0.37 [0.20, 0.71]
4.	Wang, et al.[18] (2015)	China	Cohort study	10,041 pregnant women	Pre conception, Prenatal	238	794	115	265	0.69 [0.58, 0.82]
5.	Wen, et al.[19] (2016)	Canada	Prospective cohort study	7,669 women	Early second trimester	228	7265	17	404	0.75 [0.46, 1.21]
6.	Wen, et al.[20] (2018)	China	Randomized clinical trial	1144 pregnant women	Prenatal	169	1144	156	1157	1.10 [0.90, 1.34]
7.	Zheng, et al.[21] (2020)	China	Randomized clinical trial	1,576 pregnant women	Prenatal	42	410	37	378	1.05 [0.69, 1.59]

The risk of bias analysis was conducted utilizing the RevMan 5.4 tool, developed by Cochrane, UK and presented in Figure 2 and Figure 3. In the risk of bias analysis for the studies included in the meta-analysis on folate supplementation for preventing preeclampsia, several key issues were identified. Corsi et al. (2022) demonstrated a low risk of random sequence generation and allocation concealment, but had high risks related to blinding of participants and personnel and outcome assessment, leading to an overall moderate risk of bias. The potential for bias in this study might influence the reliability of the reported outcomes.

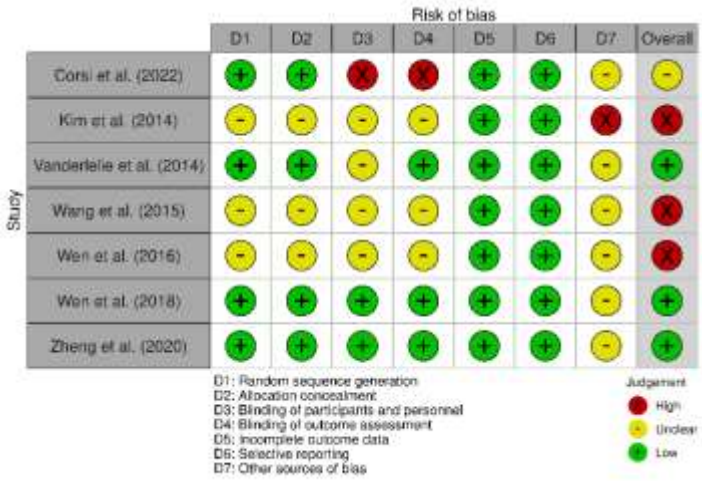

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

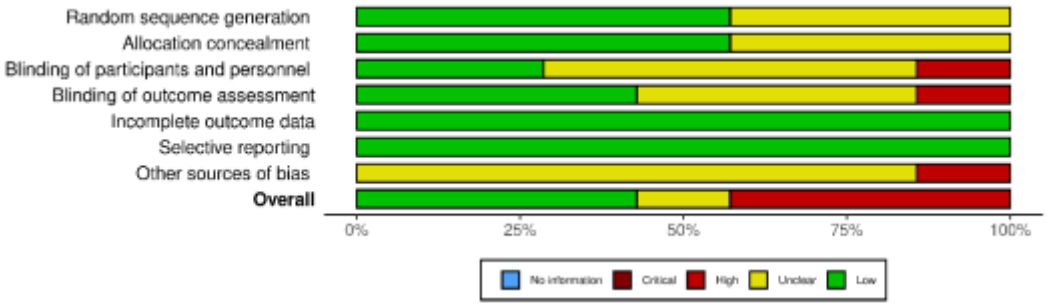

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Kim et al. (2014) and Wang et al. (2015) were assessed with high risks due to unclear methods for random sequence generation, allocation concealment, and blinding of both participants and outcome assessors. These studies also exhibited

issues with selective reporting and other sources of bias, contributing to an overall high risk of bias. The lack of transparency and methodological rigor in these studies raises concerns about the validity of their findings.

In contrast, Vanderlelie et al. (2014), Wen et al. (2018), and Zheng et al. (2020) were categorized with low risk of bias for most domains, including random sequence generation, allocation concealment, and blinding. These studies employed rigorous methodologies and addressed potential biases effectively, resulting in an overall low risk of bias. Their reliable study design and reporting enhance the credibility of their conclusions about the effectiveness of folate supplementation in preventing preeclampsia.

Effectiveness, Efficacy, and Safety of Folate Supplementation for Preeclampsia

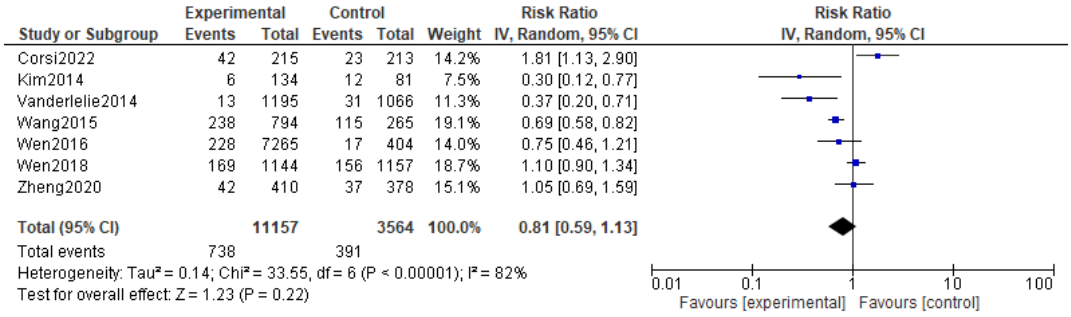

Figure 4. Forest Plot: Effectiveness, Efficacy, and Safety of Folate Supplementation for Preeclampsia

The forest plot presents data from seven individual studies assessing the effectiveness and safety of folate supplementation in preventing preeclampsia. The studies included are Corsi2022, Kim2014, Vanderlelie2014, Wang2015, Wen2016, Wen2018, and Zheng2020. The risk ratios (RR) and 95% confidence intervals (CI) for each study show a wide range of effects, from a protective effect (RR < 1) to an increased risk (RR > 1) associated with folate supplementation. For instance, Corsi2022 reports an RR of 1.81 (95% CI: 1.13, 2.90), suggesting an increased risk, while Kim2014 shows an RR of 0.30 (95% CI: 0.12, 0.77), indicating a protective effect.

The pooled risk ratio (RR) for the overall effect of folate supplementation on preeclampsia is 0.81, with a 95% CI of 0.59 to 1.13. This suggests that folate supplementation might reduce the risk of preeclampsia by 19%. However, the confidence interval crosses 1, indicating that this result is not statistically significant ($p = 0.22$). The Z-score of 1.23 further supports the lack of statistical significance, suggesting that folate supplementation does not have a conclusive effect on preeclampsia risk in the studied populations.

A critical aspect of the analysis is the high level of heterogeneity among the included studies. The I^2 value of 82% and the significant Chi^2 test ($p < 0.00001$) indicate substantial variability in the study results. This high heterogeneity suggests that the differences among the studies are significant and could stem from variations in study design, population characteristics, dosages, or other factors. The Tau^2 value of 0.14 also reflects considerable variability among the study effects.

When examining individual studies, the results are mixed. Some studies, such as Kim2014, Vanderlelie2014, and Wang2015, show protective effects with risk ratios less than 1, whereas others, like Corsi2022 and Wen2018, show an increased risk with risk ratios greater than 1. The wide confidence intervals in several studies indicate less precision in these estimates, further complicating the interpretation of the pooled result.

In conclusion, the pooled analysis does not provide strong evidence that folate supplementation is effective in reducing the risk of preeclampsia. The overall effect is not statistically significant, and the high heterogeneity suggests inconsistent results across studies. This inconsistency may be due to differences in study conditions, populations, and other factors. Given the high variability and non-significant overall effect, further research is needed to better understand the conditions under which folate supplementation might be effective. Future studies should focus on subgroup analyses and meta-regression to identify sources of heterogeneity and refine the effectiveness and safety estimates of folate supplementation for preeclampsia.

DISCUSSION

Pre-eclampsia is a multi-system disorder characterized by hypertension and potential involvement of other organ systems or the fetus, typically manifesting after 20 weeks of gestation.[22,23] It affects 5–7% of pregnancies globally and poses significant risks, including long-term health complications for mothers such as hypertension, renal disease, and cardiovascular issues, as well as adverse fetal outcomes like intrauterine growth restriction, small-for-gestational-age infants, and preterm delivery.[24]

Folate plays a significant role in preventing preeclampsia, a pregnancy complication characterized by hypertension and organ dysfunction. Adequate folate levels are essential for maintaining proper placental development, supporting antioxidant protection, and promoting healthy blood vessel function.[25] Folate deficiency can disrupt these processes, potentially leading to increased homocysteine levels and heightened risk of preeclampsia. Ensuring sufficient folate intake during pregnancy may reduce the likelihood of developing preeclampsia by supporting critical physiological functions necessary for a successful pregnancy and healthy fetal development.[26]

This systematic review and meta-analysis evaluated the effectiveness, efficacy, and safety of folate supplementation for preventing preeclampsia by synthesizing data from various study designs, including randomized controlled trials, cohort studies, and case-control studies. The analysis showed a pooled risk ratio (RR) of 0.81, with a 95% confidence interval (CI) of 0.59 to 1.13, suggesting a potential 19% reduction in preeclampsia risk with folate supplementation. However, the confidence interval includes 1, indicating that this result is not statistically significant ($p = 0.22$). The Z-score of 1.23 further supports the lack of statistical significance, implying that folate supplementation does not have a conclusive effect on preeclampsia risk in the studied populations.

Many studies involved multivitamin use with folic acid, but folic acid alone may be particularly important for preventing gestational hypertension and preeclampsia. Recent trials found no protective effect from other vitamins, and studies that focused solely on folic acid showed a lower likelihood of developing these conditions.[27] However, dosages and durations intended for neural tube defect

prevention may not be sufficient for preventing later pregnancy complications like preeclampsia, which often develops later in pregnancy. Standard recommendations of 0.4–1 mg per day, usually given only in the first trimester, may be inadequate. Women at higher risk, such as those with obesity or diabetes, might require higher doses. [28]

Findings from this analysis reveal mixed results regarding folate supplementation's effectiveness. Corsi et al. (2022) found a higher rate of preeclampsia in the folic acid group in crude analyses, but this effect was attenuated in multivariable analyses.[15] Wang et al. (2015) observed a reduced risk, though significant associations were limited to certain preeclampsia subtypes.[18] Conversely, Vanderlelie et al. (2014) and Wen et al. (2018) provided more consistent evidence, showing that high-dose folate was linked to reductions in severe gestational hypertension and preeclampsia, particularly in high-risk populations.[17,20]

Regarding safety, studies generally reported no significant adverse outcomes associated with folate supplementation. However, the variability in study design and quality, as indicated by the risk of bias analysis, suggests caution in interpreting these results. Some studies had high risks of bias, potentially affecting the reliability of their findings.

CONCLUSION

In conclusion, this meta-analysis indicates that folic acid supplementation alone does not significantly reduce pre-eclampsia risk. Overall, while evidence supports the potential benefits of folate supplementation in reducing preeclampsia risk, especially in high-risk groups, further research with robust methodologies and consistent outcome measures is needed to confirm these findings and refine clinical recommendations.

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