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Systematic Review

The comparison between folic acid supplementation compared to calcium supplementation as preeclampsia prevention: a systematic review

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Abstract
Preeclampsia is a major cause of adverse pregnancy outcomes for both mothers and infants, leading to higher rates of morbidity and mortality. Despite progress in prenatal care, the exact cause of Preeclampsia remains unknown, highlighting the need for effective prevention strategies to improve outcomes. Various nutritional interventions can be used as potential preventive measures against Preeclampsia. Among these, folic acid and calcium supplementation have garnered considerable attention. This systematic review aims to compare the effectiveness of folic acid versus calcium supplementation in preventing Preeclampsia. By synthesizing the current evidence, we seek to elucidate the relative benefits of these two interventions, thereby providing clearer guidance for clinical practice and future research. This systematic review uses PubMed Central, Springerlink, PubMed, and Google Scholar as databases, using MeSH (Medical Subject Headings) terms: 'Folic Acid', 'Calcium', and 'Preeclampsia' to extract relevant publications. Publications included were limited to English publications in the past 5 years globally. This study included 6 studies compromising 29.664 women. Prisma table is used to identify studies via databased and sorted with Rayyan.ai. Both Calcium and Folic acid supplementation in adequate dose equally needed to prevent preeclampsia. Further research is necessary to evaluate the effectiveness of therapy in equivalent subject groups. There is currently limited information on the impact of health supplements on high-risk pregnancies, including the effects of calcium supplementation.

Keywords: calcium; folic acid; preeclampsia; pregnant woman

1. Introduction

Preeclampsia defined as a new onset of hypertension and proteinuria or the new onset of hypertension plus significant end-organ dysfunction with or without proteinuria in a previously normotensive pregnant patient, generally after 20 weeks of gestation and as well as postpartum patient (August & Sibai, 2017).The World Health Organization (WHO) states that globally, preeclampsia occurs in 2% to 10% of pregnancies. The majority of reported preeclampsia cases stem from developing countries, with rates ranging from 1.8% to 16.7%, while developed countries exhibit a lower incidence at 0.4% (Khan et al, 2022). This condition constitutes 2 to 8% as pregnancy-related complications, resulting in more than 50,000 maternal fatalities and over 500,000 fetal deaths globally, emphasizing the crucial need for early identification and swift treatment to avert the associated health risks and deaths linked to preeclampsia (Bartal & Sibai, 2020).

Pregnant women face a heightened risk of nutritional deficiencies due to the increased demands of the fetus and the developing placenta on their metabolism. Nutrient deficiencies are prevalent among women of reproductive age in developing nations, encompassing both macro- and micronutrients. The association between preeclampsia and the occurrence of various micronutrient deficiencies has been documented. Consequently, inadequate nutrition during pregnancy impacts not just the mother's well-being but also for the developing fetus. To address and enhance the deficiencies in micronutrients and promote better pregnancy outcomes, supplements such as iron, folic acid, calcium, and multiple

micronutrients are used during pregnancy and prior to conception (Sher et al., 2022; Abreu et al., 2021; Tariq et al., 2021). Women classified under Advanced Maternal Age (AMA), typically over 35 years old, face a 4.5 times higher risk of experiencing preeclampsia compared to those between the ages of 25 and 29 (Tyas et al., 2019).

Calcium is a vital element that plays a key role in the mineralization of bones. Over 99% of the body's calcium is stored in bones in the form of hydroxyapatite, which not only provides structural strength to the skeleton but also acts as a reservoir for maintaining calcium levels in the blood. Calcium supplementation in pregnancy has the potential to reduce adverse gestational outcomes, in particular by decreasing the risk of developing hypertensive disorders during pregnancy, which are associated with a significant number of maternal deaths and considerable risk of preterm birth, the leading cause of early neonatal and infant mortality (Yu & Sharma, 2023). There's increasing evidence that calcium can help anticipate preeclampsia and preterm birth, especially in populations with low dietary calcium intake. Daily calcium supplementation (1.5 to 2.0 g oral elemental calcium) is recommended (WHO, 2020; Hofmeyr et al., 2018).

Folate, also known as vitamin B9, encompasses a group of water-soluble compounds crucial for DNA synthesis. It differs from folic acid (5-formyltetrahydrofolate). Folic acid is the synthetic version of folate, which converts to tetrahydrofolic acid (THF). THF participates in various methylation reactions essential for creating nitrogenous bases in DNA and RNA, and for the maturation of red blood cells (Merrell & McMurry, 2023).

Folic acid is important for early neurodevelopment and is particularly effective in preventing neural tube defects, especially spina bifida. The neural tube, which eventually forms the brain and spinal cord, completes its closure around six weeks after implantation (Ledet et al., 2024; Khalid et al., 2023; Cao et al., 2022). Multiple reports suggest that folate administration decreases the level of serum homocysteine and, therefore, reduce the risk and severity of preeclampsia (Kaldygulova et al., 2023).

While numerous journals have advocated for the connection between calcium and folic acid supplements in preventing preeclampsia, on the other hand, more recent publications argue that neither calcium nor folic acid significantly influences the prevention of preeclampsia. This study aims to summarize the folic acid and calcium supplementation outcome to prevent preeclampsia in pregnant woman.

2. Research Methods

The PRISMA protocol was used in this systematic review as its guiding framework (Page et al., 2021). The protocol was officially registered in advance. This systematic review examines the effects of supplementing with either calcium or folic acid, in varying doses (both high and low), compared to a placebo or no therapy. The study included women of reproductive age (15 to 49 years), either in the pre-pregnancy phase or during pregnancy, and focused on the reported outcomes related to preeclampsia.

The study included in this systematic review are the five years randomised controlled trials/ RCTs (2018 to 2023) of calcium and folic acid supplementation, which in the English language in search engine. The selected studies exclusively involve women of reproductive ages, centering on the impact of calcium or folic acid supplementation in comparison to placebo or alternative treatments. The interventions are administered either before conception or during pregnancy, with a specific focus on documenting the incidence of preeclampsia as the primary outcome.

The exclusion criteria applied in this review encompass non-human subjects, study designs other than clinical trials, single-arm studies wherein all enrolled participants receive identical treatments, outcomes that are not pertinent to the research objectives, and studies with unavailable full-text documentation. The primary focus of these trials is on the outcome of preeclampsia. The research was conducted through systematic searches on PubMed, Cochrane Central Register of Controlled Trials

(CENTRAL), ClinicalTrials.gov, and SpringerLink. The selected paper underwent assessment utilizing the Jadad Scale. Searches used the terms '(calcium OR folic acid) AND (eclampsia OR preeclampsia OR preeclampsia OR hypertension) AND pregnancy' with RCT restriction journal. Data were extracted by a reviewers (CA) in duplicate using the Rayyan.ai for intervention reviews. Data extracted comprised characteristic of Title, Author and Year, Type of Study, Subject Participant, Age Range, Nations, Total sample, Baseline risk of Preeclampsia (low/ high), Bacseline Calcium intake, Calcium Dose, Baseline Folic Acid intake, Folic Acid dose, added intervention, outcome / Endpoint, Timing Supplementation, Comparison (Group vs Control), Result Conclusion, and Jadad Scale. Included trials were evaluated using the Jadad Scoring or the Oxford quality scoring system.

Jadad score checklist comprised of five items of randomization, method of randomization, blinding, method of blinding, and dropouts and withdrawals, is used to assess quality. Overall, the risk of bias was considered low if the score were 3 or more, high if the risk was high for score below 3. Patients were not directly involved in this review, but results were interpreted in light of trial participant characteristics, so that future care can be personalised.

3. Results and Discussion

Of the 211 records identified, six RCTs (29,664 women) were eligible for the calcium or folic acid supplementation versus placebo/no therapy (Figure 1). Reasons for exclusion are non-pregnant woman, clearly irrelevant article and animal study.

Trials of calcium versus placebo/no therapy were primarily from multiple countries. Two trials involving sites in Argentina, Australia, Canada, Jamaica, and the UK. One Trial conducted in multiple low-income country such as South Africa, Zimbabwe, and Argentina. Two trials included specifically in China and one in China–USA. Four studies involved women aged 18 and above, two study enrolled women who specifically aged 20 and above and one study included woman of childbearing age. Four out of six trials included women identified as being at a high risk of developing preeclampsia.

The primary endpoint is preeclampsia, characterized by gestational hypertension and the presence of proteinuria after 20 weeks' gestation. Secondary outcome encompassed severe preeclampsia, preterm delivery and adverse outcome for both fetus and neonate. Additional component of the intervention were iron and multiple micronutrients. All trials defined preeclampsia by new-onset hypertension and proteinuria at $\geq$ 20 weeks of gestation (Table 1).

Theoretically, insufficient calcium intake has been implicated in the elevation of blood pressure, potentially by stimulating parathyroid hormone or renin release, resulting in increased intracellular calcium levels in vascular smooth muscle and subsequent vasoconstriction. Calcium supplementation may act by reducing parathyroid release and intracellular calcium, thereby decreasing smooth muscle contractility. This mechanism could also extend to modulating uterine smooth muscle contractility, potentially offering a preventive measure against preterm labor and delivery. Additionally, calcium supplementation may indirectly influence smooth muscle function by raising magnesium levels. Recent findings indicate that calcium supplementation affects uteroplacental blood flow, as evidenced by a reduction in the resistance index in uterine and umbilical arteries. When administered during the second half of pregnancy, supplementation seems to directly lower blood pressure rather than solely preventing the endothelial damage associated with preeclampsia.

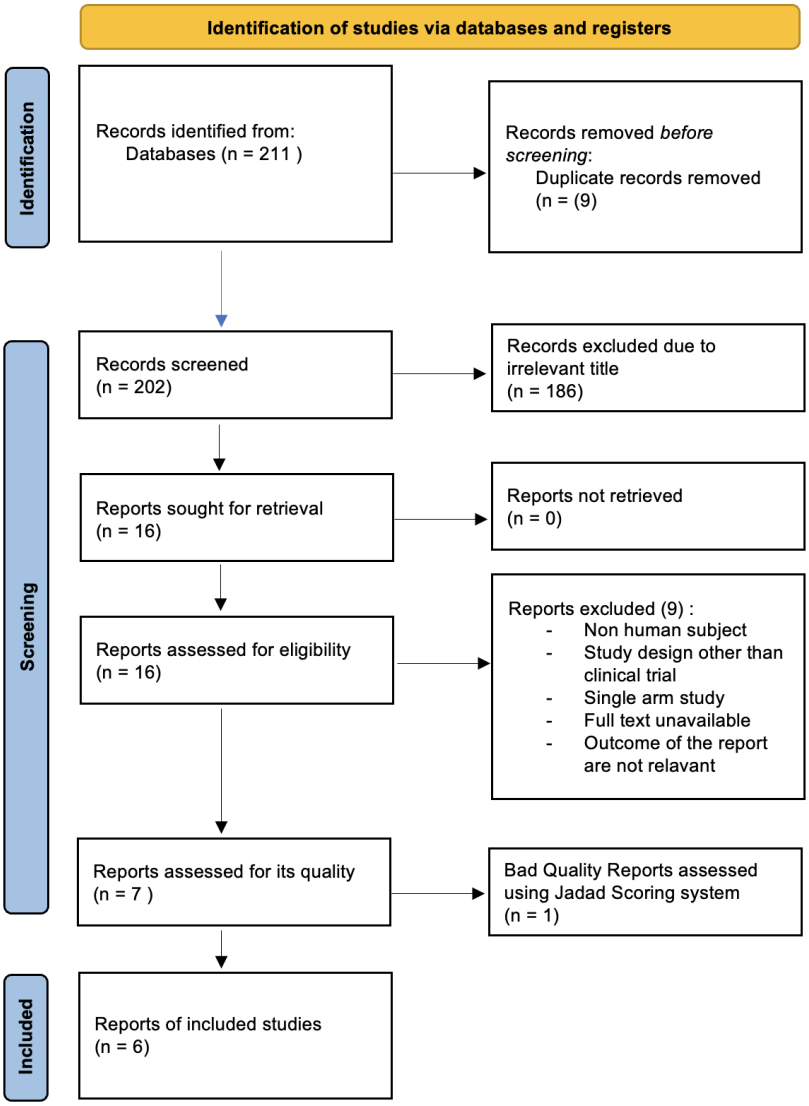

Figure 1. PRISMA-Based Workflow and Selection of Eligible Studies Included in This Systematic Review

Calcium supplementation emerges as an attractive intervention for mitigating the risk of preeclampsia in women due to its ready availability and presumed safety for both the woman and her child. At the other hand, folic acid has been known to be a very important substance in forming the neural tube (CDC, 2023). Nowadays, recent paper found that this supplement also prevents pregnancy-related complications other than neural tube defects (Greenberg et al., 2011). Folic acid supplementation has been found to lowering risk of chance to preeclampsia. This might be due to folic acid's potential to impact hyperhomocysteinemia levels, which are believed to harm the vascular endothelium in the growing placenta. Folic acid is involved in various metabolic pathways, including one-carbon metabolism, which plays a crucial role in DNA synthesis, repair, and methylation. Insufficient folate levels have been associated with endothelial dysfunction and impaired nitric oxide synthesis, which are key features of preeclampsia. By promoting endothelial function and nitric oxide production, folic acid may help mitigate the vascular dysfunction observed in preeclampsia. Moreover, folic acid supplementation has been shown to lower blood homocysteine levels. Elevated homocysteine levels have been implicated in endothelial damage, oxidative stress, and inflammation, all of which contribute to the pathophysiology of preeclampsia. Therefore, by reducing homocysteine levels, folic acid may help mitigate these deleterious effects on the vascular system and placenta. Furthermore, folic acid may

impact placental development and function, thereby influencing the risk of preeclampsia. Adequate folate levels are essential for proper placental angiogenesis and vascular remodelling. Folic acid deficiency has been associated with abnormal placental development and function, which may predispose to preeclampsia. Therefore, folic acid supplementation may help support healthy placental development and reduce the risk of preeclampsia (Kaldygulova et al., 2023; Menezo et al., 2022; De Ocampo et al., 2018).

A study conducted by Hofmeyr et al. demonstrated that calcium supplementation has a protective effect compared to placebo (Hofmeyr et al., 2018). However, the result was only borderline significant. The prevalence of Preeclampsia or pregnancy loss, or both, was 33% in the calcium group and 41% in the placebo group (risk ratio/RR 0.82 [95% confidence interval/CI 0.66–1.00]; p=0.050). No significant side effects were observed in this study.

The study participant were mothers previously diagnosed with either preeclampsia or eclampsia. According to the WHO, the minimum daily calcium requirement for pregnant women is 1200 mg, whereas non-pregnant individuals need 1000 mg per day (Willemse et al., 2020). The pregnant subjects in this study were from low-income countries, primarily in Africa, where calcium intake is often below recommended levels (Bourassa et al., 2022; Cormick et al., 2020). For populations with low calcium intake, the WHO recommends a daily dose of 1.5 to 2 grams of calcium starting from the 20th week of pregnancy. The standard recommended calcium intake requirements for these mothers were not met, which may have contributed to the borderline significance of the results. Disadvantages of this journal include a sample size that was too small, likely affecting the statistical significance of the results.

The 2022 study by Corsi et al. found that the rate of preeclampsia was significantly higher in the folic acid group compared to the placebo group in crude analyses (17.2% versus 9.9%; relative risk 1.75 [95% CI 1.06-2.88], p = .029) (Corsi et al., 2022). The folic acid dosage administered was 4.0 to 5.1 mg. However, after multivariable analyses, this effect was attenuated and no longer statistically significant (RR 1.58 [95% CI 0.95-2.63], p = .079). This is thought to be due to a different subject is used from the previous one, namely twin pregnancies, which are considered high-risk due to their nature.

The augmented maternal blood volume required to sustain twin gestations imposes additional hemodynamic demands on the maternal cardiovascular system, thereby predisposing to elevated blood pressure levels. Additionally, twin pregnancies frequently exhibit a heightened incidence of placental anomalies, including insufficient placental development or placental insufficiency, which are known contributors to the pathogenesis of preeclampsia. Moreover, women carrying twins exhibit a higher prevalence of predisposing factors for preeclampsia, such as advanced maternal age or pre-existing hypertension, thereby compounding their susceptibility to this hypertensive disorder of pregnancy. Consequently, owing to the culmination of these multifactorial elements, twin pregnancies are categorized as high-risk entities for the onset of preeclampsia.

Table 1. Selected Study of Included trial of Folic Acid- and Calcium-preeclampsia

No	Title	Author, Year	Types of Study	Study Subject	Age Range	Country / Location	Number of samples	Baseline Preeclampsia Risk : High/ Low	Baseline calcium intake	Calcium dose	Baseline folic acid intake	Folic Acid dose	Aded Intervention	Outcome/Endpoint	Timing suplementation	Comparator	Comparison (group vs control)	Result	Conclusion
1	Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial.	Hofmeyr GJ; 2019	A multicentre, double-blind, randomised, placebo-controlled trial.	Participants with previous pre-eclampsia and eclampsia	N/A	South Africa, Zimbabwe, and Argentina. Low-income countries.	651	High: previously had pre-eclampsia / eclampsia	500 mg calcium or placebo daily	500 mg	N/A	N/A	N/A	Primary outcome: **pre-eclampsia**, defined as gestational hypertension and proteinuria.	< 20 weeks (enrolment prepregnancy until 20 weeks' gestation), All participants received unblinded calcium 1·5 g daily after 20 weeks' gestation.	placebo	calcium vs placebo	Pre-eclampsia occurred in 69 (23%) of 296 participants in the calcium group versus 82 (29%) of 283 participants in the placebo group with pregnancies beyond 20 weeks' gestation	Protective, but not significant
2	Effect of high-dose folic acid supplementation on the prevention of preeclampsia in twin pregnancy.	Corsi DJ, 2022	A multicentre, randomised, placebo-controlled trial.	Twin pregnancy	18 years-old and above	Argentina, Australia, Canada, Jamaica, and the UK	428	High : Twins Pregnancy	N/A	N/A	high-dose folic acid (4.0-5.1 mg) or placebo		N/A	Primary outcome was preeclampsia, presenting as hypertension after 20 weeks' gestation with significant proteinuria. Secondary outcomes included severe preeclampsia, preterm birth, and adverse fetal and neonatal outcomes.	8 and 16 completed weeks' gestation	placebo	Folic Acid vs Placebo	rate of preeclampsia was significantly higher in the folic acid group compared to the placebo group	Folic acid and Preeclampsia not significantly related
3	The effect of folic acid throughout pregnancy among pregnant women at high risk of pre-eclampsia: A randomized clinical trial.	Zheng L, 2020	Randomized Clinical Trial	women who had pre-eclampsia or eclampsia in their last pregnancy and had a pregnancy plan	18 years-old and above	China	1576	High : previously had preeclampsia	N/A	N/A	**Low dose (LD)**(n = 788)--> 0.4 mg of FA daily from the first 3 months of pregnancy until the entire pregnancy, and the **high dose** (HD) group (n = 788) received 4 mg of FA per day.		N/A	Incidence of pre-eclampsia was reduced in the HD group with compliance >50%	entire pregnancy	Low dose vs High dose	Low Folic Acid vs High Folic Acid	incidence of pre-eclampsia was reduced in the HD group with compliance >50%	High dose Folic Acid is preventive
4	Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial	wen, 2018	Randomised, phase III, double blinded international, multicentre clinical trial	pregnant women with at least one high risk factor for pre-eclampsia	N/A	70 obstetrical centres in five countries (Argentina, Australia, Canada, Jamaica, and UK	2301	High : have risk factor for preeclampsia	N/A	N/A	(≤1.1 mg)	4 mg	N/A	N/A	N/A	Placebo	High dose Folic Acid - placebo	Supplementation with 4.0 mg/day folic acid beyond the first trimester does not prevent pre-eclampsia in women at high risk for this condition.	High doses of folic acid did not demonstrate any significantly improved outcomes.
5	Effects of prenatal micronutrients supplementation timing on pregnancy-induced hypertension: Secondary analysis of a double-blind randomized controlled trial.	Liu Y, 2021	Double-blind randomized controlled trial	nulliparous, were not morethan 20 gestational weeks confirmed via last menstrual period,	20 years old and above	China	18,775	Low	N/A	N/A	N/A	N/A	multiple micronutrients [MMN], iron-folic acid [IFA] and folic acid [FA] alone	PIH incidence	20 Weeks and above	multiple micronutrients [MMN], AND iron-folic acid [IFA]	multiple micronutrients [MMN], iron-folic acid [IFA] and folic acid [FA] alone	daily supplementation with MMN during first trimesterof pregnancy could protect against PIH. However, there was no asso-ciation between timing of supplementation with either IFA or FA andprotection against PIH	MMN , IFA, FA. FA alone paling less protecting
6	Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: A randomized clinical trial.	Chen S; 2019	Double-blind randomized controlled trial	at least one blood pressure measurement before and one after 20 weeks. one high BP measurement prior to 20 weeks was excluded	20 years old and above	Beijing | Atlanta | China | GA | USA	5933	Low	N/A	N/A	N/A	N/A	multiple micronutrients [MMN], iron-folic acid [IFA] and folic acid [FA] alone	PIH incidence	N/A	multiple micronutrients [MMN], AND iron-folic acid [IFA]	multiple micronutrients [MMN], iron-folic acid [IFA] and folic acid [FA] alone	among younger women (20e24 years of age), those who took IFA (OR ¼ 0.81, 95% CI 0.67e0.96) and MMN (OR ¼ 0.83, 95% CI 0.70e0.99) had a significantly reduced odds of PIH compared with folic acid alone	MMN , IFA, FA. FA alone paling less protecting

In the case of twin pregnancies, the efficacy of folic acid supplementation is effectively halved, even with a high dose. This reduction in individual dose potency diminishes the ability to detect significant statistical outcomes in secondary analyses. Additionally, twin pregnancies are more frequently associated with non-proteinuric preeclampsia, which may confound the results. However, these limitations could be mitigated using a randomized study design.

This study is further supported by the findings of Wen et al. which concluded that high-dose folic acid does not prevent preeclampsia in women with at least one high-risk factor for the condition (Wen et al., 2018). In their study, preeclampsia occurred in 169 out of 1144 women (14.8%) in the folic acid group and 156 out of 1157 women (13.5%) in the placebo group (relative risk 1.10, 95% confidence interval 0.90 to 1.34; P=0.37). Additionally, there was no significant difference between the groups regarding any other adverse maternal or neonatal outcomes.

Supplementation was carried out only in the first trimester. Similar to the previous study, this research utilized data from the same country samples, albeit in different years. The countries included were Canada, Argentina, Australia, Jamaica, and the UK. Thus, there were three developed countries (Canada, Australia, and the United Kingdom) and two developing countries (Argentina and Jamaica). Nutritional needs are generally better met in developed countries compared to developing ones.

A key difference is that the study by Corsi et al. focused on temporary twin pregnancies, whereas Wen et al.'s study involved a combination of high-risk factors (Corsi et al, 2022; Wen et al., 2018). Both studies, however, compared outcomes with those of placebo groups. In a study published by Zheng et al., conducted in China, the comparative efficacy of low and high dose folic acid supplementation was investigated (Zheng et al., 2020). The findings suggest that elevated folic acid dosages exhibit prophylactic effects against the onset of preeclampsia among pregnant individuals with prior preeclampsia experiences.

In the low-dose group (LD) consisting of 788 participants, individuals were administered 0.4 mg of folic acid daily from the initial three months of pregnancy throughout the entire gestation period. Conversely, the high-dose (HD) group, also comprising 788 participants, received 4 mg of folic acid per day. It was observed that the incidence of Preeclampsia was diminished in the HD group among those with a compliance rate exceeding 50%. Disparities in these findings are anticipated to arise due to variations in dietary habits among populations. China, for instance, represents a demographic characterized by lower folate intake compared to countries such as Australia, the UK, and Canada. Consequently, the observed distinctions are likely to be substantial (Colapinto et al., 2011; De Steur et al., 2010).

A limitation of the study was the recruitment of a relatively small number of disabled patients to ensure better compliance with treatment and imaging follow-up, potentially restricting the generalizability of the findings. Furthermore, throughout the course of pregnancy, the study did not impose limitations on the use of other medications by pregnant women for the treatment and management of preeclampsia. Given that the recruited participants all had a history of preeclampsia, they exhibited a high incidence of morbidity, including severe preeclampsia. The potential interaction of folic acid with other therapeutic drugs, as well as its role in the treatment of preeclampsia, remains unknown and warrants further investigation.

Both of the study by Liu et al. and Chen et al. are double blind randomized studies which has low risk of preeclampsia, different from the other four studies (Liu et al., 2021; Chen et al., 2019). The outcome counted as pregnancy-induced hypertension (PIH) incidence. Both studies compared the folic acid supplementation only to multiple micronutrients and Iron folic acid. The result come out as the supplementation folic acid only is less protecting than other two.

Here, it is suggested that the significance is not pronounced and that multivariate analysis may be preferable due to the population comprising predominantly healthy pregnant women. It is crucial to note that supplements alone do not suffice to maintain the health of pregnant women and their fetuses. Therefore, when evaluating their efficacy either independently or in conjunction with other vitamins, it becomes evident that multiple micronutrients in a healthy maternal diet yield more comprehensive data.

For calcium supplementation study, there is a lack of current data, with only one RCT meeting the selection criteria. Therefore, the risk of bias can be considered fairly high. The variability in risk factors across different studies results in a heterogeneous dataset, leading to different outcomes despite the use of folic acid interventions in high-risk pregnancies.

The major limitation of this study was the initial differences between the calcium and folic acid supplementation. Secondly, there's a multidrug supplementation RCT contained in this study, which might introduce to a potential bias. Third, each study has diverse risk factor which may contribute to potential bias. Finally, RCTs used in this study was 5 latest year which will be more precise if it use all the time study.

4. Conclusion

Both Calcium and Folic acid supplementation in adequate dose equally needed to prevent preeclampsia. Further research is necessary to evaluate the effectiveness of therapy in equivalent subject groups. There is currently limited information on the impact of health supplements on high-risk pregnancies, including the effects of calcium supplementation. Studies should further investigate the relationship between calcium supplementation and the prevention of preeclampsia.

Future research may explore the efficacy of different dosages of calcium supplements, comparing low-dose versus high-dose regimens and their impact beyond placebo comparisons. Subjects should be categorized based on risk levels, from low to high risk. Specifically, comparisons should focus on high-risk groups, such as those with a history of preeclampsia, multiple gestations, chronic hypertension, advanced maternal age, and other relevant risk factors.

Reference

Abreu, A. M., Young, R. R., Buchanan, A., Lofgren, I. E., Okronipa, H. E., Lartey, A., ... & Oaks, B. M. (2021). Maternal Blood Pressure in Relation to Prenatal Lipid-Based Nutrient Supplementation and Adverse Birth Outcomes in a Ghanaian Cohort: A Randomized Controlled Trial and Cohort Analysis. The Journal of nutrition, 151(6), 1637-1645.

August, P., & Sibai, B. M. (2017). Preeclampsia: Clinical features and diagnosis. Post TW, UpToDate. Waltham, MA: UpToDate.

Bartal, M. F., & Sibai, B. M. (2020). Preeclampsia. Protocols for High-Risk Pregnancies: An Evidence-Based Approach, 517-528.

Bourassa, M. W., Abrams, S. A., Belizán, J. M., Boy, E., Cormick, G., Quijano, C. D., ... & Weaver, C. M. (2022). Interventions to improve calcium intake through foods in populations with low intake. Annals of the New York Academy of Sciences, 1511(1), 40-58. https://onlinelibrary.wiley.com/doi/full/10.1111/nyas.14743

Cao, R., Xie, J., & Zhang, L. (2022). Abnormal methylation caused by folic acid deficiency in neural tube defects. Open Life Sciences, 17(1), 1679-1688.

Chen, S., Li, N., Mei, Z., Ye, R., Li, Z., Liu, J., & Serdula, M. K. (2019). Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: A randomized clinical trial. Clinical nutrition, 38(1), 146-151.

Colapinto, C. K., O'Connor, D. L., & Tremblay, M. S. (2011). Folate status of the population in the

Canadian Health Measures Survey. Cmaj, 183(2), E100-E106. https://www.cmaj.ca/content/183/2/E100

Corsi, D. J., Gaudet, L. M., El-Chaar, D., White, R. R., Rybak, N., Harvey, A., ... & Walker, M. (2022). Effect of high-dose folic acid supplementation on the prevention of preeclampsia in twin pregnancy. The Journal of Maternal-Fetal & Neonatal Medicine, 35(3), 503-508. https://pubmed.ncbi.nlm.nih.gov/32067533/

De Ocampo, M. P., Araneta, M. R. G., Macera, C. A., Alcaraz, J. E., Moore, T. R., & Chambers, C. D. (2018). Folic acid supplement use and the risk of gestational hypertension and preeclampsia. Women and Birth, 31(2), e77-e83.

De Steur, H., Gellynck, X., Storozhenko, S., Liqun, G., Lambert, W., Van Der Straeten, D., & Viaene, J. (2010). Health impact in China of folate-biofortified rice. Nature Biotechnology, 28(6), 554-556.

Center for Disease Control and Prevention (CDC). (2024). About folic acid. Available from https://www.cdc.gov/folic-acid/about/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/folicacid/about.html

Cormick, G., Betrán, A. P., Metz, F., Palacios, C., Beltrán-Velazquez, F., Garcia-Casal, M. D. L. N., ... & Belizán, J. M. (2020). Regulatory and policy-related aspects of calcium fortification of foods. Implications for implementing national strategies of calcium fortification. Nutrients, 12(4), 1022.

Greenberg, J. A., Bell, S. J., Guan, Y., & Yu, Y. H. (2011). Folic acid supplementation and pregnancy: more than just neural tube defect prevention. Reviews in obstetrics and gynecology, 4(2), 52.

Hofmeyr, G. J., Lawrie, T. A., Atallah, Á. N., & Torloni, M. R. (2018). Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane database of systematic reviews, (10).

Ledet III, L. F., Plaisance, C. J., Daniel, C. P., Wagner, M. J., Alvarez, I., Burroughs, C. R., ... & Varrassi, G. (2024). Spina Bifida Prevention: A Narrative Review of Folic Acid Supplements for Childbearing Age Women. Cureus, 16(1).

Kaldygulova, L., Ukybassova, T., Aimagambetova, G., Gaiday, A., & Tussupkaliyev, A. (2023). Biological role of folic acid in pregnancy and possible therapeutic application for the prevention of preeclampsia. Biomedicines, 11(2), 272.

Khalid, S. I., Thomson, K., Hunter, B. M., Garcia, R. M., Bowman, R., & Lam, S. (2023). The impact of voluntary folate fortification of corn masa flour on US pregnancies complicated by neural tube defects. Child's Nervous System, 39(7), 1813-1819.

Khan, B., Allah Yar, R., Khakwani, A. K., Karim, S., & Arslan Ali, H. (2022). Preeclampsia Incidence and its maternal and neonatal outcomes with Associated Risk factors. Cureus, 14: 11e31143.

Liu, Y., Li, N., Mei, Z., Li, Z., Ye, R., Zhang, L., ... & Serdula, M. K. (2021). Effects of prenatal micronutrients supplementation timing on pregnancy-induced hypertension: Secondary analysis of a double-blind randomized controlled trial. Maternal & Child Nutrition, 17(3), e13157.

Menezo, Y., Elder, K., Clement, A., & Clement, P. (2022). Folic acid, folinic acid, 5 methyl tetrahydrofolate supplementation for mutations that affect epigenesis through the folate and one-carbon cycles. Biomolecules, 12(2), 197.

Merrell, B. J., & McMurry, J. P. (2023). Folic acid. Encycl Toxicol Fourth Ed Vol 1-9. https://www.ncbi.nlm.nih.gov/books/NBK554487/

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj, 372.

Sher, N., Mubaraki, M. A., Zafar, H., Nazli, R., Zafar, M., Fatima, S., & Fozia, F. (2022). Effect of lipid-based multiple micronutrients supplementation in underweight primigravida pre-eclamptic women on maternal and pregnancy outcomes: randomized clinical trial. Medicina, 58(12), 1772.

Tariq, K., Fatima, S., Nazli, R., Habib, S. H., & Shah, M. (2021). Impact of Lipid-Based Nutritional Supplementation in Primi-Gravidas and Its Effect on Maternal, Birth and Infant Outcomes: a randomized controlled trial. Khyber Medical University Journal, 13(4), 187-92.

Tyas, B. D., Lestari, P., & Akbar, M. I. A. (2019). Maternal perinatal outcomes related to advanced maternal age in preeclampsia pregnant women. Journal of family & reproductive health, 13(4), 191.

Wen, S. W., White, R. R., Rybak, N., Gaudet, L. M., Robson, S., Hague, W., ... & Walker, M. C. (2018). Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. bmj, 362. https://pubmed.ncbi.nlm.nih.gov/30209050/

Willemse, J. P., Meertens, L. J., Scheepers, H. C., Achten, N. M., Eussen, S. J., van Dongen, M. C., & Smits, L. J. (2020). Calcium intake from diet and supplement use during early pregnancy: The Expect study I. European journal of nutrition, 59, 167-174.

World Health Organization (WHO. (2020). Calcium supplementation before pregnancy for the prevention of pre-eclampsia and its complications. WHO, Geneva, 1-38. https://apps.who.int/iris/bitstream/handle/10665/331787/9789240003118-eng.pdf?ua=1

Yu, E., & Sharma, S. (2018). Physiology, calcium. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482128/

Zheng, L., Huang, J., Kong, H., Wang, F., Su, Y., & Xin, H. (2020). The effect of folic acid throughout pregnancy among pregnant women at high risk of pre-eclampsia: A randomized clinical trial. Pregnancy hypertension, 19, 253-258.