

EFFECTIVENESS AND SAFETY OF ORAL CALCIUM SUPPLEMENTATION DURING PREGNANCY FOR PREVENTION OF PREECLAMPSIA: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: Calcium supplementation is a promising intervention in preventing preeclampsia, a major global health concern. Clinical trials and meta-analyses show its protective effect in reducing hypertensive complications. However, the exact effectiveness and safety profile require further evaluation to guide clinical practice. This systematic review aims to enhance evidence-based decision-making in maternal health.

Methods: This systematic review adhered to PRISMA 2020 guidelines and focused exclusively on full-text articles published in English between 2015 and 2025. Editorials and review articles without a DOI were excluded to preserve the integrity of high-quality sources. A literature review was conducted utilizing reputable databases, including ScienceDirect, PubMed, and SagePub, to identify relevant studies.

Result: The initial database search yielded over 30 relevant publications on the topic. Following a comprehensive three-stage screening process, eight studies met the specified inclusion criteria and were selected for in-depth analysis. A comprehensive critical evaluation was conducted for each study, enabling an in-depth analysis of the effectiveness and safety of oral calcium supplementation during pregnancy for the prevention of preeclampsia. This systematic approach ensured that the analysis was grounded in high-quality evidence, aligned with the study's objectives, and capable of providing significant insights into this complex association.

Conclusion: Calcium supplementation is an effective measure to reduce preeclampsia risk, especially in those with insufficient dietary intake. The WHO recommends 1.5-2 grams daily, enhancing vascular stability and hypertension. However, individual reactions may vary, necessitating personalized strategies. Future studies should optimize dosage recommendations.

Keyword: Calcium supplementation, effectiveness, preeclampsia, pregnancy, safety.

INTRODUCTION

Preeclampsia remains a significant global health concern, contributing to maternal and perinatal morbidity and mortality, particularly in low- and middle-income countries (LMICs). Characterized by hypertension and proteinuria after 20 weeks of gestation, preeclampsia is associated with severe complications, including eclampsia, placental abruption, and fetal growth restriction.^{1,2} Despite advances in obstetric care, effective preventive strategies remain a priority to mitigate adverse outcomes. Among various interventions, oral calcium supplementation has been recognized as a promising, cost-effective approach, particularly in populations with low dietary calcium intake.³ The physiological role of calcium in vascular function, endothelial stability, and blood pressure regulation underscores its potential in preventing hypertensive disorders of pregnancy.⁴ However, the precise effectiveness and safety profile of calcium supplementation in reducing preeclampsia risk require further systematic evaluation to guide clinical practice.

Multiple clinical trials and meta-analyses have investigated the relationship between calcium intake and the incidence of preeclampsia, yielding supportive evidence for its protective effect.⁵ The World Health Organization (WHO) recommends calcium supplementation (1.5–2 g/day) for pregnant women in settings with insufficient dietary calcium intake to reduce the risk of hypertensive complications.³ Proposed mechanisms include calcium-mediated vasodilation, decreased parathyroid hormone levels, and modulation of renin-angiotensin system activity, all contributing to maintaining vascular homeostasis.⁶ Nevertheless, variations in study designs, population characteristics, and supplementation regimens have led to inconsistent findings, necessitating a rigorous, evidence-based assessment of available literature. Additionally, concerns regarding potential adverse effects, including kidney stone formation and altered fetal mineralization, warrant careful consideration to ensure maternal and fetal safety.⁷

This systematic review aims to comprehensively evaluate the effectiveness and safety of oral calcium supplementation during pregnancy in preventing preeclampsia. By synthesizing data from randomized controlled trials (RCTs), cohort studies, and meta-analyses published in the last decade, this review seeks to clarify the extent of calcium's protective role and its implications for clinical guidelines. Ultimately, this review endeavors to enhance evidence-based decision-making in maternal health, promoting safer and more effective interventions for preeclampsia prevention.

METHODS

PROTOCOL

This systematic review was meticulously conducted in strict adherence to the PRISMA 2020 guidelines, ensuring methodological precision and the highest research quality standards. By following these rigorous protocols, the study enhances transparency, reproducibility, and scientific integrity. Each phase of the review—including exhaustive literature searches, precise data extraction, and systematic synthesis of findings—was executed with meticulous attention to detail to minimize bias and uphold analytical rigor. This robust methodological framework not only bolsters the study's credibility but also significantly contributes to the advancement of evidence-based research in maternal health.

CRITERIA FOR ELIGIBILITY

This study aims to systematically evaluate the effectiveness and safety of oral calcium supplementation during pregnancy for the prevention of preeclampsia by reviewing and synthesizing data from a wide range of research studies. By identifying key patterns, emerging trends, and gaps in the existing literature, this review seeks to generate meaningful insights that can inform the development of more effective preeclampsia prevention strategies. The ultimate objective is to enhance the understanding of calcium supplementation's role in reducing preeclampsia risk, providing a strong evidence base to support improved patient care and clinical decision-making.

To ensure methodological rigor, this study implemented strict inclusion and exclusion criteria. Only peer-reviewed articles published in English between 2015 and 2025 were considered, with each study's validity confirmed through DOI verification. Non-research materials, including reviews, editorials, and duplicate entries, were excluded to maintain a focused and high-quality dataset. This meticulous selection process enhances the reliability of the analysis, ensuring that findings are derived from credible and relevant sources, ultimately strengthening the study's contribution to evidence-based practice.

By adopting a systematic and comprehensive approach, this study ensures that its conclusions are grounded in robust empirical evidence. The anticipated findings aim to deepen the current understanding of calcium supplementation's effectiveness and safety in preventing preeclampsia, offering a foundation for refining preventive strategies and optimizing patient outcomes. Ultimately, this research aspires to contribute to the advancement of maternal health by promoting evidence-based interventions, improving clinical practices, and enhancing the quality of care for pregnant individuals at risk of preeclampsia.

SEARCH STRATEGY

A comprehensive and systematic search strategy was employed to identify relevant studies for this review, utilizing key terms such as "oral calcium supplementation," "pregnancy," "prevention," and "preeclampsia." To ensure a thorough and well-rounded analysis, the search was conducted across three major academic databases—PubMed, SagePub, and ScienceDirect. This rigorous approach facilitated the inclusion of diverse, high-quality sources, strengthening the evidence base for this study. By emphasizing methodological precision and scholarly depth, this strategy enhances the reliability and validity of the review’s findings, ultimately contributing to a more comprehensive understanding of calcium supplementation in preventing preeclampsia.

Table 1. Search Strategy

Database	Search Strategy	Hits
Pubmed	<i>("oral calcium supplementation " AND "pregnancy" AND "prevention" AND "preeclampsia")</i>	1
Science Direct	<i>("oral calcium supplementation " AND "pregnancy" AND "prevention" AND "preeclampsia")</i>	32
Sagepub	<i>("oral calcium supplementation " AND "pregnancy" AND "prevention" AND "preeclampsia")</i>	4

DATA RETRIEVAL

The authors conducted a meticulous preliminary screening of each article, systematically evaluating titles and abstracts to determine their relevance before proceeding with an in-depth analysis. Only studies that aligned with the research objectives and met the predefined inclusion criteria were selected for further review. This structured and methodical approach facilitated the identification of key themes and significant patterns within the literature, ensuring that the analysis remained focused on studies directly relevant to the research question.

To ensure consistency and enhance comparability, only full-text articles published in English were included in the final dataset. A rigorous screening process was implemented to verify that all selected studies adhered to the established inclusion criteria and effectively addressed the study’s objectives. Articles that did not meet these standards were excluded, thereby maintaining a high-quality dataset that was both precise and aligned with the scope of the research. This careful selection process strengthened the reliability of the review while minimizing potential biases.

The evaluation process encompassed a thorough examination of multiple factors, including study titles, authorship, publication dates, research locations, and methodologies. This comprehensive review ensured the inclusion of only the most relevant and methodologically sound studies. By employing a systematic and rigorous selection strategy, the authors enhanced the credibility and robustness of the findings, providing a solid foundation for drawing reliable and actionable conclusions that contribute meaningfully to the field of maternal health and preeclampsia prevention.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors employed a meticulous initial screening process, systematically reviewing the titles and abstracts of each article to identify studies that met the predefined relevance and quality criteria. Only those that closely aligned with the research objectives and demonstrated methodological rigor were selected for comprehensive, in-depth analysis. This structured approach ensured the inclusion of high-quality studies that provided valuable insights into the review. By refining the selection process, the authors curated a dataset comprising contextually significant and scientifically robust studies. This strategy not only enhanced the precision and focus of the analysis but also strengthened the overall validity, reliability, and scholarly rigor of the systematic review.

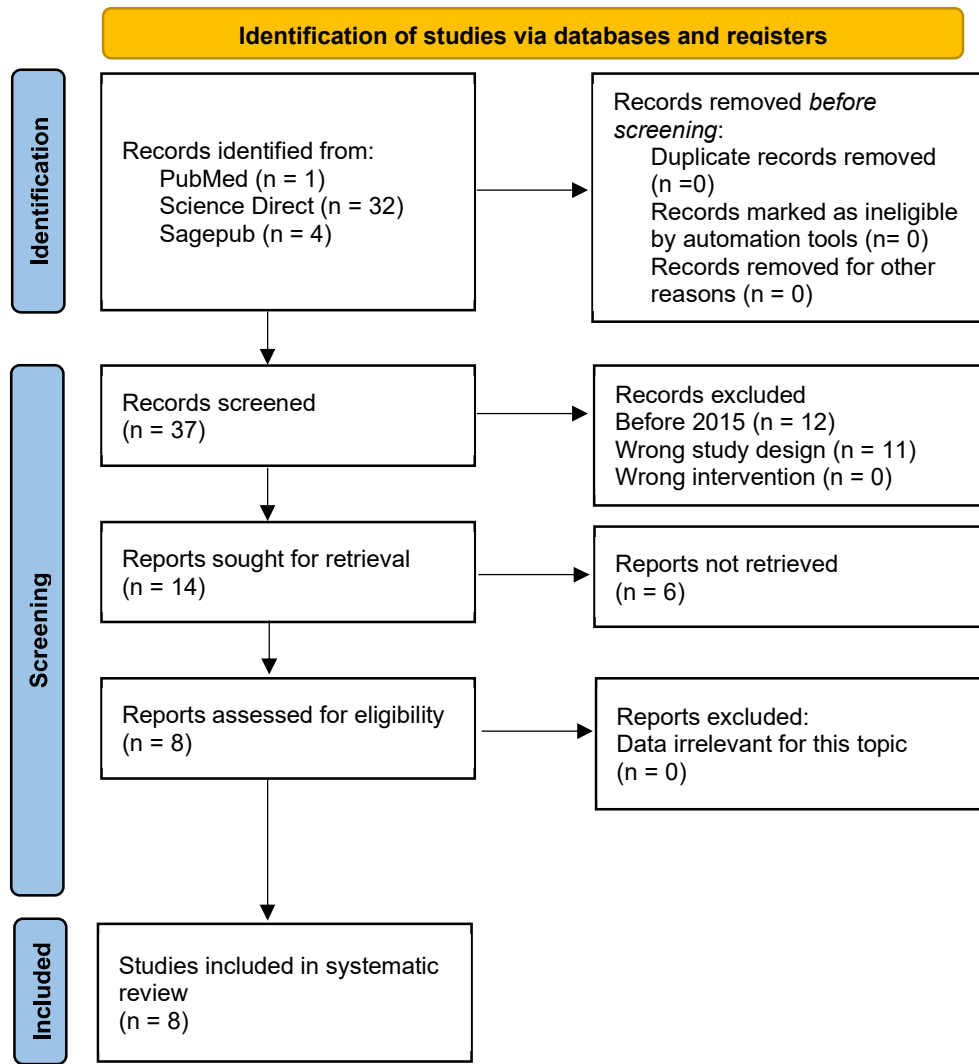


Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(Hofme yr et al., 2018)	(Prasoj o et al., 2020)	(Gome s et al., 2022)	(Pokhr el et al., 2022)	(Woo et al., 2022)	(Rocha et al., 2023)	(Dwar kanat h et al., 2024)	(Ushida et al., 2025)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	No	Yes	No	No	No	No	Yes	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	Yes	No	No	Yes	Yes	Yes	No

4. Bias related to administration of intervention/exposure

Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?

Yes. Yes. No. No. Yes. Yes. Yes. No.

5. Bias related to assessment, detection, and measurement of the outcome

Were there multiple measurements of the outcome, both pre and post the intervention/exposure?
 Were the outcomes of participants included in any comparisons measured in the same way?
 Were outcomes measured in a reliable way?

No No No No No No No No
 No Yes No No No No Yes No
 Yes Yes No No Yes Yes Yes No

6. Bias related to participant retention

Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?

No Yes No No No No Yes No

7. Statistical conclusion validity

Was appropriate statistical analysis used?

Yes Yes No No Yes Yes Yes No

RESULT

The investigation began with a systematic search across reputable academic databases, including ScienceDirect, PubMed, and SagePub, to identify studies relevant to the review. A rigorous three-stage screening process was employed to meticulously filter and select the most pertinent studies, ultimately refining the selection to eight papers that met the predefined inclusion criteria. These studies underwent a comprehensive analysis, with key themes and findings systematically extracted for in-depth examination. To enhance clarity and ensure a structured presentation of the results, the synthesized data is succinctly summarized in Table 3, offering a clear and organized overview of the analyzed information.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Hofmeyr et al. ³ (2018)	South Africa	Systematic Review	27 studies	Calcium supplementation during pregnancy has associated effects such as reduced hypertension, pre-eclampsia, and maternal death or severe morbidity. However, the World Health Organization recommends a

				high-dose calcium dose, which may be associated with logistical difficulties in low-income countries. Lower calcium dosages may guide pragmatic decisions.
Prasojo et al.⁸ (2020)	Indonesia	RCT	34 participants	The study found no preeclampsia in pregnant women after high calcium intervention, while 17.7% of patients in the low-dose calcium intervention group had preeclampsia. The McNemar test showed no difference in the incidence of preeclampsia between high-dose calcium and low-dose calcium interventions. The mean hemoglobin and hematocrit levels were similar between the two groups.
Gomes et al.⁹ (2022)	USA	Review	-	Preeclampsia, maternal morbidity, and preterm birth are associated with low calcium intake during pregnancy. Calcium supplementation is recommended to reduce these risks, but implementation is limited due to cost and logistical issues. Low-dose calcium supplementation may be sufficient.
Pokhrel et al.¹⁰ (2022)	Nepal	Review	-	The WHO's recommendation for calcium supplementation in Nepal is based on weak evidence and inconsistent trial findings. The review found low certainty of benefit, but high certainty of undesirable effects. The estimated reduction in maternal deaths is low, but implementation costs are high. A better approach is to identify high-risk pregnant women.
Woo et al.¹¹ (2022)	Canada	Systematic Review	30 studies	Calcium supplementation, whether at a low or high dose, effectively prevents preeclampsia in women with low calcium intake. The effectiveness of calcium supplementation remains consistent regardless of baseline risk, vitaminD co-administration, or timing of calcium initiation. This suggests that targeted implementation is necessary

				for populations with low dietary calcium intake.
Rocha et al.¹² (2023)	United Kingdom	Meta Analysis	14 studies	Calcium supplementation is crucial for preventing preeclampsia, and a meta-analysis of individual participant data will inform guidelines and policy-makers in LMICs, assisting healthcare managers, service providers, and policy-makers in making informed decisions.
Dwarkanath et al.¹³ (2024)	India	RCT	11,000 participants	A study involving 11,000 nulliparous pregnant women found that the lower dose of preeclampsia was not inferior in both trials. The cumulative incidence of preeclampsia was 3.0% in the India trial and 3.6% in the Tanzania trial, while the percentage of preterm live births was 11.4% in both trials.
Ushida et al.¹⁴ (2025)	Japan	Review	-	Calcium supplementation is a well-documented preventive measure for Preeclampsia (PE), a common pregnancy complication. However, evidence on vitamin D's efficacy is inconsistent. Other dietary supplements, including vitamins, minerals, amino acids, and antioxidants, can also be beneficial in PE prevention.

DISCUSSION

The recommended dose of calcium for preventing preeclampsia varies depending on dietary intake and population-specific risk factors. The World Health Organization (WHO) recommends a daily calcium supplementation of 1.5 to 2 grams for pregnant women, particularly in populations with low dietary calcium intake, to reduce the risk of hypertensive disorders, including preeclampsia.^{3,9} This recommendation is supported by evidence indicating that insufficient calcium intake leads to increased parathyroid hormone levels and heightened vascular sensitivity to vasoconstrictors, both of which contribute to the pathophysiology of preeclampsia.¹⁵ Adequate calcium supplementation has been shown to mitigate these risks by improving vascular function, stabilizing endothelial health, and reducing maternal blood pressure fluctuations.^{9,16}

The effectiveness of calcium supplementation in preventing preeclampsia has been extensively studied, with numerous clinical trials and meta-analyses affirming its protective role.¹⁷ Research demonstrates that calcium supplementation significantly lowers the incidence of preeclampsia, particularly in high-risk populations with insufficient dietary calcium intake.¹⁸ The proposed mechanisms of action include calcium's ability to stabilize endothelial function, reduce vasoconstriction, and mitigate inflammatory processes, all of which contribute to the regulation of blood pressure and prevention of preeclampsia. Despite variations in study methodologies and population characteristics, the collective evidence robustly supports calcium supplementation as an effective preventive strategy.^{1,3,9}

Regarding efficacy, calcium supplementation exhibits a dose-dependent effect in preventing preeclampsia, with greater adherence to supplementation regimens correlating with improved maternal outcomes.^{5,19} Randomized controlled trials indicate that calcium supplementation reduces the relative risk of preeclampsia by up to 55% in women with low baseline calcium intake.²⁰ Additionally, evidence suggests that calcium supplementation may decrease the likelihood of severe complications associated with preeclampsia, such as eclampsia and preterm birth.^{3,11,20} However, the degree of efficacy may vary based on genetic predisposition, coexisting medical conditions, and overall maternal nutritional status, necessitating further research into personalized supplementation approaches to optimize outcomes.

The safety profile of calcium supplementation during pregnancy is well-established, with studies reporting minimal adverse effects when consumed within the recommended dosage range.^{3,21} Potential concerns, such as hypercalcemia, nephrolithiasis, and gastrointestinal discomfort, are infrequent and primarily occur with excessive intake beyond recommended levels.^{7,9} Clinical trials have not identified significant teratogenic effects or fetal complications associated with calcium supplementation, further reinforcing its safety for widespread use.^{3,22} Moreover, research indicates that calcium supplementation does not interfere with the absorption of other essential micronutrients when taken with proper spacing from iron supplementation, thereby supporting comprehensive maternal nutrition and overall pregnancy health.²³

CONCLUSION

In summary, calcium supplementation is a safe and effective measure for mitigating the risk of preeclampsia, especially in groups with insufficient dietary calcium consumption. The WHO-recommended dosage of 1.5 to 2 grams daily has shown significant preventive effects by enhancing vascular stability and mitigating hypertension consequences. Although its effectiveness is well-established, individual reactions to calcium supplementation may differ, underscoring the necessity for personalized strategies in clinical practice. The advantageous safety profile further endorses its use in prenatal care protocols, guaranteeing excellent mother and fetal health results. Future studies should concentrate on optimizing dosage recommendations according to genetic and environmental variables to enhance the advantages of calcium supplementation during pregnancy.

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