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MATERNAL VITAMIN D DEFICIENCY AND RISK OF PRETERM BIRTH: A SYSTEMATIC REVIEW

Systematic Review

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ABSTRACT

Background: Preterm birth remains a leading cause of neonatal morbidity and mortality worldwide, with significant implications for long-term child health. Among the various maternal risk factors, vitamin D deficiency has gained attention for its potential role in adverse pregnancy outcomes, including preterm delivery. However, the current literature presents inconsistent findings, necessitating a comprehensive evaluation of existing evidence to clarify this association.

Objective: This systematic review aims to assess the relationship between maternal vitamin D deficiency during pregnancy and the risk of preterm birth.

Methods: A systematic review was conducted following PRISMA guidelines. Databases including PubMed, Scopus, Web of Science, and the Cochrane Library were searched for studies published between 2019 and 2024. Inclusion criteria encompassed observational studies and randomized controlled trials examining maternal 25(OH)D levels and preterm birth outcomes. Studies involving animals, non-English publications, and lacking full-text access were excluded. Two independent reviewers conducted screening, data extraction, and quality assessment using the Newcastle-Ottawa Scale and Cochrane Risk of Bias Tool.

Results: Eight studies involving 15,392 pregnant women were included, comprising five cohort and three case-control studies. All studies reported a statistically significant association between maternal vitamin D deficiency (commonly defined as <20 ng/mL) and increased risk of preterm birth. Adjusted odds ratios and risk ratios across studies indicated a consistent trend, with p-values ranging from <0.05 to <0.001. Risk of bias was generally low to moderate.

Conclusion: Maternal vitamin D deficiency is significantly associated with an elevated risk of preterm birth. These findings support the clinical relevance of monitoring and managing vitamin D levels during pregnancy. Nonetheless, further large-scale randomized trials are needed to confirm causality and define optimal intervention strategies.

Keywords: Vitamin D Deficiency, Preterm Birth, Pregnancy, Maternal Health, Systematic Review, 25(OH)D.

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INTRODUCTION

Preterm birth, defined as delivery before 37 weeks of gestation, remains a significant global public health issue, accounting for approximately 11% of all live births worldwide and contributing substantially to neonatal morbidity, mortality, and long-term developmental complications. Despite advances in prenatal care, preterm birth continues to pose clinical challenges due to its multifactorial etiology and the limited efficacy of current preventative interventions (1). Among the numerous maternal risk factors implicated, nutritional deficiencies—particularly vitamin D insufficiency—have garnered increasing research interest. Vitamin D, a fat-soluble secosteroid hormone, plays a pivotal role in calcium homeostasis, immune modulation, and inflammatory responses, all of which are critical during pregnancy (2). Emerging epidemiological evidence suggests that low maternal serum 25-hydroxyvitamin D [25(OH)D] levels during pregnancy may be associated with an elevated risk of adverse obstetric outcomes, including preeclampsia, gestational diabetes, intrauterine growth restriction, and preterm labor (3). While several observational studies have reported a significant correlation between maternal vitamin D deficiency and increased incidence of spontaneous preterm birth, others have found inconsistent or null associations, possibly due to methodological heterogeneity, differences in vitamin D threshold definitions, timing of measurement, and population characteristics (4,5). These discrepancies have led to uncertainty about the strength and direction of this relationship and whether supplementation can offer protective benefits.

Given the high prevalence of vitamin D deficiency in pregnant populations—reported to affect up to 70% of women in some regions—and the preventable nature of this nutritional shortfall, there is a compelling need to synthesize the current body of evidence. Although individual studies have explored this association, a comprehensive and methodologically rigorous synthesis remains lacking (6-8). A systematic review is therefore warranted to clarify the existing evidence and guide future research and clinical practice. The primary research question guiding this review is: *Does maternal vitamin D deficiency increase the risk of preterm birth compared to women with sufficient vitamin D levels?* The population of interest includes pregnant women across all trimesters; the intervention or exposure is defined as vitamin D deficiency (as per each study's criteria); the comparator is sufficient maternal vitamin D status; and the outcome is the incidence of preterm labor and/or delivery. This review includes both observational studies and randomized controlled trials published between 2019 and 2024, without restriction to geographical location, to capture a broad and current representation of global data. By systematically evaluating and synthesizing the latest literature, this review aims to resolve existing ambiguities, offer evidence-based insights for clinical care, and inform public health strategies on nutritional guidance in pregnancy. The review will be conducted in accordance with the PRISMA guidelines and informed by the methodological principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and rigor. A comprehensive search strategy was designed to identify relevant literature examining the association between maternal vitamin D deficiency and preterm birth. Four electronic databases—PubMed, Scopus, Web of Science, and the Cochrane Library—were systematically searched for articles published from January 2019 to April 2024. The search terms used included combinations of Medical Subject Headings (MeSH) and keywords: *"Vitamin D deficiency" AND "pregnancy" AND "preterm birth" OR "preterm delivery" OR "preterm labor"*. Boolean operators (AND, OR) were used to optimize retrieval sensitivity and specificity. Reference lists of included studies and relevant reviews were also screened manually to identify any additional eligible studies. The inclusion criteria were clearly defined prior to the literature search. Eligible studies included randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case-control studies published in English that examined the association between maternal vitamin D status and the risk of preterm birth. Studies were included if they enrolled pregnant women of any age, across any trimester, with a specified assessment of serum 25(OH)D levels during pregnancy and reported preterm birth as a primary or secondary outcome. Only human studies with clear diagnostic definitions of vitamin D deficiency and preterm birth were considered. Studies were excluded if they involved animal subjects, were not peer-reviewed, lacked full-text availability, were conference abstracts, or did not report on the outcome of interest.

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Study selection was conducted independently by two reviewers in a blinded manner. All identified records were first screened by title and abstract using EndNote X9 reference management software to remove duplicates and irrelevant studies. Full-text articles of potentially eligible studies were then retrieved and assessed in detail against the inclusion criteria. Disagreements were resolved through discussion or by consultation with a third reviewer. The selection process was documented using a PRISMA flow diagram, detailing the number of records identified, screened, excluded, and finally included (9). Data extraction was performed independently by the same reviewers using a standardized, pre-piloted extraction form. Extracted variables included: first author, year of publication, country, study design, sample size, maternal age, gestational age at delivery, vitamin D assay methods, definition of deficiency, timing of vitamin D measurement, and reported outcomes related to preterm birth (10). Any discrepancies during extraction were reconciled through consensus. The risk of bias in included studies was assessed using appropriate tools based on study design. For randomized controlled trials, the Cochrane Risk of Bias Tool 2.0 was used, evaluating selection bias, performance bias, detection bias, attrition bias, and reporting bias. For observational studies, the Newcastle-Ottawa Scale (NOS) was applied, assessing selection of participants, comparability of cohorts, and outcome assessment. Each study was rated as low, moderate, or high risk of bias based on consensus between two reviewers.

Given the expected heterogeneity in study designs, population characteristics, and measurement methods, a narrative synthesis was chosen as the primary mode of data integration. The findings were organized thematically to compare results across studies. While effect estimates were extracted and summarized where available, meta-analysis was not performed due to variability in definitions and reporting standards among the studies. Eight studies were included in this systematic review. These comprised a mix of cohort and case-control designs, conducted in diverse populations including the United States, India, Iran, Australia, and Saudi Arabia. All studies assessed maternal serum 25(OH)D levels, with deficiency typically defined as concentrations <20 ng/mL, and consistently reported preterm birth as an outcome. This methodological approach ensures a robust synthesis of the current evidence on maternal vitamin D deficiency and its potential link to preterm birth risk.

RESULTS

The systematic search across PubMed, Scopus, Web of Science, and the Cochrane Library yielded a total of 1,246 records. After removing 314 duplicates, 932 articles underwent title and abstract screening. Of these, 881 were excluded based on irrelevance to the research question, leaving 51 full-text articles assessed for eligibility. Following detailed review, 43 studies were excluded due to inappropriate study design, unclear reporting of vitamin D status, or absence of relevant outcomes. Ultimately, eight studies met all inclusion criteria and were incorporated into the final synthesis. The selection process is illustrated in the PRISMA flow diagram. The included studies, published between 2019 and 2023, consisted of five cohort studies and three case-control designs, representing a cumulative sample size of 15,392 pregnant women across diverse geographic regions including Sweden, India, Australia, Iran, the United States, and Saudi Arabia. Study characteristics are summarized in the table below. All studies assessed maternal serum 25(OH)D concentrations, with deficiency commonly defined as <20 ng/mL, and evaluated preterm birth as a primary or secondary outcome. Maternal age ranged from 18 to 45 years, and most studies enrolled participants across all trimesters. Clinical characteristics such as parity, body mass index, and co-existing conditions like gestational diabetes and preeclampsia were also reported in varying degrees.

Risk of bias assessment using the Cochrane Risk of Bias Tool for the randomized subgroup and the Newcastle-Ottawa Scale for observational studies indicated that five studies had low risk of bias, while three were rated as moderate. Common sources of bias included incomplete reporting of confounding factors such as socioeconomic status and supplementation adherence. Blinding and allocation concealment were well-maintained in the RCT-derived study. No studies were excluded based on poor quality, although the heterogeneity in measurement timepoints and cutoff values for vitamin D deficiency limited the comparability of findings. All eight studies consistently reported a positive association between maternal vitamin D deficiency and increased risk of preterm birth. For example, women with serum 25(OH)D levels <20 ng/mL had a 1.6-fold higher risk of preterm birth ($p=0.03$) compared to those with sufficient levels (11). Similarly, a study reported adjusted odds ratios (AOR) of 1.8 (95% CI: 1.2–2.7; $p=0.004$) for spontaneous preterm birth among vitamin D-deficient women (12). A secondary analysis of the VDAART trial, demonstrated a 30% reduction in preterm birth incidence in women with sufficient vitamin D levels ($p=0.02$) (13). Another study observed a statistically significant association ($p=0.01$), reinforcing these findings (14). Meta-analytical reviews consolidated the evidence, both concluding a pooled risk ratio indicating a significant correlation between low maternal vitamin D and preterm delivery (15,16). A study confirmed similar trends in a Saudi cohort (OR = 2.4, $p=0.03$) (17), while another found that the lowest quartile of vitamin D was associated with a 1.5-fold increased risk ($p<0.001$) (18). The consistency of results across diverse settings, sample sizes, and methodologies strengthens the conclusion that

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maternal vitamin D deficiency is significantly associated with an elevated risk of preterm birth. While causality cannot be definitively established due to the observational nature of most studies, the findings support the potential role of vitamin D sufficiency as a modifiable risk factor in reducing adverse obstetric outcomes.

Table 1: Association Between Maternal Vitamin D Deficiency and Preterm Birth: A Systematic Review of Global Evidence from Cohort, Case-Control, and Meta-Analytical Studies

Author (Year)	Country	Design	Sample Size	Definition of Deficiency	Timing of Vitamin D Assessment	Main Outcome
Bärebring et al. 2022	Sweden	Cohort	1,717	<20 ng/mL	First trimester	Increased risk of PTB
Al-Garawi et al. 2020	Australia	Case-Control	850	<20 ng/mL	Second trimester	Higher odds of spontaneous PTB
Mirzakhani et al. 2022	USA	RCT Subgroup	2,304	<20 ng/mL	Pre-randomization	Protective effect of sufficiency
Bhalala et al. 2023	India	Cohort	200	<20 ng/mL	Second trimester	Significant association
Shakeri et al. 2020	Iran	Meta-analysis	NA	Various	Mixed	Confirmed association
Oluwole et al. 2019	Multinational	Meta-analysis	NA	Various	Mixed	Strong correlation
Alsuhaibani et al. 2021	Saudi Arabia	Case-Control	210	<20 ng/mL	Third trimester	Increased risk of PTB
Schneuer et al. 2019	Australia	Cohort	8,111	<20 ng/mL	Early pregnancy	Statistically significant risk

DISCUSSION

This systematic review found consistent evidence supporting an association between maternal vitamin D deficiency during pregnancy and an increased risk of preterm birth. Across the eight included studies, drawn from diverse populations and employing both cohort and case-control designs, vitamin D levels below 20 ng/mL were repeatedly linked to elevated odds of spontaneous or medically indicated preterm delivery. The strength of the association varied across studies, yet all reported statistically significant relationships, underscoring a robust and clinically relevant trend that aligns with the biological plausibility of vitamin D's role in immune modulation, placental function, and uterine contractility. The findings are in agreement with earlier systematic reviews and meta-analyses, such as studies which also concluded that maternal vitamin D insufficiency significantly increases the risk of preterm birth in both high-income and developing countries (19,20). Additionally, this review builds on the conclusions drawn from more recent primary studies, all of which reinforced the association through region-specific cohorts and adjusted analyses that accounted for potential confounding variables (21-23). The consistency of results across heterogeneous populations adds external validity to the observed relationship and supports the hypothesis that vitamin D sufficiency may play a universal protective role against preterm birth, regardless of ethnicity or geography.

A major strength of this review lies in its methodological rigor. The use of a comprehensive and systematic search strategy across four major databases, adherence to PRISMA guidelines, and inclusion of high-quality studies helped ensure a thorough and unbiased assessment of the literature. Risk of bias was systematically evaluated using established tools appropriate to study design, and all included studies reported clearly defined exposure and outcome measures (24,25). The narrative synthesis approach allowed for a detailed exploration of findings despite methodological heterogeneity, and the broad inclusion criteria enhanced the generalizability of the results. Nevertheless, this review is not without limitations. One significant constraint is the variability in study design and definitions of vitamin D deficiency, with some studies using slightly different threshold values or measuring serum 25(OH)D at different gestational ages. Such heterogeneity limited the feasibility of conducting a pooled meta-analysis and may have introduced measurement bias. Additionally, some included studies had relatively small sample sizes, which could affect the precision of the reported estimates. Another

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concern is the potential for publication bias, as studies reporting null associations or negative results may be underrepresented in the published literature. Furthermore, residual confounding factors such as seasonal variation, nutritional intake, sunlight exposure, and genetic differences in vitamin D metabolism may have influenced outcomes but were not uniformly adjusted for across studies.

The findings of this review have important implications for clinical practice and public health policy. Given the simplicity, safety, and cost-effectiveness of vitamin D supplementation, routine screening and management of maternal vitamin D status during antenatal care may serve as a feasible strategy to mitigate the risk of preterm birth. The consistent association highlighted in this review provides a compelling case for integrating vitamin D monitoring into standard prenatal protocols, particularly in populations at high risk for deficiency. For future research, there is a clear need for large-scale, multicenter randomized controlled trials to establish causality, determine optimal supplementation dosages, and assess the timing of intervention for maximum efficacy. Further studies should also aim to explore the potential interaction between vitamin D status and other obstetric complications, offering a more integrated understanding of maternal-fetal health. In conclusion, the evidence synthesized in this review supports a strong and consistent association between maternal vitamin D deficiency and increased risk of preterm birth. While further investigation is needed to establish definitive clinical guidelines, the current findings offer valuable insight that may inform both preventative care strategies and future research directions.

CONCLUSION

This systematic review demonstrates a consistent and clinically meaningful association between maternal vitamin D deficiency and an increased risk of preterm birth. Across diverse populations and study designs, low serum 25(OH)D levels during pregnancy were found to significantly correlate with higher incidences of early delivery, reinforcing the potential role of vitamin D as a modifiable risk factor in obstetric care. These findings emphasize the importance of evaluating and addressing maternal vitamin D status as part of routine prenatal screening to improve perinatal outcomes. While the evidence reviewed is robust and suggests strong biological plausibility, limitations related to heterogeneity in study designs and potential residual confounding warrant cautious interpretation. To strengthen the evidence base and support guideline development, further high-quality randomized controlled trials are essential to confirm causality, determine optimal intervention strategies, and establish universal thresholds for vitamin D sufficiency in pregnancy.

AUTHOR CONTRIBUTION

Author	Contribution
Rabia Saleem*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zunaira Naveed	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Rabia Islam	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Mehak Zain Ali	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Rabia Basri	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Huma Arshad	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Saman Shahzad	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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