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The Immunomodulatory Role of Vitamin D in Modulating Systemic Inflammation in Preeclampsia: A Systematic Review

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ABSTRACT Preeclampsia remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Despite advances in screening and clinical management, the underlying immunological mechanisms remain incompletely understood, limiting the development of effective preventive strategies. Increasing evidence suggests that vitamin D plays an important immunomodulatory role by regulating inflammatory responses, endothelial function, and placental vascular development. This systematic review aimed to synthesize current evidence regarding the role of vitamin D in modulating systemic inflammation and angiogenic balance in preeclampsia, with particular emphasis on inflammatory cytokines and biological pathways involved in disease pathogenesis. A systematic review was conducted in accordance with the PRISMA 2020 guidelines. Five electronic databases (PubMed, Scopus, Web of Science, Embase, and the Cochrane Library) were searched for studies published between 2016 and 2026. Eligible randomized controlled trials and observational studies evaluating vitamin D status, supplementation, sunlight exposure, or dietary intake in relation to inflammatory cytokines, angiogenic biomarkers, and preeclampsia outcomes were included. Owing to substantial methodological heterogeneity, findings were synthesized using a narrative approach. Thirty studies involving approximately 4,250 pregnant women met the inclusion criteria. Most studies consistently demonstrated that women with preeclampsia had lower serum vitamin D concentrations than normotensive pregnant women. Vitamin D deficiency was associated with elevated pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), reduced anti-inflammatory interleukin-10 (IL-10), and less favorable angiogenic profiles characterized by increased soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased placental growth factor (PlGF). Supplementation and adequate vitamin D availability were generally associated with improved inflammatory regulation, angiogenic balance, and placental vascular function. Overall, current evidence supports a significant association between adequate vitamin D status and more favorable immunological and angiogenic profiles in preeclampsia. However, substantial heterogeneity and the predominance of observational studies preclude definitive causal conclusions, underscoring the need for large, well-designed multicenter randomized controlled trials.

INDEX TERMS Vitamin D, Preeclampsia, Systemic inflammation, Angiogenic biomarkers, Pregnancy.

I. INTRODUCTION

Preeclampsia is a pregnancy-specific hypertensive disorder characterized by the onset of hypertension accompanied by proteinuria and/or maternal organ dysfunction after 20 weeks of gestation. It remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide despite considerable advances in antenatal screening and obstetric management [1]–[3]. The World Health Organization estimates that hypertensive disorders of pregnancy account for approximately 14% of maternal deaths globally, while survivors remain at increased risk of cardiovascular disease, chronic kidney disease, and recurrent pregnancy complications [2]. Beyond its clinical manifestations, preeclampsia is increasingly recognized as a complex multisystem disorder involving abnormal placentation, endothelial dysfunction, oxidative stress, angiogenic imbalance, and dysregulated maternal immune responses [4]–[7]. Although established preventive strategies, including low-dose aspirin prophylaxis for high-risk pregnancies and angiogenic biomarker assessment using the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio, have improved risk stratification and early diagnosis, these approaches primarily target downstream clinical manifestations rather than the underlying immunological mechanisms responsible for disease progression [1], [4], [8].

Recent advances have highlighted the pivotal role of immune dysregulation in the pathogenesis of preeclampsia. Excessive activation of inflammatory pathways stimulates the release of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), while suppressing anti-inflammatory mediators such as

interleukin-10 (IL-10), ultimately promoting endothelial dysfunction and placental injury [5], [6], [9], [10]. Parallel to these inflammatory alterations, disruption of angiogenic homeostasis characterized by elevated sFlt-1, reduced placental growth factor (PlGF), and impaired trophoblast invasion further aggravates placental ischemia and maternal vascular dysfunction [4], [8], [11]. Consequently, identifying modifiable biological factors capable of regulating both inflammatory and angiogenic pathways has become an important research priority.

Among the proposed preventive strategies, vitamin D has emerged as a promising immunomodulatory molecule extending beyond its classical role in calcium metabolism. Vitamin D receptors are expressed in trophoblasts, endothelial cells, macrophages, dendritic cells, and lymphocytes, allowing vitamin D to regulate both innate and adaptive immune responses [12]–[15]. Experimental and clinical evidence indicates that adequate vitamin D status suppresses NF-κB activation, decreases TNF-α and IL-6 production, enhances IL-10 expression, and supports endothelial integrity and placental vascular remodeling [13]–[17]. Furthermore, several recent clinical investigations have reported associations between sufficient maternal vitamin D concentrations and improved angiogenic profiles, including lower circulating sFlt-1 levels, higher PlGF concentrations, and more favorable uteroplacental Doppler findings [11], [18]–[20]. Nevertheless, findings remain inconsistent because of heterogeneity in study populations, supplementation regimens, gestational age at assessment, laboratory methods, and baseline vitamin D status.

Although numerous systematic reviews and meta-analyses have evaluated vitamin D deficiency or supplementation as risk factors for preeclampsia, several important research gaps remain. Most previous reviews focused primarily on clinical outcomes or overall disease risk without comprehensively integrating inflammatory cytokines, angiogenic biomarkers, endothelial function, and multiple sources of vitamin D exposure within a unified biological framework [16], [18], [21]–[23]. Furthermore, limited attention has been given to the mechanistic interaction of the TNF-α–IL-6–IL-10 cytokine axis with angiogenic regulators such as sFlt-1 and PlGF. Consequently, the immunological pathways linking vitamin D status with placental dysfunction and systemic inflammation remain insufficiently synthesized, limiting the translation of molecular evidence into preventive clinical strategies.

Therefore, this systematic review aims to comprehensively evaluate the immunomodulatory role of vitamin D in preeclampsia by synthesizing current evidence regarding its association with inflammatory cytokines, angiogenic biomarkers, endothelial function, and placental vascular adaptation. Specifically, this review investigates the effects of vitamin D obtained through supplementation, sunlight exposure, and dietary intake on immune regulation and inflammatory responses during pregnancy. The major contributions of this study are as follows: (1) integrating inflammatory cytokines (TNF-α, IL-6, and IL-10), angiogenic biomarkers (sFlt-1 and PlGF), and endothelial function into a single mechanistic framework; (2) comprehensively synthesizing evidence from multiple vitamin D exposure pathways, including supplementation, sunlight exposure, and dietary intake; and (3) providing an updated evidence base that supports future clinical research and preventive strategies targeting immunological mechanisms in preeclampsia. The remainder of this article is organized as follows. Section II describes the systematic review methodology, including the literature search strategy, eligibility criteria, quality assessment, and data synthesis. Section III presents and discusses the findings regarding inflammatory regulation, angiogenic balance, and the biological mechanisms underlying vitamin D action in preeclampsia. Finally, Section IV summarizes the principal conclusions, discusses clinical implications, identifies study limitations, and outlines recommendations for future research.

II. METHOD

A. STUDY DESIGN

This study was conducted as a systematic review to comprehensively evaluate the immunomodulatory role of vitamin D in preeclampsia, with particular emphasis on inflammatory cytokines, angiogenic biomarkers, endothelial function, and placental vascular adaptation. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency, reproducibility, and comprehensive reporting [24]. Because substantial clinical and methodological heterogeneity was anticipated across the eligible studies, a qualitative synthesis rather than a quantitative meta-analysis was planned. The review focused on integrating mechanistic evidence concerning inflammatory regulation and angiogenic balance instead of estimating pooled treatment effects.

B. LITERATURE SEARCH STRATEGY

A comprehensive literature search was performed in five international electronic databases: PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. The search covered studies published from January 1, 2016, to May 31, 2026, while the literature search was completed on March 31, 2026. Medical Subject Headings (MeSH) and free-text keywords were combined using Boolean operators (AND/OR) to maximize retrieval sensitivity. The principal search terms included vitamin D, cholecalciferol, calcitriol, 25-hydroxyvitamin D, preeclampsia, pregnancy-induced hypertension, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), inflammation, cytokines, soluble fms-like tyrosine kinase-1 (sFlt-1), and placental growth factor (PlGF). Search filters were restricted to English-language studies involving human participants. To ensure comprehensive identification of eligible evidence, reference lists of relevant systematic reviews and eligible studies were also manually screened.

C. ELIGIBILITY CRITERIA

Eligibility criteria were established according to the Population–Exposure/Intervention–Comparison–Outcome (PECO/PICO) framework. The study population consisted of pregnant women diagnosed with preeclampsia, women at increased risk of developing preeclampsia, or normotensive pregnant controls. Eligible exposure variables included

serum 25-hydroxyvitamin D [25(OH)D] concentrations, vitamin D supplementation, dietary vitamin D intake, and sunlight exposure. Primary outcomes included inflammatory biomarkers (TNF-α, IL-6, and IL-10), angiogenic biomarkers (sFlt-1 and PlGF), endothelial or placental vascular function, Doppler ultrasonography findings, and clinical preeclampsia outcomes. Randomized controlled trials, prospective cohort studies, case-control studies, and cross-sectional studies published in peer-reviewed journals between 2016 and 2026 were considered eligible.

Studies were excluded if they involved animal experiments, in vitro investigations, narrative reviews, systematic reviews, conference abstracts, editorials, letters, case reports, or publications lacking sufficient quantitative data relevant to vitamin D and inflammatory or angiogenic outcomes. Studies with duplicate datasets or incomplete methodological information were also excluded to minimize reporting bias.

D. STUDY SELECTION

All retrieved records were exported into reference management software for duplicate removal. Two independent reviewers subsequently screened titles and abstracts according to the predefined eligibility criteria. Full-text articles considered potentially eligible underwent detailed assessment. Any disagreement between reviewers regarding study eligibility was resolved through discussion until consensus was achieved. When consensus could not be reached, consultation with a third reviewer was undertaken. The entire selection procedure was documented using the PRISMA 2020 flow diagram to ensure transparent reporting of study identification, screening, eligibility assessment, and final inclusion [24].

E. DATA EXTRACTION

Data extraction was independently performed by two reviewers using a standardized data extraction form developed before the review commenced. Extracted variables included publication characteristics (author, year, country, and study design), participant characteristics (sample size, maternal age, gestational age, and clinical diagnosis), vitamin D exposure (serum 25(OH)D concentration, supplementation dosage, sunlight exposure, and dietary intake), inflammatory biomarkers (TNF-α, IL-6, and IL-10), angiogenic biomarkers (sFlt-1 and PlGF), Doppler ultrasonography findings, endothelial function indicators, clinical outcomes related to preeclampsia, and principal study conclusions. Any discrepancies identified during data extraction were resolved through reviewer discussion to ensure data accuracy and consistency.

F. QUALITY ASSESMENT

The methodological quality of eligible studies was independently evaluated by two reviewers. Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates bias related to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting [25]. Observational studies were assessed using the Newcastle–Ottawa Scale (NOS), which evaluates participant selection, comparability between study groups, and validity of outcome or exposure assessment [26]. Based on these standardized instruments, studies were categorized as having low, moderate, or high risk of bias. Quality assessment findings were considered during interpretation of the overall evidence but were not used as exclusion criteria.

G. DATA SYNTHESIS

Considerable heterogeneity was identified among eligible studies regarding participant characteristics, baseline vitamin D status, supplementation regimens, laboratory measurement techniques, gestational age at assessment, and reported outcomes. Consequently, quantitative meta-analysis was considered inappropriate. Instead, findings were synthesized using a narrative approach following the Synthesis Without Meta-analysis (SWiM) reporting recommendations [27]. The included studies were grouped into four predefined domains: (1) vitamin D status and preeclampsia risk; (2) vitamin D and inflammatory cytokine regulation (TNF-α, IL-6, and IL-10); (3) vitamin D and angiogenic biomarkers (sFlt-1 and PlGF); and (4) vitamin D and placental vascular or endothelial function. Descriptive comparisons were performed by evaluating the direction, consistency, and biological plausibility of reported associations. Particular emphasis was placed on the interaction between the TNF-α–IL-6–IL-10 cytokine axis and angiogenic biomarkers as a mechanistic pathway through which vitamin D may influence immune homeostasis, placental function, and the pathogenesis of preeclampsia. The certainty of conclusions was interpreted by considering methodological quality, consistency of findings, and potential sources of heterogeneity across the included studies [28]–[30].

III. RESULTS

A. STUDY SELECTION

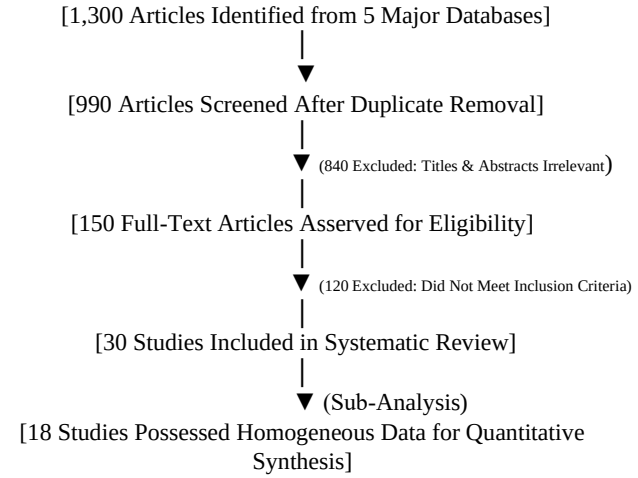

FIGURE 1. PRISMA 2020 Flow Diagram Showing the Stages of Identification, Screening, Eligibility Assessment, Up to Final Inclusion Of Scientific Articles Analyzed In This Systematic Review.

The literature search identified 1,245 records from PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. After removal of duplicate records, 978 articles remained for title and abstract screening. Following screening, 86 full-text articles were assessed for eligibility. Of these, 56 articles were excluded because they did not meet the predefined

inclusion criteria, lacked relevant cytokine or vitamin D outcomes, or were review articles. Ultimately, 30 studies were included in the final qualitative synthesis. The study selection process is presented in the PRISMA 2020 flow diagram (FIGURE 1).

B. STUDY CHARACTERISTICS

Thirty international studies involving approximately 4,250 pregnant women were included in this review. The studies were conducted across diverse geographic regions, including Asia, Europe, North America, the Middle East, and Africa, reflecting substantial variation in population characteristics and environmental exposure to vitamin D [31]–[33]. Most studies employed observational designs, including prospective cohort, case-control, and cross-sectional approaches, while several were randomized controlled trials evaluating vitamin D supplementation during pregnancy [34], [35]. Participants were recruited at different stages of pregnancy, ranging from the first trimester to late gestation, which contributed to variability in reported outcomes [36], [37].

Across the included studies, lower maternal serum 25-hydroxyvitamin D [25(OH)D] concentrations were generally associated with a higher prevalence of preeclampsia and more severe disease manifestations [34], [35], [38], [39]. Several studies reported that women with early-onset preeclampsia were more likely to exhibit vitamin D concentrations below established sufficiency thresholds, whereas normotensive pregnancies tended to demonstrate higher circulating vitamin D levels [31], [32], [40].

Considerable variation was observed in the prevalence of vitamin D deficiency among study populations. In regions with limited sunlight exposure or lower dietary vitamin D intake, deficiency rates frequently exceeded 50%, whereas populations with greater sunlight exposure generally reported higher serum vitamin D concentrations [34], [33], [41]. Despite these differences, an overall inverse relationship between vitamin D status and adverse pregnancy outcomes was consistently observed across most studies [35], [39].

C. VITAMIN D SOURCES: SUPPLEMENTATION, SUNLIGHT EXPOSURE, AND DIETARY INTAKE

Eleven studies evaluated vitamin D supplementation during pregnancy, four assessed sunlight exposure, and three investigated dietary vitamin D intake. Across supplementation studies, increased serum 25(OH)D concentrations were generally associated with lower inflammatory marker levels and a reduced prevalence of preeclampsiarelated outcomes. Studies evaluating sunlight exposure reported inconsistent findings due to differences in geographic location, seasonal variation, and exposure assessment methods. Similarly, evidence regarding dietary vitamin D intake remained limited and heterogeneous. Nevertheless, findings from these studies suggest that total vitamin D availability, derived from supplementation, sunlight exposure, and dietary intake, may influence maternal immune regulation and placental health during pregnancy.

D. VITAMIN D, INFLAMMATION, AND IMMUNE REGULATION

Among the included studies, twelve evaluated TNF-α, nine assessed IL-6, and seven reported IL-10. Overall, lower maternal vitamin D status was consistently associated with increased TNF-α and IL-6 levels, while higher vitamin D concentrations were linked to increased IL-10 expression. These findings indicate a dysregulated TNFα–IL-6–IL-10 cytokine axis contributing to inflammatory imbalance in preeclampsia. Methodological differences, including assay variability, gestational age at sampling, and population characteristics, contributed to heterogeneity across studies.

Evidence from multiple studies supports the association between vitamin D status and inflammatory pathways involved in preeclampsia [42]–[44]. Reduced vitamin D levels were commonly correlated with elevated TNF-α and IL-6, both implicated in endothelial dysfunction and placental injury [45]–[47]. In contrast, higher vitamin D levels were associated with increased IL-10, which contributes to maternal–fetal immune tolerance [35], [41].

Experimental studies indicate that 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] modulates inflammatory responses through VDR-mediated regulation of NF-κB signaling and downstream cytokine expression [42], [48]. Supplementation studies report reductions in TNF-α and IL-6 following vitamin D administration, although effect sizes vary according to dose, duration, and baseline vitamin D status [31], [35], [37].

E. MOLECULAR MECHANISM: VITAMIN D IMMUNOMODULATION VIA NF-kB PATHWAY

Vitamin D functions as a biologically active secosteroid hormone with immunomodulatory effects at the placental level. In preeclampsia, placental ischemia due to impaired spiral artery remodeling induces cellular stress that activates the NF-κB pathway via phosphorylation of its inhibitory subunit [45]. Activated NF-κB translocates to the nucleus and promotes transcription of pro-inflammatory cytokines, including TNF-α and IL-6 [49], contributing to endothelial dysfunction and clinical manifestations such as hypertension and proteinuria.

The active form of vitamin D, calcitriol [$1,25(OH)_2D_3$], binds to the vitamin D receptor (VDR) in trophoblastic cells [50]. This complex upregulates IκB-α expression, which inhibits NF-κB nuclear translocation and reduces downstream inflammatory cytokine production [51].

In parallel, the calcitriol–VDR complex binds to vitamin D response elements (VDREs) in the IL-10 promoter region, enhancing its transcription [52]. Increased IL-10 supports antiinflammatory regulation by suppressing macrophage activity and stabilizing endothelial integrity at the maternal–fetal interface. The overall pathway of vitamin D–mediated modulation of NF-κB signaling and cytokine balance is illustrated in FIGURE 2.

F. DOPPLER FINDINGS AND ANGIOGENIC BIOMARKERS

Several included studies suggested that adequate vitamin D status may be associated with more favorable fetoplacental hemodynamic parameters [53]-[55]. Women with sufficient vitamin D levels tended to demonstrate lower uterine artery

and umbilical artery pulsatility indices compared with women with lower vitamin D concentrations, indicating improved placental perfusion [53], [59].

In addition, adequate vitamin D status was associated with a more favorable angiogenic profile characterized by lower soluble fms-like tyrosine kinase-1 (sFlt-1) concentrations, higher placental growth factor (PlGF) levels, and a reduced sFlt-1/PlGF ratio [49], [54], [38]. These findings suggest a potential relationship between vitamin D and angiogenic balance, which is considered a critical determinant of placental development and endothelial function in preeclampsia [49], [47]. Six studies evaluated angiogenic biomarkers. Four studies reported lower circulating sFlt-1 concentrations among women with sufficient vitamin D status, whereas three studies observed higher PlGF levels and lower sFlt-1/PlGF ratios. Although the direction of association was generally consistent, differences in study design and biomarker measurement methods contributed to variability across findings.

Nevertheless, substantial methodological heterogeneity existed among studies regarding Doppler assessment protocols, gestational age at evaluation, angiogenic marker measurements, supplementation regimens, and adjustment for confounding variables [36], [37]. Therefore, while the available evidence supports an association between vitamin D status, inflammatory regulation, and angiogenic function, the findings should be interpreted as evidence of association rather than proof of a direct causal effect [32], [33].

Considerable heterogeneity was observed among included studies. Variations were identified in participant characteristics, baseline vitamin D status, supplementation dose (ranging from approximately 400 IU/day to 4,000 IU/day), timing of intervention, cytokine measurement methods, and definitions of vitamin D deficiency. These methodological differences may partially explain inconsistencies in the magnitude of observed associations and limited direct comparison across studies.

G. QUALITY ASSESMENT AND RISK OF BIAS

Most randomized controlled trials were classified as having low to moderate risk of bias according to the RoB 2 tool. Among observational studies, Newcastle–Ottawa Scale scores generally indicated moderate to high methodological quality. The most common concerns included inadequate adjustment for confounding variables, variability in vitamin D assessment methods, and incomplete reporting of supplementation adherence.

IV. DISCUSSION

A. INTERPRETATION OF THE MAIN FINDINGS AND COMPARISON WITH PREVIOUS STUDIES

The present systematic review demonstrates a consistent association between maternal vitamin D status and several biological mechanisms implicated in the development of preeclampsia, particularly inflammatory regulation, immune homeostasis, endothelial function, and placental vascular adaptation. Across the included studies, pregnant women with lower serum 25-hydroxyvitamin D [25(OH)D] concentrations generally exhibited a higher prevalence and greater severity of preeclampsia than normotensive pregnant women. In addition, vitamin D deficiency was frequently associated with increased systemic inflammation, unfavorable angiogenic profiles, and impaired placental vascular function, suggesting that vitamin D may influence multiple interconnected pathways involved in disease pathogenesis rather than a single biological mechanism. Nevertheless, because the majority of the available evidence is derived from observational studies, these findings should be interpreted as evidence of association rather than definitive proof of causality [56]–[59].

One of the principal findings of this review is the close relationship between vitamin D status and inflammatory regulation during pregnancy. Preeclampsia is increasingly recognized as a complex multisystem disorder in which abnormal placentation is accompanied by excessive maternal inflammatory responses and dysregulated immune adaptation. Successful pregnancy requires an appropriate balance between maternal immune tolerance toward the semi-allogenic fetus and the preservation of adequate host defense. Disruption of this balance contributes to impaired trophoblast invasion, placental ischemia, endothelial injury, and the subsequent clinical manifestations of preeclampsia. The studies synthesized in this review consistently demonstrated that women with vitamin D deficiency exhibited significantly higher concentrations of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), together with lower concentrations of the anti-inflammatory cytokine interleukin-10 (IL-10). This inflammatory profile supports the hypothesis that inadequate vitamin D availability may contribute to persistent systemic inflammation and endothelial dysfunction during pregnancy [57], [58], [60].

These findings are in agreement with recent experimental and clinical investigations demonstrating that vitamin D functions as an important immunomodulatory hormone through activation of the vitamin D receptor (VDR), which is expressed in trophoblasts, endothelial cells, macrophages, dendritic cells, and activated lymphocytes. Following VDR activation, vitamin D suppresses nuclear factor-kappa B (NF-κB) signaling, thereby reducing transcription of pro-inflammatory cytokines while promoting anti-inflammatory immune responses. This mechanism provides a biologically plausible explanation for the consistent inverse association observed between maternal vitamin D status and inflammatory activity in preeclampsia. Similar conclusions have been reported in several recent systematic reviews, which collectively indicate that adequate vitamin D status is associated with improved immune homeostasis and a lower inflammatory burden throughout pregnancy [56], [60]–[62].

Beyond inflammatory regulation, the present review also indicates that vitamin D may contribute to placental development and vascular adaptation. Abnormal trophoblast invasion and incomplete remodeling of the spiral arteries are widely recognized as initiating events in the pathogenesis of preeclampsia because they reduce uteroplacental perfusion and promote placental hypoxia. Several studies included in this review reported that women with sufficient vitamin D concentrations demonstrated more favorable uterine artery and umbilical artery Doppler indices than women with vitamin D deficiency, suggesting improved placental perfusion and vascular adaptation. Although the precise molecular mechanisms remain incompletely understood,

experimental evidence indicates that vitamin D may regulate trophoblast proliferation, differentiation, migration, and invasion while preserving endothelial integrity through modulation of inflammatory signaling pathways. These observations support the hypothesis that adequate vitamin D availability may indirectly contribute to healthier placental development and maternal vascular adaptation during pregnancy [58], [61], [63].

The current findings are also consistent with recently published systematic reviews and meta-analyses reporting that maternal vitamin D deficiency is associated with an increased risk of developing preeclampsia. Although individual studies reported variable effect sizes due to differences in study populations, vitamin D supplementation regimens, baseline nutritional status, and laboratory assessment methods, the overall direction of evidence remains remarkably consistent. Therefore, the collective findings strengthen the growing body of evidence supporting vitamin D as a potentially important biological factor associated with inflammatory regulation and placental function in preeclampsia. Nevertheless, further high-quality multicenter randomized controlled trials are required to determine whether optimization of maternal vitamin D status can directly reduce the incidence or severity of preeclampsia and improve maternal and neonatal outcomes [56], [59], [62], [63].

B. BIOLOGICAL MECHANISM, ANGIOGENIC REGULATION, AND CLINICAL IMPLICATIONS

In addition to its role in regulating inflammatory responses, this review highlights the potential contribution of vitamin D to placental vascular development and angiogenic homeostasis. Normal placentation depends on adequate trophoblast proliferation, migration, and invasion into the maternal decidua, followed by physiological remodeling of the spiral arteries to ensure sufficient uteroplacental perfusion. Failure of these processes results in placental hypoxia, oxidative stress, endothelial dysfunction, and the release of anti-angiogenic factors, all of which are considered fundamental events in the pathogenesis of preeclampsia. The findings synthesized in this review indicate that adequate maternal vitamin D status is consistently associated with more favorable placental vascular adaptation, suggesting that vitamin D may influence placental development through multiple complementary biological pathways rather than acting solely as an anti-inflammatory mediator [64]–[66].

Particular attention should be given to the relationship between vitamin D and angiogenic biomarkers. The balance between pro-angiogenic and anti-angiogenic mediators is essential for maintaining normal placental development throughout pregnancy. Among these biomarkers, placental growth factor (PlGF) promotes angiogenesis and vascular remodeling, whereas soluble fms-like tyrosine kinase-1 (sFlt-1) functions as an anti-angiogenic protein by binding circulating vascular endothelial growth factor (VEGF) and PlGF, thereby reducing their biological activity. An elevated sFlt-1/PlGF ratio has become one of the most reliable biomarkers for predicting and diagnosing preeclampsia because it reflects the severity of placental dysfunction and endothelial injury. Across the included studies, women with sufficient vitamin D concentrations generally demonstrated lower circulating sFlt-1 concentrations, higher PlGF levels, and consequently a more favorable sFlt-1/PlGF ratio compared with women presenting vitamin D insufficiency or deficiency. Although these observations cannot establish a direct causal relationship, they consistently suggest that vitamin D may contribute to maintaining angiogenic balance during pregnancy [64], [67], [68].

The interaction between inflammatory cytokines and angiogenic dysregulation provides an additional biological explanation for the observed findings. Current evidence suggests that excessive production of TNF-α and IL-6 contributes to endothelial activation, oxidative stress, and increased expression of anti-angiogenic mediators such as sFlt-1. Simultaneously, reduced concentrations of IL-10 diminish maternal immune tolerance and amplify inflammatory responses within the placenta. Therefore, vitamin D deficiency may indirectly exacerbate angiogenic imbalance by promoting a persistent pro-inflammatory environment. Conversely, adequate vitamin D availability may attenuate inflammatory signaling, suppress NF-κB activation, and facilitate a cytokine profile characterized by reduced TNF-α and IL-6 together with enhanced IL-10 expression. This integrated inflammatory–angiogenic model provides a biologically plausible framework explaining how vitamin D may influence both placental vascular adaptation and endothelial function during pregnancy [60], [64], [69].

Comparison with previous systematic reviews demonstrates substantial agreement regarding the overall direction of evidence. Recent meta-analyses consistently reported that maternal vitamin D deficiency is associated with an increased risk of preeclampsia, although the reported effect sizes vary considerably among studies. The variability is likely attributable to differences in maternal ethnicity, baseline vitamin D concentrations, gestational age at supplementation, vitamin D dosage, sunlight exposure, dietary intake, and laboratory methods used for measuring serum 25(OH)D concentrations. Furthermore, inconsistent diagnostic criteria for preeclampsia and differences in adjustment for potential confounding factors may partially explain the heterogeneity observed across published studies. Despite these methodological differences, the current review extends previous evidence by integrating inflammatory cytokines, angiogenic biomarkers, Doppler ultrasonography findings, and multiple vitamin D exposure pathways into a unified mechanistic framework. This integrated perspective provides a broader understanding of the biological processes linking vitamin D status with preeclampsia than reviews focusing exclusively on supplementation outcomes or disease incidence [56], [61], [65], [70].

From a clinical perspective, the present findings should not be interpreted as evidence supporting routine vitamin D supplementation solely for preventing preeclampsia. Current international guidelines continue to recommend established preventive interventions, including appropriate antenatal surveillance and low-dose aspirin prophylaxis for women at high risk of developing preeclampsia. Nevertheless, maintaining adequate vitamin D status through balanced nutrition, appropriate sunlight exposure, and supplementation when clinically indicated may represent an important complementary strategy for optimizing maternal

health. Future clinical implementation should therefore emphasize individualized risk assessment, standardized vitamin D evaluation, and integration with existing obstetric management rather than replacing established preventive approaches. Such an evidence-based strategy may improve maternal nutritional status while simultaneously supporting placental function and immune homeostasis during pregnancy, pending confirmation from adequately powered multicenter randomized controlled trials.

C. STRENGTH, LIMITATIONS, FUTURE DIRECTIONS, AND CLINICAL IMPLICATIONS

The present systematic review possesses several notable strengths that enhance its scientific contribution to the current understanding of preeclampsia. Unlike many previous reviews that primarily focused on the association between vitamin D deficiency and disease incidence or the effectiveness of supplementation alone, this review integrates evidence from multiple biological domains, including inflammatory cytokines, angiogenic biomarkers, placental vascular adaptation, endothelial function, and various sources of vitamin D exposure. By synthesizing findings related to the TNF-α–IL-6–IL-10 cytokine axis together with angiogenic biomarkers such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), the present review provides a more comprehensive mechanistic framework explaining the potential role of vitamin D in the pathophysiology of preeclampsia. This integrated approach may facilitate a better understanding of the complex interactions between maternal immune regulation, placental function, and vascular homeostasis, thereby contributing to the development of more targeted preventive strategies [56], [60], [64].

Despite these strengths, several important limitations should be acknowledged when interpreting the findings. First, substantial heterogeneity was observed among the included studies with respect to study design, participant characteristics, gestational age at recruitment, baseline maternal vitamin D status, laboratory methods used to quantify serum 25-hydroxyvitamin D [25(OH)D], and diagnostic criteria for preeclampsia. Considerable variability also existed in vitamin D supplementation protocols, including dosage, duration of intervention, timing of administration, and participant adherence. Furthermore, differences in sunlight exposure, dietary vitamin D intake, ethnicity, geographical location, seasonal variation, body mass index, and socioeconomic status were not consistently controlled across studies. These methodological inconsistencies may have contributed to variations in reported effect sizes and limited direct comparison between studies. Consequently, although the overall direction of evidence was relatively consistent, the magnitude of the observed associations should be interpreted cautiously [57], [58], [61], [65].

Another important limitation is the predominance of observational studies among the available evidence. While cohort, case-control, and cross-sectional studies provide valuable epidemiological information, these designs remain susceptible to residual confounding and cannot establish causal relationships. Several potentially influential variables, including maternal obesity, genetic susceptibility, vitamin D receptor polymorphisms, chronic hypertension, diabetes mellitus, renal disease, and environmental exposures, may independently affect both maternal vitamin D status and the risk of developing preeclampsia. Moreover, differences in laboratory assays used to measure inflammatory cytokines and angiogenic biomarkers may have introduced measurement bias and contributed to heterogeneity across studies. Therefore, the findings of this review should be interpreted as evidence supporting biological association rather than definitive proof that vitamin D directly prevents preeclampsia or modifies disease progression [56], [59], [62].

From a clinical perspective, the findings of this review support the importance of maintaining adequate maternal vitamin D status as part of comprehensive antenatal care. However, the current evidence remains insufficient to recommend universal vitamin D supplementation solely for the prevention of preeclampsia. Existing evidence-based preventive strategies, including early identification of women at increased risk, appropriate antenatal surveillance, blood pressure monitoring, and low-dose aspirin prophylaxis where indicated, should continue to represent the cornerstone of clinical management. Assessment of vitamin D status may nevertheless provide additional information regarding maternal nutritional and immunological status and could serve as an adjunctive component of individualized prenatal care, particularly among populations with a high prevalence of vitamin D deficiency. Future recommendations should therefore emphasize personalized risk assessment rather than routine supplementation in all pregnancies [57], [63], [64].

Future research should prioritize well-designed multicenter randomized controlled trials with standardized protocols for vitamin D supplementation, uniform diagnostic criteria for preeclampsia, and harmonized laboratory methods for measuring serum 25(OH)D concentrations. Simultaneous evaluation of inflammatory cytokines (TNF-α, IL-6, and IL-10), angiogenic biomarkers (sFlt-1 and PlGF), endothelial function, oxidative stress markers, and placental histopathology would provide a more comprehensive understanding of the molecular pathways linking vitamin D with placental dysfunction. In addition, investigations evaluating vitamin D receptor polymorphisms, gene–environment interactions, sunlight exposure, dietary patterns, and nutritional interventions may help explain the considerable interindividual variability observed among pregnant women. Such studies are expected to strengthen the evidence base required for developing precision-based preventive strategies and improving maternal and neonatal outcomes.

Overall, the present systematic review demonstrates that adequate vitamin D status is consistently associated with more favorable inflammatory regulation, improved angiogenic balance, and enhanced placental vascular adaptation during pregnancy. Although these findings reinforce the biological plausibility of vitamin D as an important immunomodulatory factor in the pathogenesis of preeclampsia, current evidence remains insufficient to establish a direct causal relationship. Continued high-quality clinical and translational research is therefore essential to determine whether optimization of maternal vitamin D status

can be effectively incorporated into evidence-based strategies for reducing the global burden of preeclampsia and improving pregnancy outcomes.

V. CONCLUSION

Conclusion

This systematic review aimed to comprehensively evaluate the relationship between maternal vitamin D status, inflammatory biomarkers, angiogenic regulation, and the development of preeclampsia by synthesizing evidence from recent international studies. Following a structured literature search and study selection process, **30 eligible studies involving approximately 4,250 pregnant women** were included in the qualitative synthesis. Overall, the evidence consistently demonstrated that lower maternal serum 25-hydroxyvitamin D [25(OH)D] concentrations were associated with an increased risk and greater severity of preeclampsia. Women with vitamin D deficiency generally exhibited elevated concentrations of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), together with reduced levels of the anti-inflammatory cytokine interleukin-10 (IL-10), indicating disruption of maternal immune homeostasis. Furthermore, adequate vitamin D status was consistently associated with more favorable angiogenic profiles, including lower circulating soluble fms-like tyrosine kinase-1 (sFlt-1) concentrations, higher placental growth factor (PlGF) levels, and a reduced sFlt-1/PlGF ratio, which collectively reflect improved placental vascular adaptation and endothelial function. Several studies also reported better uterine artery Doppler findings among pregnant women with sufficient vitamin D concentrations, supporting the biological role of vitamin D in placental development and vascular remodeling. Although the overall findings provide strong evidence of an association between vitamin D status and the inflammatory and angiogenic pathways involved in preeclampsia, considerable heterogeneity among study designs, supplementation protocols, laboratory methods, participant characteristics, and potential confounding factors precludes definitive conclusions regarding causality. Therefore, vitamin D should currently be regarded as a promising complementary biomarker and potential supportive strategy for optimizing maternal health rather than a standalone intervention for preventing preeclampsia. Future research should prioritize large-scale multicenter randomized controlled trials with standardized vitamin D supplementation protocols, harmonized diagnostic criteria, and integrated evaluation of inflammatory cytokines, angiogenic biomarkers, placental function, genetic susceptibility, and long-term maternal and neonatal outcomes. Such investigations will strengthen the evidence base necessary for developing personalized preventive strategies and improving the clinical management of preeclampsia.

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DATA AVAILABILITY

All data analyzed during this study are included in the published articles cited in this manuscript. Additional information is available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTION

Author 1 conceptualized the study, designed the research methodology, conducted the literature search, screened and selected eligible studies, performed data extraction and synthesis, interpreted the findings, and prepared the original manuscript draft. Author 2 contributed to the study design, validated the methodology, critically reviewed the extracted data, and revised the manuscript for important intellectual content. Author 3 supervised the overall research process, provided scientific guidance, verified the interpretation of the findings, and approved the final version of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

DECLARATIONS

ETHICAL APPROVAL

Not applicable. This study is a systematic review based exclusively on published literature and did not involve human participants, animals, or identifiable personal data.

CONSENT FOR PUBLICATION PARTICIPANTS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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