Metabolism Open 25 (2025) 100350

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

The role of vitamin D deficiency in placental dysfunction: A systematic review

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ARTICLE INFO

Keywords:
Vitamin D deficiency
Placental dysfunction
Pregnancy outcomes
Angiogenesis
Immune regulation

ABSTRACT

Introduction: Vitamin D plays a critical role in pregnancy, supporting placental function via angiogenesis, immune regulation, and nutrient transport. Deficiency in vitamin D during gestation is associated with complications such as preeclampsia, intrauterine growth restriction (IUGR), and preterm birth. However, the mechanisms linking vitamin D deficiency to placental dysfunction remain inadequately understood, highlighting the need for systematic evaluation.

Methods: A systematic review was conducted in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with searches in PubMed, Scopus, and Web of Science for studies published within the last 20 years. Inclusion criteria targeted human studies examining the association between vitamin D and placental function, including randomized controlled trials, cohort studies, and case-control studies. A total of 10 studies were included following rigorous screening and quality assessment.

Results: Findings from human studies indicate that maternal vitamin D deficiency significantly impairs placental function by reducing vascular integrity, downregulating nutrient transporters, and promoting inflammation. Mechanistic evidence highlights decreased expression of vascular endothelial growth factor (VEGF) and increased inflammatory cytokines in vitamin D-deficient pregnancies. Supplementation with active vitamin D [1α,25(OH)2D3] mitigated these adverse effects, restoring placental growth, improving nutrient transport, and reducing inflammation. Notably, population-specific differences and sex-specific responses to vitamin D sufficiency were observed.

Conclusions: Vitamin D is essential for optimal placental function and pregnancy outcomes. This review underscores the need for standardized supplementation protocols and further research into long-term and population-specific effects of vitamin D. Addressing these gaps can inform targeted interventions to reduce pregnancy complications and improve maternal-fetal health.

1. Introduction

Vitamin D, a fat-soluble secosteroid hormone, is well-recognized for its pivotal role in calcium and phosphate homeostasis, immune modulation, and cellular differentiation [1,2]. Its importance becomes even more pronounced during pregnancy, a period marked by profound physiological changes to support both maternal and fetal health. During gestation, vitamin D contributes to critical processes such as fetal skeletal development, regulation of maternal immune tolerance to the semi-allogenic fetus, and maintenance of optimal placental function. These roles underscore its broader significance in ensuring a healthy pregnancy and favorable outcomes for both mother and child [3].

The placenta is a transient yet essential organ unique to pregnancy. It serves as the critical interface between the maternal and fetal systems. Its multifaceted functions include facilitating the transfer of nutrients and oxygen from the mother to the fetus, eliminating fetal waste products, and orchestrating complex endocrine signaling to sustain pregnancy [4,5]. However, disruptions in placental activity have been strongly linked to adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction (IUGR), and preterm birth. These complications significantly contribute to maternal and neonatal morbidity and mortality on a global scale, posing substantial challenges to

This article is part of a special issue entitled: Vitamin D published in Metabolism Open.

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https://doi.org/10.1016/j.metop.2025.100350
Received 28 December 2024; Received in revised form 24 January 2025; Accepted 24 January 2025
Available online 31 January 2025

healthcare systems [6,7].

Emerging evidence highlights the potential role of vitamin D in modulating placental health. Specifically, vitamin D deficiency during pregnancy has been implicated in impairments of trophoblast invasion, angiogenesis, and immune regulation, which are vital for normal placental development and function [8]. Trophoblast invasion is crucial for anchoring the placenta to the uterine wall and establishing adequate blood flow to support fetal growth [9]. Angiogenesis, the formation of new blood vessels, ensures the placenta's capacity to supply nutrients and oxygen to the growing fetus [10]. Additionally, immune regulation mediated by the placenta is essential for protecting the pregnancy from maternal immune responses that might otherwise reject the fetus [11].

Despite advancements in understanding the role of vitamin D in pregnancy [12], its direct influence on placental function remains incompletely understood. This knowledge gap limits the ability to develop evidence-based, targeted interventions aimed at mitigating complications related to placental dysfunction. Addressing this gap is imperative, as enhancing our understanding of vitamin D's role in placental biology could inform novel strategies to reduce the incidence of adverse pregnancy outcomes and improve maternal-fetal health worldwide.

While several studies have investigated the association between vitamin D deficiency and adverse pregnancy outcomes [13–15], the underlying mechanisms linking vitamin D status to placental dysfunction are not fully elucidated. Additionally, heterogeneity in study designs, population characteristics, and methods of assessing vitamin D levels presents challenges in synthesizing the existing evidence.

This systematic review aims to critically appraise and synthesize the current evidence on the role of vitamin D deficiency in placental dysfunction. By examining clinical and mechanistic studies, the review seeks to provide a comprehensive understanding of this relationship and identify areas for future research.

2. Methods

2.1. Search strategy

We conducted a comprehensive search using the following electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search strategy incorporated key terms and their combinations, including "vitamin D", "calcitriol", "placental dysfunction", "placental insufficiency", "placental pathology", and "pregnancy outcomes". We applied filters for studies published in the last 20 years. We have also registered this systematic review in International Prospective Register of Systematic Reviews (PROSPERO) with ID number CRD42024626920.

2.2. Inclusion criteria and exclusion criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Studies were included in the review if they met the following criteria: a) Investigated the relationship between vitamin D levels and placental dysfunction; b) Conducted on human populations and designed as randomized controlled trials (RCTs), cohort studies, case-control studies, or cross-sectional studies and c) Published in the English language.

Studies were excluded if they: a) Were conducted on non-human subjects and b) Lacked clear outcomes related to placental function.

2.3. PRISMA process

The PRISMA process is illustrated in Fig. 1.

2.4. Identification

We conducted a comprehensive search across multiple databases, including PubMed, Scopus, and Web of Science, yielding 450 records. We identified an additional 30 records through manual searches and reference lists of relevant articles. This resulted in a total of 480 records.

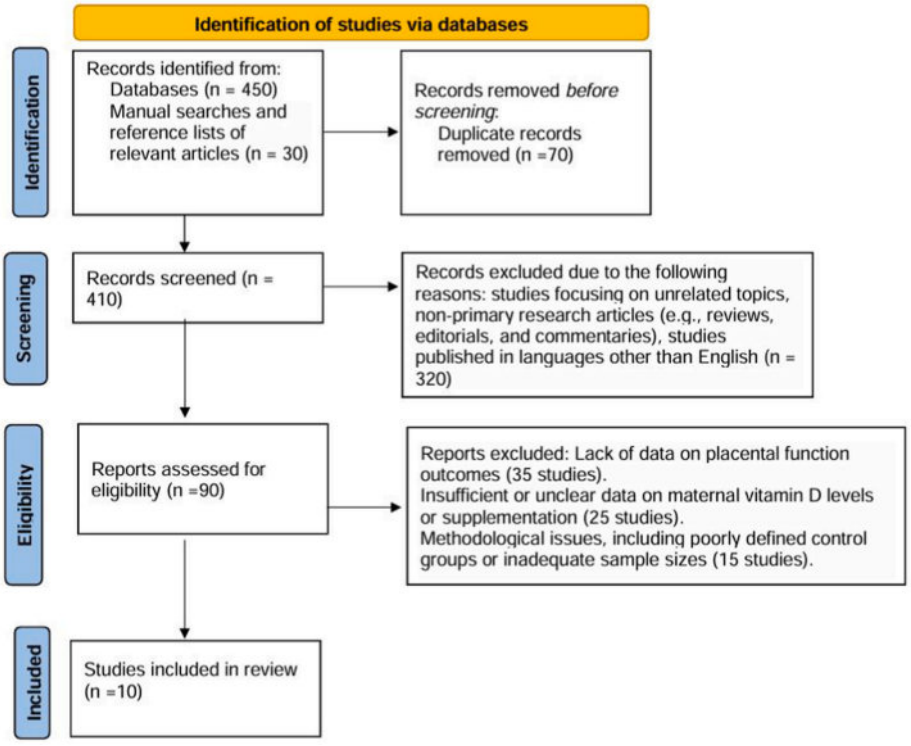

Fig. 1. PRISMA process.

2.5. Screening

After the removal of 70 duplicates, we screened 410 records by titles and abstracts. During this stage, we excluded 320 records based on the following reasons: a) Studies focusing on unrelated topics; b) Non-primary research articles (e.g., reviews, editorials, and commentaries) and c) Studies published in languages other than English. This left 90 articles for full-text review.

2.6. Eligibility

We assessed the full texts of 90 articles for eligibility. Of these, we excluded 80 articles for the following reasons: a) Lack of data on placental function outcomes (35 studies); b) Insufficient or unclear data on maternal vitamin D levels or supplementation (25 studies); c) Methodological issues, including poorly defined control groups or inadequate sample sizes (15 studies) and d) Non-primary research such as opinion papers or position statements (5 studies).

2.7. Inclusion

Finally, 10 studies met all inclusion criteria and were included in the qualitative synthesis.

2.8. Methodological quality assessment

Two authors independently assessed the quality of the included studies. No discrepancies were found between their evaluations, eliminating the need for arbitration. We evaluated the methodological quality of the studies using appropriate tools tailored to the study designs. For randomized controlled trials (RCTs), we employed the Cochrane Risk of Bias (RoB 2.0) tool [17]. We applied the Newcastle-Ottawa Scale (NOS) [18] and the Joanna Briggs Institute (JBI) Critical Appraisal Tool for cohort and case-control studies [19]. The quality assessment of the included studies is provided in Supplementary File 1.

2.9. Data extraction

Two independent reviewers extracted data from each included study. The extracted data comprised the first author, publication year, country, study design, sample characteristics (e.g., size and subgroups), outcomes measured and main findings.

Discrepancies between reviewers were resolved through consensus. In cases where agreement was not reached, a third reviewer was consulted to ensure accuracy and consistency in the extracted data.

3. Results

The studies included [20–29], collectively demonstrate the pivotal role of maternal vitamin D levels in placental function. The studies represent a diverse range of research designs and geographic contexts, including RCTs, cohort studies, and case-control studies conducted in the USA, Korea, Denmark, and France. Sample sizes ranged from small, targeted studies of 43 participants to large-scale cohort analyses involving up to 2146 participants. Summary of the studies' characteristics is displayed in Table 1.

Awe et al. [20] and Schulz et al. [27] demonstrated significant downregulation of antiangiogenic markers such as Soluble Fms-like Tyrosine Kinase-1 (sFlt-1) in vitamin D-sufficient mothers, underscoring its critical role in angiogenesis regulation and placental vascular integrity. Similarly, Cho et al. [21] identified vitamin D deficiency as a contributor to gestational diabetes mellitus (GDM) through elevated placental Cytochrome P450 Family 24 Subfamily A Member 1 (CYP24A1) expression, which may disrupt vitamin D metabolism and placental function.

Gernand et al. [22] found that maternal vitamin D sufficiency reduced placental vascular pathology risk in male pregnancies and lowered the incidence of small for gestational age (SGA) births, indicating a sex-specific protective effect. He et al. [23] and Mead et al. [24] reported improved placental structural parameters, such as increased villous surface density and higher placental weight, in vitamin D-sufficient mothers, although histological changes remained minimal. Phillips et al. [25] added that vitamin D sufficiency enhanced placental mitochondrial function and reduced inflammatory markers, further supporting its pivotal role in maintaining placental performance.

Raia-Barjat et al. [26] highlighted a fivefold increased risk of placenta-mediated complications (PMCs) in vitamin D-deficient mothers, emphasizing the severe consequences of deficiency on placental health. Vestergaard et al. [28] provided compelling evidence that high-dose vitamin D supplementation significantly reduced pre-eclampsia, fetal growth restriction, and other adverse outcomes by improving angiogenic balance and placental function, suggesting policy-level benefits. Lastly, Gernand et al. [29], Collaborative Perinatal Project) demonstrated that maternal vitamin D sufficiency was associated with enhanced fetal growth metrics, such as increased birth weight and head circumference, further highlighting its importance in mitigating placental dysfunction.

4. Discussion

This study investigated the relationship between maternal vitamin D levels and placental function, focusing on the regulatory role of vitamin D in angiogenesis, immune modulation, and overall placental health. The findings demonstrated that vitamin D sufficiency during pregnancy is significantly associated with improved placental vascular integrity, reduced expression of antiangiogenic markers such as sFlt-1, and enhanced structural parameters, including villous surface density. Furthermore, vitamin D sufficiency correlated with reduced inflammation, improved mitochondrial function, and better neonatal outcomes, emphasizing its multifaceted role in maintaining placental performance.

Vitamin D deficiency has been closely associated with significant disruptions in placental function, including impaired angiogenesis, immune regulation, and nutrient transport [30]. Studies demonstrate that maternal vitamin D deficiency decreases the expression of vascular endothelial growth factor (VEGF), which is critical for vascular development in the labyrinth zone of the placenta. The labyrinth zone is a highly vascular region responsible for nutrient and gas exchange between the mother and fetus. Insufficient vascular development in this region leads to vascular insufficiency, mirroring adverse pregnancy outcomes such as IUGR and preeclampsia observed in vitamin D-deficient pregnancies [30]. Vitamin D plays a pivotal role in regulating trophoblast invasion, a process essential for anchoring the placenta to the uterine wall and establishing adequate maternal-fetal circulation. The inhibition of trophoblast invasion under vitamin D-deficient conditions suggests a critical link between maternal vitamin D status and placental attachment abnormalities, ultimately contributing to adverse perinatal outcomes [30].

Additionally, vitamin D deficiency has been shown to modulate glucocorticoid signaling, significantly impacting fetal exposure to stress hormones. A key finding is the reduced expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in vitamin D-deficient placentas. This enzyme normally inactivates maternal glucocorticoids, thereby protecting the fetus from excessive exposure to stress hormones. Its reduced expression leads to increased fetal glucocorticoid exposure, disrupting normal fetal growth and development. This dysregulation is further compounded by elevated maternal glucocorticoid levels often associated with vitamin D deficiency, which may trigger placental inflammation and vascular insufficiency [30].

Vitamin D deficiency during gestation has profound implications for both placental function and fetal development, as demonstrated also by experimental mouse models. The study by Chen et al. [31] found that vitamin D deficiency significantly reduced fetal weight and crown-rump

Table 1
Summary of the studies' characteristics.

N	Authors	Year	Study Type	Country	Sample (Subjects and Comparators)	Measurements	Outcomes	Main Findings
1	Awe et al. [20]	2020	Randomized, Placebo-Controlled Clinical Trial	USA	43 pregnant women aged 18–45; randomized to receive placebo or 4000 IU/day vitamin D3 plus standard prenatal vitamins (400 IU vitamin D3). Subgroups based on maternal vitamin D sufficiency: sufficient (≥100 nmol/L) vs. deficient (<100 nmol/L).	Placental mRNA expression of sFlt-1, Flt-1, Sam68; maternal vitamin D levels at baseline and delivery; gene correlations by race/ethnicity (African American, Caucasian, Hispanic American).	Differential expression levels of sFlt-1, Flt-1, and Sam68 based on vitamin D sufficiency. Strong correlations observed between Sam68 and sFlt-1 mRNA levels across populations.	Vitamin D sufficiency was associated with lower placental mRNA levels of Sam68 and sFlt-1. Vitamin D sufficiency was associated with a 3.3-fold decrease in sFlt-1, 2.6-fold decrease in Flt-1, and 6.3-fold decrease in Sam68 expression. These results suggest a potential regulatory role for vitamin D in angiogenesis-related pathways crucial for placental function.
2	Cho et al. [21]	2013	Case-Control Study	Korea	60 pregnant women: 40 with normal pregnancies and 20 with gestational diabetes mellitus (GDM). Maternal serum and placental tissue samples collected at delivery.	Maternal serum vitamin D (25(OH)D) levels; placental expression of VDR, CYP27B1, and CYP24A1 using PCR, Western blot, and immunohistochemistry.	Women with GDM had significantly lower serum 25(OH)D levels and higher prevalence of vitamin D deficiency (85 %) compared to controls (27.5 %). Placental CYP24A1 expression and protein levels were significantly elevated in GDM.	Vitamin D deficiency is associated with GDM. Elevated placental CYP24A1 may contribute to decreased maternal vitamin D levels, as it deactivates both 25(OH)D and 1,25(OH)2D. This suggests a role for placental vitamin D metabolism in GDM pathophysiology.
3	Gernand et al. [22]	2013	Multicenter Cohort Study	USA	2048 singleton term pregnancies from the Collaborative Perinatal Project (1959–1966); maternal vitamin D levels measured at ≤26 weeks gestation. Placental pathology analyzed for vascular lesions.	Maternal serum 25(OH)D; placental vascular pathology (e.g., infarcts, thrombosis); infant sex and birth weight.	Maternal 25(OH)D ≥ 80 nmol/L reduced placental vascular pathology risk in male pregnancies by 49 %. No association was observed in female pregnancies. Birth weight was significantly lower in female pregnancies with placental pathology and maternal vitamin D deficiency.	Higher maternal vitamin D levels (≥80 nmol/L) were protective against placental vascular pathology in male pregnancies but not female pregnancies. Placental pathology associated with lower birth weight only in female pregnancies with vitamin D deficiency.
4	He et al. [23]	2020	Nested Case-Control Study (VDAART)	USA	47 placentas from singleton pregnancies, subgrouped by maternal vitamin D levels: sufficient (>32 ng/mL) vs. insufficient (<32 ng/mL). 27 placentas analyzed for histopathology; 11 for RNA sequencing.	Placental histopathology (e.g., chorioamnionitis, villous density); maternal serum 25(OH)D levels (baseline, third trimester); gene expression profiles (RNA sequencing).	Higher villous surface density in sufficient 25(OH)D group (third trimester); significant gene expression differences (CNTN5, INTS9, vWF, MACC1, ARMS2); no significant histopathological differences except for increased multinucleated trophoblastic giant cells in the sufficient group.	Maternal vitamin D sufficiency had limited effects on placental structure but modulated gene expression. Higher villous surface density suggested enhanced maternal-fetal transport capacity. Chronic chorioamnionitis was associated with offspring asthma.
5	Mead et al. [24]	2023	Secondary Analysis of RCT (Kellogg Pregnancy Study)	USA	115 placentas from singleton pregnancies, subgrouped by maternal vitamin D supplementation: 400 IU/day (control) vs. 4400 IU/day (intervention). Serum 25(OH)D levels categorized as deficient (<20 ng/mL), insufficient (20–32 ng/mL), and sufficient (>32 ng/mL).	Placental weight, maternal serum 25(OH)D levels, and placental pathologies (vascular and inflammatory) categorized using Amsterdam Consensus Criteria.	Maternal 25(OH)D levels positively correlated with placental weight ($p = 0.0009$). No significant differences in placental lesions by treatment group. Placentas in intervention group had fewer lesions but the trend was not significant.	Elevated maternal serum 25(OH)D levels associated with increased placental weight but not with adverse morphology. Findings emphasize the importance of adequate vitamin D supplementation during pregnancy for healthy placental development.

(*continued on next page*)

Table 1 (*continued*)

N	Authors	Year	Study Type	Country	Sample (Subjects and Comparators)	Measurements	Outcomes	Main Findings
6	Phillips et al. [25]	2022	Cross-Sectional Study with In Vitro Analysis	USA	Placental samples and maternal blood collected from 57 normal-weight (NW) and obese (OB) women undergoing C-section; in vitro experiments with cytotrophoblasts treated with calcitriol (active vitamin D).	Maternal and fetal serum 25 (OH)D levels; placental VDR and CYP27B1 expression; mitochondrial function (oxygen consumption); inflammatory markers (NLRP3, IL-18).	Maternal BMI negatively correlated with vitamin D levels in maternal and cord blood. Vitamin D sufficiency improved placental mitochondrial respiration and reduced IL-18 expression in cytotrophoblasts.	Maternal obesity reduced placental VDR expression and mitochondrial function. Vitamin D supplementation increased VDR levels, enhanced mitochondrial respiration, and reduced inflammation in placental cells.
7	Raia-Barjat et al. [26]	2021	Prospective Multicenter Cohort Study	France	182 pregnant women at high risk for placenta-mediated complications (PMCs). Subgrouped based on serum 25(OH) D levels: deficient (<20 ng/mL), insufficient (20–29 ng/mL), sufficient (≥30 ng/mL).	Maternal serum 25(OH)D levels (measured at five time points during pregnancy); PMC occurrence, including preeclampsia (PE), intrauterine growth restriction (IUGR), and other complications.	At 32 weeks, vitamin D deficiency increased the risk of PMCs fivefold compared to sufficient levels (RR: 5.14; 95 % CI: 1.50–17.55). Late PMCs were more strongly associated with low vitamin D than early PMCs.	Vitamin D deficiency (<20 ng/mL) at 32 weeks was a strong predictor of PMCs, especially late-onset complications (beyond 34 weeks). This highlights the potential protective role of vitamin D in maintaining placental performance and reducing PMC risks.
8	Schulz et al. [27]	2017	Randomized Controlled Trial (RCT)	USA	43 placentas from singleton pregnancies, subgrouped by maternal serum 25(OH) D levels: sufficient (≥100 nmol/L) vs. deficient (<100 nmol/L). Maternal serum vitamin D was supplemented with either 400 IU or 4400 IU/day.	Placental mRNA expression of angiogenic biomarkers (sFlt-1, VEGF, PGF), hormones (hPL, PRB), and vitamin D metabolism genes (CYP27B1, CYP24A1); maternal and fetal vitamin D levels.	Maternal 25(OH)D sufficiency significantly downregulated sFlt-1 and VEGF gene expression compared to deficiency. PRB and hPL were significantly upregulated in vitamin D sufficient mothers.	Maternal vitamin D sufficiency was associated with reduced antiangiogenic markers (sFlt-1) and improved placental gene expression profiles, highlighting its protective role against vascular complications such as preeclampsia.
9	Vestergaard et al. [28]	2023	Double-Blinded Randomized Controlled Trial (GRAVITD Study)	Denmark	2000 pregnant women (gestational weeks 10–14) randomized to 90 μg/day vitamin D (intervention) vs. 10 μg/day (control). Maternal serum levels and placental samples collected at delivery.	Maternal serum 25(OH)D, placental function (angiogenic markers, vitamin D metabolism genes), and pregnancy outcomes: preeclampsia (PE), fetal growth restriction (FGR), gestational diabetes mellitus (GDM).	Higher maternal 25 (OH)D levels associated with reduced PE and FGR incidence, improved placental function, and better neonatal outcomes. Secondary outcomes included fewer adverse events in intervention group.	High-dose vitamin D supplementation (90 μg/day) reduced adverse pregnancy outcomes related to placental dysfunction (PE, GDM, FGR) and enhanced placental angiogenic and vitamin D metabolism gene expression. Findings suggest modifying national guidelines for vitamin D supplementation in pregnancy.
10	Gernandet al. [29]	2013	Observational Cohort Study (Collaborative Perinatal Project)	USA	2146 singleton term pregnancies (1959–1965); subgrouped by maternal serum 25(OH) D levels: sufficient (≥37.5 nmol/L) vs. deficient (<37.5 nmol/L). Maternal serum collected at ≤26 weeks of gestation.	Maternal serum 25(OH)D levels, birth weight, head circumference, placental weight, placental-to-fetal weight ratio, and SGA.	Maternal vitamin D sufficiency was associated with higher birth weight (+46g), larger head circumference (+0.13 cm), and reduced risk of SGA by 50 % in the first trimester. No association was observed with placental weight or placental-to-fetal weight ratio.	Maternal 25(OH)D levels ≥37.5 nmol/L were positively associated with physiological fetal growth and negatively associated with SGA risk, but not with placental weight or morphology. Findings emphasize the role of maternal vitamin D status in early pregnancy for fetal growth outcomes.

1,25(OH)2D - 1,25-Dihydroxyvitamin D; **25(OH)D** - 25-Hydroxyvitamin D; **ARMS2** - Age-Related Maculopathy Susceptibility 2; **BMI** - Body Mass Index; **C-section** - Cesarean Section; **CI** - Confidence Interval; **CNTN5** - Contactin 5; **CYP24A1** - Cytochrome P450 Family 24 Subfamily A Member 1; **CYP27B1** - Cytochrome P450 Family 27 Subfamily B Member 1; **FGR** - Fetal Growth Restriction; **Flt-1** - Fms-like Tyrosine Kinase-1; **GDM** - Gestational Diabetes Mellitus; **hPL** - Human Placental Lactogen; **IL-18** - Interleukin-18; **INTS9** - Integrator Complex Subunit 9; **IU** - International Units; **IUGR** - Intrauterine Growth Restriction; **MACC1** - Metastasis Associated in Colon Cancer 1; **mRNA** - Messenger RNA; **NG** – Nanogram; **nmol/L** - Nanomoles per Liter; **NLRP3** - NOD-, LRR- and Pyrin Domain-Containing Protein 3; **PCR** - Polymerase Chain Reaction; **PE** – Preeclampsia; **PGF** - Placental Growth Factor; **PMC** - Placenta-Mediated Complications; **PRB** - Progesterone Receptor Beta; **RCT** - Randomized

Controlled Trial; **RNA** - Ribonucleic Acid; **RR** - Relative Risk; **Sam68** - Src-associated in Mitosis 68; **sFlt-1** - Soluble Fms-like Tyrosine Kinase-1; **SGA** - Small for Gestational Age; **VEGF** - Vascular Endothelial Growth Factor; **VDAART** - Vitamin D Antenatal Asthma Reduction Trial; **VDR** - Vitamin D Receptor; **vWF** - Von Willebrand Factor.

length, both key markers of IUGR. Mechanistically, vitamin D deficiency was shown to impair placental development by reducing placental weight, diameter, and cell proliferation in critical regions such as the labyrinth layer, which mediates nutrient and oxygen exchange between the mother and fetus [31]. Moreover, nutrient transporters such as glucose transporter 1 (GLUT1), sodium-coupled neutral amino acid transporter 2 (SNAT2), and fatty acid transport protein 4 (FATP4), essential for glucose, amino acid, and fatty acid transfer, were downregulated in vitamin D-deficient mice, further compromising placental function. This dysfunction was accompanied by a marked decrease in angiogenic and growth factors, including vascular endothelial growth factor alpha (VEGF-α), placental growth factor (PGF), and insulin-like growth factor 2 (IGF2), which are pivotal for placental vascularization and overall development [31].

In addition to structural and functional disruptions, vitamin D deficiency was found to induce placental inflammation, as evidenced by upregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 alpha (IL-17α), and interferon-gamma (IFN-γ), as well as chemokines such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), and keratinocyte-derived chemokine (KC). The nuclear translocation of nuclear factor kappa B (NF-κB) p65, a key transcriptional regulator of inflammation, was significantly higher in the placentas of vitamin D-deficient mice compared to controls, suggesting a mechanistic link between vitamin D deficiency and inflammation-mediated placental insufficiency [31]. Human data corroborated these findings, showing higher levels of inflammatory markers and reduced placental diameter in vitamin D-deficient pregnancies compared to controls. Notably, supplementation with 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3], the active form of vitamin D, mitigated many of these adverse effects, restoring placental growth, nutrient transporter expression, and reducing inflammation [31].

This systematic review has several notable strengths. A comprehensive and rigorous search strategy was employed, incorporating multiple databases, including PubMed, Scopus, and Web of Science, alongside manual searches of reference lists. This ensured the inclusion of diverse geographic and research contexts, enhancing the reliability and generalizability of the findings. Adherence to PRISMA guidelines further strengthened the review's methodological rigor, providing transparency in the selection and evaluation of studies. The review's multifaceted focus on angiogenesis, immune modulation, and nutrient transport offered an integrated perspective on the critical role of vitamin D in placental physiology. Moreover, the robust quality assessment process, which utilized established tools such as the Cochrane Risk of Bias tool and Newcastle-Ottawa Scale, bolstered the internal validity of the review. By integrating both clinical and mechanistic evidence, the review provided a comprehensive understanding of vitamin D's role in placental health, while also highlighting population-specific variations, such as sex-specific vascular responses, which emphasize the need for tailored interventions. The findings have significant policy implications, particularly regarding the potential role of high-dose vitamin D supplementation in reducing pregnancy complications like preeclampsia and fetal growth restriction.

This systematic review highlights several critical areas for future research to address the limitations and knowledge gaps identified in the literature. Longitudinal studies are essential to elucidate the long-term effects of maternal vitamin D sufficiency on offspring health, particularly concerning fetal programming and its influence on chronic diseases later in life. Understanding how maternal vitamin D levels impact transgenerational health outcomes could provide valuable insights into preventive strategies for at-risk populations.

Population-specific studies are necessary to explore variations in outcomes based on genetic predispositions, dietary habits, environmental exposures, and sex-specific differences in placental function. These factors may significantly influence how vitamin D sufficiency impacts pregnancy outcomes, and understanding them could inform tailored supplementation guidelines. Furthermore, large-scale, RCTs are needed to standardize dosage, timing, and duration of vitamin D supplementation during pregnancy. This standardization would allow for clearer guidelines on how to optimize maternal and fetal health outcomes.

Mechanistic research focusing on human placentas is imperative to delineate the causal pathways linking vitamin D deficiency to placental dysfunction. Current findings are predominantly based on animal models or observational studies, leaving gaps in understanding how vitamin D modulates specific pathways such as angiogenesis, immune regulation, and glucocorticoid signaling in humans. Exploring these mechanisms could identify novel therapeutic targets for intervention.

Lastly, future research should prioritize examining the combined effects of vitamin D sufficiency with other micronutrients or prenatal health interventions. Integrative approaches could provide a broader understanding of maternal-fetal health dynamics and offer holistic strategies for mitigating placental dysfunction and associated adverse pregnancy outcomes.

4.1. Limitations

Despite these strengths, the review has several limitations that must be acknowledged. Significant heterogeneity in study designs, population characteristics, and measures of vitamin D status complicated the synthesis of findings and limited the strength of pooled conclusions. Furthermore, the exclusion of non-English studies and non-human research may have overlooked valuable insights into vitamin D's effects on placental biology. Only 10 studies met the inclusion criteria, which raises concerns about the breadth of evidence and potential publication bias. Additionally, most included studies lacked longitudinal follow-up, limiting the understanding of the long-term implications of maternal vitamin D sufficiency for offspring health. The focus on vitamin D deficiency (<20 ng/mL) without sufficient exploration of insufficiency (20–30 ng/mL) represents another critical gap, particularly as insufficiency is more prevalent and may also impact placental function.

Moreover, inconsistent reporting of vitamin D supplementation regimens across studies, including variations in dosage, timing, and duration, posed challenges to the development of standardized recommendations. Confounding factors, such as maternal comorbidities, dietary habits, and environmental exposures, were not consistently controlled, potentially biasing results. While animal studies provided robust mechanistic insights, human studies were largely observational, leaving causal pathways linking vitamin D deficiency to placental dysfunction incompletely understood. Small sample sizes in several clinical studies further reduced statistical power, limiting the reliability of subgroup analyses, such as sex-specific effects. Collectively, these limitations underscore the need for further high-quality research to standardize methodologies, explore long-term effects, and address confounding variables.

5. Conclusions

Vitamin D deficiency during pregnancy is increasingly recognized as a critical factor contributing to placental dysfunction, with implications for adverse maternal and fetal outcomes. This systematic review highlights the multifaceted role of vitamin D in regulating key placental functions, including angiogenesis, immune modulation, nutrient

transport, and glucocorticoid signaling. The findings emphasize that maternal vitamin D sufficiency is associated with improved placental vascular integrity, reduced inflammation, and better neonatal outcomes, underscoring its importance for optimal pregnancy health. However, significant gaps in the current literature remain, particularly in understanding the long-term and population-specific effects of vitamin D, as well as the mechanisms linking its deficiency to placental insufficiency. Addressing these gaps through robust, standardized research is essential to developing evidence-based strategies for mitigating pregnancy complications and improving maternal and neonatal health worldwide.

CRediT authorship contribution statement

Eleni Gerovasili: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antigoni Sarantaki:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Data curation. **Anastasia Bothou:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Data curation. **Anna Deltsidou:** Writing – review & editing, Visualization. **Aikaterini Dimitrakopoulou:** Writing – review & editing, Visualization, Conceptualization. **Athina Diamanti:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

There was no source of funding for this research.

Conflict of interest

The authors declare no competing interests.

Acknowledgements

During the preparation of this work, AI tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the final content of the present manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2025.100350.

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