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# Correlation of Maternal Vitamin D Deficiency with Hypertensive Disorders of Pregnancy

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**Abstract**

**Background**: Hypertensive disorders of pregnancy (HDP), especially pre-eclampsia (PE), are major causes of maternal and perinatal morbidity and mortality. Emerging evidence suggests maternal vitamin D deficiency (VDD) may be associated with increased risk of HDP.

**Objective**: To review and synthesize current evidence on the correlation between maternal vitamin D deficiency and hypertensive disorders of pregnancy.

**Methods**: Narrative systematic-review style synthesis of observational studies, randomized controlled trials (RCTs), and meta-analyses published through 2025 using PubMed/PMC and major journal databases.

**Keyoutcomes**: incidence of gestational hypertension (GH) and pre-eclampsia (PE) in relation to maternal serum 25-hydroxyvitamin D (25(OH)D) levels and effects of vitamin D supplementation.

**Results**: Multiple observational studies and meta-analyses report an inverse association between maternal 25(OH)D and risk of pre-eclampsia; several RCTs and pooled analyses indicate that vitamin D supplementation during pregnancy may reduce PE risk, though heterogeneity exists regarding dose, timing, and study quality. Mechanistic studies propose immunomodulatory, anti-inflammatory and placental angiogenesis pathways whereby vitamin D could influence HDP pathogenesis. Not all studies agree: some recent pooled analyses and cohort studies report non-significant associations or effect modification by baseline vitamin D status and geographic/seasonal factors.

**Conclusions**: The preponderance of evidence supports a correlation between low maternal vitamin D status and increased risk of pre-eclampsia, and some trials/meta-analyses indicate potential benefit from supplementation. However, heterogeneity in study design, supplementation regimens, and confounding limits definitive causal claims. Larger, well-powered randomized trials with standardized dosing and timing, and mechanistic work, are needed to guide specific clinical recommendations.

**Keywords:** Vitamin D, 25-hydroxyvitamin D, pre-eclampsia, gestational hypertension, hypertensive disorders of pregnancy, pregnancy, supplementation.

## Introduction

Hypertensive disorders of pregnancy (HDP), particularly pre-eclampsia, affect an estimated 2–8% of pregnancies worldwide and are a leading cause of maternal and perinatal morbidity and mortality. [1] Research has focused on maternal risk factors and pathophysiologic mechanisms—placental dysfunction, endothelial injury, and exaggerated inflammatory responses—many of which are plausibly influenced by vitamin D biology. Vitamin D (measured as serum 25-hydroxyvitamin D, 25(OH)D) has

roles beyond calcium homeostasis, including immunomodulation, regulation of angiogenic factors, and trophoblast function, mechanisms relevant to HDP pathogenesis. [2][3]

Vitamin D deficiency (VDD) is common in pregnant populations globally, with prevalence estimates varying by region, skin pigmentation, sun exposure and supplementation practices. Observational epidemiology, mechanistic studies, and randomized trials over the last decade have explored whether maternal VDD correlates with higher incidence of gestational hypertension and pre-eclampsia. This review synthesizes the evidence and highlights gaps for future research.

## Methods

A targeted literature search was carried out in PubMed/PMC and major journal sites for articles published up to 2025 addressing maternal vitamin D status and hypertensive disorders of pregnancy. Search terms included "vitamin D", "25-hydroxyvitamin D", "pregnancy", "preeclampsia", "gestational hypertension", "vitamin D supplementation", and combinations thereof. Both observational studies (cohort, case-control) and interventional trials (RCTs) plus systematic reviews / meta-analyses were included to form a narrative synthesis. Priority was given to higher-quality evidence (large cohorts, meta-analyses, RCTs) and influential mechanistic/review papers.

## Results

### 1. Observational evidence: association between low maternal 25(OH)D and HDP

Several cohort and case–control studies report lower mean maternal 25(OH)D among women who later develop pre-eclampsia compared with normotensive controls and an inverse relationship between 25(OH)D concentration and PE risk. Large cohort analyses (including multi-thousand subject studies) have described a significant association between mid-pregnancy vitamin D deficiency and increased PE incidence even after adjustment for some confounders, though residual confounding (BMI, ethnicity, season) remains a challenge. [2][4][5]

However, not all observational studies find consistent results: some report no significant association between vitamin D and pregnancy-induced hypertension (PIH) after adjustment, suggesting heterogeneity by population, baseline vitamin D status, or study timing of measurement (first vs second trimester). [6]

### 2. Mechanistic plausibility

Vitamin D acts via the vitamin D receptor (VDR) which is expressed in placental tissue; proposed mechanisms linking VDD to HDP include modulation of immune responses (shifting away from pro-inflammatory cytokine profiles), regulation of angiogenic/anti-angiogenic factors (VEGF, sFlt-1, soluble endoglin), and effects on trophoblast invasion and placentation. These mechanisms support biological plausibility for an influence of vitamin D on early placental development and subsequent risk of pre-eclampsia. [7][8]

### 3. Randomized trials and supplementation studies

Randomized trials of vitamin D supplementation in pregnancy have primarily targeted neonatal bone outcomes and general maternal–fetal health; only a subgroup of RCTs have hypertensive disorders as primary or secondary outcomes. Several pooled analyses and RCT meta-analyses indicate that vitamin D supplementation during pregnancy is associated with a reduced risk of pre-eclampsia (estimates vary; some pooled results suggest ~30–45% relative risk reduction), particularly when higher doses (≥2000 IU/day or higher cumulative dosing) and early initiation are used. [9][10][11]

Notably, large trials such as MAVIDOS and several others did not uniformly demonstrate BP-lowering effects across all subgroups, and some analyses show benefit mainly in vitamin D–deficient populations or in seasonal/latitude-specific subgroups. The heterogeneity in dose, timing (first vs second trimester), baseline vitamin D status, and trial endpoints complicates direct comparison. [12][13]

**4. Recent high-quality meta-analyses and systematic reviews**

Multiple recent reviews/meta-analyses (2017–2025) converge on an association between low maternal vitamin D and higher PE risk; more recent pooled RCT meta-analyses also suggest supplementation reduces PE incidence, though they flag heterogeneity and risk of bias in included trials. Some analyses emphasize that benefits are more pronounced when baseline deficiency is common and when supplementation is compared with placebo rather than low-dose vitamin D controls. [9][4][5][14]

## Discussion

### Strength of evidence

There is consistent epidemiologic evidence of an inverse correlation between maternal 25(OH)D levels and the risk of pre-eclampsia across many settings, supported by mechanistic plausibility. Several RCTs and meta-analyses support a protective effect of supplementation against pre-eclampsia, particularly when started early and used at sufficient doses. [9][7][5]

### Limitations and heterogeneity

Measurement timing: Studies measure 25(OH)D at different gestational ages; early placentation-related mechanisms would predict a critical window in early pregnancy. [12]

Confounding: BMI, ethnicity/skin pigmentation, socioeconomic status, and seasonal sunlight exposure confound associations and are inconsistently controlled. [2][14]

Supplementation heterogeneity: Trials vary widely in dose (400 IU to large intermittent boluses), regimen, and co-interventions (calcium), making pooled estimates noisy. [9][11]

Outcome definitions: Some studies group gestational hypertension and pre-eclampsia, while others focus on PE alone; differential effects may exist. [13]

### Clinical implications

Given the observational and trial evidence, correcting maternal vitamin D deficiency in pregnancy is reasonable as part of antenatal care, particularly in populations with high prevalence of deficiency. However, definitive universal recommendations (specific dose and timing) to prevent HDP require stronger, consistent RCT evidence targeting hypertensive endpoints as primary outcomes. Current systematic reviews indicate potential benefit but highlight the need for standardized, well-powered trials. [9][8]

### Research recommendations

Large, multi-centre RCTs with primary endpoints of HDP/preeclampsia, stratified by baseline vitamin D status. [7][12]

Studies focusing on timing (preconception/first trimester vs later) and dose-finding to determine minimal effective regimen with safety monitoring. [11][3]

Mechanistic studies linking maternal supplementation → placental biomarkers (sFlt-1, endoglin, exosomal signaling) → clinical endpoints. [8]

## Conclusion

The balance of evidence supports a correlation between maternal vitamin D deficiency and increased ri-

sk of pre-eclampsia, and some randomized evidence suggests supplementation may reduce PE incidence. Heterogeneity in studies—regarding population, measurement timing, supplementation dose/timing, and outcome definitions—limits definitive causal claims and prevents strong universal dosing recommendations solely for HDP prevention at present. Addressing these gaps with well-designed trials and mechanistic studies should be prioritized.

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