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Adverse Maternal Outcomes Associated with Vitamin D Deficiency

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Abstract:

Vitamin D deficiency is highly prevalent among pregnant women globally, particularly in regions with limited sunlight exposure, darker skin pigmentation, cultural clothing practices, and insufficient dietary intake. Maternal vitamin D levels influence calcium homeostasis, immune responses, angiogenesis, placental development, and metabolic regulation. Deficiency during pregnancy has been linked to increased risk of hypertensive disorders, altered glucose regulation, increased susceptibility to infections, and psychological disturbances. Understanding these associations is essential to improving maternal outcomes and guiding antenatal care protocols.

Keywords: Vitamin D deficiency; pregnancy outcomes; gestational diabetes mellitus; preeclampsia; cesarean section; postpartum depression; maternal morbidity; antenatal care.

Introduction:

Vitamin D plays a fundamental physiological role during pregnancy, contributing to calcium metabolism, immune regulation, vascular endothelial integrity, and placental function. Deficiency during pregnancy is common worldwide, with prevalence rates exceeding 40–60% in many populations, especially in the Middle East and South Asia, where sunlight exposure and dietary intake are often inadequate. Low levels of 25-hydroxyvitamin D have been increasingly associated with metabolic, inflammatory, and vascular dysregulation, which can predispose pregnant women to a range of adverse outcomes **(1).**

A growing body of evidence links maternal vitamin D deficiency to complications such as preeclampsia, gestational diabetes mellitus, preterm labor, increased cesarean delivery rates, and postpartum depression. Vitamin D's influence on endothelial health, insulin sensitivity, cytokine balance, and placental development provides a plausible mechanistic explanation for these associations **(2).** Despite expanding evidence, screening and supplementation strategies remain variable across clinical guidelines, highlighting the need for increased awareness and standardized recommendations to reduce preventable maternal morbidity.

Preeclampsia

The protective role of vitamin D in preeclampsia can be explained by multiple mechanisms. One of them is the immunomodulatory role of calcitriol in regulating immune response. Defective control of effector T cells by regulatory T cells can lead to poor placental invasion, thereby leading to the release of placenta-derived vasoconstrictive factors, and consequently maternal hypertension and proteinuria**.** Vitamin D helps in maintaining the immune homeostasis and thus prevents placental vasoconstriction and ultimately, preeclampsia**.** Also, vitamin D regulates the endothelial and vascular smooth muscle cell proliferation and therefore, plays a role in regulating blood pressure through RAAS (Renin-Angiotensin-Aldosterone system)**.**

Vitamin D has also been found to regulate angiogenesis via its receptor elements in VEGF promoter and stimulating the expression of VEGF in vascular smooth muscle cells. Calcitriol also helps to prevent cholesterol uptake by the macrophages and vascular smooth muscle cells of the arterial walls, which is the observed pathology in utero placental vessels of patients with preeclampsia **(3)**. Several observational studies were recently performed to investigate an association between vitamin D deficiency and preeclampsia but the findings have been inconsistent.

Eleven observational studies have examined the association between preeclampsia and vitamin D **(4)** carried out a nested case control study in Canada and concluded that vitamin D deficiency (<30 ng/ml) was associated with increased risk of preeclampsia (adjusted Odd's Ratio (OR), 2.23; 95% Confidence Interval (CI) 1.29–3.83).

Similar results were also reported by other recent studies **(5**).

On the contrary**, Bomba-Opon et al., (6)** measured the 25OHD levels in 280 pregnant women in Poland and found no association between vitamin D levels and markers of preeclampsia, including Pregnancy-associated plasma protein A (PAPP-A), Placenta Growth Factor (PlGF), uterine artery pulsatility index and mean arterial pressure. Similarly, **Schneuer et al., (7)** reported no increased risk of preeclampsia in vitamin D deficient pregnant women in a nested case control study conducted in 5109 pregnant women. Some other studies also described comparable outcomes **(8).**

Karamali et al., (9) conducted a double blind placebo-controlled RCT in pregnant women at risk of preeclampsia determined by abnormal uterine artery waveform, and reported no significant change in blood pressure with vitamin D supplementation.

When combined supplementation of vitamin D and calcium was given in an interventional study to at-risk preeclampsia patients, significant improvement in the outcomes with reduced systolic and diastolic blood pressure was observed in the vitamin D and calcium supplemented group compared to the placebo group **(10)**.

Similarly, **Asemi et al., (11)** also reported positive outcomes on supplementation with vitamin D (400 IU) and multi-minerals (800 mg calcium, 200 mg magnesium, 8 mg zinc) over 9 weeks compared to placebo in at-risk preeclampsia patients. Cochrane review on vitamin D supplementation studies reported that women who receive vitamin D supplementation had lower risk of preeclampsia but with only borderline significance (RR 0.52, CI 0.25–1.05), whereas combined vitamin D and calcium supplementation significantly reduces the risk of preeclampsia (Risk Ratio (RR): 0.51, CI 0.32–0.80) **(12).**

Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus is defined as hyperglycemia from glucose intolerance that develops or is first diagnosed during pregnancy **(13)**. Vitamin D plays a role in glucose homeostasis by multiple mechanisms **(14).** Firstly, it regulates the calcium levels, which in turn regulates insulin production and secretion by the endocrine pancreas **(15)**. It also improves the sensitivity of the target cells like adipose tissue, liver and skeletal muscles to insulin **(14)**. Through its role in regulation of immune cells, it protects β cells from detrimental immune attacks and even enhances their function **(15)**. Vitamin D deficiency or the dysfunction of vitamin D receptors relates to the pathogenesis of type 1 and type2 diabetes, but its role in gestational diabetes mellitus (GDM) remains inconclusive.

Eight observational studies have been recently conducted to study the association of vitamin D with GDM. **Arnold et al., (16)** conducted a nested case control study in the United States among pregnant women and reported an inverse relationship between vitamin D status in early pregnancy and risk of gestational diabetes. 5 ng/ml increase in vitamin D3 levels was associated with reduction in GDM risk by 14%. Similar effects were reported by **Lacroix and colleagues, (17**) in a prospective observational study in Canada and in a cross sectional observational study in Arab women **(14)**. On the contrary, multiple studies failed to establish a role of vitamin D in the prevention of GDM **(18)**. The lack of consistent findings calls for large-scale prospective studies to evaluate the role of vitamin D in GDM.

Cesarean section (C-section)

Vitamin D receptors are present on smooth muscle cells, including uterine muscles, and skeletal muscle cells. Vitamin D regulates the contractile proteins of uterine myometrial cells **(19).** Vitamin D deficiency, therefore, may decrease the strength of the contractile muscles, causing prolonged labor or obstructed labor, indicating the need for C-section **(20).** Vitamin D deficiency has also been postulated to cause malformation of pelvis, which is yet another indication for C-section **(21)**.

Few studies have analyzed the association between vitamin D levels and cesarean sections. Recently, five observational studies were conducted with mixed outcomes **(19)**. In a prospective cohort study conducted in Spain in 2,382 mother child pairs, **Rodriguez et al., (22)** reported that adequate vitamin D (25 OHD ≥ 30ng/ml) decreased the risk of C-section by obstructed labor (RR=0.60, 95% CI 0.37, 0.97). In a multiethnic Asian cohort study conducted by GUSTO study group **(19)**, it was found that low vitamin D levels were associated with increased risk of emergency C-sections in Chinese and Indian women, and not in Malay women and overall there was no significant association. No association between vitamin D deficiency and risk of C-section was reported in other recent studies **(20)**.

Preterm Delivery

One of the most common causes for preterm delivery is infection **(23)**. Vitamin D, through its role in anti-inflammatory pathways via nuclear factor-kB inhibition, could play a role in decreasing the incidence of infections thereby, preterm births **(24)**. But the exact role of vitamin D in the pathogenesis of preterm birth has not yet been clearly defined.

Few recent interventional studies on vitamin D supplementation examined its role in the prevention of preterm births. **Hossain et al., (25**) carried out a RCT of routine care (200 mg ferrous sulfate and 600 mg calcium) vs. vitamin D3 supplementation (4,000 IU daily) from 20 weeks of gestation till delivery in 207 pregnant women and reported comparable outcomes in both the groups (p >0.05). **Mojibian et al., (26)** also reported similar findings. On the contrary **Sablok et al., (27)** found decreased incidence of preterm delivery in the group with vitamin D supplementation (8.3%) compared to no intervention (21.1%) though it was not statistically significant.

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