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Vitamin D deficiency: its causes and complication in pregnancy.

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Abstract : Vitamin D (VD), a fat-soluble vitamin, serves a key function in in cell differentiation, immune system function, and brain development, making its status during pregnancy essential for maternal health and fetal growth. Low VD levels are linked to adverse outcomes such as preeclampsia, low birth weight, neonatal hypocalcemia, impaired growth, and increased risk of autoimmune diseases. This review highlights the impact of maternal VD deficiency on complications like gestational diabetes, hypertension, intrauterine growth restriction, miscarriage, stillbirth, and preterm birth. It also explores underlying mechanisms, including immune modulation, cytokine regulation, hormone function, and placental health, to support strategies for improving pregnancy outcomes through better VD management.

1.Introduction:

VD or 1, 25 – trihydroxy cholecalciferol is a vitamin that dissolves in fat involved in the absorption and homeostasis of bone minerals. It is considered as the steroid prohormone, that it's precursor is cholesterol and the dietary form are either ergosterol(vit – D2) and cholecalciferol (vit – D3).

Besides the purpose of bone homeostasis VD has a marked role in regulating immune response and reducing inflammation. Other function that has role of VD are muscle function and heart health maintenance and also may help in reducing blood pressure. The classical and non-classical mechanisms of this hormone influence calcium balance, immune function, cell growth and specialization, as well as responses to infection and the emergence of cancer [1]. The primary aim of this study is to review VD metabolism during pregnancy and breastfeeding, by examining the prevalence of VD deficiency and its causes and possible complications affecting both the mother and fetus.

2. VD Metabolism:

To comprehend the distinct aspects of VD metabolism during pregnancy, it is essential to begin by reviewing the normal physiological processes of VD metabolism in the human body[2-5]. VD refers to a group of compounds with similar biological roles. Around 80–90% of VD in the body is synthesized in the skin as cholecalciferol (VD3) through exposure to UVB(Ultra Violet B) sunlight, while a smaller portion comes from diet—either as VD3 from animal sources or VD2 (ergocalciferol) from plants and fungi. Both forms are inactive and require two hydroxylation steps in the liver and kidneys to become active. UVB rays convert skin-derived proVD3 into precholecalciferol, which quickly becomes cholecalciferol with body heat[6].

VD from animal (D3), plant (D2) sources, and skin synthesis enters the bloodstream and binds to VD binding protein (VDBP) for transport to the liver. There, it undergoes its first hydroxylation by the enzyme CYP2R1, forming 25(OH)D (calcidiol). This is then transported to the kidneys, where CYP27B1 catalyzes a second hydroxylation, producing $1,25(OH)_2D$ (calcitriol), the active form of VD. Calcitriol binds to the VD receptor (VDR), triggering gene expression that regulates bone, mineral metabolism, and various other biological functions.

Serum levels of active VD [$1,25(OH)_2D$] are mainly regulated by parathyroid hormone (PTH), calcium, phosphate, and by $1,25(OH)_2D$ itself. Through feedback, high levels of $1,25(OH)_2D$ activate the enzyme CYP24A1, which breaks down VD into inactive forms, and suppress CYP27B1 activity, thereby reducing further production of active VD.

3. VD Metabolism during Pregnancy:

During pregnancy, notable changes in VD metabolism occur, including: (a) a steady rise in maternal serum concentrations of 1,25-dihydroxyVD [1,25$(OH)_2$D], which does not pass through the placenta, (b) heightened activity of the CYP27B1 enzyme in both the maternal kidneys and placenta, (c) increased levels of VD-binding protein (VDBP) in the mother, and (d) a decline in the breakdown of 1,25$(OH)_2$D[7,8]. The placenta plays a crucial role in regulating and transferring VD to the fetus, as both the maternal (decidual) and fetal (trophoblastic) components express VD receptors (VDR) and the CYP27B1 enzyme, which facilitates the reconfiguration of 25-hydroxy VD [25(OH)D] into its active form, 1,25$(OH)_2$D[9,10].

During pregnancy, the body's requirement for VD rises. However, about 70% of expectant mothers experience VD deficiency, 21% have insufficient levels, and only 7.3% maintain adequate VD status[11]. VD influences several key reproductive and placental processes, including decidualization, implantation, the production of human placental lactogen (hPL), the secretion of human chorionic gonadotropin (hCG), regulation of progesterone and estrogen, calcium transport across the placenta, and placental immune function[12]. The presence of polycystic ovary syndrome (PCOS) and VD deficiency—either separately or in combination—can elevate the threat of pregnancy complications, whereas maintaining sufficient VD levels (above 75 nmol/L) may help reduce these risks.

VD levels have been linked to various pregnancy-related complications. Measurements taken in the early trimester (with average levels of 10.1 ng/mL compared to 15.7 ng/mL) reveal a link with the later formation of gestational diabetes mellitus (GDM), typically diagnosed between the 24th and 26th weeks of pregnancy. This association appears to be independent of traditional risk factors such as obesity or a previous history of GDM. A notably higher percentage of women diagnosed with GDM were found in the VD deficient group compared to those with sufficient VD levels (87.1% vs. 68.7%) [13,14].

Recent research and meta-analyses suggest that higher VD levels during pregnancy may lower the risk of preeclampsia, though more clinical studies are needed[16]. Some large observational studies, however, did not find a clear link, especially in healthy women[17]. VD may offer protection by promoting Th2-dominance and reducing placental genes like sFLT-1 and VEGF, which are linked to preeclampsia[15,18-20]. Deficiency has also been connected with recurrent miscarriage and infertility, likely due to its role in regulating inflammatory cytokines (IL-2, IFN-γ, TNF-α). VD levels below 50 nmol/L have been linked to a higher risk of miscarriage, mainly in early pregnancy [21-23] .

VD needs are elevated during key life stages such as fetal development, infancy, childhood, puberty, and pregnancy. Beyond its role in calcium absorption and bone health, VD is also linked to various non-skeletal conditions. Recent studies suggest that supplementation during pregnancy may reduce complications like preeclampsia, cesarean delivery, and gestational diabetes, especially in VD-deficient mothers[19,24-26]

4. Reason for VD deficiency

VD is obtained from both dietary sources and sunlight exposure, with sunlight being the primary contributor. In fact, just 30 minutes of midday sun in the summer can produce around 50,000 IU of VD in individuals with light skin. The main cause of VD deficiency is insufficient sunlight exposure, which can be worsened by dietary limitations, particularly among vegetarians and vegans. This issue is more pronounced in individuals with darker skin, who naturally produce less VD from sunlight[60 – 63], and in those who have limited sun exposure due to lifestyle, cultural practices, or geographic location. Ethnic groups such as people from the Indian subcontinent and the Middle East[64 – 67] are especially vulnerable to deficiency. In recent years, VD deficiency has become increasingly common[68,69], contributing to a resurgence of conditions like rickets in the UK and other developed nations[70]. Pregnant women from non-Western backgrounds living in northern Europe are particularly at risk, and VD deficiency during pregnancy is now considered a widespread and ongoing public health concern[71].

5. Complications of VD deficiency during pregnanacy:

5.1:Recent research shows that VD receptors are found in various cell types, including those involved in glucose metabolism, such as muscle cells and pancreatic beta cells[27,28]. VD directly influences beta cell function and is essential for normal insulin secretion by the pancreas[29]. A deficiency in VD has been linked to disruptions in blood glucose levels, insulin production, and insulin sensitivity in target tissues[30]. Supplementing VD in individuals with type 2 diabetes and a deficiency has been shown to improve both insulin secretion and sensitivity. This has led to the theory that gestational diabetes mellitus (GDM) may stem from insulin resistance triggered by pregnancy, combined with inadequate insulin secretion. Recent meta-analyses have examined the relationship between serum VD levels and the risk of developing gestational diabetes mellitus (GDM), and have confirmed a significant association between the two[31-34]

5.2:Pregnancy-induced hypertension (PIH) is linked to a high risk of serious complications for both mother and baby, along with increased mortality. Numerous studies have connected VD to PIH[35,36]. It may help by promoting trophoblast repair, supporting angiogenesis, and aiding in endothelial healing. Additionally, VD might

lower the risk of PIH by regulating placental calcium transport and immune system function[37,38]. A slight increase in VD intake was linked to a modest reduction in the occurrence of PIH, suggesting a limited but possible connection between VD levels and pregnancy-related hypertension. Pregnant and breastfeeding women face a higher risk of VD deficiency due to greater nutritional demands. This aligns with earlier studies indicating that low VD levels may be associated with a higher risk of developing PIH[39-41].

5.3:Preeclampsia, the most severe form of pregnancy-induced hypertension, has been consistently linked to disruptions in calcium and VD metabolism during late pregnancy. These include reduced urinary calcium excretion (hypocalciuria) [42-45] and low levels of serum 1,25-dihydroxyVD [46-49]. A recent nested case-control study found that women who later developed preeclampsia had lower levels of 25(OH)D early in pregnancy, suggesting that VD deficiency may occur before symptoms appear and could play a role in the development of the condition[50]. There are studies showing no significant association between preeclampsia and VD in first trimester of pregnancy, rather women with VD sufficiency in their last trimester of pregnancy had a lower risk of preeclampsia [51].

5.4:Low VD levels have been associated with a higher risk of respiratory tract infections. Specifically, an inverse relationship has been found between VD (25(OH)D) levels in cord blood and the likelihood of upper respiratory infections in early infancy, with increased infections observed during the first three months and wheezing by 15 months of age[52]. Newborns with VD levels below 20 ng/mL had a sixfold greater risk of developing respiratory syncytial virus bronchiolitis by age one, compared to those with levels above 30 ng/mL[53]. VD supplementation, particularly in cases of severe deficiency, has shown effectiveness in preventing acute respiratory infections. In the context of asthma, prenatal VD intake may help lower the risk of wheezing in children, as low 25(OH)D3 levels are strongly linked to asthma development[54, 55].

5.5:VD deficiency has also been linked to atopic dermatitis, with affected individuals often showing lower-than-normal serum VD levels[56]. One study indicated that VD supplementation could help children with winter-related dermatitis[57]. Calcitriol, the active form of VD, suppresses dendritic cell maturation, which can dampen acquired immune responses and potentially increase the risk of autoimmune diseases like diabetes mellitus, multiple sclerosis, and inflammatory bowel disease. Moreover, although current evidence is limited and not yet conclusive, VD deficiency may also be associated with a higher risk of cancer, musculoskeletal pain, migraines, and mental health conditions such as schizophrenia, dementia, and depression[58, 59]. More research is needed to clarify these potential connections.

5.6: VD deficiency is increasingly recognized as a contributing factor to the development of cardiovascular diseases [72,73]. Research indicates that low VD levels can lead to high blood pressure by promoting vasoconstriction and increasing vascular resistance [74]. Additionally, VD deficiency has been linked to a higher risk of mortality from cardiovascular conditions and cancer [72,75]. Numerous studies have demonstrated that reduced sun exposure—and consequently lower serum levels of 25(OH)D—is associated with an elevated risk of heart attacks, strokes, circulatory disorders, and peripheral vascular disease [76,77].

5.7: Spontaneous abortion and stillbirth are serious pregnancy complications that can lead to psychological stress in future pregnancies [78]. A cross-sectional study conducted in China found that pregnant women with low VD levels had a 1.71 times higher risk of spontaneous abortion (95% CI: 1.2–2.4), based on serum 25OHD levels measured in 60 first-time pregnant women carrying singletons at 7–9 weeks of gestation [79]. Similarly, research by Barebring et al. [80] showed that higher VD levels in early pregnancy were linked to a decreased risk of spontaneous abortion, with each 1 nmol/L rise in serum 25OHD levels reducing the risk by 1% (OR = 0.989, 95% CI: 0.98–1.00; $p < 0.05$).

Tables 1 present a summary of observational studies that examined the association between serum 25(OH)D levels or maternal VD intake and the risk of gestational diabetes and hypertensive disorders.

table 1:

Author	Year	Design	n	Gestational Age	Outcome	SignificantAssociation
Achkar [40]	2015	Nested case-control	2144	<20 weeks	Risk of PE was higher at 25(OH)D concentrations <25 nmol/L (OR 24.04, 95% CI: 2.1, 274.8)	Yes
Álvarez-Fernández [44]	2015	Retrospective cohort	257	9–12 & 20–41 weeks	Risk of late onset PE was higher at 25(OH)D concentrations <50 nmol/L (OR 4.6, 95% CI: 1.4, 15)	Yes
Mohaghegh [56]	2015	Case-control	91	Delivery	Mean SD 25(OH)D status was lower in women with than without PE (38 34 vs. 58 38 nmol/L)	Yes
Pena [54]	2015	Cross-sectional	179	Delivery	Preeclamptic mothers had a higher rate of 25(OH)D <50 nmol/L than those without PE (50% vs. 23%)	Yes
Bärebring [35]	2016	Prospective cohort	2000	First & third trimester	An increase in 25(OH)D of 30 nmol/L was associated with lower odds of PE (OR 0.22, 95% CI: 0.084, 0.581) but not PIH alone	Yes
Mircea Iurciuc 1, Florina Buleu	2024	Prospective cohort	187	second trimester	Significant differences regarding the augmentation index (Aix) brachial, PWVao, heart rate, and systolic or diastolic BP with more increased values for the HTN group vs. the preeclampsia group in the current research ($p < 0.001$).	YES
Pingping Wang1*,JinYao2	2025	Prospective	180	after 20 weeks	there is a significant negative correlation between 25-hydroxyVD and D-dimer (r=-0.365, P<0.001), and a negative correlation with MPV (r=-0.496, P<0.001).	YES
Meng-Xi Zhang 1,:, Guo-Tao Pan	2015	meta-analysis	9209		A noteworthy decrease of 4.93 nmol/L (95% CI, 6.73, 3.14) in serum 25(OH)D was demonstrated in the participants with GDM, and moderate heterogeneity was observed ($I2 = 61.40\%$, $p = 0.001$)	yes

6. conclusion:

Different studies suggest the requirement of VD during pregnancy and the complications of VD deficiency during pregnancy. The study shows the increased risk of GDM , the VD levels of pregnant women with preeclampsia show a positive correlation with those of their newborns, suggesting that the newborn's VD status may be reliably assessed based on the mother's VD levels in cases of pregnancy-induced hypertension (PIH). Previous studies suggests a detailed study is advisory on viatamine D deficiency: its causes and complication in pregnancy .

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