Chapter

Role of Vitamin D in Preeclampsia

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Abstract

Pathogenesis of preeclampsia involves immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, hypertension that may be affected by vitamin D. Human placenta expresses all the components for vitamin D signaling: Vitamin D receptor (VDR), retinoid X receptor (RXR), 1-alpha- hydroxylase (CYP27B1) and 24- hydroxylase (CYP24A1). Vitamin D binding protein plays a role in binding and transportation of 25 hydroxyvitamin D [25(OH)D] and $1,25(OH)_2D_3$. Vitamin D is activated by 25-hydroxylase (CYP2R1) and 1-alpha -hydroxylase (CYP27B1) and is degraded by 24-hydroxylase (CYP24A1). Vitamin D supplementation is not recommended by WHO for pregnant women and allows recommended nutrient intake (RNI) of 200 IU (5 μg) per day. Further research requires serum 25(OH)D analysis and assessment of maternal and infant outcomes; pre-conceptional vitamin D status.

Keywords: Vitamin D, vitamin D receptor, cytochrome P450, pregnancy, preeclampsia, cord blood

1. Introduction

Pathogenesis of preeclampsia involves immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, hypertension that may be affected by vitamin D [1]. Preeclampsia complicates 2–8% of pregnancies globally and the incidence continues to increase worldwide. Preeclampsia (PE) is associated with significant maternal morbidity and mortality.

2. Pathogenesis of preeclampsia

Numerous pathophysiologic abnormalities have been suggested to explain the mechanisms of the origin of preeclampsia. Despite intensive research efforts, the etiology and pathogenesis of PE are not completely understood. The development of preeclampsia is influenced by genetic, immunologic, and environmental risk factors suggesting a multifactorial origin. Currently, there is no single reliable, cost-effective screening test for preeclampsia. A baseline laboratory evaluation is performed early in pregnancy in women who are at high risk for preeclampsia.

It is obvious that no single mechanism is responsible for this syndrome. The initiating abnormality is failed vascular remodeling of the vessels that supply the placental bed (stage 1). This was linked to the maternal syndrome of preeclampsia (stage 2). Two key features in the pathogenesis of preeclampsia are shallow endovascular cytotrophoblast invasion in the spiral arteries and endothelial cell dysfunction.

According to Barker's theory (also, called fetal programming or fetal origins of disease), origin of some adulthood chronic diseases such as cardiovascular diseases, hypertension and diabetes have their origin in intrauterine life. This hypothesis suggests that the intrauterine environment in which the fetus develops may be responsible for complications in adult life. Changes occurring in intrauterine environment and that somehow could disrupt normal development of the fetus can trigger metabolic changes, which may result in the development of long-term disorders. Preeclampsia has implications for future pregnancies and future cardiovascular risk.

3. Vitamin D metabolism during pregnancy

Since fetus completely relies on the maternal stores for its growth and development, vitamin D status during pregnancy has an important effect on this. During early pregnancy, $1,25(OH)_2D$ increases and they continue to increase until delivery. This increase in $1,25(OH)_2D$ is dependent on the available 25(OH)D levels and are independent of calcium metabolism (**Figure 1**).

The primary role of vitamin D in pregnancy is immunomodulatory in addition to its classical calcium regulatory function. According to Barker's hypothesis, the developmental origins of adult disease lie mainly in prenatal factors such as nutritional insults occurring during pregnancy and/or early infancy period [2].

Vitamin D metabolism during pregnancy and fetal development is different as compared with non-pregnant state, The conversion of vitamin D to 25(OH)D is unchanged during pregnancy. The conversion of 25(OH)D to $1,25(OH)_2D$ during pregnancy is unique and unparalleled during life and at no other time during life 25(OH)D is so closely linked with $1,25(OH)_2D$ production.

During pregnancy, the rise in $1,25(OH)_2D$ in the mother and fetus is dependent on substrate availability i.e., 25(OH)D, and this is largely independent of calcium

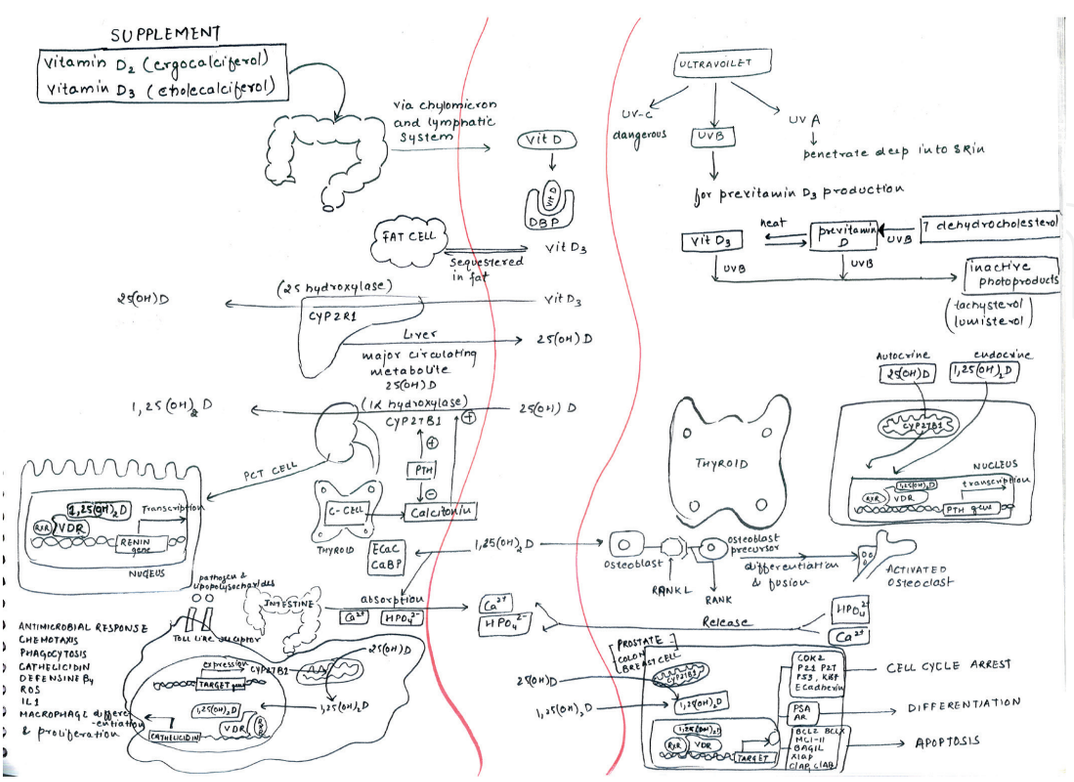

Figure 1.
Overview of vitamin D metabolism, its role and mechanism of action.

homeostasis. The $1,25(OH)_2D$ serum concentrations double by 12th weeks of gestation and continue to rise two- to threefold from the non-pregnant baseline rising (to over 700 $pmol \cdot L^{-1}$) attaining levels that would be toxic due to hypercalcemia to the non-pregnant individual, but which are essential during pregnancy. Neither in the mother nor in the fetus during the pregnant state, this conversion seems to be controlled by classic calcium homeostatic mechanisms. Calcium homeostasis, however, is not linked with this increase in $1,25(OH)_2D$, because there is no increase in calcium demand by either the mother or fetus at 12 weeks of gestation. In contrast, the increased $1,25(OH)_2D$ levels remain sustained during pregnancy and during lactation these levels are not sustained when the maternal calcium demands are high.

The mechanism of uncoupling of calcium metabolism from $1,25(OH)_2D$ generation during pregnancy and not lactation is not clear. It could be due to the fact that $1,25(OH)_2D$ is an important immune modulator involved in maternal tolerance to the foreign fetus since pregnant women with preeclampsia have a clinical picture of inflammation and vasculitis, vitamin D deficiency has been implicated and vitamin D is a known modulator of inflammation [3].

Experimental animal studies have also strongly shown that vitamin D deficiency is a potential mechanism of placental dysfunction and respiratory maturation [4].

There is disruption of endothelial stability and an enhancement of "vascular leak" during preeclampsia and experimental animal models of preeclampsia have clearly demonstrated that endothelial instability leads to placental ischemia [5].

Vitamin D_3,$25(OH)D_3$ and $1,25(OH)_2D_3$ stabilize endothelium and endothelium "leak" through non-genomic mechanisms and on equal molar basis, vitamin D_3 has more potent action as compared to $25(OH)D_3$ or $1,25(OH)_2D$. Vitamin D_3 is the most accessible form for cell membrane and it exists mainly bound to VDBP in circulation and only miniscule amount of vitamin D_3 exist in the free form. Vitamin D_3 has a longer half-life following its endogenous synthesis (in skin) as compared to the exogenous vitamin D taken orally and the half-life of 25(OH)D is weeks. Vitamin D_3 when given at physiological doses of 4 000 $IU \cdot d^{-1}$ or greater circulates in the "free" form at significant levels to be available to membrane insertion and subsequent endothelial stabilization that is likely to have profound effects on several disease processes. Recent studies have implicated maternal vitamin D deficiency as a risk factor for abnormal fetal growth patterns, adverse birth outcomes, increased risk of preterm birth. and reproductive failure [6, 7].

1,25-dihydroxyvitamin D [$1,25(OH)_2D$] is primary bioactive form, and it does not readily cross the placenta, umbilical cord concentrations of its precursor, 25(OH)D, are similar to maternal concentrations. Placenta modulates circulating vitamin D metabolites in pregnant women and favors the uptake of DBP-bound $25(OH)D_3$ through a specific receptor system (LRP2-CUBN) and has CYP27B1 activity.

Both maternal decidua and fetal trophoblast have detectable CYP27B1 activity and they express VDR. Placental production of $1,25(OH)_2D$ has been documented to be essential for immunosuppressive effects required for immune tolerance of implantation. Vitamin D may have a more extensive role in placental function, including trophoblastic differentiation and extravillous trophoblast invasion of the decidua and myometrium and a fundamental role in the process of conception, implantation and development of the placenta itself. However, the precise role of vitamin D in the process of implantation remains unclear.

Studies have shown that $1,25(OH)_2D$ regulates homeobox gene HOXA10 expression in human endometrial stromal cells which is important for the development of endometrial development and implantation. Animal studies have shown that female rats on a vitamin D-deficient diet had overall reduction of fertility and failure of implantation and administration of $1,25(OH)_2D$ corrected this.

In addition, vitamin D via its immunomodulatory actions may also influence implantation indirectly. Decidual synthesis of $1,25(OH)_2D$ has the potential to influence uterine natural killer cells, dendritic cells, macrophages and T-cells throughout pregnancy, including inhibition of Th1 cytokines and promotion of Th2 cytokines, that have a significant role in the process of implantation [8].

Obesity is also a major contributing factor to vitamin D status in pregnant women that causes lowering of 25(OH)D levels in pregnant women with high body mass index (BMI).

4. Vitamin D signaling in pregnancy

Vitamin D signaling is important for normal placental function and fetal growth. Vitamin D maintains healthy cellular functions and redox and Ca^{2+} signaling systems and increases expression of both Nrf2 and the anti-aging protein Klotho, a major regulator of Ca^{2+} and redox signaling. Declining vitamin D levels reduces the stability of this regulatory signaling network and may cause many of the major diseases linked to vitamin D deficiency which are associated with a dysregulation in both ROS and Ca^{2+} signaling [9].

Also, vitamin D signaling depends on availability and turnover of active vitamin D receptor (VDR) ligand 1,25-dihydroxycholecalciferol and efficiency of VDR transactivation. Net availability of active hormone depends on the delivery of substrate and the balance of activating and inactivating enzymes, mainly secosteroid metabolizing p450 enzymes (e.g., various hydroxylase enzymes: 25 hydroxylase, 24 hydroxylase and 1- alpha hydroxylase). Out of these hydroxylases, 1- alpha hydroxylase is expressed in kidney and released in systemic circulation to serve as a critical activating enzyme in circulation. It is also synthesized in target tissues and activates local secosteroid. 1- alpha hydroxylase in kidney is upregulated by low calcium intake and parathyroid hormone inactivates both phosphatonins [10] as well as proinflammatory signal transduction downregulates its expression.

Transactivation of VDR depends on exact molecular structure, nuclear translocation, and presence of heterodimer retinoid X-receptor (RXR) and other nuclear cofactors to regulate gene expression, however, membrane receptor for these effects is not yet identified.

Rickets is a syndrome of impaired vitamin D signaling due to vitamin D_3 deficiency and can be caused by inherited defects of the cascade, nutritional deficits, lack of sunlight exposure, malabsorption, and underlying diseases like chronic inflammation. Vitamin D signaling is complex and modulated at multiple levels.

$1,25\ (OH)_2\ D$ can diffuse freely across the plasma membrane and binds its high-affinity nuclear receptor (VDR, vitamin D receptor) to mediate its effects transcriptionally and post transcriptionally. In the transcriptional pathway, $1,25(OH)_2D$ bind to VDR and forms a heterodimer complex (VDR- RXR complex) with retinoid X receptor (RXR). The VDR-RXR complex binds to vitamin D response element (VDRE) in the promoter region to regulate the target expression of vitamin D. Also, there is non-transcriptional pathway of vitamin D signaling having modulatory effects via binding of calcitriol- VDR complex with caveolae to stimulate signaling cascades namely, protein kinase C and mitogen-activated protein kinase. These signaling cascades regulate various cellular functions such as proliferation, differentiation, invasion, and apoptosis. Altered VDR expressions have been associated with various cancers, however, role of VDR and vitamin D signaling in pregnancy is poorly understood.

5. Vitamin D- induced genomic alterations during pregnancy

Vitamin D supplementation during pregnancy appears to affect genetic information of several highly functional modules related to systemic inflammation and immune responses and implicates the emergence of a distinctive immune response in women destined to develop preeclampsia [11].

Both non-genomic and genomic actions of vitamin D can affect epigenetic regulation of fetal development, and dynamic changes occur in epigenetic markers namely, methylation, hydroxylation, post translational modifications (covalent modifications) various short and long RNAs that regulate the transcriptional gene activity during the acquirement of specific cellular functions. A subset of epigenetics are programmed during early pregnancy that are stably maintained into adulthood [12].

6. Role of vitamin D binding protein (VDBP) in PE

VDBP is plasma carrier protein that binds metabolites of vitamin D to be transported in the body. Vitamin D-binding protein [VDBP, group-specific component (GC) of serum (GC-globulin)] is encoded by the GC gene. VDBP is synthesized mainly in liver and synthesized in adipose tissue, kidneys, and gonads. VDBP is 58 kDa glycosylated alpha-globulin composed of 458 amino acid residues in length and it folds into a triple-domain structure bound by disulphide bonds.

VDBP has immunomodulatory properties and is involved in chemotaxis of fatty acids and endotoxins. Immunological role for VDBP in pre-eclampsia in VDBP of placental origin has been documented as autoimmune target of autoantibodies in the sera of pre-eclamptic women compared with the sera of healthy non-pregnant women. Maternal obesity is associated with adverse health effects for both mother and newborn along with increased inflammation seems to be an important pathological mechanism for detrimental effects of obesity during pregnancy. However, role of vitamin D in the process is still remains to be clarified.

VDBP-macrophage activating factor (DBP-MAF) is involved in bone metabolism. VDBP has been shown to increase drastically during pregnancy as compared to non-pregnant women, reaching their peak in early third trimester and with the lowest level at approximately 36 weeks gestation. This increase is associated with increased total 25(OH)D and decreased free and bioavailable 25(OH)D to increase the capacity to store and metabolize more vitamin D to maintain sufficient concentration of vitamin D throughout pregnancy and lactation to support their increased requirements.

The increase in VDBP during pregnancy could also occur in response to rising estrogen. VDBP has been reported to increase when oestrogens levels are increased in conditions such as high stress states, some ovarian tumors and hormone replacement therapies.

Fetus obtains its supply of vitamin D via placenta which has also been shown to express VDBP. Placental cells express the components of vitamin D signaling including VDR and VDBP and can synthesize and respond to $1,25(OH)_2D_3$ and $24,25(OH)_2D$. The maternal vitamin D compounds may enter the placental cells by endocytosis of 25(OH)D-VDBP and/or by diffusion of the free hormone to be transformed into $1,25(OH)_2D_3$ or $24,25(OH)_2D$, however, the exact mechanism is not known. Without VDBP maternally derived 25(OH)D may not enter placental cells and its transformation into the active form of vitamin D and its transport to the fetus for utilization would not be possible.

SNPs of three genes involved in vitamin D metabolism including GC have been implicated in pre-eclampsia risk. GC-1 phenotype has been identified as a genetic marker for early detection for women at risk of pre-eclampsia. This has been shown that in South African (HIV endemic region) pregnant women complicated by pre-eclampsia that two SNPs of GC gene (rs4588 and rs7041) are more frequently present.

Status of VDBP and total 25(OH)D in preeclampsia is still not clear. Few studies have reported that different VDBP plasma concentrations in women who developed pre-eclampsia as compared to pregnant normotensive controls and no correlations have been noted between VDBP and total 25(OH)D. The increased oxidative stress in pregnancy may be responsible for the altered concentration of VDBP and vitamin D metabolism in placentae in preeclampsia. Moreover, proteinuria in preeclampsia have been shown to cause urinary loss of VDBP as compared to normotensive pregnancies possibly due to disruption of vitamin D metabolism and function through reduced VDBP.

Current evidence suggests that VDBP has been implicated in pregnancy, but its exact role is not yet fully understood. More focused studies are needed to address these limitations to disentangle the functions of VDBP and to clarify its role as a measure of vitamin D status and an important novel biomarker of pregnancy and reproductive outcomes.

7. Role of cytochrome P450 in PE

Two hepatic P450 enzymes catalyzing 25-hydroxylation of vitamin D_3 (VD_3) exist in mammalian liver namely, mitochondrial, and microsomal enzymes. Mitochondrial vitamin D_3 25-hydroxylase is apparently identical with CYP27A.

VD_3 is activated to 1α,25-dihydroxyvitamin D3 (1,25-D_3) by cytochrome P450 2R1 (CYP2R1)/CYP27A1 and CYP27B1 (1-alpha-hydroxylase) sequentially and deactivated by multiple enzymes including CYP3A4. 1,25-D_3 can activate the transcription of CYP3A genes. Activated vitamin D receptor (VDR) forms a heterodimer with retinoid X receptor α (RXRα) to recruit co-activators and translocate this to the nucleus for its binding to specific vitamin D responsive elements (VDRE), and thus activates the gene transcription. This transactivation effect modulates the nutrient bioavailability and drug metabolism. Also, extrarenal expression of CYP27B1 (1-alpha-hydroxylase) generates $1,25(OH)_2D$ in numerous target tissues including the placenta and brain. Vitamin D receptor (VDR) regulates cytochrome P450 3A (CYP3A) expression in human and VDR-response elements are found in the promoter region of CYP3A genes [13].

8. Vitamin D supplementation in pregnancy

Vitamin D dysregulation during pregnancy has been linked to adverse effects on placental function and pregnancy and there is requirement for adequate vitamin D status across gestation. Pregnant women are at high risk of vitamin D deficiency (VDD) and VDD during pregnancy is associated with increased risk of gestational diabetes and preeclampsia. Since preeclampsia can affect offspring health resulting in low birth weight, poor skeletal health, impaired brain development, autoimmune disease, obesity, and insulin resistance.

Randomized controlled trials investigating vitamin D supplementation during pregnancy have revealed that increased vitamin D supplementation decreased complications of pregnancy and C-section births and improve birth outcome data.

Recent randomized controlled trials involving vitamin D supplementation in high-risk pregnancies have demonstrated decreased cesarean section rate and maternal hospitalization, decreased macrosomia and hospitalization in newborns of women with gestational diabetes. Favorable effects on insulin metabolism parameters, serum HDL cholesterol and total cholesterol concentrations in women with pre-eclampsia risk factors were also reported [14].

9. WHO recommendations

Vitamin D supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes [15].

Remarks:

- These recommendation do not propose any alterations in the prevalent WHO recommendation regarding vitamin D supplementation during pregnancy as per WHO ANC guidelines.

- According to WHO guidelines on healthy eating, the pregnant women should receive adequate nutrition and consumption of healthy, balanced diet, according to WHO guidance on healthy eating during pregnancy.

- Since sunlight is one of important source of vitamin D and it is not known that how much duration of sunlight is required. This depends on various variables namely, amount of skin being exposed to sunlight, time of day, altitude and seasonal variations, pigmentation of skin (in darker skin, less vitamin D is synthesized by pigments are synthesized as compared to lighter pigments) and sunscreen use also decreases its production.

- In the cases of documented vitamin D deficiency or in pregnant women, vitamin D supplements may be given as per the guidelines of WHO

*This is an extract from the relevant guideline (https://www.who.int/publications-detail-redirect/9789240008120).

10. Future research

The complexity of vitamin D metabolism and functions involved in placental development are still to be fully elucidated and they are likely to be a key component of future studies of vitamin D in pregnancy. Further studies of vitamin D and adverse events in early pregnancy are required.

This needs to be clarified in future studies that how variations in vitamin D system in placenta and fetal trophoblast cells can affect implantation and regulate maintenance of a successful healthy pregnancy.

Role of vitamin D in maternal obesity is still not clear. Only a limited number of reports of vitamin D deficiency and miscarriage are available, and such studies need to be expanded by including more rigorous supplementation trials.

The mechanism of alteration of offspring epigenetic status by maternal VDD and the physiological impact of these epigenetic modifications remains uncertain. Future studies are needed to elucidate the mechanism and searching the windows for effective timely intervention via supplementation. Since VDD critically affects developmental programming of short- and long-term offspring metabolic and

neurobehavioral health, potentially via epigenetic mechanisms, exploration of mechanisms of non-genomic or genomic effects of vitamin D is required.

11. Conclusions

A proper understanding of causal mechanisms that lead to adverse health in offspring born to VDD mothers is required for early diagnoses and improving treatment during pregnancy so as to prevent later adverse DOHaD (developmental origins of adult disease) effects in at-risk offspring and mothers in future. Some genetic variants of VDBP have also been reported to be associated with these adverse outcomes. Further studies are required to explore more accurate VDBP assays and exploring ethnic variation and potential confounders are needed to clarify whether VDBP is associated with reproductive health and pregnancy outcomes, and the mechanisms underlying these relationships and possible role of vitamin D during pregnancy to prevent adverse fetal and maternal outcome.

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Conflict of interest

None. There is no conflict of interest.

Notes/thanks/other declarations

None.

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