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A comprehensive review of vitamin D level in third trimester of pregnancy: Suggestive of pharmacological intervention to override preeclampsia

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Abstract
Preeclampsia is a serious pregnancy complication, untreated preeclampsia can develop into eclampsia. Prevention of preeclampsia (PE) remains one of the most significant problems in perinatal medicine. Due to the possible unpredictable course of hypertension in pregnancy, primarily PE and the high complication rate for the mother and fetus/newborn, it is urgent to offer pregnant women in high-risk groups effective methods of preventing the PE development or delaying its appearance. In addition, due to the association of PE with an increased risk of developing cardiovascular diseases in later life, effective preeclampsia prevention could also be important in reducing their incidence. Ideal PE prophylaxis should target the pathogenetic changes leading to the development of PE and be safe for the mother and fetus, inexpensive and freely available. Currently, the only recognized method of PE prevention recommended by many institutions around the world is the use of a small dose of acetylsalicylic acid in pregnant women with risk factors. Unfortunately, some cases of PE are diagnosed in women without recognized risk factors and in those in whom prophylaxis with acetylsalicylic acid is not adequate. Hence, new drugs which would target pathogenetic elements in the development of preeclampsia are studied. Vitamin D seems to be a promising agent due to its beneficial effect on placental implantation, the immune system, and angiogenic factors. Studies published so far emphasize the relationship of its deficiency with the development of PE, but the data on the benefits of its supplementation to reduce the risk of PE are inconclusive. In the light of current research, the key issue is determining the protective concentration of vitamin D in a pregnant woman.

Keywords: Preeclampsia, pregnancy, vitamin D

Introduction
The Vitamin D status in pregnant women is also essential for the fetus. In early pregnancy, 25(OH)D crosses the placenta from mother to fetus, and the level measured in cord blood at birth depends on maternal status being on average at 80% of the value of the mother [1]. If the mother is deficient, the same occurs to the fetus [2]. The placenta and fetal tissues express 1α-hydroxylase leading to bioactive Vitamin D in the fetal circulation. The classic effects of Vitamin D deficiency during pregnancy and in neonates have been late hypocalcemia and nutritional rickets. Vitamin D is known to boost innate immunity by regulating production of anti-microbial peptides [3]. Several studies demonstrated that prenatal Vitamin D status plays a role in the offspring's susceptibility to develop asthma later in life [4, 5, 6]. It could also contribute to the destructions of beta cells of pancreas due to its action in type 1 helper lymphocytes and cytokines [7].

Vitamin D deficit during mother's pregnancy could also be a risk factor for multiple sclerosis in adult life because it influences early brain development, playing a relevant role in neuronal differentiation and synaptic functions [8]. Vitamin D plays a significant role in fetal skeletal growth and mineralization. Skeletal formation begins in the embryonic period, but the main period of skeletal mineralization (80%) is during the third trimester [9]. Skeletal mineralization in the uterus is primarily determined by the fetal plasma ionic calcium (Ca^{2+}) concentration, which is dependent on placental Ca^{2+} transfer and fetal calciotropic hormones [10]. An optimal supply of energy and essential nutrients is necessary for appropriate intrauterine fetal growth and development. The role of vitamin D in maintaining calcium concentration in the body is considered essential for regularized musculoskeletal growth; it is hypothesized that concentration of maternal vitamin D level can control neonates' bone development, length, and density.

A prospective cohort study conducted by Sarma *et al*. [11] concluded that healthy skeletal development of fetus is significantly altered by vitamin D insufficiency. Length of femur bone and infant length at birth are also affected and these lengths might be shorter in neonates born to vitamin D-deficient mothers, thus depicting a significant relation [11].

Vitamin D plays a significant role in fetal skeletal growth and mineralization. Skeletal formation begins in the embryonic period, but the main period of skeletal mineralization (80%) is during the third trimester [12]. Skeletal mineralization in the uterus is primarily determined by the fetal plasma ionic Ca^{2+} concentration, which is dependent on placental Ca^{2+} transfer and fetal calciotropic hormones. The level of Ca^{2+} transport across the placenta is strongly regulated by plasma membrane calcium-dependent ATPases (PMCA 1–4) gene expression [13].

Vitamin D physiology

Vitamin D (VD) is a fat-soluble steroid hormone mainly existing in two isoforms: cholecalciferol (VD3) and ergocalciferol (VD2 [14]. Vitamin D2 is synthesized by the irradiation of ergosterol in yeast, while vitamin D3 is generated from 7-dehydrocholesterol after ultraviolet (UV)-B irradiation in the human skin. Although vitamin D2 and D3 were considered equally active for many years, current knowledge indicates that the potency of vitamin D2 is less than one third that of vitamin D3 [15-18]. Vitamin D3 is the main form of vitamin D in humans [19]. A 20-min long whole-body exposure to the summer sun is able to produce up to 250 µg of vitamin D3 [20, 21], which yields the recommended serum level (>30 ng/mL) of its metabolite and systemic indicator, 25-hydroxyvitamin D [25(OH)D], which is also known as calcifediol or calcidiol [22]. Vitamin D3 is also present in small amounts in the diet of animal origin (e.g. fatty fish and fish liver oil, egg yolk, or dairy products). Over the past decade, another form of vitamin D was discovered in mushrooms, particularly those exposed to UV light. This so-called vitamin D4 (22-dihydroergocalciferol) is derived from its precursor, 22,23-dihydroergosterol [23].

Biosynthesis

During the first step of VD3 biosynthesis, the penetration of ultraviolet B (UVB) radiation with a wavelength of 290–315 nm into epidermis stimulates the photoconversion of 7-dehydrocholesterol into pre-VD3 (precalciferol) and subsequently calciol, which is then metabolized by hydroxylation reactions catalyzed by cytochrome P450 monooxygenases (CYP) CYP2R1 and CYP27A1 in the liver to form 25-hydroxyvitamin D3 (calcidiol). Calcidiol is further hydroxylated by calcidiol-1α -hydroxylase (CYP27B1) to 1α,25-dihydroxyvitamin D3 (calcitriol), the most active form of VD3 in the body [24, 25]. Although the kidneys are the primary site for the synthesis of circulating active calcitriol, recent research indicates that several other cell types, including prostate, placenta, brain, lung, immune cells, and myocytes, that also express 1α-hydroxylase, enable the local conversion of calcidiol to its active form [26, 27]. Renal CYP27B1 is stimulated by the parathyroid hormone (PTH), hypocalcemia and hypophosphatemia and receives negative feedback from 1,25(OH)2D3 as well as hypercalcemia [28].

Mechanism of action

The biological actions of calcitriol are mediated through the vitamin D receptor (VDR), which is a transcription factor regulating gene expression. The VDR is a member of the nuclear receptor (NR) family that include receptors for retinoic acid, thyroid hormone, steroid hormones, and adrenal steroids [29]. Once calcitriol binds to the VDR, it forms a heterodimer with another NR, the retinoic acid X receptor (RXR), and then translocates to the nucleus, resulting in the VD response elements (VDREs) recognition, binding, and subsequent target gene activation. The calcitriol/VDR/RXR/VDREs complex regulates the transcription of many genes, including the activation of calbindin (CALB), cathelicidin (CAMP), transforming growth factor β (TGFB), and nerve growth factor (NGF) as well as the repression of parathyroid hormone (PTH) and CYP27B13] [30].

Functions of vitamin D

It has been known for almost a century that the central role of VD3 is the mineral homeostasis and regulation of bone growth [31]. In addition to its classical roles in bone metabolism, growing evidence shows that VD3 exerts other essential physiological functions in the human body. For instance, it regulates the proliferation, differentiation, and apoptosis of normal and malignant cells [32]. Moreover, the expression of the VDR and CYP27B1 in certain types of immune cells implies the potential roles of VD3 in the modulation of the immune function [33]. Furthermore, calcitriol, as a neurosteroid hormone, exerts various actions in the central nervous system (CNS): it affects brain development, maintains adult brain function, and protects the brain from aging [25, 34]. Vitamin D association with brain development can be predicted by the findings that enzymes metabolizing vitamin D, CYP27B1 and CYP24A1, are localized in brain cells like the cortex region and Purkinje cells, indicating the independent role of vitamin D in brain. It is also involved in the regulation of neurotrophins, neuroimmunity, and neurotransmission in the brain [19].

Vitamin D helps in maintenance phosphorus balance, the regulations of calcium and phosphorus homeostasis are closely related, and the calciotropic hormones, PTH and 1α,25-dihydroxyvitamin D, can also control serum phosphorus [35]. Vitamin D also regulates blood pressure, Another meta-analysis of four prospective and 14 cross-sectional studies also reported an inverse relationship between circulating 25-hydroxyvitamin D and hypertension [36].

Disorders of vitamin D consumption

Vitamin D toxicity induces abnormally high serum calcium concentration (hypercalcemia), which could result in bone loss, kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. Hypercalcemia has been observed following daily doses of greater than 50,000 IU of vitamin D [37]. The Food and Nutrition Board of the IOM conservatively set the tolerable upper intake level (UL) at 4,000 IU/day (100 µg/day) for all adults. Certain medical conditions can increase the risk of hypercalcemia in response to vitamin D, including primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma [38]. People with these conditions may develop hypercalcemia in response to any increase in vitamin D nutrition and should consult a qualified health care provider regarding any increase in vitamin D intake**.**

In the past few years, vitamin D malnutrition has become prevalent among populations of different countries, races, and age groups, especially among women of reproductive age (WRA) [39, 40] Factors associated with vitamin D insufficiency are substantial use of sun protection beauty products, insufficient exposure to sunlight, use of tobacco, obesity, insufficient vitamin D intake or intestinal malabsorption, seasonal variation that is observed at temperate latitudes, and some pathological

conditions like kidney or liver failure, chronic inflammation, and use of contemporary medications [41-43]. In those with vitamin D deficiency, increasing 25(OH)D concentrations via D3 supplements or sufficient daily sun exposure reduces the risks and the severity of multiple disorders, including type 2 diabetes, hypertension, metabolic syndrome, obesity, cancer, and infections [44, 45].

Preeclampsia

Preeclampsia (PE) is a multifaceted syndrome that complicates approximately 3–5% of all pregnancies [46, 47]. It is primarily identified by the onset of hypertension after the 20th week of gestation and is frequently accompanied by dysfunction in multiple organs, including the kidneys, liver, blood, brain, and placenta [48, 49]. The clinical presentation of PE can vary significantly, ranging from mild to severe, with severe cases leading to life-threatening complications for both the mother and the fetus [49]. Women who have experienced PE are at an increased risk for chronic conditions such as chronic hypertension, cardiovascular disease, stroke, metabolic syndrome, cognitive impairment, and end-stage renal disease [50-53]. Moreover, PE poses significant risks to the fetus and the newborn. Infants born to mothers with PE are at an elevated risk for both immediate and long-term health issues. In the short term, these infants may suffer from complications related to preterm birth and intrauterine growth restriction [54]. In the long term, they are more susceptible to neurodevelopmental impairments, diabetes mellitus, coronary heart disease, and hypertension [55-57].

Risk factors for PE include a history of PE in previous pregnancies, chronic hypertension, preexisting diabetes, kidney disease, autoimmune disorders, obesity, advanced maternal age, multiple pregnancies, and certain genetic predispositions [47, 58, 59]. Additionally, first-time pregnancies and assisted reproductive technologies are associated with a higher risk of developing PE [47, 60, 61].

Preeclampsia etiology

Despite extensive research, the precise mechanisms that lead to the development of PE remain largely unclear. It is widely recognized that the condition originates from abnormal placentation early in pregnancy, which subsequently leads to widespread endothelial dysfunction. This dysfunction results in the clinical manifestations of the disease, including hypertension and organ damage [47, 60].

Understanding its etiology is essential for developing effective preventive and therapeutic strategies [61]. Several hypotheses have been proposed to explain the development of PE, each highlighting different aspects of its pathogenesis [62]. The two-stage hypothesis suggests that PE develops in two stages: impaired placentation due to inadequate trophoblast invasion, leading to poor spiral artery remodeling and placental hypoxia, followed by a maternal systemic response involving the release of anti-angiogenic factors (soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)), causing widespread endothelial dysfunction and systemic inflammation [63, 64]. The genetic and epigenetic hypothesis focuses on genetic predispositions and epigenetic changes, suggesting that genetic variants in both the mother and fetus affect placental development, while epigenetic modifications (DNA methylation, histone modification) influence gene expression related to immune response and angiogenesis [65, 66]. The immunological hypothesis argues that abnormal maternal immune adaptation to the fetus triggers PE. The maternal immune system fails to adequately tolerate fetal antigens, leading to an imbalance in immune cells (natural killer (NK) cells and regulatory T cells (Tregs)) and resulting in inflammatory responses and inadequate spiral artery remodeling [67]. The angiogenic imbalance hypothesis highlights the disruption of balance between pro-angiogenic factors (vascular endothelial growth factor (VEGF), placental growth factor (PlGF)), and anti-angiogenic factors (sFlt-1, sEng), impairing blood vessel formation and function, which results in endothelial dysfunction and reduced placental perfusion [68]. The placental hypoxia and oxidative stress hypothesis suggests that oxidative stress due to placental hypoxia contributes to PE. Placental hypoxia increases the production of reactive oxygen species (ROS), which damage placental and maternal endothelial cells, impairing their function [69]. The metabolic syndrome hypothesis links preeclampsia to metabolic syndrome and associated conditions, including obesity, insulin resistance, and hypertension. Metabolic disturbances lead to systemic inflammation and endothelial dysfunction, contributing to PE development [70]. Additionally, PE is likely caused by a combination of factors. The environmental factors hypothesis emphasizes the impact of endocrine disruptors such as BPA and phthalates on hormone signaling pathways, inducing oxidative stress and inflammation affecting placental and vascular function. The hormonal imbalance hypothesis discusses the roles of estrogens and androgens in regulating angiogenic factors, endothelial function, and immune responses, with disruptions leading to oxidative stress, inflammation, and endothelial dysfunction. The infection and inflammation hypothesis suggests maternal infections and inflammation contribute to PE by inducing systemic inflammatory responses, increasing cytokine production, and causing placental inflammation from conditions such as periodontal disease, urinary tract infections, and COVID-19. The intestinal dysbiosis hypothesis proposes that maternal intestinal dysbiosis affects pregnancy outcomes by altering gut microbiota, increasing intestinal permeability, and modulating the immune system, leading to systemic inflammation and contributing to PE. The sleep disorders hypothesis links sleep disorders during pregnancy, such as sleep apnea and altered sleep patterns, to increased PE risk through increased sympathetic activity and inflammation. The fetal factors hypothesis explores how fetal conditions like hydrops fetalis, viral infections, trisomy 13, and complications from multiple gestations can lead to placental and systemic effects contributing to PE. The autoimmune disorders hypothesis examines how autoimmune conditions with chronic immune activation, autoantibody production, and systemic inflammation increase the risk of PE. The endocrine disorders hypothesis investigates how endocrine disorders like hyperparathyroidism, Cushing's syndrome, and hyperaldosteronism cause hormonal imbalances, leading to altered vascular reactivity, increased blood pressure, and electrolyte disturbances. Finally, the placental aging hypothesis attributes PE to placental aging, characterized by telomere shortening, cellular senescence, oxidative stress, and impaired placental function, increasing PE risk [60, 62, 71].

PE can be categorized into early-onset and severe, with the latter exhibiting clinical features such as blood pressure exceeding 160/100 mmHg, visual disturbances, fetal growth restriction (FGR), and headaches. It progresses to a severe kind with major or long-term implications if left untreated [72]. FGR is one of the most worrisome consequences of PE for the fetus, which refers to a fetus that does not achieve its biological growth potential during pregnancy, often manifested by fetal ultrasound estimates of body mass or abdominal circumference below the 10th

percentile for gestational age [73]. Infants affected by FGR have a high chance of feeding difficulties, temperature instability, glucose instability, and jaundice [74]. They are also at risk of neurological handicaps and chronic diseases including metabolic, cardiac, neurodevelopmental, reproductive, and psychiatric disorders in their adulthood [75]. Thus, fetus with FGR would have potential lifelong consequences.

Vitamin D roles in pregnancy

Maintaining adequate vitamin D levels during pregnancy is vital for ensuring optimal health outcomes for both the mother and fetus. The active form of vitamin D, 1,25-dihydroxyvitamin D, plays an important role in regulating various genes essential for immune function and cell differentiation, which are critical processes during pregnancy [76, 77].

It is clear that vitamin D deficiency during pregnancy is common throughout the world yet what effect does deficiency have on the mother and her developing fetus? There is a strong relationship between maternal and fetal (cord blood) circulating 25(OH)D levels [78-81] such that maternal vitamin D deficiency is mirrored by neonatal vitamin D deficiency. With severe maternal vitamin D deficiency, the fetus rarely may develop rickets in utero with manifestation at birth [82].

While there can be some calcium loss during pregnancy through fetal demands and increased urinary calcium excretion which increases with advancing pregnancy, there is a rebound effect such that multiparous women are not at increased risk of osteopenia compared with nulliparous women. Throughout gestation, if a woman is vitamin D deficient, it appears to impact fetal bone health more than maternal [83-85].

A systematic review and meta-analysis of 31 observational studies on maternal vitamin D status and pregnancy outcomes indicated that vitamin D insufficiency may be associated with gestational diabetes mellitus, preeclampsia, and bacterial vaginosis in pregnant women. Low maternal serum vitamin D during pregnancy was also linked to an increased risk for small-for-gestational age infants and low-birth-weight infants, but not for Cesarean section [86]. However, the number of intervention trials is currently too limited to draw conclusions as to whether vitamin D supplementation during pregnancy might reduce the incidence of the above-mentioned adverse outcomes [87].

A few observational studies have given rather weak evidence in support of a relationship between maternal vitamin D sufficiency during pregnancy and incidence of respiratory conditions and allergies in children [88].

Considering the part of vitamin D in regulating auto- and cellular immunity abnormalities, it is assumed that it may lower the chances of frequent pregnancy loss. Lower concentration of serum vitamin D in initial pregnancy signifies the risk of abortion [89].

Emerging research suggests a potential link between these conditions, indicating that vitamin D deficiency may contribute to the development of gestational diabetes and exacerbate its effects. Vitamin D deficiency influences the risk of GDM are not yet fully understood [90]. However, it has been demonstrated that 1,25(OH)2D3 affects both beta cell activity and insulin resistance [91-93]

The mechanisms underlying the association between 25(OH)D deficiency and an increased risk of cesarean section are complex and require further investigation. One potential explanation for this association is the presence of vitamin D receptors in skeletal muscle [94], which can lead to proximal muscle weakness (especially pelvic muscle [95]. and suboptimal muscle function and strength in individuals with vitamin D deficiency [95-96]. Additionally, calcium levels, which are regulated by 25(OH)D, play a critical role in smooth muscle performance during labor initiation [97].

Vitamin D may affect myometrial contractility via two pathways: involving the intracellular vitamin D receptor and changes in the calcium metabolism [98]. *In vitro* studies have demonstrated that vitamin D regulates contractile proteins in myometrial cells [99]. Mothers with asthma had 2 times higher risk of having a child with asthma or recurrent wheeze before the age of 3 years than did mothers without asthma. However, this risk among mothers with asthma was substantially attenuated if they were Vitamin D sufficient at early and late pregnancy. Therefore, women with asthma who start their pregnancies with high levels of Vitamin D and remain Vitamin D sufficient throughout pregnancy are likely to experience a reduced risk of asthma or recurrent wheeze in their children before 3 years of age [100].

A cross-sectional study concluded that severe deficiency of vitamin D has damaging effects during early embryonic stages and can lead to loss of pregnancy [101]. Thus, it is recommended to modulate vitamin D intake to avoid spontaneous pregnancy loss.

Postpartum depression

Postpartum depression (PPD), an acute mental condition, occurs after child delivery characterized by behavioral and emotional disturbance. There are several pathways that contribute to functions of vitamin D in depression pathogenesis. First, vitamin D plays a key role as a neurosteroid hormone regulating healthy nervous homeostasis and growth, providing protection and neuroplasticity [102]. Moreover, vitamin D also serves as an antioxidant by maintaining glutathione level in the brain. It influences the production of mood-directing hormones, dopamine and norepinephrine, in the brain [103]. In addition, it was also found that vitamin D regulates calcium ions in nerve cells that control the development of depressive symptoms. Thus, decreased vitamin D concentration increases neural calcium, leading to depression [103]. Furthermore, vitamin D receptors are located in the hippocampus and cingulate cortex of brain, which are involved in processing, memory storage, and planning [101]. Endocrine Society recommends supplementation of vitamin D (2000 IU) during gestational and lactation period to meet elevated demands that may avoid the symptoms of PPD. Hence, vitamin D may play an important role in maintaining overall cognitive functions.

Collectively, these data suggest that vitamin D deficiency states during pregnancy are associated with alteration in lung structure and function and increased inflammation, contributing to asthma, which manifests well after birth, and further suggests epigenetic mechanisms of action of vitamin D.

Conclusion

Overall, there is no consistent evidence that vitamin D supplementation during pregnancy has clinically meaningful health benefits for pregnant women and infants in the general population. However, research in this field should focus on conducting adequately powered trials with high-quality assessment of maternal outcomes including GDM and hypertensive disorders of pregnancy**.** Despite advances in understanding its pathophysiology, effective prevention and treatment strategies remain limited. Continued research is essential to develop targeted therapies that can improve outcomes for both mothers and their babies **.**In conclusion, low vitamin D levels were associated with preeclampsia among women with early-onset preeclampsia and/or whose children

were born SGA. Preeclampsia is not a homogenous condition and more studies are needed before vitamin D supplementation during pregnancy can be recommended. The results stress the importance that future studies, epidemiological studies as well as randomized trials, should not treat preeclampsia as a homogeneous pregnancy complication**.** The present results argue in favour of vitamin D supplementation in pregnant woman and clearly suggest that the risks of preeclampsia, preterm delivery and caesarean delivery are lower when the serum vitamin D level is maintained in the normal range throughout pregnancy**.**

Conflict of Interest
Not available

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