EFFECT OF VITAMIN D DEFICIENCY IN PREGNANT WOMEN

Sadiq Nazim Abdel Amir Hamad  
AL_muthanna, University College of Science _Department Of Biology  
Sadeknazim451@gmail.com  

Sarah Ibrahim Mutar Aswad  
University of anbar College of Science Biology department  
Sarahibrahim20181995@gmail.com  

Hawraa Ayed Halil Khanzeer Al-Qadisiyah  
University College of Science _Department Of Biology  
hooorey51@gmail.com  

Alina Shahab Qahtan Yahya  
Al-Mustansiriya University, Bachelor of Life Sciences, Biotechnology  
alinashahab360@gmail.com  

Mohammed Jassim Mohammed Ali  
Madenat Alelem University College Department of biology  
evavovehc51998@gmail.com

Abstract: Vitamin D deficiency (VDD) in pregnant women and their children is an important health problem with severe consequences for the health of both. Thus, the objectives of this review were to reassess the magnitude and consequences of VDD during pregnancy, lactation and infancy, associated risk factors, prevention methods, and to explore epigenetic mechanisms in early fetal life capable of explaining many of the non-skeletal benefits of vitamin D (ViD).  

Keywords: -

Introduction  
Vitamin D deficiency (VDD) is identified as a public health problem in many countries, and pregnant women have been identified as a high-risk group, among whom the prevalence of VDD ranges between 20 and 40%. While it is acknowledged that vitamin D (ViD) supplementation is effective in preventing the VDD, many children are born with this deficiency, raising questions as to how and why VDD affects the pregnancy, the fetus and the newborn's health. The increase in the number of studies on this subject shows conflicting results on the association between 25(OH)D levels in pregnancy and adverse effects on maternal and fetal health, both skeletal and non-skeletal (autoimmune diseases, cardiovascular diseases, diabetes and certain types of cancer through "fetal imprinting"). Vitamin D deficiency has been linked to...
many metabolic and cardiovascular diseases (CVD), and therefore supplemental vitamin D has been used in the treatment and prevention of these diseases. This fat-soluble vitamin is a steroid hormone that is endogenously produced in the skin of humans. Initially, researchers have focused on a link between low levels of vitamin D and the occurrence of bone disease, as vitamin D has been primarily known for its role in regulating calcium homeostasis and bone metabolism. Data from the 2005–2006 National Health and Nutrition Examination Survey indicate that vitamin D deficiency, defined as a serum 25-hydroxyvitamin D levels ≤ 20 ng/mL (50 nmol/L), is common among adults aged 20 years and over in the United States (US), with 41.6% of adults reporting a vitamin D deficiency.  

**Literature Review**

2.1 Physiology and vitamin D metabolism

There are two sources of ViD for humans. An exogenous one is provided by the diet in the form of vitamins D2 and D3. In the endogenous production, cholecalciferol (D3), the main source of ViD, is synthesized in the skin by the action of ultraviolet B (UVB) radiation through the photolysis of 7-dehydrocholesterol and transformed into vitamin D3. Sufficient exposure to sunlight or UVB radiation is up to 18IU/cm2 in 3 hours. This process takes place in two phases: the first one occurs in the deep layers of the dermis and consists in the photo conversion of 7-dehydrocholesterol into pre-vitamin D or pre-calciferol (Fig. 1).
In the second phase, there is a chemical isomerization depending on body temperature, and pre-vitamin D slowly and progressively turns into vitamin D3, which has high affinity for the ViD carrier protein (DBP), and the pre-vitamin D, with lower binding affinity, remains in the skin.\textsuperscript{4} Upon reaching the skin capillary network, ViD is transported to the liver and binds with DBP, where it starts its metabolic transformation.\textsuperscript{4}

The two types of ViD undergo complex processing to be metabolically active.\textsuperscript{5} Initially, the pre-hormone is hydroxylated in the liver at the carbon 25 position through the action of vitamin D-25-hydroxylase 1a (1-OHase), which constitutes an enzyme system dependent on cytochrome P-450 (CYP27B) present in liver microsomes and mitochondria, and originates 25-hydroxyvitamin D (25(OH)D), the most abundant circulating form of ViD.\textsuperscript{4} Its mean blood concentration is 20-50ng/mL (50-125nmol/L) and it has an average life of approximately 3-4 weeks.\textsuperscript{4} It is estimated that its circulating pool is in dynamic equilibrium with reserves of 25(OH)D (muscle and adipose tissue), which makes blood levels a reliable indicator of the state of the ViD reserves in the body.\textsuperscript{4} Under normal circumstances, the percentage of conversion into 25(OH)D is low, with a distribution of almost 50% in the fat and muscle compartments. When there is excess intake of ViD, most of it is stored in the fatty deposits.\textsuperscript{4} As 25(OH)D has low biological activity, it is transported to the kidney where it undergoes the second hydroxylation, and then the active forms are obtained: calcitriol (1a-dihydroxyvitamin D) (1.25(OH)2D) and 24.25-dihydroxyvitamin D (24.25(OH)2D), through the respective action of enzymes 1-OHase and vitamin D-24-hydroxylase (24-OHase) present in mitochondria of cells of the proximal convoluted tubule.\textsuperscript{5}

DBP and 25(OH)D are filtered by the glomerulus and absorbed in the proximal tubule by low-density lipoprotein receptors, which regulate the uptake of the

25(OH)D-DBP complex within the tubule cells and the subsequent hydroxylation to 1.25(OH)2D.\textsuperscript{4} 1-OHase is also found in other tissues that express ViD receptors, such as the placenta, colon, activated mononuclear cells and osteoblasts, which could produce 1.25(OH)2D with local autocrine or paracrine function.\textsuperscript{6} Several factors regulate the levels of 1.25(OH)2D: 1-OHase, whose hydroxylation is activated by the Parathyroid hormone (PTH), and calcitonin, which is inhibited by serum levels of calcium, phosphorus and 1.25(OH)2D itself, and whose average life is 15 days.\textsuperscript{6}

Blood levels of phosphorus have a direct action, without the intervention of PTH, and hypophosphatemia increases the production of 1.25(OH)2D.

Thus, in addition to the main action of ViD in maintaining physiological levels of calcium and phosphorus capable of allowing metabolism, neuromuscular transmission and bone mineralization, the presence of ViD receptors in bone, bone marrow, cartilage, hair follicle, adipose tissue, adrenal gland, brain, stomach, small intestine, distal kidney tubule, colon, pancreas (B cells), liver, lung, muscle, activated B and T lymphocytes, heart cells, vascular smooth muscle cells, gonads, prostate, retina, thymus and thyroid glands has been described, which reinforce such diverse and important ViD functions (Fig. 2).\textsuperscript{5} Figure 3 summarizes the mechanisms involved in the control of serum calcium and phosphorus levels.\textsuperscript{7}

2.2 Risk factors for ViD deficiency

The main source of ViD for children and adults is exposure to sunlight, so the main cause of VDD is the decrease of its endogenous production. Any factor that affects the transmission of UVB radiation or interferes with its skin penetration will determine the reduction of 25(OH)D.\textsuperscript{4}

Among these risk factors are:
• Use of sunscreen with a protection factor of 30 reduces the synthesis of ViD in the skin, above 95%

• Individuals with darker skin have natural sun protection, as melanin absorbs UVB radiation, and thus they need 3-5 times longer sun exposure to synthesize the same amount of ViD than individuals with light skin

• Skin aging as well as age decrease the capacity of the skin to produce ViD due to lower availability of 7-dehydrocholesterol

• Skin damage such as burns decrease ViD production

2.3. Vitamin D deficiency in pregnancy and fetal programming

During fetal life, the body tissues and organs go through critical development periods that coincide with periods of rapid cell division. Fetal programming is a process through which a stimulus or insult, during a certain development period, would have effects throughout life. This term is used to describe the mechanisms that determine fetal adaptation to changes that accompany the gene-environment interaction during specific periods of fetal development.

It has been demonstrated that nutritional and environmental exposures during these sensitive periods of life may influence fetal growth and the development of physiological functions of organs and systems. Permanent changes in many physiological processes of this programming can modify the expression patterns of genes, with consequent influence on phenotypes and functions (epigenetic mechanisms).

Thus, the closer to fertilization these changes take place, the greater the potential for epigenetic changes and their correspondence in newborns to occur in response to environmental changes. These changes in placenta/embryo/fetus provide a plausible explanation for the concept of fetal origin of adult diseases.

It is currently recognized that nutrition in early life and other environmental factors play a key role in the pathogenesis and predisposition to diseases, which seem to propagate to subsequent generations. Epigenetic modifications establish a link with the nutritional status during critical periods of development and cause changes in gene expression that can lead to the development of disease phenotypes.

Recent evidence indicates that nutrients can modify the immune and metabolic programming during sensitive periods of fetal and postnatal development. Thus, modern diet patterns could increase the risk of immune and metabolic dysregulation associated with the increase of a wide range of noncommunicable diseases. Among these nutrients, ViD is emphasized, and its effects on fetal programming and gene regulation might explain why it has been associated with many health benefits throughout life.

There seems to be a window of early development in life that can shape the nature of the immune response in adulthood, and thus early life factors that predispose individuals to chronic lung disease would not be limited to the post-natal period, as evidence indicates that there are intrauterine effects such as maternal smoking, diet and ViD that influence the development of the
lung and the subsequent development of asthma and chronic obstructive pulmonary disease.16, 17

As much of the reprogramming that occurs during childhood may go unnoticed until adulthood, the better understanding of the interaction between genetics and epigenetics in critical time windows of development would improve our capacity to determine individual susceptibility to a wide range of diseases.13 Although these epigenetic changes appear to be potentially reversible, little is known about the rate and extent of improvements in response to positive environmental changes, including nutrition, and to what extent they depend on the duration of exposure to a deficient maternal environment also remains unknown.18 Thus, it can be observed that, in spite of all this new range of information, maternal nutrition has received little attention in the context of implementation of effective prevention goals (MDG, Millennium Development Goals). This could be attributed to the lack of a solid and strong foundation to justify the enormous effort required to improve the nutritional status of all women of reproductive age.19 To elucidate the true role of nutritional epigenetics13, 14 in fetal programming of pregnant women, especially those with VDD, would allow the use of effective prevention measures to improve maternal and fetal health and prevent the development of future chronic diseases.

2.4. Vitamin D and calcium metabolism in pregnancy

During pregnancy and lactation, significant changes in calcium and ViD metabolism occur to provide for the needs required for fetal bone mineralization. In the first trimester, the fetus accumulates 2-3mg/day of calcium in the skeleton, which doubles in the last trimester.1 The pregnant woman's body adapts to the fetal needs and increases calcium absorption in early pregnancy, reaching a peak in the last trimester.1 The transfer is counterbalanced by increased intestinal absorption and decreased urinary excretion of calcium. Plasma levels of 1.25(OH)2D increase in early pregnancy, reaching a peak in the third trimester and returning to normal during lactation. The stimulus for increased synthesis of 1.25(OH)2D is unclear, considering that PTH levels do not change during pregnancy.1 A potent stimulus to placental transfer of calcium and placental synthesis of ViD is the PTH-related peptide (PTHrP), produced in the fetal parathyroid and placental tissues, which increases the synthesis of ViD.1 The PTHrP can reach the maternal circulation and it acts through the PTH/PTHrP receptor in the kidney and bones, being a mediator in the increase of 1.25(OH)2D and helping in the regulation of calcium and PTH levels in pregnancy.1 Other signals involved in the regulation process include prolactin and the placental lactogen hormone, which increase intestinal calcium absorption, reduce urinary calcium excretion and stimulate the production of PTHrP and 1.25(OH)2D. Moreover, the increase in the maternal blood levels of calcitonin and osteoprotegerin protects the mother's skeleton from excessive calcium resorption.1 Additionally, during lactation, there is a relative estrogen deficiency, caused by elevated levels of prolactin, which determines bone resorption and suppression of PTH levels. PTHrP levels are elevated and act as a substitute for PTH, while maintaining urinary calcium absorption and bone resorption.1

2.5. Implications of vitamin D deficiency in pregnancy

Recent studies emphasize the importance of non-classical roles of ViD during pregnancy and in the placenta and correlate VDD in pregnancy with preeclampsia, insulin resistance, gestational diabetes, bacterial vaginosis and increased frequency of cesarean delivery.20 ViD supplementation reduces the risk of preeclampsia. Studies in women with preeclampsia have shown low urinary excretion of calcium, low ionized calcium levels, high levels of PTH and low levels of 1.25(OH)2D.21 An association between maternal VDD (<50nmol/L) and increased risk of gestational diabetes (OR:2.66, 95% CI: 1.01 to 7.02),22 as well as the fact that VDD is an independent risk factor for bacterial vaginosis in pregnancy23 have also
been documented. A recent randomized and controlled study showed that supplementation with 4,000IU/d during pregnancy was associated with reduced risk of combined morbidities, such as maternal infections, cesarean section and preterm delivery.21-24

A prospective study showed that cesarean delivery is four times more common in women with VDD (<37.5nmol/L) when compared to women with normal levels of ViD (OR: 3.84, 95% CI: 1.71 to 8.62).25

2.6. Implications of vitamin D deficiency in lactation and childhood

Adequate levels of ViD are also important for the health of the fetus and the newborn, and poor skeletal mineralization in utero due to VDD can be manifested in the newborn as congenital rickets, osteopenia or craniotabes.1

Maternal VDD is one of the main risk factors for VDD in childhood, as in the first 6-8 weeks of life newborns depend on the ViD transferred across the placenta while in the womb. This association is linear,26 and the 25(OH)D levels of the newborn correspond to 60-89% of maternal values.2

These levels decrease on the 8th week and, therefore, exclusively breastfed infants have an increased risk of VDD, as human milk has a low concentration of ViD (approximately 20-60IU/L: 1.5-3% of the maternal level). This concentration is not sufficient to maintain optimal levels of ViD, especially when exposure to sunlight is limited,27 and may induce seizures caused by hypocalcemia and dilated cardiomyopathy.1 Observational studies have shown that low levels of ViD during pregnancy and VDD in childhood are related to the increase in other non-skeletal manifestations,2 such as a higher incidence of acute lower respiratory tract infections and recurrent wheezing in the first five years of life.28

Contradictory results are observed in relation to the increased risk of allergic diseases such as asthma, eczema and rhinitis in the presence of VDD.29 However, a cohort study showed increased asthma and eczema among children whose mothers had high serum levels of 25(OH)D during pregnancy.30 Japanese schoolchildren that received ViD supplementation (1,200IU/d) had a 42% reduction in the incidence of type A Influenza.1 A cohort study showed that supplementation with 2,000IU/d of ViD during the first year of life was associated with a reduction in the incidence of type I diabetes during a 30-year follow up.31

2.7. Vitamin D deficiency, insufficiency and sufficiency

The cutoff point to define the ViD status based on the values of 25(OH)D is debatable. There are currently two criteria:

- The Committee of the Institute of Medicine (IOM, USA)32 considers values lower than 20ng/mL (50nmol/L) as indicators of VDD, with 10ng/mL (25nmol/L) being considered severe VDD, and 10-19ng/mL (25-49nmol/L) being considered ViD insufficiency. ViD levels <10ng/mL are associated with rickets and osteomalacia in adults and children. Between 10-19ng/mL, there is increased rate of bone resorption and increased risk of secondary hypoparathyroidism. Thus, the IOM recommends a threshold level of 20ng/mL as adequate to maintain bone health at all ages.

- The Endocrine Society (USA) proposes VDD in the presence of ViD levels inferior to 20ng/mL and ViD insufficiency between 20-30ng/mL (50-75nmol/L).33 In clinical practice, a patient would have sufficient levels when the concentration of 25(OH)D were greater than 30ng/mL. Several authors support this concentration cutoff for
musculoskeletal health and mineral metabolism (prevention of rickets and osteomalacia, elevated PTH levels, osteoporotic fractures and falls among the elderly) 34 The main differences between the IOM32 and the Endocrine Society 33 are the overall health endpoints. The IOM makes recommendations to ensure skeletal health and suggests there is lack of evidence to support recommendations of potential non-skeletal benefits of ViD, considering that individuals with levels inferior to 20ng/mL are not deficient, as 97% of individuals with these levels have adequate bone health.32 The Endocrine Society 33 considers that serum levels superior to 30ng/mL bring greater benefits to health in general, when compared to a level of 20ng/mL, and that skeletal health is not guaranteed with levels inferior to 30ng/mL; these data are supported by three supposed observations:

- The increase in PTH reaches a plateau when serum 25(OH)D is ≥30ng/mL;
- There is a decrease in the risk of fractures in individuals with levels ≥30ng/ml;
- Calcium absorption is maximal for serum levels of 30ng/mL.

2.8. Basic Physiology of Vitamin D and the Endothelium

The majority of vitamin D in the body is obtained through the sunlight-initiated biosynthesis in the skin. When the skin is exposed to the sun, a cholesterol precursor, 7-dehydrocholesterol, is converted to previtamin D3 and vitamin D3 (cholecalciferol) by ultraviolet B (UVB) radiation and thermal stimulation, respectively 12. Less than 30% of vitamin D can be obtained through diet 13. Vitamin D found in foods can exist in two forms: Vitamin D2 (ergocalciferol), found in vegetable sources such as sun-dried mushrooms; and vitamin D3, found mostly in oil-rich fish. Both vitamin D2 and D3 go through hydroxylation twice to become the biologically active form, namely 1α,25-dihydroxyvitamin D3 (1α,25(OH)2D3 or calcitriol) 14. The first phase of hydroxylation occurs in the liver in which vitamin D is converted to calcidiol 25(OH)D by 25-hydroxylase, and the second phase of hydroxylation, catalyzed by 1α-hydroxylase, occurs mainly in the kidney, which produces 1α,25(OH)2D3 from 25(OH)D; 1α,25(OH)2D3 then exerts biological actions by binding to nuclear VDR or plasma membrane VDR. The principal biological actions of 1α,25 (OH)2D3 are mediated by the nuclear VDR through which 1α,25(OH)2D3 controls gene expression. The ligand-bound nuclear VDR translocate into the nucleus and form homodimers or heterodimers with the retinoid X receptor (RXR). After this nuclear dimerization, the homodimers or VDR-RXR heterodimers bind to specific enhancer elements found in the promoter region of vitamin D-regulated genes, referred to as vitamin D response elements (VDRE), thus activating the expression of specific target genes 15. The genomic action of vitamin D is involved in expression of over 200 genes, the functional activities which play essential roles in various physiological processes including homeostatic control of bone metabolism, immune cell growth, and regulation of vascular tone 5,16,17. Activation of the plasma membrane VDR can elicit an intracellular signal transduction pathway independent of the VDRE 18,19, although most biological actions of calcitriol are attributed to activation of the nuclear VDR given that the nuclear VDR effectively responds to 1α,25 (OH)2D3 at sub-nanomolar concentrations 20. Vitamin D has been implicated in various biological activities within the body, and as such, VDR have been found in most tissues and cells 21. The most well-known action of vitamin D is associated with the homeostasis of calcium and bone mineralization, with vitamin D and VDR primarily functioning to promote calcium absorption in the intestines 22. Vitamin D is an essential component necessary for the development, growth, and mineralization of bone during the formative years of childhood; however, vitamin D continues to play a crucial role maintaining optimal bone health throughout the lifespan in adults of all ages 23. Both genomic and non-genomic actions of vitamin D are mediated by the VDR, and ligand-activated VDRs are involved in physiological processes through regulation of transcriptional
activity of target genes or activation of intracellular second messengers 24,25. While vitamin D plays important roles in various cellular functions, the action of vitamin D can be inhibited by a number of factors such as reduced biosynthesis of vitamin D, a lack of vitamin D hydroxylases in the cells, and reduced VDR content; thus, the impaired vitamin D action may contribute to the development of many chronic diseases including osteoporosis, diabetes, atherosclerosis, ED, and cancer 26.

2.9. Pregnancy

In 2019, two Cochrane analyses on vitamin D and pregnancy were published. They suggested that vitamin D supplementation may reduce gestational diabetes, low birthweight, and preeclampsia, but a higher than currently recommended dose appeared to have no additional benefit except for possible further reduction of gestational diabetes 35, 36. However, several studies in recent years have highlighted that women are at high risk for vitamin D deficiency, and this is associated with adverse pregnancy outcomes, including preeclampsia and gestational diabetes 37–38. It has been demonstrated that vitamin D supplementation is able to reduce adverse pregnancy outcomes when a higher level is achieved, with an increasing efficacy when the target level is raised from 20 to 40 ng/mL or 50 ng/mL. Interestingly, the maximum change is achieved 6–8 weeks after initiating the treatment, likely exerting the genomic actions of vitamin D 39–40. Three major adverse pregnancy outcomes appear to improve with vitamin D supplementation: a 60% reduction in preeclampsia, a 50% reduction in gestational diabetes, and a 40% reduction in preterm delivery 41. These data are consistent with previous work on the topic 42. Moreover, following the genomic and epigenetic effects of vitamin D supplementation, vitamin D deficiency during pregnancy also seems able to induce specific genomic pathways relevant to autoimmune disease in childhood and later in life 43,44. The placenta can convert 25(OH)D to the active form 1,25(OH)2D, similarly to the kidneys; therefore, more basic research should shed light in the future on the specific vitamin D metabolism during pregnancy 43. The FDA has recently approved the statement “Pregnant women who have higher serum vitamin D levels have a decreased risk of preterm birth.” Taking into account the recent literature, vitamin D deficiency is associated with worse outcomes during pregnancy, and at least 400–600 IU of daily vitamin D supplementation is reasonable for women with a vitamin D level <40 ng/mL, with higher required doses in more severe deficiency 43

Conclusion

VDD in pregnant women and their children is a major health problem, with potential adverse consequences for overall health. Prevention strategies should ensure the ViD sufficiency in women during pregnancy and lactation. Evidence-based interventions to improve maternal and fetal nutrition, such as for ViD, are accompanied by a decrease of the impact on the health of their children

References


[16]. Shrimpton R: Global policy and programme guidance on maternal nutrition: what exists, the mechanisms for providing it, and how to improve them? Paediatr Perinat Epidemiol. 2012;26 (S1):315-25


