

# Vitamin D – a novel role in pregnancy

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*Vitamin D regulates placental development and function. It is a potent regulator of the immune system-stimulating antimicrobial responses while suppressing inflammation. Its deficiency has been linked to increased risk of serious chronic and inflammatory diseases. Vitamin D deficiency during pregnancy increases susceptibility to infection and inflammation, leading, in turn, to outcome like preterm birth or preeclampsia. Pregnant women with darker skin pigmentation are more likely to be vitamin D deficient, particularly when living in regions with low exposure to sunlight. It is possible that during pregnancy, a primary non-infectious inflammatory process is activated by vitamin D deficiency. Combined assessment of vitamin D deficiency and inflammatory markers in early pregnancy or during different stages of pregnancy may facilitate the recognition of the risk of complications.*

*Keywords: vitamin D, pregnancy, immune response.*

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**Introduction.** Beyond its classical effects on bone and calcium homeostasis causing rickets and osteoporosis, vitamin D has become increasingly recognized as a potent regulator of multiple physiological functions above. Vitamin D can be obtained from limited food sources, such as fatty fish and fish oil, and, today, from dietary supplements or we can also make it ourselves, through a chemical reaction that happens in the skin when it is exposed to ultraviolet B (UVB) light especially to meet the increased demands of pregnancy.

The vitamin D deficiency epidemic during pregnancy is caused by a lack of adequate sunlight exposure needed to synthesize vitamin D<sub>3</sub> (cholecalciferol) in the skin, coupled with oral intakes that are too low even with regular use of prenatal vitamins containing 400 IU vitamin D<sub>3</sub> [1] Vitamin D deficiency during pregnancy has been linked with a number of serious short- and long-term health problems in offspring, including im-

paired growth, skeletal problems, type 1 diabetes, asthma, and schizophrenia [2].

**Functional aspects of vitamin D.** Vitamin D in humans, refers to Vitamin D<sub>3</sub>, which is also known as cholecalciferol. In response to UVB light, it is created by skin cells called keratinocytes utilizing 7-dehydrocholesterol, a product of cholesterol. This version has no biological activity in the body till this molecule is modified primarily in the liver, by a series of related enzymes for hydroxylation, to generate 25-hydroxyvitamin D<sub>3</sub> (25(OH)D<sub>3</sub>). The 25(OH)D<sub>3</sub> made by the liver is nonetheless the major circulating form of vitamin D. When it is needed in the body, a final conversion to the biologically active form by the enzyme 1 $\alpha$ -hydroxylase (CYP27b1), is required to become 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D<sub>3</sub>). This was first discovered in the kidney, and renal processing is responsible for generating much of the body's circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> supply [3] (Fig. 1).

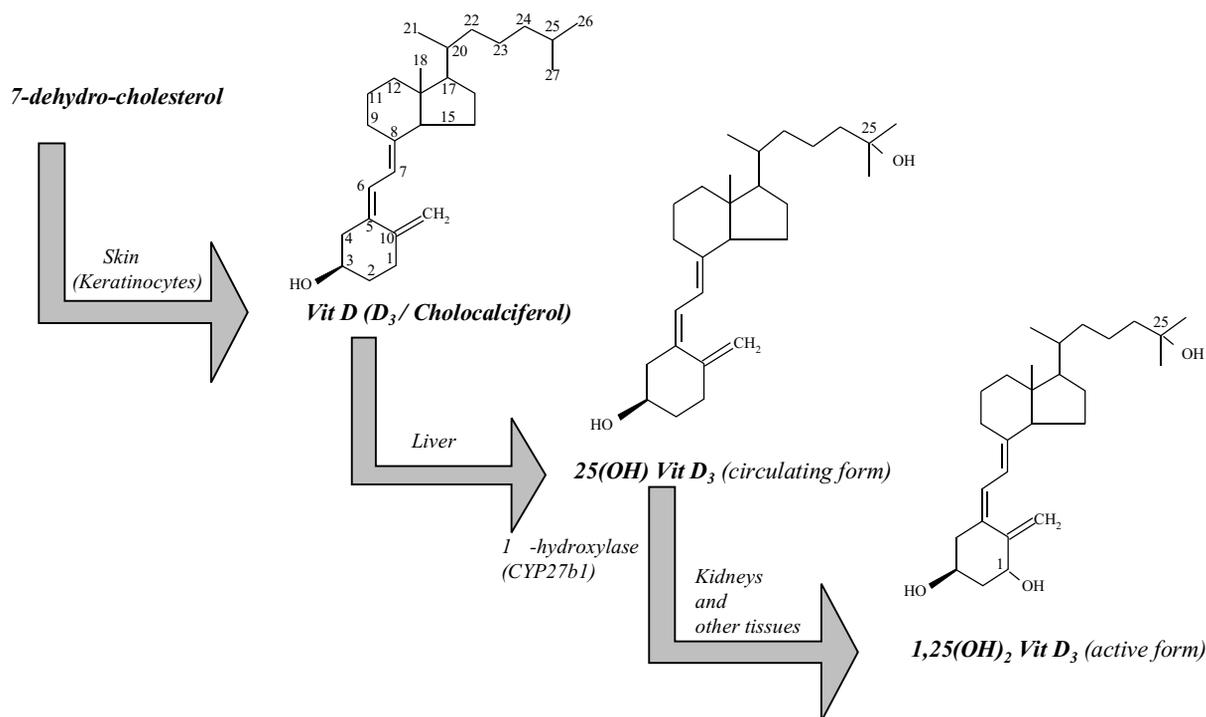


Fig. 1. Skin keratinocytes convert 7-dehydrocholesterol to vitamin D in response to sunlight exposure. This is converted to the circulating form 25(OH)D<sub>3</sub> in liver and to 1,25(OH)<sub>2</sub>D<sub>3</sub> in the target tissues

The active form of vitamin D, the 1,25(OH)<sub>2</sub>D<sub>3</sub> molecule virtually functions as an «on/off» switch for genes of every tissue in the human body. This form of vitamin D acts by attaching to the vitamin D receptor (VDR), which serves as a transcription factor inside a cell's nucleus. Once bound to 1,25(OH)<sub>2</sub>D<sub>3</sub>, the VDR protein makes a complex with retinoid-x receptor (RXR). This complex now binds to a specific region of the cell's DNA adjacent to a target gene. Their attachment to the DNA induces cellular machinery to begin transcribing the neighboring gene to a specific protein.

Recently, many other tissues, including cells of the immune system and the skin, have been identified to perform the conversion of 25(OH)D<sub>3</sub>. Skin is therefore unique among organs in that it is capable of manufacturing biologically active 1,25(OH)<sub>2</sub>D<sub>3</sub> in the presence of UVB light from start to finish, although local production of 1,25(OH)<sub>2</sub>D<sub>3</sub> from circulating in other tissues is a substantial source of vitamin D's biological activity.

By inducing a cell to make a particular protein, 1,25(OH)<sub>2</sub>D<sub>3</sub> affects a range of cellular function, and this ability to trigger gene activity in different tissues is the basis of vitamin D's enormous physiological ef-

fects. Precisely, vitamin D is manufactured in one tissue and circulates through the body influencing many other tissues, and VDR is a nuclear receptor that responds to powerful steroidal hormones such as estrogen and testosterone [4].

Although at least 1,000 different genes are believed to be regulated by 1,25(OH)<sub>2</sub>D<sub>3</sub>, including several involved in the body's calcium processing that account for D's well-known role in bone formation as well as genes with critical roles in a variety of cellular defenses.

**Circulating levels of 25(OH)D<sub>3</sub> – the biomarker of vitamin D status.** Circulating levels of 25(OH)D<sub>3</sub> are a direct reflection of vitamin D status, which depends on access to vitamin D either through exposure to sunlight or through dietary intake whereas serum concentrations of 1,25(OH)<sub>2</sub>D<sub>3</sub>, are primarily defined by the endocrine regulators of renal CYP27b1 activity. The net effect of this is that vitamin D status can vary significantly in populations as a consequence of geographical, social or economic factors. Until recently, rickets was considered to be the only significant clini-

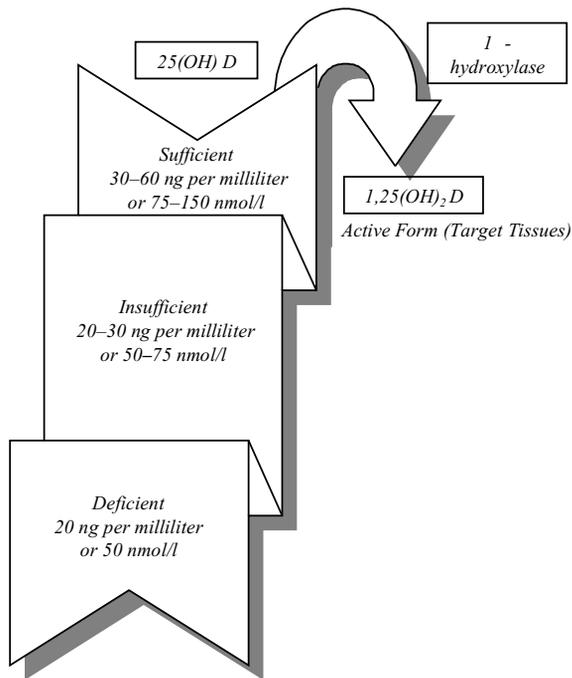


Fig. 2. Deficient and Sufficient levels of circulating vitamin D for getting converted to the active form by the action of 1-hydroxylase

cal consequence of low serum 25(OH)<sub>2</sub>D<sub>3</sub>. However, an entirely new perspective on vitamin D deficiency has arisen from the observation that serum 25(OH)<sub>2</sub>D<sub>3</sub> levels correlate inversely with serum parathyroid hormone below a threshold of 80 nmol/l 25(OH)<sub>2</sub>D<sub>3</sub> [5]. This has led to a complete re-evaluation of the optimal serum level of 25(OH)<sub>2</sub>D<sub>3</sub> so that serum concentrations of 25(OH)<sub>2</sub>D<sub>3</sub> up to 75 nmol/l are now considered to be inadequate and are more commonly referred to as vitamin D «insufficiency» as opposed to «deficiency» [6]. A 25(OH)<sub>2</sub>D<sub>3</sub> level of 30 ng per milliliter (75 nmol/l) or higher provides adequate substrate for 1-OHase to convert 25(OH)<sub>2</sub>D<sub>3</sub> to its active form, 1,25(OH)<sub>2</sub>D<sub>3</sub> [6]. We categorized the serum levels of 25(OH)<sub>2</sub>D<sub>3</sub> as: less than 50 nmol/l (< 20 ng per milliliter) as deficient, 50–75 nmol/l (< 20–30 ng per milliliter) as insufficient, and 75–150 nmol/l (< 30–60 ng per milliliter) as sufficient (Fig. 2).

Once 1,25(OH)<sub>2</sub>D<sub>3</sub> completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (24-OHase), which enhances the catabolism of 1,25(OH)<sub>2</sub>D<sub>3</sub> to biologically inert 1,24,25-trihydroxyvitamin D.

Locally produced 1,25(OH)<sub>2</sub>D<sub>3</sub> does not enter the circulation and has no influence on calcium metabolism. Therefore circulating levels of 25(OH)<sub>2</sub>D<sub>3</sub> are a direct reflection of vitamin D status, which depends on access to vitamin D either through exposure to sunlight or through dietary intake.

**Vitamin D requirements during pregnancy.** In addition to causing poor global mineralization of the skeleton, vitamin D deficiency has implications for numerous other nonskeletal health outcomes. *In utero* or early life vitamin D deficiency has been linked to an increased risk of type 1 diabetes [7], asthma [8], and schizophrenia [9, 10].

Fascinating new data also show that vitamin D regulates placental development and function [11], which suggests that maternal vitamin D status may be associated with adverse outcomes of pregnancy, such as miscarriage, preeclampsia, and preterm birth.

Preterm delivery in the environment of infection is believed to result from the actions of pro-inflammatory cytokines secreted as part of the maternal and/or fetal host response to microbial invasion [12, 13]. Enhanced expression of the pro-inflammatory cytokines IL-1, IL-6 and TNF are associated with preterm delivery [14]. Such cytokines have been detected in elevated concentrations in the amniotic fluid and plasma of women with preterm labor and human gestational tissues are potentially rich sources of inflammatory cytokines [15]. These cytokines can be induced by a number of stimuli, including bacterial endotoxins, and they have been shown to promote spontaneous labor and rupture of membranes via their actions on the gestational tissues [16–18].

Several studies have reported altered levels of CYP27b1 in placentas from preeclampsia pregnancies [19, 20]. Furthermore, in a recent nested case-control study of pregnant women Bodnar and colleagues showed that vitamin D deficiency significantly increases the risk of preeclampsia [1]. This coupled with evidence of the prevalence of vitamin D insufficiency in pregnant mothers – particularly African-American mothers [1] – has supported a role for vitamin D sufficiency in protecting against this prevalent complication of pregnancy [21]. There was no significantly altered expression of vitamin D receptor (VDR) or CYP27b1 in pregnancies with intrauterine growth restriction

(IUGR) [22]. More recent studies of vitamin D insufficiency during pregnancy and lactation have served to underline the magnitude of the problem [1, 3, 4, 23, 24].

Our research group recently reported vitamin deficiency in cohort study of spontaneous preterm pregnancies ( $N = 27$ ) compared to matched case controls ( $N = 32$ ) in an NIH Behavior In Pregnancy Study (BIPS). In the study, serum samples were collected in 528 ethnically diverse women at 18–20 weeks (T1), 28–30 weeks (T2) and 34–36 weeks (T3). Circulating levels of vitamin D ( $25(\text{OH})\text{D}_3$ ) were significantly lower at each visit in the cases who subsequently delivered preterm. The levels indicated deficient in controls. Subsequent visits also showed lower levels in the PTB cases compared to the control group. We assessed the involvement of vitamin D in the occurrence of IL-6 levels in women with spontaneous preterm birth. At all three time intervals, significantly higher levels of IL-6 were associated with the preterm birth cases as compared to the controls [25]. Significantly higher levels of this pro-inflammatory cytokine, IL-6 were found in subjects with IUGR as compared with controls. This also correlated with lower serum vitamin D levels in this cohort. It is possible that a non-infectious inflammatory response is activated by vitamin D deficiency that is a marker of risk for or causative in preterm birth or development of IUGR [26].

**Racial disparity in vitamin D synthesis.** Since the most important source of vitamin D is the skin's synthesis of the vitamin from UVB solar radiation [27]. Any process that reduces UVB photons from entering the epidermis will diminish cholecalciferol (vitamin  $\text{D}_3$ ) production. The skin pigment melanin absorbs UVB photons and can reduce vitamin  $\text{D}_3$  synthesis by .90 % [28]. Consequently, African Americans are at high risk of vitamin D deficiency.

According to CDC, 42 % of African-American women in US between the ages of 15–49 years are deficient in vitamin D (less than 20 ng per milliliter of serum levels) [29]. Nevertheless, it is also clear that some groups are more at risk of vitamin D insufficiency than others. The 1988–1994 National Health and Nutrition Examination Survey revealed that 42 % of African-American women of child-bearing age had  $25(\text{OH})\text{D}_3$  levels that were lower than 50 nmol/l, half the current

optimal target level. This compares with only 4 % of white women [23].

We recently reported vitamin deficiency in cohort study of African-American pregnancies compared to Caucasians. Although the cohort used had women who delivered at term, the levels of  $25(\text{OH})\text{D}_3$  in Caucasians were significantly lower in the subjects with infection than the ones without ( $p < .001$ ). Women with vitamin D insufficiency in the second trimester were more likely to develop infection during pregnancy but not subjects with sufficient vitamin D at T1. The proportion of infection percent in the Caucasian and African-American groups was significantly different at all the time periods as well as their levels of  $25(\text{OH})\text{D}_3$ . African Americans show a trend to have higher proportion of infections than the Caucasian group at all three visits and had significantly lower  $25(\text{OH})\text{D}_3$  ( $p < .001$ ) at these visits [30].

Our results reveal a positive association between  $25(\text{OH})\text{D}_3$  concentrations and elevated risk of infection [31]. Vitamin D insufficiency may, therefore be involved in the pathogenesis of maternal infection during pregnancy. Vitamin D levels could modulate this infection susceptibility during pregnancy.

In another study, approximately 29 % of Black pregnant women and 5 % of white pregnant women residing in the northeastern United States had vitamin D deficiency, i. e. serum  $25(\text{OH})\text{D}_3$  of less than 50 nmol/l, whereas 54 % of Black women and 47 % of white women had serum  $25(\text{OH})\text{D}_3$  levels indicative of vitamin D insufficiency, i. e.  $25(\text{OH})\text{D}_3$  of 50–75 nmol/l [1].

**Immunomodulation by vitamin D.** Recently vitamin D deficiency and even insufficiency has become a worldwide issue affecting the populations across the globe. The broader implications of vitamin D restrictions especially with the growing trend of sun-blocks, have become more evident. Vitamin D status has been found to be a major contributing factor to immune response [32]. Precisely, the active form of vitamin D,  $1,25(\text{OH})_2\text{D}_3$  has been shown to be the key modulator of immune responses [33, 34]. The degree to which inflammatory pathways play a role in labors that are not associated with clinical signs of infection is unknown, however even normal labor shares certain characteristics with inflammatory processes.

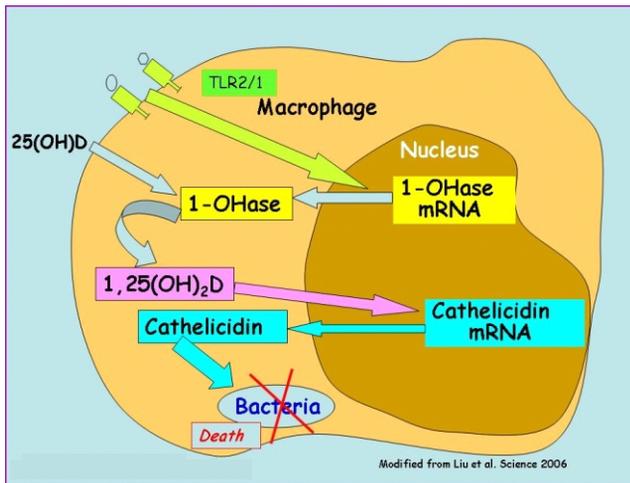


Fig. 3. Macrophage cells respond to bacterial cell walls by manufacturing both VDR proteins and the enzyme (1-OHase) that converts circulating  $25(\text{OH})\text{D}_3$  into the biologically active  $1,25(\text{OH})_2\text{D}_3$ . These events induced the immune cells to start producing cathelicidin that demonstrates antimicrobial activity against a variety of bacteria

Liu [35] substantially advanced this line of investigation by showing that human immune cells respond to infection by manufacturing both vitamin D receptor proteins and the enzyme that converts circulating  $25(\text{OH})\text{D}_3$  into the biologically active  $1,25(\text{OH})_2\text{D}_3$  and to induce the immune cells to start producing cathelicidin. Cathelicidin, the naturally produced antimicrobial agent that acts against a variety of bacteria, explaining the tuberculosis sunshine cure: the sun-soaked skin could boost their immune cells to generate the natural antibiotic that fought of the tuberculosis bacteria bacteria (TB) (Fig. 3).

In particular, the active form of vitamin D,  $1,25(\text{OH})_2\text{D}_3$  has been shown to be a key modulator of immune responses [36, 37]. Both the receptor for  $1,25(\text{OH})_2\text{D}_3$ , VDR [36, 38] and the enzyme that catalyzes the synthesis of  $1,25(\text{OH})_2\text{D}_3$  from precursor  $25(\text{OH})\text{D}$ , CYP27b1 [39, 40] are abundantly expressed by cells from the immune system. The presence of CYP27b1 in macrophages [41] and dendritic cells [42] indicates that local (autocrine  $25(\text{OH})\text{D}_3$  or paracrine) synthesis of  $1,25(\text{OH})_2\text{D}_3$  is a pivotal feature of vitamin D action within the immune system.

**Placental production of vitamin D.** The placenta was one of the first extra-renal sites shown to synthesize  $1,25(\text{OH})_2\text{D}_3$  from  $25(\text{OH})\text{D}_3$  [43, 44]. Organiza-

tion of 1 -hydroxylase, the enzyme needed to convert  $25(\text{OH})\text{D}_3$  to the active form is localized both in maternal decidua and fetal trophoblasts and is more abundant in first and second trimester. We detected highest levels of  $25(\text{OH})\text{D}_3$  at 18–20 weeks of pregnancy in the study as well as control group. This could also be due to the presence of VDR in the placenta as has been suggested by [45].

This means that vitamin D functions in an autocrine fashion at the fetal-maternal interface [45]. One possible explanation is that  $1,25(\text{OH})_2\text{D}_3$  functions as a regulator of placental calcium transport in addition to an immunomodulatory function [46].

From the studies highlighting immunological function of the heterogeneous cells that make up the placenta, maternal and fetal cells are able to mediate innate [47, 48] and adaptive [49, 50] immune responses. Furthermore, a series of studies using human placentas [11, 22] have demonstrated the expression of CYP27b1 (gene for producing the enzyme 1 -hydroxylase) in decidua (maternal tissue) and trophoblast (fetal tissue) [11, 22]. Within deciduas, CYP27b1 is expressed by both stromal cells and macrophages, while in trophoblasts CYP27b1 is localized predominantly in the syncytiotrophoblast (the cells that form the barrier between maternal and fetal blood) [22]. In primary cultures of human decidual cells, both  $1,25(\text{OH})_2\text{D}_3$  and  $25(\text{OH})\text{D}_3$  (the latter metabolized endogenously to  $1,25(\text{OH})_2\text{D}_3$ ) induced expression of antimicrobial cathelicidin, but suppressed the inflammatory cytokine production [32].

Within the decidua, the gene expression for this enzyme (CYP27b1) was identified in decidual stromal cells as well as the decidual macrophages, suggesting a possible immunomodulatory function for localized synthesis of  $1,25(\text{OH})_2\text{D}_3$  [11, 22]. Vitamin D – the trigger for antibacterial/anti-inflammatory responses in decidual and trophoblastic cells.

Analysis of decidual cells *in vitro* has endorsed a possible role for  $25(\text{OH})\text{D}_3$  and  $1,25(\text{OH})_2\text{D}_3$  as modulators of immune responses in maternal tissue [32]. Human decidual cells from 1<sup>st</sup> trimester placentas incubated for 24 hrs with  $25(\text{OH})\text{D}_3$  or  $1,25(\text{OH})_2\text{D}_3$  showed induction of cathelicidin and suppression of cytokines such as IL-1, TNF and IL-4 [32]. The fact that a physiological dose of  $25(\text{OH})\text{D}_3$  (100 nmol/l) was as ef-

fective as a pharmacological dose of  $1,25(\text{OH})_2\text{D}_3$  (100 nmol/l), underlines the importance of localized (placental) versus endocrine (systemic) synthesis of  $1,25(\text{OH})_2\text{D}_3$ .

Using primary human placental tissue and trophoblastic cells it has been shown that the fetal side of the placenta also induces cathelicidin-mediated antibacterial response to treatment with vitamin D metabolites. Collectively these data indicate that exogenous  $1,25(\text{OH})_2\text{D}_3$  or locally metabolized  $25(\text{OH})\text{D}_3$  are capable of inducing anti-bacterial and anti-inflammatory responses in both the maternal and fetal components of the placenta [22].

In addition to stromal and trophoblastic cells, the placenta is made up of an array of leukocytes that are fundamental to the immunology of gestation. We have shown that the most abundant of the decidual immune cells, uNK, do not express CYP27b1 [22] but are potential targets for paracrine responses to  $1,25(\text{OH})_2\text{D}_3$  synthesized by stromal cells or macrophages. By contrast, decidual macrophages express abundant levels of CYP27b1 and may therefore support the same auto-crine vitamin D-induced innate immunity demonstrated in peripheral blood-derived macrophages. In the case of the latter we have shown that specific antibacterial responses such as toll-like receptor (TLR)-mediated induction of cathelicidin are highly dependent on vitamin D status [51].

When a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or pathogen-associated molecular patterns such as lipopolysaccharide, the signal up-regulates expression of the VDR and 25-hydroxyvitamin, the enzyme D-1 -hydroxylase (1-OHase).  $1,25(\text{OH})_2\text{D}_3$  travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*.

Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the VDR and is strongly up-regulated in myeloid cells by  $1,25$ -dihydroxyvitamin  $\text{D}_3$  [51]. It is also likely that the  $1,25(\text{OH})_2\text{D}_3$  produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate

immunoglobulin synthesis. The autocrine synthesis of  $1,25(\text{OH})_2\text{D}_3$  that drives innate immune responses is dependent on the availability of substrate  $25(\text{OH})\text{D}_3$  (Fig. 3). It has been shown that Caucasian levels of cathelicidin production were 3-times higher than those in African Americans [51]. *In vitro* supplementation of  $25(\text{OH})\text{D}_3$  to the African-American serum was able to restore cathelicidin expression to levels similar to the ones for Caucasians establishing that vitamin D deficiency compromises innate immune responses to infection [52].

The placenta is one of the first tissues shown to be capable of synthesizing  $1,25(\text{OH})_2\text{D}_3$  with 1 -hydroxylase receptor activity detected both in maternal decidua and fetal trophoblast [19].

The net effect is that vitamin D status can vary significantly in populations as a consequence of stress from social, behavioral or economic factors. Sensitivity of parathyroid hormone to the threshold of 80 nmol/l of  $25(\text{OH})\text{D}_3$  has led to re-evaluation of the optimal level up to 75 nmol/l are now considered to be inadequate and are more commonly referred to as vitamin D insufficiency as opposed to deficiency [53].

A newborn's vitamin D stores are completely reliant on vitamin D from the mother [13]. Not surprisingly, poor maternal vitamin D status during pregnancy is a major risk factor for infant rickets [54]. This could be indicative of the fact that fetal programming is associated with the increased risk of common diseases in adult life.

Ч. П. Арора, К. Дж. Хобель

Нова роль вітаміну D при вагітності

Резюме

*Вітамін D регулює розвиток і функцію плаценти. Він є потужним регулятором імунної системи, що стимулює антибактеріальну відповідь та пригнічує запалення. Його дефіцит пов'язаний із зростанням ризику серйозних хронічних і запальних захворювань. Протягом вагітності дефіцит вітаміну D підвищує сприйнятливість жінок до інфекцій і запалення, спричиняє передчасні пологи та преєклампсію. Вагітні жінки з темнішою шкірою, які живуть у місцях з низьким рівнем сонячного світла, частіше страждають від дефіциту вітаміну D. При вагітності можлива активація первинного неінфекційного запального процесу внаслідок дефіциту вітаміну D. Виявлення дефіциту вітаміну D і запальних маркерів на різних стадіях вагітності може полегшити розпізнавання ризику будь-яких ускладнень.*

*Ключові слова: вітамін D, вагітність, імунна відповідь.*

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Новая роль витамина D при беременности

Резюме

Витамин D регулирует развитие и функцию плаценты. Он является мощным регулятором иммунной системы, стимулируя антибактериальный ответ и подавляя воспаление. Его дефицит связан с увеличением риска серьезных хронических и воспалительных заболеваний. Во время беременности дефицит витамина D увеличивает восприимчивость женщины к инфекциям и воспалению, вызывает преждевременные роды и преэклампсию. Беременные женщины с более темной кожей, живущие в областях с низким уровнем солнечного света, чаще подвержены дефициту витамина D. При беременности возможна активация первичного неинфекционного воспалительного процесса вследствие дефицита витамина D. Выявление дефицита витамина D и воспалительных маркеров на различных стадиях беременности может облегчить распознавание риска всевозможных осложнений.

Ключевые слова: витамин D, беременность, иммунный ответ.

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