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## VITAMIN D - DEFICIENCY STATES: SOME ASPECTS OF INFLUENCE TO THE COURSE AND OUTCOME OF PREGNANCY

## ВИТАМИН D – ДЕФИЦИТНОЕ СОСТОЯНИЕ: НЕКОТОРЫЕ АСПЕКТЫ ВЛИЯНИЯ НА ТЕЧЕНИЕ И ИСХОД БЕРЕМЕННОСТИ

G. S. Manasova, A. A. Zelinsky, O. N. Kazarenko, C. C. Globa

Г. С. Манасова, А. А. Зелинский, О. Н. Казаренко, С. С. Глоба

Odessa National medical university, Odessa, Ukraine;

Communal Health Protection Institution “Maternity Hospital N 5”, Odessa, Ukraine

Одесский национальный медицинский университет, г. Одесса, Украина;

КУ «Родильный дом № 5», г. Одесса, Украина

**Summary.** The article presents a review of literature on vitamin D-deficiency during pregnancy: preeclampsia, intrauterine growth retardation. Some aspects of vitamin D impact to a pregnant woman immune system, realization of intrauterine infection in the form of early neonatal sepsis; and the development of somatic pathology in children born from mothers with vitamin D-deficient status are discussed.

**Keywords:** vitamin D- deficiency, pregnancy.

**Реферат.** В статье представлен обзор литературы по проблемам витамин D-дефицитного статуса во время беременности: преэклампсии беременных, задержки внутриутробного развития плода. Представлены отдельные аспекты влияния витамина D на состояние иммунной системы беременной, на реализацию внутриутробного инфицирования в виде раннего неонатального сепсиса, а также развитие соматической патологии у детей, рожденных от матерей с витаминD-дефицитным статусом.

**Ключевые слова:** витамин D- дефицит, беременность.

In recent years, vitamin D (VD) biological effects attract attention of the numerous scientists of the world. In the 80-s of the last century it was found that VD's conversion to active hormonal form – 1,25 dioxivitamin D (1,25 (OH)<sub>2</sub>D) [1,2] is the necessary condition for its important role implementation in the regulation of calcium-phosphorus metabolism and optimal bone state. In future, VD itself was considered as a prohormone and its active metabolite – dihydroxy-VD - as a hormone. The discovery of specific vitamin D-receptor (VDR) contributed to it, too [3].

VDRs are found in almost all organs and tissues of a body, their expression is carried out by almost all nucleus - containing cells [4 ]. Now it is proved that, due to the wide representation of the VDR in a body, the regulation of 10% of the all human genes is carried by VD.

VD deficiency is observed in more than 30% of the adult population and it is the real medical and social problem [5, 6].

Regulation of VDRs expression is one of the basic mechanisms of the target cells response for calcitriol and various versions of different organs functional response [7, 8].

The presence of the mitochondrial enzyme 1- $\alpha$ -hydroxylase in the implementation of the biological effects of calcitriol is worth special noticing. This enzyme catalyzes hydroxylation of 25-hydroxyvitamin D to its active form – 1,25-dihydroxyvitamin - D<sub>3</sub> (1,25 (OH)<sub>2</sub>D) not only in the renal tubules, intestine, bone and cartilage tissue, but also in the cells of skin, nervous system, spleen, lymph nodes, skeletal muscle, lung, liver, monocytes, macrophages, stem cells etc. [9].

The presence of 1- $\alpha$ -hydroxylase in kidneys and in the other organs indicates the presence of other sources of VD hormonal forms and demonstrates the importance of this vitamin for the performance of various organs and tissues of a body [6].

The presence of the VDR directly into the reproductive organs - uterus, ovaries, pituitary and placenta tissues – is interesting at evaluation of the mechanisms ensuring optimal female reproductive health. In these reproductive organs 1-a-hydroxylase is also synthesized [10, 11, 12].

The participation of VD in the estradiols synthesis, receptors to which are identified in the myocardiocytes and endothelial cells identified, are interesting from the point of view of obstetricians and gynecologists. Perhaps, calcitriol deficit breaks estrogens' synthesis, which may lead to placental dysfunction and development of other complications of gestation [13, 14].

The theory of so-called “epigenetic programming” or “fetal programming” is currently widespread. It is based on the causation of a fetal development on the environment in which it grows, and the impact of these conditions on morbidity risk both in childhood and future life. Thus, in the number of studies it has shown that the children of VD-deficient women more likely to develop chronic diseases such as asthma, diabetes mellitus type 1, schizophrenia and etc. [15, 16, 17, 18, 19].

Active forms of the VD can regulate the transcription of genes responsible for the formation of the gestational immune tolerance, implantation and invasion of trophoblast, and further angiogenesis [20]. Evans K.N. et al. (2004) found that expression of RNA (mRNA) 1- $\alpha$ -hydroxylase messenger in the first and

second trimesters of pregnancy exceeds its expression in the 3rd trimester, while expression of mRNA-VD takes place to a lesser extent compared with 1- $\alpha$ - hydroxylase throughout the whole pregnancy [21, 22]. Apparently, in the phase of implantation and placentation, when angiogenesis of uteroplacental system is in its most active stage, a pregnant woman needs more 1,25-dihydroxyvitamin-D<sub>3</sub>.

Late onset gestosis of pregnant is an immediate problem of obstetrics. None of the existing theories of the etiopathogenic mechanisms of this gestational process complication development is perfect. Taking into account the currently known role of VD in the genesis of cardiovascular diseases, obstetricians pay particular attention to the study of its role in the pathogenesis of preeclampsia (PE) during pregnancy.

The main prerequisite for the role of VD study in the development of the late gestosis, was the discovery of its receptors in the endothelial cells, cardiomyocytes, vascular smooth muscle. These data indicate VD's active participation in the regulation of the enzymatic processes in cardiovascular system [23, 24, 25].

In the studies of Li Y.C. et al. (2004) it has been demonstrated that VD is RAS potent endocrine regulator and rennin's direct suppressor [26]. VD directly suppresses rennin's expression, and this suppression does not depend on VD effect on calcium metabolisms, the circulating blood volume and blood osmotic state [27].

Another study demonstrated that 1,25-dihydroxyvitamin-D blocks activation of RAS in mesangial and juxtaglomerular kidney cells, induced by hyperglycemia and transforming growth factor ( $\beta$ - (TGF- $\beta$ ) [28]. The authors concluded that VD sufficient level provides reno protective effect in diabetic nephropathy.

In addition to the impact on RAS, VD through vascular endothelial growth factor (VEGF) can inhibit the vascular smooth muscle cells proliferation and thus regulates blood pressure. In this way VD improves endothelium-dependent vasodilatation, inhibits anticoagulant activity and improves blood rheology. The angiogenic abilities of endothelial progenitor cells are improved under the influence of VD [29].

According to Deb D.K, Sun T, Wong K.E et al. (2010), VD renoprotective effect is performed by protecting podocytes and blocking of transforming growth factor (TGF- $\beta$ ) in glomeruli, as well as the blocking of the epithelial-mesenchymal transition of fibroblasts in renal tubules. This mechanism can significantly reduce the development of the tubulointerstitial fibrosis. In addition, VDR agonists have potent anti-inflammatory action due to suppression of pro-inflammatory cytokines activity both in glomerular, and tubulointerstitial renal zone [30].

Now, the role of VD in the pathogenesis of cardiovascular disease is under constant study. The dependence of coronary heart disease, myocardial infarction, hypertension, and other cardiovascular diseases development on VD deficiency is mentioned in many works [24, 31, 32, 33, 34, 35]. Further study continuation are required the mechanisms of VD' participation in the development of PE.

There is a number of studies showing that due to the anti-inflammatory action of 1,25 (OH)<sub>2</sub> – VD and reducing of tissue damage in chronic diseases [36, 37], inhibition of myocytes proliferation [38],

slowing of atherosclerotic vascular changes, regression of hypertrophic changes in myocardial muscle [39], severity of heart failure eventually decreases [40].

From obstetricians' point of view both generalized endothelial dysfunction and inflammation take part in PE development, therefore the development of new methods of gestation complications prevention is a problem of top urgency. Violation of nidation, implantation and placentation underlies the mechanisms that cause the pathological angiogenesis and development of the variety of pregnancy complications, including PE [41,42].

It is an active part of 1,25-dihydroxy-VD in the pathogenesis of cardiovascular diseases which formed the basis of numerous studies searching the tie of 1,25-dihydroxy-VD deficiency and PE development.

The scientists from the Graduate School of Public Health of Pittsburgh University have examined 700 PE women and 3000 healthy women. They have found that vitamin D deficiency increases PE risk by 40%. Even its minimum deficiency nearly doubles the risk of late gestosis. In addition, the authors showed that the children born by PE mothers, risk of early neonatal mortality increases fivefold [43].

In the work of E. N Vasilyeva, T. G Denisova, E. N. Shamitova et al. (2015) VD, VD - binding-protein and endothelin -1-38 have been examined in the blood of pregnant women ND IT WAS found that these women have a pronounced deficiency of VD. The level of VD binding-protein, as well as the endothelin's level ( hypertensive action messenger ) was a little bit increased in these patients. The comparative assessment of the newborns showed that the infants in the preeclampsia group has certain problems in perinatal period (violation of adaptation, hypocalcemia, etc.) which were 2,75 times more frequent than in the control group [44].

According to another study, VD level reduction in the blood during pregnancy below 20 ng / ml is associated with 4-fold increase of severe PE, and its content less than 15 ng / ml increases PE risk by 5 times [45,46, 47].

Bodnar L. M. et al. (2007) examined the effect of VD-deficiency on PE development in primigravidae with singleton pregnancy from 16 weeks of pregnancy to the delivery date. PE early development ( pregnancy induced hypertension and proteinuria) was the main selection criterion. VD level in serum of the women with the later developed PE, was initially less: 45.4 nmol/l (95% CI) 38,6-53,4 nmol/l, compared to 53.1 and 47.1-59.9 nmol/L in the control group (p <0.01). Dose-dependent relation between 25(OH) D serum concentration before 22 weeks and PE development risk has been established. The newborns of the mothers with PE had 25(OH) D level less than 37.5nmol/l twice oftener than the newborns from control group [45].

The VD deficiency during pregnancy can act as PE independent risk factor. Probably, it is necessary to consider the prescribing of VD supplements for the prevention of gestation complications and fetuses successful development [48, 49, 50] from pregnancy early stages.

The violation of the angiogenesis with the subsequent placentation's problems and endothelial dysfunction are the main syndromes of the maternal body in preeclampsia, which takes place in 3-7% of pregnant women [51, 52].

The exact mechanisms of VD participation in PE genesis are not sufficiently clear, however, its role in cardiovascular disease pathogenesis is perfectly visible.

There are data showing that PE is accompanied by the marked changes in VD and calcium metabolism. It is possible that PE development at VD deficiency is associated with its calcium-regulating function [53].

There are indications of VD-deficiency relation and PE development, but there is no accurate information about the role of placental VD-metabolic system in the course of normal or PE - complicated pregnancy. It is assumed, that PE is the second phase of VD-deficiency-induced disease [54, 55, 56].

The initial step in the placental dysfunctions formation is a violation of its perfusion properties, mostly due to the abnormal implantation. In the second stage of the pathological process is already taking place endothelial dysfunction leads to the multisystem disorders and the generalized activation of the inflammatory process [57].

The normal placentation and its further development provides favorable outcome of pregnancy. It is placental dysfunction that has an important role in PE pathogenesis. There is evidence that this condition correlates with vitamin D decrease in the maternal-placental blood flow. As we have already noted, during pregnancy not only kidneys are the site of VD synthesis but also trophoblast cells: placenta and decidual tissue can produce and secrete 1,25 (OH) 2D3 [58, 59].

The detection of 1 $\alpha$ -hydroxylases gene transcription and receptors VD-expression in trophoblast allowed to suggest that VD plays the role of metabolic processes autocrine regulator [60, 61].

In experimental studies it has been shown that VD may modulate macrophages' activity and cytokines' production, regulate by this way the maternal and placental immunologic and inflammatory responses. It was revealed that in PE 1 $\alpha$ -hydroxylases expression and activity in the syncytiotrophoblast are limited. It is known, that in normal pregnancy development balance preservation between Th2- and Th1-cytokines has an important role, and provides the tolerance of implantation. VD deficiency may impair paradigm Th2/Th1 with proinflammatory cytokines activation and development of systemic inflammatory reaction which characterizes PE. In addition, through the direct effect to the angiogenesis gene transcription, including vascular endothelial growth factor (VEGF), VD deficiency may also affect the formation of endothelial dysfunction [62, 63].

Infectious pathology has a special role in a woman's health, besides it has huge medical-social significance, also. According to the data of leading perinatologists, intrauterine infection remains the problem with non-optimal level of solution [64].

According to the data of different authors, 27 - 37% of alive neonates demonstrate varying clinical signs of intrauterine infection. In perinatal losses infectious diseases cause from 11% to 45% of fatalities and take 1 – 3 places, while stillbirths account for 15-17%.

TORCH-infection's agents are worth special attention as etiological causes of intrauterine infection and their pathogens perforate placental barrier: every second sick newborn is the carrier of either cytomegalovirus or herpes or other TORCH infection. The frequency of early neonatal mortality and morbidity is 5.3 - 27.4% [65].

Among VD's many functions its participation in formation a body's immune response is an important one: the level of vitamin D functionality is associated with the risk of infection (acute respiratory viral infections, tuberculosis), chronic inflammation (Crohn's disease), allergic (asthma) and autoimmune diseases development. In particular, VD inhibits genes expression to transferrin. on the macrophages It is known that transferrins participate in providing innate immunity by reducing free iron ions concentration, which, in its turn, inhibits the bacterial growth. Transferrins concentration reduces significantly in inflammatory processes, nephrotic syndrome, cirrhosis, hemochromatosis and other pathologies [66].

It is also known, that VD inhibits CD23-cells formation: their soluble form acts as a low affinity receptor for immunoglobulin E (Ig E). This C - selective receptor is present on the surface of 30% of B-lymphocytes, 1% of T-cells and monocytes (in patients with allergies this percentage significantly increases). Production CD23 cells is enhanced under the influence of IL-4. It was found that soluble CD23-cells very high levels in the synovial fluid are observed in rheumatoid arthritis [67]. This observation allows us to consider VD as immunomodulatory agent.

VD inhibits T-helper cells activity and proliferation, the main function of which is to strengthen the adaptive immune response. This function of VD-hormone depends on the concentration of interleukin-1 (IL-1), the active pro-inflammatory cytokine. at low concentrations of IL-1 VD enhances T-helper cells proliferation by 50 times; at its high concentration it increases their induction, but blocks proliferation. At optimal (physiological) concentrations VD suppress both induction and proliferation of T-helpers. At deficiency of VD there is no sufficient stimulatory effects on monocytes and macrophages [68].

Calcitriol induces Ca-binding proteins synthesis: that of gastrointestinal epithelium's calbindinum, neurons, parvalbulinum and muscles tissue troponin as well as calcimedinum in tissues, including lymphoid tissue, which is important in inflammatory processes [69, 70, 71].

Thus, VD causes decrease of cells proliferation, induces terminal differentiation of normal and abnormal cells, including tumor cells, exhibits certain immunosuppressive effects and restricts some types of inflammatory response [72].

Influence of a pregnant woman VD-status on fetus' condition is noteworthy. Thus, there is dependence of children born with low relative to gestational age body mass with VD- deficiency state of mother's body. In the works of Baker A.M. et al. (2010), Robinson C.J. et al. (2011) is shown that the early onset of pregnancy late gestosis followed by birth of low-weight infants there is either failure or deficiency

of 25(OH)D<sub>3</sub>. The authors of this research direction suggest that the participation of VD in metabolic processes and impact on the fetuses [73, 74] is realized via placental mechanisms.

VD has a definite role in the development of the early neonatal sepsis (ENS) in premature neonates (M. Cetinkaya, F. Cekmez et al., 2014), and sepsis's severity depends on VD's concentration in blood. In the examination of 50 children with clinical and laboratory results of the ENS (main group) and 50 healthy children without any clinical or laboratory signs of infection (control group) it has been revealed that 25-hydroxyvitamin D (25-OHD) level was significantly lower in children and their mothers in ENS group. Maternal and neonatal levels of 25-OHD were significantly higher in summer and in regular supplements of VD during pregnancy. In ENS group severe deficiency of VD has been identified. Newborns' level of 25-OHD had a positive correlation with its level in mothers. The authors suggest that VD supplements during pregnancy may help to prevent early septic complications in mature newborns [75].

There is an interesting prospective research where its authors study high doses of VD effect in the anthropometric data of the children and their further physical and mental development. Prospective survey of 596 children was carried out in the neonatal period, at the age of 9 months and 9 years. The children's general physical mental development, anthropometric data, echocardiographic examination, dual energy absorptiometry, blood pressure and thickness of the intima-media ration has been assessed. 25(OH) VD level was determined before labours in mothers. It has been revealed that the children of mothers with 25 (OH) VD level over 75 nmol/l had an increased risk of eczema at the age of 9 months ( $p = 0, 025$ ) and asthma at the age of 9 years old ( $p = 0,038$ ) compared to the children whose mothers' VD concentration was less than 30 nmol /l. The authors concluded that VD high levels (more than 75 nmol / L) during pregnancy does not affect a child's intelligence, psychological health, cardiovascular system and do not increase atopic dermatitis risk, but the authors emphasize the necessity of further researches [76].

In 2014, at the annual meeting of the American Society of Anesthesiologists it has been reported that VD-scarce condition during pregnancy contributes to woman's depressive status, more severe pain during childbirth. The authors carried out the comparative study of the women with VD different status; during research all the women ( $n=93$ ) had epidural analgesia of 0,2% ropivacaine solution without addition of opioids. It turned out that at the lower level of VD a woman needs more pain medication. Besides that, the authors found that the VD-deficient women had a lower contractile ability of the uterus reduced, which significantly increases the frequency of surgical delivery [77].

The adverse effects of VD deficiency to the women during pregnancy and the relationship of this deficiency with the development of gestation complications such as intrauterine growth retardation, preeclampsia, neonatal hypocalcaemia, gestational diabetes, premature birth, perinatal infection, as well as autoimmune pathology risk were indicated in the studies of Brannon P.M. (2012), Yoder M.C. et al. (2012), Mulligan M. L. et al. (2010), Maladkar M. I. et al (2015). The authors also noted that the widespread use of multivitamin complexes in the antenatal stage is not sufficient to the adequate levels of VD maintain [78, 79, 80].

In the study of the possible relationship of VD deficiency and thyroid dysfunction during pregnancy in a group of women of northeast China the following data have been established. 25-hydroxyvitamin D average level in the first trimester was significantly lower than that in the next two trimesters ( $p < 0.01$ ), whereas the difference between the second and third trimesters have not been identified. At 96%, 78% and 76% of the women respectively trimester levels of 25-hydroxyvitamin D was less  $\leq 50$  nmol/l. The relationship between 25-hydroxyvitamin D and calcium blood levels in the first and second trimester, and the dependence of VD levels on the seasons was established. NS statistical relationship ( $p = 0.024$ ) of 25-hydroxyvitamin D and triiodothyronine only in the first trimester has been found. There was no dependence between concentrations of phosphates, parathyroid hormone and other thyroid hormones and 25-hydroxyvitamin D level [81].

Thus to determine the optimal 25 (OH) D<sub>3</sub> level to implement reproductive potential and body's needs during a woman's whole life [82] becomes important.

Despite the attention of the scientists to the problem of VD-deficiency, particularly in the field of perinatal medicine, there is a certain lack of large-scale randomized clinical trials and experimental observations of high quality, establishing VD deficiency connection with adverse consequences for the health of a woman and child.

Taking into account the prevalence of VD - deficiency, the opportunities of diagnosis, prevention and treatment of this condition, the value of the further researches increases.

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