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IBI (India) = 4.260
OAJI (USA) = 0.350

SOI: [1.1/TAS](https://doi.org/10.1/TAS) DOI: [10.15863/TAS](https://doi.org/10.15863/TAS)

International Scientific Journal Theoretical & Applied Science

p-ISSN: 2308-4944 (print) e-ISSN: 2409-0085 (online)

Year: 2020 Issue: 10 Volume: 90

Published: 30.10.2020 <http://T-Science.org>

QR – Issue



QR – Article



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THE EFFECT OF VITAMIN D DEFICIENCY ON THE FORMATION OF THE REPRODUCTIVE SYSTEM IN GIRLS

Abstract: The article discusses literature data highlighting modern ideas about the role of vitamin D in the implementation of its nonclassical effects associated with a number of somatic pathologies and impaired reproductive system function. The effect of vitamin D deficiency on the development of obesity, insulin resistance, hypertensive conditions, cancer of various localization is described. A decrease in vitamin D supply is associated with endometrioid disease, metabolic disorders in polycystic ovaries.

Key words: Reproductive health, pathology, metabolism, localization, vitamin D.

Language: English

Citation: Isroilova, G., Azimova, K., & Amonova, M. (2020). The effect of vitamin D deficiency on the formation of the reproductive system in girls. *ISJ Theoretical & Applied Science*, 10 (90), 381-385.

Soi: <http://s-o-i.org/1.1/TAS-10-90-65> **Doi:**  <https://dx.doi.org/10.15863/TAS.2020.10.90.65>

Scopus ASCC: 2700.

Introduction

Although the importance of vitamin D in calcium phosphate homeostasis was proven early in its study, the understanding of the molecular biology of vitamin D remained undiscovered until the late 1960s. An important step in solving this problem was the study [1], which studied the stages of vitamin D metabolism and proved its nuclear localization in various tissues [2, 3]. The sequence of steps in the study of vitamin D has contributed to a better understanding of the multiple roles of vitamin D in biological responses. In the last decade, the non-skeletal effects of vitamin D have been in the

spotlight, and the accumulated literature data support the idea of the importance of vitamin D for various organs and systems other than the skeleton [4, 5].

The term "vitamin D" is a group of several forms of vitamin D that are similar in chemical structure (secosteroids) and exist in nature:

- vitamin D1 (this was the name of the substance discovered in 1913 by E.V. McCollum in cod liver fat, which is a compound of ergocalciferol and lumisterol in a 1:1 ratio);

- vitamin D2 - ergocalciferol, formed from ergosterol under the influence of sunlight, mainly in

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plants; is, along with vitamin D3, one of the two most common natural forms of vitamin D;

- vitamin D3 - cholecalciferol, formed in the body of animals and humans under the influence of sunlight from 7-dehydrocholesterol; it is considered to be the "true" vitamin D, while others in this group are considered modified derivatives of vitamin D;

- vitamin D4 - dihydrotachysterol or 22,23-dihydroergocalciferol;

- vitamin D5 - sitocalciferol (formed from 7-dehydrositosterol).

Vitamin D is traditionally referred to as a fat-soluble vitamin. However, unlike all other vitamins, vitamin D is not actually a vitamin in the classical sense of the term, since it is biologically inactive. Vitamin D is converted into 1,25-dihydroxyvitamin D3 as a result of two successive hydroxylation reactions with the participation of enzymes 25- and 1 α -hydroxylases in the liver and kidneys. Due to metabolism in the body, vitamin D turns into an active - hormonal form and has a variety of biological effects, interacting with specific receptors (VDR) localized in the nuclei of cells of many tissues and organs [6]. In this respect, the active metabolite of vitamin D behaves like a true hormone, which is why it was named D-hormone.

Vitamin D2 enters the human body from food and is metabolized to form derivatives that have an effect similar to the metabolites of vitamin D3, providing no more than 5-10% of the need. Its main sources are cereal products, fish oil, butter, margarine, milk, egg yolk, etc.

The second natural form of vitamin D, vitamin D3, or cholecalciferol, is formed from a precursor in the dermal layer of the skin - provitamin D3 (7-dehydrocholesterol) under the influence of short-wave ultraviolet B radiation.

The 1,25-dihydroxyvitamin D3 receptors (VDR) provide the ability to generate biological responses in more than 40 target tissues.

The cellular effects of vitamin D and its metabolites are very complex and are carried out mainly through intranuclear VDRs mediated by a ligand-activated transcription factor, which belongs to nuclear hormone receptors [3]. Binding of a ligand to a receptor initiates a cascade of events that include receptor phosphorylation and nuclear translocation, recruitment and then heterodimerization with the 9-cis retinoic receptor (RXR). The VDR / RXR heterodimer, in turn, forms a complex with vitamin D binding protein (VDR) and a co-regulatory protein that bind with a vitamin D reactant element in the promoter region of target genes, which allows regulating the transcription of tissue-specific genes [7]. The genomic pathway leading to changes in gene transcription takes from several hours to several days [8]. Although the effect of active 1,25 (OH) 2D on target cells primarily reflects genomic activity, more recent data indicate the presence of an additional non-

genomic signaling mechanism through the membranes associated with the steroid-coupled rapid response receptor (MARRS), which leads to a faster response, from seconds to several minutes [9, 8]. This mechanism has been suggested in a variety of tissues, including the intestines, bones, parathyroid glands, liver, monocytes, and pancreatic beta cells [3, 10]. At the same time, VDR signaling is also associated with the expression of the CYP19 (aromatase) gene, which functionally unites vitamin D with the family of reproductive steroid hormones [11, 12]. An important role in the biological action of vitamin D is also played by the enzymes CYP27B1 and CYP24A1, which regulate the synthesis and catabolism of the vitamin in the liver and kidneys.

Studies investigating the supply of vitamin D in the population in various countries have shown a high prevalence of vitamin D deficiency in both northern and southern regions. Data collected from the North American National Health and Nutrition Examination Survey has recorded a 4-fold increase in the prevalence of vitamin D deficiency in the US population over the past 10-15 years [13]. Thus, it is alarming to find that populations with the highest physiological requirements for vitamin D — pregnant women, newborns, children and adolescents — are also at high risk of vitamin D deficiency [14].

Suboptimal dietary vitamin D intake, increased environmental pollution, lifestyle changes (limiting sun exposure), and a concomitant increase in sunscreen use due to carcinogenic alertness are considered as causes of a vitamin D deficiency pandemic. The inverse relationship between serum 25 (OH) D levels and body mass index (BMI) is also well described. Although the "cause and effect" of this relationship is unclear, obesity is recognized as an independent risk factor for vitamin D deficiency. One mechanism for lowering circulating 25 (OH) D levels in overweight and obese people is the sequestration of a fat-soluble vitamin in adipose tissue. The rising prevalence of obesity may partly explain the upward trend in vitamin D deficiency, which in turn may itself be a contributing factor to the rise in the obesity pandemic. There is a point of view that secondary hyperparathyroidism arising as a consequence of vitamin D deficiency stimulates the activity of 1- α hydroxylase, contributing to a compensatory increase in the level of 1,25 (OH) 2D. Recent in vitro experiments have shown that 1,25 (OH) 2D induces an increase in the concentration of calcium ions within adipocytes, which in turn can stimulate lipogenesis and inhibit lipolysis. One hypothesis for obesity is associated with abnormal as well as decreased signaling of the leptin receptor. In mice with removed leptin receptors, it has been shown that leptin and its related receptor can also regulate renal synthesis of CYP27b1 and 1,25 (OH) 2D [10].

There is no unified data on the optimal level of 25 (OH) D measured in blood serum. However,

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according to most experts, the normal content of 25 (OH) D in blood serum is 25-40 ng / ml, D-vitamin deficiency is at 20-10 ng / ml, and D-deficiency is at a level less than 10 ng / ml. ... Intoxication with vitamin D is observed when the level of 25 (OH) D is higher than 150 ng / ml [11].

The term D-hormone deficiency mainly denotes a decrease in its intake and formation in the body of 25 (OH) D and 1 α , 25 (OH) 2D₃, as well as a violation of its reception.

Large-scale studies in recent years have revealed a link between vitamin D deficiency and the prevalence of a number of diseases. An association of the risk of developing cancer and autoimmune diseases with vitamin D deficiency and geographical latitude has been noted. To date, the expression of vitamin D receptors has been found in cancer of various localizations: melanoma, breast cancer, adenocarcinoma of the colon, endometrial and prostate cancer, bladder cancer, and the relationship of these diseases with vitamin D deficiency is being actively studied [3,11].

There is growing scientific evidence that increasing your vitamin D intake reduces your risk of chronic disease. For example, it has been shown that prescribing vitamin D in a dose of 2000 IU / day to children in the first year of life reduces the risk of developing type 1 diabetes mellitus by 80% over the next 20 years. In addition, children in the same cohort who had vitamin D deficiency during their first year of life had a 4-fold increased risk of developing type 1 diabetes. Increasing vitamin D intake lowers the risk of developing rheumatoid arthritis [7,11].

How is it possible that vitamin D can have such a wide range of therapeutic effects? The fact is that VDRs are present in most cells and tissues of the body, and 1,25 (OH) 2 D is one of the most powerful regulators of neoangiogenesis and growth of both normal and cancerous cells [11,4]. It is likely that with an increase in vitamin D intake or exposure to sunlight, there is an increase in the blood concentration of 25 (OH) D over 30 ng / ml, which is so necessary for maximum extrarenal synthesis of 1.25 (OH) 2D in various tissues and cells of the body. including the colon, mammary glands, prostate, lungs, activated macrophages and parathyroid cells, is reasonable. The local production of 1,25 (OH) 2D is considered important for the retention of cell growth and possibly prevents the transformation of a normal cell into an autonomous and uncontrolled cancer cell [11,8].

Since VDR and 1 α -hydroxylase are found in reproductive tissue, including the ovaries, uterus, placenta, and pituitary gland, an association of vitamin D with reproductive health is clear. There is evidence that vitamin D has a definite effect on IVF outcomes, the development of polycystic ovary syndrome (POS) and endometriosis, and overall steroidogenesis in healthy women. In a study of 84 infertile women

undergoing IVF, women with higher serum and follicular fluid 25 (OH) D levels were more likely to become clinically pregnant after IVF, and high vitamin D levels improved the results of controlled ovarian hyperstimulation. [11,10].

Polycystic ovary syndrome (POS) is the most common endocrine disorder in women of reproductive age. POS is characterized by increased secretion of androgens by the ovaries and adrenal glands, symptoms of hyperandrogenism, insulin resistance, an increased risk of developing type 2 diabetes, menstrual and reproductive disorders in women. Overall, POS is the most common cause of anovulatory infertility in women [4,12]. Studies concerning vitamin D supply in patients with POS have shown a direct relationship between vitamin D levels and metabolic disturbances, insulin resistance, increased body mass index (BMI), triglycerides, total testosterone and dehydroepiandrosterone in the blood. Research is currently underway on genes involved in the synthesis, hydroxylation and transport of vitamin D in POS. Vitamin D supplementation or vitamin D₃ analogs have positive effects on insulin secretion, lipid profile, glucose and C-peptide reduction, menstrual cycle, and follicular development. The presence of obesity in patients was a significant factor in these studies. An association between vitamin D levels and insulin resistance was observed only in obese patients. Lower serum levels of 25 (OH) D₃ were found in obese women with POS (13.1 \pm 3.9 ng / ml), while in non-obese women it was significantly higher (20.2 \pm 8.4 ng / ml). Perhaps it is obesity, but not the presence of POS, that determines this deficiency [6,12].

There are data on the association of endometriosis with the metabolism of vitamin D and there are two arguments in favor of the existence of such a relationship: VDR and 1 α -hydroxylase are present in the endometrium and, possibly, the endometrium serves as a site of extrarenal synthesis and an object of exposure to vitamin D. Since endometriosis is associated with significant immune disorders, it can be assumed that vitamin D is involved in local immunosuppression in the development of endometriosis. It should be noted that a significantly higher concentration of VDR and 1 α -hydroxylase receptors was found in the endometrium of women with endometriosis compared to healthy women, with a different content of vitamin D-binding protein. It is this protein that is directly related to the stimulation of macrophage activity. This finding could explain the effect of vitamin D on local immunosuppression promoting endometrial cell implantation.

The study of the role of vitamin D in pregnancy is of particular interest. It has been shown that 1,25 (OH) 2 D₃ regulates the release and secretion of human chorionic gonadotropin in syncytiotrophoblast and increases placental production of sex steroids. It

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turned out that calcitriol promotes the transport of calcium to the placenta, stimulates the release of placental lactogen, and also regulates the expression of HOXA10 (a gene that determines the development of genital organs) in stromal cells of the human endometrium. Expression of HOXA10 is of some importance for the development of the endometrium and improves the susceptibility to implantation [9]. The serum vitamin D level of women in the third trimester of pregnancy is 2 times higher than that of non-pregnant women.

Vitamin D deficiency causes a number of adverse pregnancy complications: hypertension and especially preeclampsia (PE), an increase in the frequency of caesarean section and spontaneous preterm birth, the development of bacterial vaginosis in early pregnancy, and gestational diabetes mellitus. Preeclampsia is one of the most common obstetric complications and contributes significantly to maternal and fetal morbidity and mortality. Although the etiology is not entirely clear, impaired trophoblast invasion, low placental perfusion, endothelial dysfunction, and oxidative stress are the mechanisms underlying preeclampsia. The presence of vitamin D and its receptors in the placenta, as well as the ability of vitamin D to modulate immune, inflammatory and vascular reactions, allow substantiating the role of vitamin D deficiency in pregnant women in the pathogenesis of preeclampsia. High vitamin D levels in women are associated with a lower incidence of preeclampsia and lower blood pressure. A 25 (OH) D3 content during pregnancy of less than 20 ng / ml is associated with a 4-fold increase and less than 15 ng / ml with a 5-fold increase in severe preeclampsia. A study of 23,423 nulliparous women in Norway showed a 27% reduction in the risk of PE in women who received 400-600 IU of vitamin D per day compared with women who did not receive the supplements [11].

While the role of vitamin D in the development of hypertensive conditions during pregnancy is not in doubt, the study of the relationship of vitamin D with gestational diabetes mellitus (GDM) gives conflicting results. In a study in women with vitamin D deficiency in the early stages, the risk of developing GDM was found to be 2.66 times higher than in pregnant women with normal vitamin D levels. Two other studies failed to identify an association between vitamin D content and the subsequent risk of GDM [11, ten].

There are convincing data on the association of vitamin D deficiency with an increase in the frequency of caesarean section in pregnant women. A recent observation found a 4-fold increase in the likelihood of caesarean section in women with low vitamin D (<13.5 ng / ml) at the time of labor compared with women with higher vitamin D. D on the contractile activity of the myometrium. Myometrium contractility depends on the release of ionized calcium

in muscle cells, and this process is regulated by vitamin D [8].

Activated T and B lymphocytes also have a VDR, and therefore 1,25 (OH) 2D is a very effective modulator of the immune system. Vitamin D is able to inhibit the proliferation of T-helper 1 (Th1) and limit the production of cytokines such as interferon gamma (IFN- γ), interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF- α). On the other hand, vitamin D induces type 2 T-helper cytokines, which have a protective effect on pregnancy. Given these immune effects of vitamin D, it has been suggested that vitamin D may act as an immune regulator during implantation and play an important role in reproductive function. In early pregnancy, the trophoblast produces and responds to vitamin D, which has a local anti-inflammatory response and induces the growth of decidual tissue for a successful pregnancy [12,7].

A recent study showed a 17% increase in preterm birth rates among black women without concurrent chorioamnionitis with vitamin D levels <15ng / ml. In a cohort of 82,213 singleton infants, they found evidence that vitamin D and seasonal exposure to sunlight are related to preterm birth. The prevalence of spontaneous preterm labor (SPD) was lowest among women who conceived in summer and fall, and highest at early pregnancy in winter and spring. Research has provided compelling evidence that adequate vitamin D may protect against premature birth [12,11]. A retrospective study by Japanese authors found lower values of 25 (OH) D among women who were hospitalized for preterm labor early in the third trimester of pregnancy [13.1].

What is the link between vitamin D deficiency and preterm labor? It can be mediated by other complications of pregnancy - preeclampsia, placental insufficiency and bacterial vaginosis, in the development of which the role of vitamin D deficiency has been practically proven. At the same time, the potential of vitamin D in a key influence on the parameters of innate immunity, systems and regulation of the activity of cellular immunity may be of independent importance in reducing the risk of SPR. It is possible that vitamin D can reduce the risk of SPR by decreasing the activity of the myometrium.

Deficiency of vitamin D deserves special attention with a predisposition to a spectrum of diseases of infectious etiology, including bacterial vaginosis (BV). Disruption of the normal balance of vaginal microflora with an increased growth of anaerobic bacteria leads to an increase in the production of pro-inflammatory cytokines, prostaglandins and phospholipase A2 [13,7]. The relationship between BV and vitamin D status was studied in a study of 3,500 women (pregnant and non-pregnant). A decrease in vitamin D (25 (OH) D <30 ng / ml) has been identified as an independent risk factor for BV in pregnant women. Bodner et al. in a

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prospective cohort study of 469 pregnant women in the first trimester showed that the mean serum 25 (OH) D concentration below 11.8 ng / ml was detected in bacterial vaginosis, while in women with normal vaginal microflora it was more than 16 ng / ml. Approximately 57% of women with low 25 (OH) D levels (<8ng / ml) suffered from persistent BV compared with 23% of women with normal (> 30 ng / ml) serum vitamin D levels [14.5]. These studies clearly show an association between vitamin D deficiency and BV in pregnant women, which increases the risk of miscarriage by 7 times.

Available evidence points to a biologically significant role for vitamin D in women's reproductive health. In addition to classic diseases such as

osteoporosis and osteomalacia, vitamin D deficiency in women is beginning to be associated with lower fertility and an increased risk of adverse pregnancy outcomes. However, the results of studies examining the relationship between 25 (OH) D levels and the incidence of adverse pregnancy outcomes are not always unambiguous. The reason for this is the small sample size, inadequate control of external factors, and significant heterogeneity of the studied populations [14,13]. The optimal reproductive serum 25 (OH) D3 levels, especially during pregnancy, for the nonclassical effects of vitamin D are unclear. The solution is likely to be large-scale randomized clinical trials with practical public health outcomes.

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