**Pathogenetic role of vitamin D deficiency in the development of menstrual dysfunction in pubertal girls: a literature review**

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**ABSTRACT**

In the literature review, 50 scientific sources surrounding the problem of vitamin D deficiency, 80% of which amounted to the issuance of the last 5 years, have been analyzed. Despite the impact of vitamin D deficiency on the health of children and adolescents has been studied for a long time, the information on the role of vitamin D in the formation of menstrual function in pubertal girls is scant and ambiguous. Among the hypotheses of menstrual dysfunction with vitamin D deficiency, neurohumoral regulation of the hypothalamic-pituitary-ovarian system is considered to be essential due to the localization of vitamin D receptors (VDR), unlike other vitamins, in the nuclei of various tissues and organs. However, in the last 10 years, data on the role of genetic polymorphism of the VDR gene in the pathogenesis of various manifestations of menstrual dysfunction have been accumulated. Some studies indicated a beneficial effect of cholecalciferol on such menstrual dysfunctions as oligomenorrhea and dysmenorrhea. Regarding numerous data on the role of vitamin D, both traditional and recently published, there is a strong correlation between vitamin D deficiency and other various factors, determining a wide range of polymorphic clinical manifestations where menstrual dysfunction is essential in girls at the age of puberty.

**Introduction**

The urgency of the problem has arisen from the high prevalence of menstrual dysfunction ranged from 20 to 30–48% in the structure of gynecological diseases in adolescent girls, which is a common reason to visit a pediatric gynecologist in 60% of cases [1]. Aggressive environmental factors, such as stress, malnutrition and deficiency of essential vitamins and minerals, have proven to exert a great influence on the reproductive health in girls. Uncompensated deficit in certain substances causes not only functional but metabolic disturbances. Among these essential substances, vitamin D is known to perform many functions as vitamin D receptors are found in various tissues of the body, including female reproductive organs.

The data on the role of vitamin D in the formation of menstrual function are ambiguous. According to some studies, the role of vitamin D deficiency in the development of menstrual disorders in women was considered to be proven; therefore, in these disorders, high-dose vitamin D had to be administered [2]. However, according to other authors, the level of vitamin D (in combination with calcium) was of no clinical significance and a positive correlation with the function of the reproductive organs was not found [3]. A direct correlation between vitamin D levels and metabolic and hormonal disorders, such as insulin resistance, an increase in serum total testosterone and dehydroepiandrosterone (DHEA) was shown. Moreover, the authors noted that administration of vitamin D supplements or its analogs had a positive effect on insulin secretion, lipid profile, decrease in glucose and C-peptide levels, restoration of the menstrual cycle and development of follicles [4]. However, the data on the role of vitamin D in the development of reproductive disorders in adolescents are insufficient and clinical guidelines on the need for vitamin D supplements in adolescent girls with vitamin D deficiency and menstrual dysfunction are absent.

**Epidemiological factors of vitamin D deficiency**

According to the numerous studies, nowadays the prevalence of vitamin D deficiency in different countries accounts for at least 50% [5]. Taking into consideration that human body produces vitamin D only when UV rays heat the skin, deficit conditions are prevalent especially in countries with few sunny days. However, the studies on vitamin D deficiency among residents of different countries have shown its high prevalence not only in the northern but also in the southern latitudes, which was associated with additional risk factors for the development of deficit conditions. Therefore, the southern countries of Saudi Arabia and the Middle East also face with epidemic of vitamin D deficiency [6].

Over the past 10–15 years, among the US population, a fourfold increase in the prevalence of vitamin D deficiency has been registered [7]. Studies conducted in North London recruiting 56 adolescent patients between 2012 and 2014 showed a significant vitamin D deficiency in 81.5% [8].
In Russia, this problem is particularly relevant as most of its territory lies above the 42 degrees parallel contributing to a lower level of insolation. Thus, in adolescents of the Perm Territory, a decreased level of calcidiol (<50 nmol/L) was found in 47%, and in the Republic of Komi, vitamin D deficiency in children reached up to 86% in the autumn, and 98% in early spring [9].

Studying the prevalence of vitamin D deficiency in the modern world, we have especially paid attention to lifestyle, eating habits, genetic and other risk factors. In the modern society, spending most of time indoors (work, studies, etc.) and having unbalanced diet are widely distributed throughout the world.

In recent years, generally accepted risk factors are thought to be not only the region with low insolation, but also female gender, low socioeconomic status, obesity, frequent use of carbonated soft drinks, lack of daily intake of multivitamin supplements, poor health education, lack of evidence-based recommendations on daily intake of vitamin D [10].

**The role of vitamin D in the development of menstrual function**

Vitamin D, unlike other vitamins, has a variety of biological effects based on the interaction with the specific receptors, localized in the cell nuclei of many tissues and organs [11]. Some researchers believed that vitamin D receptors and vitamin D metabolizing enzymes (24-hydroxylase and 1-a-hydroxylase) were found in the ovaries and in the normal endometrium, as well as in the eutopic and ectopic endometrium in women with endometriosis [12]. Since vitamin D receptors were found in the ovaries, uterus, placenta and pituitary gland, the connection between vitamin D and reproductive health is evident.

Moreover, data on the role of vitamin D in the pathogenesis of menstrual dysfunction was insufficient presumably due to not enough research and contradictory information about the correlation between vitamin D and metabolic and genetic disorders in adolescent girls [13]. Thus, some studies clearly demonstrated a negative impact of vitamin D deficiency on ovarian function, as it was revealed in the VDR mRNA expression in human ovaries through both receptor mechanism and hormones in hypothalamo–pituitary–ovarian axis.

However, there is still no consensus on the mechanisms and extent of the impact of vitamin D deficiency on steriodogenesis, follicular development and ovarian reserve [14]. Some researchers explained the connection between vitamin D levels in serum and menstrual function through mediated mechanisms. In the literature, there were too few data on the correlation between the level of vitamin D and insulin resistance, an increase in serum total testosterone and DHEA [15].

In one Russian study, emphasizing the importance of thyroid diseases in vitamin D deficiency and establishing a significant correlation between reduced levels of vitamin D and elevated levels of anti-TPO antibodies [16], it was proved that hypothyroidism in combination with vitamin D deficiency more often led to various menstrual dysfunctions, for example, oligomenorrhea [9].

Examining the reproductive system, clinical manifestations are generally considered to be dysmenorrhea with pain syndrome, different types of premenstrual syndrome and oligomenorrhea. According to some studies, the severity of manifestations were significantly decreased if high-dose cholecalciferol was prescribed [17,18].

In iodine-deficient regions, timely correction of macro- and micronutrients deficit is especially important to establish a normal menstrual function. Some authors stressed upon the necessity of iodine medications intake of at least 100 mg per day for children in iodine-deficient regions, as well as vitamin and mineral supplements with micronutrients [19]. To prevent reproductive disorders, vitamin D has to be administered immediately, as soon as its deficiency is established [20].

However, another authors believed that vitamin D had no clinical significance in the development of various types of dysmenorrhea and premenstrual syndrome in adolescent girls, but had only a long-term, mediated effect on the reproductive function [21].

Vitamin D deficiency and its clinical manifestations indirectly led to a number of interrelated symptoms and syndromes, as well as other macro- and micronutrients deficit, which somewhat changed and aggravated the clinical picture of the initial deficit. [22].

Other researchers kept under review the role of genetic polymorphism of the VDR gene in the pathogenesis of various clinical manifestations of vitamin D deficiency [23,24]. Polymeric genetic variants were proved to exert both qualitative and quantitative impact on the levels of cholecalciferol. Thus, a high incidence of vitamin D deficiency was revealed in carriers of VDR gene bb BsmI genotype of the polymorphic marker. It was shown that the carriage of polymorphic variants of genes was associated with different levels of serum vitamin D [25], and VDR BsmI gene polymorphism was significantly associated not only with vitamin D deficiency but also with insulin resistance [26].

A significant correlation between the variations in the VDR gene and a high risk of a decrease in circulating active form of vitamin D (1.5–3.7 times) was demonstrated [27]. Therefore, the mechanism underlying the correlation between vitamin D deficiency and menstrual dysfunction should be considered unspecified.

**Correction of vitamin D deficiency as prevention of menstrual dysfunction in adolescent girls**

Due to various reasons, the effective communication between different medical specialists and continuation of follow-up older children have been lost, resulting in the lack of recommendations and little information about the need to prescribe vitamin D supplements for children older than one year. However, one of the most important stages in the development is the pubertal period, when harmonious uninterrupted functioning of all body systems is extremely necessary and deficit in various macro- and micronutrients resulting in a decreased adaptation to changing functional parameters of the body could cause dysfunction of any systems.

According to the clinical guidelines of the Russian Association of Endocrinologists (2015), a widespread screening of vitamin D deficiency was not recommended [28]. It was indicated only for patients with the risk factors such as bone diseases, age over 60 years, obesity, as well as for pregnant and breastfeeding women with risk factors and refused low-dose vitamin D intake. However, regarding the disappointing statistics on a steady increase in vitamin D deficiency among the population of different countries, and the role of vitamin D in the development of menstrual function in girls, the American Association of Endocrinologists recommended low-dose vitamin D to achieve a serum level of 75 nmol/L. Thus, children under one-year old should be prescribed 400–1000 MM (safe maximum dose up to 4000 IU), adults older than 18 years – 1500–2000 IU (safe maximum dose up to 10,000 IU) of cholecalciferol. [29] However, researchers still have not developed unified dosages and schemes for prescribing low- and high-dose vitamin
D, and there is no unified scale to assess the level of cholecalciferol deficiency in the serum.

In the viewpoint of most experts, the level of calcidiol less than 20 ng/ml (50 nmol/l) should be regarded as vitamin D deficiency, keeping in mind the correlation of serum calcidiol with the level of parathyroid hormone, which returns to normal values only at serum vitamin D levels of 30–40 ng/ml (75–100 nmol/l) [30].

Giving recommendations about vitamin D supplements, it is certainly necessary to consider its initial levels, and medical history of gastrointestinal, liver and kidney diseases [31].

The toxicity of medications containing various forms of vitamin D still remains an unresolved issue. However, a number of authors proved that daily intake of 10,000IU of vitamin D did not cause hypercalcemia and an increase in calcium excretion by the kidneys. By all means, the prescription of low- and high-dose vitamin D should be considered individually, after detection of serum vitamin D and regular urine tests. With respect to the prevalence of the problem and proved correlation between vitamin D deficiency and various menstrual dysfunctions, screening is needed to reveal and prevent this disorder among girls at the age of puberty [32].

The impact of vitamin D on the trophologic status is also important as an intake of vitamin D supplements or its analogs demonstrated a positive effect on insulin secretion, lipid profile, decrease in glucose and C-peptide levels, and, in turns, on the menstrual cycle and the development of follicles [33].

Many researchers agreed about the necessity to review the recommendations on prescribing low-dose vitamin D to children of different ages [34].

A particular attention shall be drawn to girls at the pubertal period, since adolescents require vitamin D supplements during their intensive growth, but they extremely rare take low-dose Vitamin D to prevent deficiency [35].

Conclusions

Regarding numerous contemporary data on the role of vitamin D, both traditional and recently published, a strong correlation between vitamin D deficiency and other factors, determining a range of polymorphic clinical manifestations such as menstrual dysfunction has been found in girls at the age of puberty.

With respect to the prevalence of vitamin D deficiency not only in the countries of the northern latitudes, as well as its high incidence among children of different ages and lack of clinical recommendations for the administration of vitamin D supplements to adolescents, the development of guidelines is the main objective of ongoing and planned research.

Disclosure statement

The authors report no conflicts of interest.

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