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The Role of Vitamin D In The Regulation Of Steroid And Folliculogenesis Processes, In The Development Of Hormonal Disorders In Endocrine Infertility In Women Living In The Aral Sea Region

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Abstract

The study of the literature and our own observations allow clude that the determination of the level of vitamin D in with endocrine infertility, the study of its role in the sis and influence on the course of the disease is relevant. iency may play a key role in the pathogenesis of obstetric ological diseases such as infertility and preeclampsia. l diabetes mellitus, polycystic ovary syndrome, fibroids, dometriosis. It should be emphasized that in infertility, the of reproductive system disorders can be achieved not only min D. However, the addition of vitamin D is a safe and atment that can have a positive effect on reproductive vomen living in the Aral Sea region.

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Keywords:

PCOS. 25 (OH) D. NOXA10, 3β -HSD.GSD

Introduction: The factor, the deficiency of which leads to the development of rickets, was discovered and named vitamin D about 100 years ago. The data obtained subsequently proved that this substance is necessary for the normal development and functioning of bone tissue, and is also a hormone that mediates various effects in other tissues of the body. In this regard, a detailed study of the physiological role of vitamin D in the body, its importance in the functioning of tissues and organs, as well as the contribution that changes in its metabolism make to the development of chronic diseases, the course and outcome of pregnancy, is of considerable interest. Achieving tissue-specific results when correcting vitamin D levels raises the question of the possible advisability of carrying out preventive and therapeutic measures in appropriate conditions [17]. Vitamin D deficiency is observed in 75% of the world's inhabitants, among whom the majority are women and children. It is known that it is involved in calcium-phosphorus metabolism and affects bone mineral density, therefore it is widely used for the prevention and treatment of rickets in children, osteoporosis in adults [16].

For a long time, the effect of vitamin D was studied mainly in children, but recently interest in the role of vitamin D in the body has been steadily growing. Of particular interest are the endocrine

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regulatory systems associated with a wide tissue expression of enzymes of vitamin D metabolism, as well as the ways in which vitamin D enters the cell and the signaling pathways activated [4]. Determining the values of vitamin D levels that mediate its extraosseous effects can be used to develop appropriate recommendations for correcting vitamin D levels. Studies of the effect of vitamin D on immune function are of interest, as well as the relationship of vitamin D with skin, nervous system, cardiovascular system, and obesity. and diabetes mellitus, cancer, reproductive function[5], prevention of falls and improved quality of life[18].

Vitamin D affects the reproductive health of women[9]. In women with polycystic ovary syndrome (PCOS), low levels of 25-hydroxyvitamin D (25(OH)D) are associated with obesity, metabolic and hormonal disorders, and vitamin D intake may help regulate the menstrual cycle and metabolism. Moreover, vitamin D may affect the steroidogenesis of sex hormones (estradiol and progesterone) in healthy women [5], while high levels of 25(OH)D may be in women with endometriosis. Systematic reviews point to lower levels of 25(OH)D in women with PCOS and an inverse relationship between blood levels of 25(OH)D and the severity of metabolic disorders in women with PCOS. Meta-analyses of RCTs indicate a positive effect of vitamin D on follicular development and menstrual cycle characteristics, but do not show improvement in metabolism. In a retrospective analysis of RCTs, the level of 25(OH)D was an independent predictor of successful induction of ovulation in infertile women with PCOS []. % [twenty]. 1,25(OH)2D3 regulates the expression of human chorionic gonadotropin, regulates the expression of HOXA10 in human endometrial stromal cells.

Infertility is a problem affecting about 10–15% of couples. Given this high prevalence of infertility, as well as vitamin D3 deficiency in healthy young women [6] and the possible role of vitamin D3 in human reproduction, the development of new therapeutic approaches, such as vitamin D3 supplementation, is needed. in the treatment of reproductive disorders.

The involvement of vitamin D in steroidogenesis is confirmed by in vitro studies, in which the enzyme 1α-hydroxylase (converting vitamin D25(OH) to calcitriol) and VDR were found in ovarian granulosa cells [7]. It has been suggested that vitamin D may play a role in modulating the levels of key enzymes in steroidogenesis (3β-HSD). Z. Merhi et al. [20] showed that in vitro vitamin D increased 3β-HSD mRNA gene expression and progesterone synthesis from pregnenolone in human granulosa cells. Thus, the diverse functions of vitamin D, which are realized through genomic and non-genomic mechanisms, suggest its possible epigenetic and allosteric role in the regulation of steroidogenesis processes [11].

Diseases leading to normogonadotropic anovulation include PCOS, obesity, type 1 or 2 diabetes, endometriosis, chronic salpingo-oophoritis, and autoimmune oophoritis [23–26]. According to I.P. Nikolaenkov et al. [15], in 48.8% of patients with PCOS, a reduced aromatase activity of follicles is determined, indicating the role of primary ovarian factors in the pathogenesis of the disease. Most patients with PCOS have normogonadotropic anovulation [27-30]. Metabolic disorders in women with PCOS are associated with low serum levels of vitamin 25(OH)D [2, 31]. Thus, in patients with PCOS, a direct correlation was observed between vitamin D deficiency and insulin resistance, obesity, and hyperandrogenemia [31, 32]. According to a randomized study conducted by A.M. Belenchia et al. [32], in young women with PCOS and overweight, the use of natural vitamin D preparations improved insulin sensitivity and weight loss. In the study of E.I.

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Abashova et al. [33] in 50% of patients with PCOS and overweight, the use of tableted cholecalciferol in combination with a low-calorie diet and dosed physical activity helped to reduce weight []. In patients with normogonadotropic anovulation, it is possible to restore a full-fledged ovulatory cycle with the help of stable remission or compensation of the underlying disease [14]. A possible cause of primary ovarian disorders in women may be a defect in the enzymes responsible for steroidogenesis in the ovaries [5].

Vitamin D from the skin or food is processed in the liver by the enzyme 25-hydroxylase. The biological effects of vitamin D are mediated by the vitamin D receptor (RVD), which is distributed in various tissues, including the skeleton and parathyroid glands, as well as reproductive organs [16]. In women, RVD mRNA expression was found in the ovaries [19], in mixed ovarian cells, and in a purified culture of granulosa cells, which indicates its role in sex hormone steroidogenesis [20]. In addition, RVDs have been found in the pituitary and endometrium in women [19]. The action of vitamin D is associated with male and female reproductive function at various levels. The exact role of 1,25(OH)2D locally synthesized in reproductive tissues is not well defined, but may include effects on follicle development and uterine maturation. DBP may contribute to the development of infertility as a factor associated with endometriosis. In this regard, in women with this variant of the DBP gene, the phagocytic activity of macrophages is reduced, which can contribute to the implantation of endometrioid tissue in the abdominal cavity and the development of endometriosis. Women with endometriosis have higher levels of macrophages and cytokines in the peritoneal fluid.

Endometriosis in 56.3% of women is combined with normogonadotropic anovulation [1]. The development of normogonadotropic anovulation in external genital endometriosis is due to folliculogenesis disorders: the number of preovulatory follicles decreases, their growth and development are disturbed. Data on the association of endometriosis with vitamin D metabolism is scarce, but there are two points in favor of this association: 1) PFDi 1α-hydroxylase has been shown to be expressed in the endometrium, indicating that the endometrium is an extrarenal local site of vitamin D synthesis and action; and 2) vitamin D is involved in the regulation of the immune system [1].

In a study involving 87 women with endometriosis and 53 healthy women, Somiglianaetal. observed an association of high levels of 25(OH)D with a significantly increased risk of endometriosis, as well as a biological gradient showing higher levels of 25(OH)D in women with advanced disease. The role of vitamin D3 in pregnant women is discussed in detail in the works of Lewis S. et al. [13]. It is well established that vitamin D deficiency is common among pregnant women, and pregnant women have significantly lower levels of 25(OH)D compared to non-pregnant controls. Moreover, maternal vitamin D deficiency may be independently associated with an increased risk of gestational diabetes mellitus (GDM). In a cohort study of mothers and children conducted in Norway (NorwegianMotherandChildCohortStudy), which involved 23423 previously nulliparous pregnant women, low vitamin D3 intake was associated with an increased risk of developing preeclampsia [98]. Vitamin D3 supplementation resulted in a 50% reduction in preterm birth, a 25% reduction in maternal infectious complications, and a 30% reduction in comorbidities (DM, hypertension, and preeclampsia) [13].

In a survey of 800 pregnant women living in St. Petersburg and the Leningrad Region[12], vitamin D deficiency and deficiency occurred in 100% of women with infertility; in patients with

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miscarriage, vitamin D deficiency and deficiency was observed 6 times more often; pregnant women with preeclampsia were 5 times more likely to have low vitamin D levels; in physiological pregnancy, vitamin D deficiency was detected in only 18.5% of women []. baby tissues (MAVIDOS) showed that when taking 1000 IU of colecalciferol during pregnancy, in general, there was no increase in bone mass compared with placebo, but in children born in winter, an increase in BMD of almost 10% was noted; the efficacy and safety of taking 1000 IU of cholecalciferol to compensate for vitamin D deficiency in pregnant women has also been shown [78]. Various factors influence adverse pregnancy outcomes, some of which we can prevent by giving women of reproductive age a balanced diet with adequate amounts of micronutrients (minerals and vitamins). They allow the body to synthesize enzymes, hormones and other substances necessary for the proper growth and development of the fetus. The consumption of vitamin-mineral complexes (VMC) by a woman reduces the risk of miscarriage by an average of 55%. Micronutrient deficiencies are common even in developed countries. 20 years ago, the UN and WHO postulated that in developing countries it is preferable to give pregnant women multivitamins.

In the Aral Sea region, this deficiency should not be widespread, however, despite the fact that the inhabitants of Central Asia receive a lot of sunlight, the prevalence of micronutrient deficiencies is no less than among the inhabitants of the northern regions. In addition, the natural absorption of the vitamin decreases over the years, and people with dark skin absorb it more slowly. Negative aspects for the perception of useful sunlight are unfavorable ecology, for example, air pollution and other problems associated with the drying of the Aral Sea [3]. Therefore, even in the summer months, not always and not everyone can stock up on cholecalciferol. The benefits of taking fish oil, which contains a large amount of vitamin D, have been proven. But fish is not available in sufficient quantities for all residents of the Aral Sea region. It is paradoxical that the inhabitants of the Aral Sea region are not active consumers of fish. According to our data obtained as a result of a survey of the population of the Khorezm region, to the question: what products are most often consumed in your family, only 0.3% of respondents named fish products. D2 (ergocalciferol) enters the body along with the usual food. However, few animal foods are known to be fortified with vitamin D: fatty fish (herring, sardines, salmon, mackerel, tuna, halibut), lamb, eggs (yolk), butter, cream, sour cream, hard cheese, beef liver, seafood, cod liver, red caviar, fish oil. In a limited amount, the vitamin is present in plant foods: chanterelle mushrooms, oatmeal, potatoes, oranges, parsley, broccoli, nuts, vegetable oils. For residents of the Khorezm region, as well as other residents of the Aral Sea region, only eggs and potatoes can be attributed to the usual food. In addition, violations of the rules of cooking can lead to the destruction of useful vitamins, including vitamin D3.

It has been found that the beneficial properties of some types of food are enhanced when it is irradiated with ultraviolet rays, and vitamin D can be synthesized by living cells under the influence of sunlight. D3 (cholecalciferol) is called "solar" because it is formed in the skin due to ultraviolet radiation. To do this, children and adults should be in the sun for about 15-30 minutes several times a week. However, intense production of vitamin D occurs during unhealthy hours, from 11:00 to 14:00, when the skin needs protection. foods rich in it, some of which also contain cholesterol. What prevents the residents of the sunny Prearalie from getting enough D3 and other micronutrients? According to the World Health Organization (WHO), intestinal diseases are one of the urgent problems in the Central Asian region. The most severe and prognostically unfavorable

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disease among them is celiac disease [2], the prevalence of which in the general population is 1% [5]. Chronic enterocolitis affects 12 to 34% of the population. These diseases are the direct cause of micronutrient deficiencies, including vitamin D3.

Calciferol controls the work of the immune, cardiovascular, endocrine, hormonal, nervous systems; maintains the level of innate immunity; acts as a hormone (D-hormone) [21], which regulates carbohydrate and other types of metabolism; is responsible for the blood levels of minerals such as calcium and phosphorus, which contribute to the preservation and strengthening of musculoskeletal tissue (bones, joints, muscles, teeth), is important for the musculoskeletal system, including correct posture. It regulates more than 200 genes, has anti-inflammatory, antitumor, immunomodulatory efficacy, and slows down the aging process. It is considered a vitamin for women's health.

Vitamin D is able to perform the functions of progesterone from the luteal phase to gestation. Both molecules are characterized by synergistic action. Calcitriol promotes the growth of the endometrium, supports the process of implantation and the course of pregnancy through different but similar pathways used by progesterone [19]. bone tissue, restores the body of a woman after childbirth[20].

The reasons why this substance is not enough for a woman's body can be [8]:

• inadequate production of D2 by exposure to the sun;

• winter-spring period of the year (from October to March);

• mono-diets, protein diets, unbalanced nutrition, vegetarianism, pregnancy;

• breastfeeding: in the first 6 months of feeding, the level of vitamin D in a woman drops sharply, which provokes a loss of calcium 4 times more than during childbearing;

• mature age (after 50 years);

• the presence of diseases of the liver and kidneys, gallbladder, small intestine;

• excess weight;

• lack of physical activity;

• taking antacids (which reduce high levels of acidity in the stomach) and cholesterol medications;

• chronic diseases of the endocrine system, gallbladder, pancreatitis, etc.

The correlation between seasonality and the number of daylight hours with fertility in humans has been studied. While nearly all research has focused on the effects of visible light via retino-hypothalamic connections or melatonin secreted in the absence of visible light, the role of vitamin

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D3 is hardly recognized. However, some studies suggest an association of vitamin D3 with human fertility. Serum 25(OH)D levels reflect seasonal fluctuations, with high levels in summer and autumn and low levels in winter and spring. In the Nordic countries, where there is a strong seasonal contrast in the amount of light, conception rates decrease during the dark winter months, while conception rates peak during the summer, leading to a maximum birth rate in the spring. Moreover, in northern countries, ovulation rates and endometrial receptivity decrease during the long, dark winters. There are several possible explanations for these findings, including changes in the hypothalamic-pituitary axis, neurotransmitters in the brain such as serotonin, dopamine, and endogenous opioids. This fact may also be partly explained by the seasonal variation in vitamin D levels, which may affect several pathways, including changes in endometrial and oocyte development. There is evidence that vitamin D3 has some impact on women's reproductive health, including IVF outcomes, PCOS, and endometriosis.

According to the latest recommendations from the Institute of Medicine and the Society of Endocrinologists [10], there are currently no specific recommendations for prescribing vitamin D3 to women or men suffering from endocrine disorders, including infertility or hypogonadism. In a 2011 report by the Institute of Medicine, the recommended level of 25(OH)D is at least 50 nmol/L20 ng/mL) [10]. The report states that daily intake of vitamin D should be 600 IU for those under 70 years of age and 800 IU for the older age group in the general population, which is in line with the recommended daily allowance. The Endocrine Practice Guidelines Committee suggests a daily intake. vitamin D3 in the range of 1500-2000 IU for adults from 18 years to 70 years. According to the 2015 clinical guidelines of the Russian Association of Endocrinologists, vitamin D status should be assessed by determining the level of 25(OH)D in blood serum according to international standards (Vitamin D External Quality Assessment Scheme, National Institute for Standard sand Technology).

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