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ТИББИЁТДА ЯНГИ КУН
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A BIOCHEMICAL MARKER OF PREMATURE BIRTH

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✓ ***Resume***

Vitamin D deficiency is a real pandemic in the modern world. Vitamin D deficiency is today a global health problem affecting more than 2.3 billion people worldwide.

It should be recognized that this disorder is of interest to both obstetrician-gynecologists and other specialists, since vitamin D deficiency is associated with oncological, neurological, cardiovascular and autoimmune diseases, as well as various pathologies in the field of obstetrics and gynecology. Recently, there has been a sharp increase in interest in the "hormone D" - calcitriol and its receptors (VDR) as risk factors for the development of a number of obstetric complications. Vitamin D receptors have been found in the ovaries, uterus, placenta, and pituitary gland. According to some studies, vitamin D deficiency during pregnancy increases the risk of preterm birth. It is involved in the processes of angiogenesis, inhibition of cell proliferation, maintains genetic homeostasis and final differentiation of fetuses, affects the production of macrophages, the functioning of the pancreas, and the reninangiotensin system.

Key words: vitamin D deficiency, 25-hydroxyvitamin D, general risk groups, pregnancy, preterm birth.

БИОХИМИЧЕСКИЙ МАРКЁР ПРЕЖДЕВРЕМЕННЫХ РОДОВ

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✓ ***Резюме***

Дефицит витамина D является настоящей пандемией в современном мире. Недостаток витамина D сегодня является глобальной проблемой здравоохранения, затронувшей более 2.3 млрд жителей планеты . Следует признать, что это нарушение вызывает интерес как акушеров-гинекологов, так и других специалистов, поскольку дефицит витамина D ассоциирован с онкологическими, неврологическими, сердечно-сосудистыми и аутоиммунными заболеваниями, а также различные патологии в сфере акушертва и гинекология. В последнее время резко вырос интерес к «гормону D» – кальцитриолу и его рецепторам (VDR) как факторам риска развития целого ряда акушерских осложнений. В яичниках, матке, плаценте и гипофизе найдены рецепторы к витамину D. Согласно некоторым исследованиям, дефицит витамина D во время беременности повышает риск преждевременных родов. Он участвует в процессах ангиогенеза, ингибирования пролиферации клеток, поддерживает генетический гомеостаз и окончательную дифференцировку плодов, оказывает влияние на продукцию макрофагов, работу поджелудочной железы и ренинангиотензиновой системы.

Ключевые слова: дефицит витамина D, 25-гидроксивитамин D, общие группы риска, беременность, преждевременные роды

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✓ ***Rezyume***

D vitamini tanqisligi rivojlanayotgan dunyoda haqiqiy pandemiya hisoblanadi. D vitamini tanqisligi bugungi kunda butun dunyo bo'ylab 2,3 milliarddan ortiq odamni qamrab olgan global sog'lik muammosidir. Shuni tan olish kerakki, bu o`zgarish ham akusher-ginekologlar, ham boshqa mutaxassislar uchun qiziqish uyg'otadi, chunki D vitamini etishmovchiligi onkologik, nevrologik, yurak-qon tomir va autoimmun kasalliklar, shuningdek, akusherlik va ginekologiya sohasidagi turli patologiyalar bilan bog'liq. So'nggi paytlarda bir qator akusherlik asoratlarining rivojlanishi uchun xavf omillari sifatida "gormon D" - kaltsitriol va uning retseptorlari (VDR) ga qiziqish keskin ortdi. D vitamini retseptorlari tuxumdonlar, bachadon, platsenta va gipofiz bezida topilgan.Ba'zi tadqiqotlarga ko'ra, homiladorlik davrida D vitamini etishmasligi erta tug'ilish xavfini oshiradi. angiogenez jarayonlarida, hujayra proliferatsiyasini inhibe qilishda ishtirok etadi, genetik gomeostazni va homilaning yakuniy differentsiatsiyasini saqlaydi, makrofaglar ishlab chiqarishga, oshqozon osti bezi faoliyatiga va renin-angiotensin tizimiga ta'sir qiladi.

Kalit so'zlar: D vitamini etishmovchiligi, 25-gidroksivitamin D, umumiy xavf guruhlari, homiladorlik, erta tug'ilish.

Relevance

The incidence of vitamin D deficiency in the population ranges from 20% to 90% [2]. The prevalence of vitamin D deficiency and insufficiency during pregnancy ranges from 19.0 to 96.0% in Europe, 27.0 to 91.0% in the United States, 39.0 to 65.0% in Canada, 25.0 to 87.0% in Australia and New Zealand, and 45.0 to 100.0% in Asia [5]. According to a meta-analysis of 195 studies on vitamin D status from 44 countries involving more than 168,000 participants, mean serum 25-hydroxyvitamin D (25(OH)D) levels in the population ranged widely from 1.9 to 54.6 ng/ml. However, 37.3% of researchers reported vitamin D deficiency (< 20 ng/ml) in the population. It has been shown that vitamin D deficiency in pregnant women is associated with an increased risk of threatened preterm labour, development of placental insufficiency, pre-eclampsia, gestational diabetes mellitus, bacterial vaginosis, uterine contractile dysfunction, and increased incidence of caesarean section. In the fetus and neonate, it leads to low birth weight, decreased intrauterine hip height, infantile heart failure, craniotabes, acute lower respiratory tract infection, and hypocalcaemia. Vitamin D deficiency is among the negative factors affecting female reproductive health [7,11].

This review focuses on calcitriol-dependent mechanisms in the pathogenesis of obstetric complications such as spontaneous miscarriage, preterm labour, fetal growth retardation, pre-eclampsia, perinatal infections and gestational diabetes mellitus [23]. In the light of recent advances, the role of vitamin D in the regulation of reproductive function has been proven. As a steroid hormone, this vitamin is essential for a wide range of physiological processes. Vitamin D deficiency is currently a worldwide health problem and accounts for a very large percentage of acute and chronic pathology. It actively influences various metabolic processes, takes part in the regulation of cell growth and functioning in the human body (6). It has been reported that pregnant women with serum vitamin D concentration less than 20 ng/ml are 3.81 times more likely to have preterm labour than women with vitamin D concentration above 40 ng/ml(18). Inadequate vitamin D levels in pregnant women and their children is an important problem in maternal and child health services, leading to unfavourable consequences for overall health. The role of vitamin D in women's reproductive health is of great interest. It is noted that insufficient vitamin D in the fetal body may not only be accompanied by insufficient mineralisation of bone tissue, but also lead to metabolic disorders, hypocalcaemic convulsions, increased incidence of bronchopulmonary dysplasia, necrotizing enterocolitis and sepsis in newborn children, and in the future - to impaired physical and neuropsychiatric development, increased risk of a number of diseases (infectious, allergic, etc.). The issues of optimal dosing regime of vitamin D during pregnancy and in newborn children are discussed.

Adequate vitamin D intake and serum concentrations are important for bone health and calcium-phosphorus metabolism, as well as for optimal function of many organs and tissues. Most epidemiological studies show that vitamin D deficiency has a high prevalence in the population.

Vitamin D is formed in the skin under the influence of UVA or from food, and then a chain of metabolic processes occurs with the formation of active vitamin D metabolites, which together with parathyroid hormone and calcitonin provide regulation of calcium and phosphate metabolism - the so-called classical vitamin D action. In pregnant women, syncytiotrophoblast is one of the sources of calcitriol production. During pregnancy, closer to 12 weeks, the concentration of 1,25(OH)2D more than doubles, which confirms the important role of vitamin D in supporting gestation and controlling fetal development. It regulates decidualisation, implantation, and placental lactogen expression. In addition, vitamin D affects the secretion of progesterone and estriol, human chorionic gonadotropin (hCG), calcium uptake by the placenta and placental immunomodulation Decreased vitamin D synthesis is noted at high latitudes (closer to the polar regions), especially during winter months, high levels of atmospheric pollution, dense cloud coverage of the earth, clothing-covered skin, use of sunscreen and swarthy skin type. Currently, there has been a significant evolution in

the knowledge of vitamin D, with clarification of metabolic pathways and new receptor-mediated mechanisms of immunological action (anticarcinogenic, immunomodulatory, anti-inflammatory, etc.). Thanks to the research of many scientific groups, the understanding of the role of vitamin D in the body has changed significantly in recent decades (21). Thus, it has been shown that active metabolites of vitamin D have an effect on numerous physiological processes. Currently, the term vitamin D unites more than 6 molecules of similar nature, of which 2 steroidal prohormone molecules - D2 and D3 - have the greatest biological significance. Vitamins D2 and D3 are biologically inert. Two successive hydroxylations are required to convert them into the active form of D-hormone (1,25(OH)2D), which binds to its receptors in tissues. The first occurs in the liver, and under the action of the mitochondrial enzyme vitamin-D-25-hydroxylase (CYP27A1) D3 is converted to 25-hydroxyvitamin D (25(OH))D), also known as calcidiol. A second hydroxylation occurs in the kidneys, resulting in the synthesis of the biologically active 1,25-dihydroxyvitamin D(1,25(OH)2D), or calcitriol, under the action of mitochondrial 1α-hydroxylase (CYP27B1). The enzyme 1α-hydroxylase is also found in many other tissues, which contributes to the local conversion of 25(OH)D to activeVitamin D levels influence 172 major physiological indicators of human health associated with the risk of various diseases and The vitamin D receptor (vitamin D receptor, VDR) is found in more than 38 organs and tissues [20].

There are ≪classical≫ effects of D-hormone associated with its influence on calcium-phosphorus metabolism and bone mineral density, and ≪nonclassical≫ biological effects. The ≪nonclassical≫ (extraosseous) effects of D-hormone include inhibition of cell proliferation and angiogenesis, stimulation of insulin and cathelicidin (antimicrobial peptides) production, inhibition of renin production, anti-inflammatory, immunomodulatory, antibacterial, antitumour and a number of other properties. Similar results were obtained in a study by some co-authors, which indicates that vitamin D in granulosa cells of human ovaries in vitro stimulates the production of estradiol, estrone, progesterone, insulin-like growth factor [1,19]. Reports on the prevalence of vitamin D deficiency and insufficiency in different countries of the world show the wide prevalence of this problem among different population groups, regardless of the standard of living in the country and its geographical location In the epidermis, cholecalciferol binds to vitamin D-binding protein and 70% of it from the bloodstream goes to the liver, and the other part goes to fat cells, where vitamin D depot is formed. It has been shown that when human skin is exposed to sunlight at a single erythemal dose, the vitamin D3 content in the blood increases as much as after ingestion of 10,000 IU of vitamin D3 [3]. However, the development of hypervitaminosis D during prolonged insolation does not occur due to the blocking of excess vitamin D from the skin into the bloodstream and its transformation into inactive compounds. With age, the content of7-dehydrocholesterol in the epidermis decreases, respectively, the synthesis of vitamin D3 decreases and after 65 years of age its level decreases more than 4 times 25-hydroxycholecalciferol is considered the most accurate indicator of vitamin D level. This is because 25(OH)D is characterised by a long half-life (about 3 weeks). The 25(OH)D level reflects the rate of accumulation of both endogenous and exogenous vitamin D. In addition, 25(OH)D synthesis in the liver is predominantly regulated by the substrate, i.e. the inactive form of vitamin D, and is less subject to humoral influences Thus, 25(OH)D is the transport form of vitamin D, and 1,25(OH)2D is its hormonal form, the mechanism of action of which is similar to the classical action of steroid hormones. The rate of formation of 1,25(OH)2D depends on the serum concentration of calcium, phosphate, and parathyroid hormone (PTH). In patients with cystic fibrosis, cholestasis, and adults, it is likely to be increased [9].

The 500 IU per day currently used is sufficient to maintain optimal Ca and P metabolism but insufficient to fulfil the non-calcaemic functions of cholecalciferol. The main manifestations of the activity of its metabolites in the body are: regulation of mineral metabolism, especially calcium and phosphorus; regulation of bone growth, bone remodelling and repair; inhibition of the renin-angiotensin system; anti-inflammatory, regulation of cell growth and differentiation, angiogenesis; regulation of neuromuscular conduction [13].

In pregnancy, vitamin D favourably affects the mother-placenta-fetus system, participating: in the process of implantation; in the formation of the placental complex; in the regulation of an adequate immune response to the forming pregnancy; in the normal development of the bone and cartilage skeleton of the fetus; in providing local immunity in the vagina [22].

Vitamin D avitaminosis is the condition when blood concentrations of 25(OH)D are below 10 ng/ml. The range of serum concentrations of 25(OH)D from 10 to 20 ng/ml corresponds to the concept of hypovitaminosis. At concentrations of 20-30 ng/ml we can speak of a reduced content of the vitamin in the body. The normal content of 25(OH)D is from 30 ng/ml to 100 ng/ml (more than 100 - a possible toxic effect) [10].

When prescribing vitamin D preparations, laboratory monitoring is recommended 2-3 months after the start of treatment. To assess vitamin D status in pregnant women, the total concentration of 25(OH)D [25(OH)D2 and D3] in serum was determined by enzyme immunoassay method [7].

The results of 25(OH)D levels were assessed according to European guidelines. Vitamin D levels <20 ng/ml were diagnosed as vitamin D deficiency, 20-30 ng/ml as deficiency (suboptimal status), and 30-100 ng/ml as optimal. To prevent vitamin D deficiency, pregnant and lactating women should receive at least 800-1,200 IU of vitamin D daily. 90 pregnant women were observed, the women received 5,000 IU of vitamin D daily until 26 weeks of pregnancy, while the control group (44 patients) received placebo. As a result, the women who received placebo had statistically higher development than the main group (35.9 % vs. 10.9 $P < 0.005$), indicating the efficacy of vitamin D prescription in the prevention of preterm labour in the first and second trimesters of pregnancy [8, 12].

Conclusion

Summarising the available data, it can be assumed that women at risk of pre-eclampsia, gestational diabetes mellitus, habitual miscarriage, placental insufficiency and IUI should take at least 4000 IU of vitamin D during pregravidarial preparation and early in pregnancy. For healthy women with vitamin D levels of 25-30 ng/ml, 2000 IU may be used, and over 30 ng/ml - the currently recommended -1000 IU(170). Prevention of prematurity is a global priority; thus, women at risk of vitamin D deficiency may be screened and prescribed vitamin D supplements in the future.

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