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## DEVELOPMENT OF PREMATURE BIRTH

*Sharipova N.M.*

*Bukhara State Medical Institute, Bukhara, Uzbekistan.*

**Relevance.** The relevance of premature birth remains one of the problems of modern obstetrics, which remains one of the most important causes of perinatal morbidity and mortality. The problem of preterm birth (PB) continues to worry not only the obstetric community, but also the state as a whole, because PB is an important socio-economic problem, poses a threat to the life of mother and child, leads to early perinatal mortality and (or) disability of premature infants. Calcitriol and its receptors (VDR) as risk factors for the development of a number of obstetric complications. We know that the etiology of preterm birth is multifactorial, and the influence of vitamin D cannot be excluded. During pregnancy, closer to 12 weeks, the concentration of 1,25(OH)<sub>2</sub>D more than doubles, which confirms the important role of vitamin D in supporting gestation and controlling processes fetal development. It regulates decidualization, implantation, and expression of placental lactogen. In addition, vitamin D influences the secretion of progesterone and estriol, human chorionic gonadotropin (hCG), placental calcium uptake, and placental immunomodulation (1,16).

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

## Развитие преждевременных родов

Шарипова Н.М.

Бухарский государственный медицинский институт,  
Бухара, Узбекистан.

**Актуальность.** Актуальность преждевременных родов остаются одной проблем современного акушерства которого остается в числе важнейших причин перинатальной заболеваемости и смертности. Проблема преждевременных родов (ПР) не перестает волновать не только акушерское сообщество, но и государство в целом, потому что ПР являются важной социально-экономической проблемой, несут угрозу жизни матери и ребенка, приводят к ранней перинатальной смертности и (или) к инвалидизации недоношенных детей. Мы знаем, что этиология преждевременных родов многофакторна, и не исключено влияние витамина D. Во время беременности, ближе к 12 нед, концентрация 1,25(OH)<sub>2</sub>D увеличивается более чем вдвое, что подтверждает важную роль

витамина D в поддержке гестации и контроле процессов развития плода. Он регулирует децидуализацию, имплантацию, экспрессию плацентарного лактогена. Кроме того, витамин D влияет на секрецию прогестерона и эстриола, хорионического гонадотропина человека (ХГЧ), на поглощение кальция плацентой и плацентарную иммуномодуляцию (1,16).

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

The incidence of vitamin D deficiency in the population varies from 20% to 90% (2). The prevalence of vitamin D deficiency and insufficiency during pregnancy ranges from 19.0 to 96.0% in Europe, from 27.0 to 91.0% in the United States, from 39.0 to 65.0% in Canada, in Australia and New Zealand - from 25.0 to 87.0% and in Asia - from 45.0 to 100.0% (5). According to a meta-analysis of 195 vitamin D status studies conducted in 44 countries and involving more than 168,000 people, the average serum level of 25-hydroxyvitamin D (25(OH)D) in the population varies widely from 1.9 to 54.6 ng/ml. At the same time, 37.3% of researchers reported vitamin D deficiency (<20 ng/ml) in the population. It has been shown that vitamin D deficiency in the body of a pregnant woman is associated with an increased risk of premature birth, the development of placental insufficiency, preeclampsia, gestational diabetes mellitus, bacterial vaginosis, impaired contractile activity of the uterus, and an increase in the frequency of cesarean sections. In the fetus and newborn it leads to low birth weight, decreased femoral growth in utero, infant heart failure, craniotabes, acute lower respiratory tract infection, and hypocalcemia. Vitamin D deficiency is considered to be a negative factor affecting women's reproductive health (7,11).

The review is devoted to calcitriol-dependent mechanisms of the pathogenesis of such obstetric complications as spontaneous miscarriage, premature birth, fetal growth restriction, preeclampsia, perinatal infections and gestational diabetes mellitus. In light of the achievements of recent years, the role of vitamin D in the regulation of reproductive function has been proven. As a steroid hormone, this vitamin is necessary for a wide range of physiological processes. Vitamin D deficiency is currently a worldwide health problem and causes a very large percentage of acute and chronic pathologies. It actively influences various metabolic processes and takes part in the regulation of cell growth and functioning in the human body (6). It was reported that pregnant women with serum vitamin D concentrations less than 20 ng/mL were 3.81 times more likely to have preterm birth than women with vitamin D concentrations greater than 40 ng/mL (18).

Vitamin D is formed in the skin under the influence of ultraviolet radiation or comes from food, then a chain of metabolic processes occurs with the formation of active metabolites of vitamin D, which, together with parathyroid hormone and

calcitonin, provide regulation of calcium and phosphate metabolism - the so-called classical action of vitamin D. In pregnant women, syncytiotrophoblast is one of the sources of calcitriol production. During pregnancy, closer to 12 weeks, the concentration of  $1,25(\text{OH})_2\text{D}$  more than doubles, which confirms the important role of vitamin D in supporting gestation and controlling fetal development processes. It regulates decidualization, implantation, and expression of placental lactogen. In addition, vitamin D affects the secretion of progesterone and estriol, human chorionic gonadotropin (hCG), calcium absorption by the placenta and placental immunomodulation. Thus, active metabolites of vitamin D have been shown to affect numerous physiological processes. Currently, the term vitamin D combines more than 6 molecules of a similar nature, of which 2 molecules of steroid prohormones - D<sub>2</sub> and D<sub>3</sub> - have the greatest biological significance. Vitamins D<sub>2</sub> and D<sub>3</sub> are biologically inert. To convert them into the active form of D-hormone ( $1,25((\text{OH}))_2\text{D}$ ), which binds to its receptors in tissues, two successive hydroxylations are necessary. The first occurs in the liver and is converted by the mitochondrial enzyme vitamin D 25-hydroxylase (CYP27A1) to 25-hydroxyvitamin D ( $25((\text{OH}))\text{D}$ ), also known as calcidiol. The second hydroxylation occurs in the kidneys, resulting in the synthesis of biologically active 1,25-dihydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ), or calcitriol, under the action of mitochondrial  $1\alpha$ -hydroxylase (CYP27B1). The enzyme  $1\alpha$ -hydroxylase is also found in many other tissues, which contributes to the local conversion of  $25(\text{OH})\text{D}$  to active Vitamin D levels influence 172 key physiological indicators of human health associated with the risk of developing various diseases and the 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 “non-classical” biological effects. The “non-classical” (extraosseous) effects of D-hormone include inhibition of cell proliferation and angiogenesis, stimulation of the production of insulin and cathelicidins (antimicrobial peptides), inhibition of renin production, anti-inflammatory, immunomodulatory, antibacterial, antitumor and a number of other properties.

Similar results were obtained in a study by some co-workers, which indicates that vitamin D in human ovarian granulosa cells in vitro stimulates the production of estradiol, estrone, progesterone, and insulin-like growth factor 1 (19). Reports on the prevalence of vitamin D deficiency and insufficiency in various countries around the world show the widespread 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 comes from the bloodstream to the liver, and the other part goes to fat cells, where a vitamin D depot is formed. It has been shown that when human skin is exposed to sunlight at a single erythemal dose, the level of vitamin D<sub>3</sub> in the blood increases in

the same way as after ingestion of 10,000 IU of vitamin D<sub>3</sub> (3). However, the development of hypervitaminosis D during prolonged sun exposure does not occur due to blocking the entry of excess vitamin D from the skin into the bloodstream and its transformation into inactive compounds. With age, the content of 7-dehydrocholesterol in the epidermis decreases; accordingly, the synthesis of vitamin D<sub>3</sub> decreases and after 65 years its level decreases by more than 4 times. 25-hydroxycholecalciferol is considered the most accurate indicator of vitamin D levels. This is because 25(OH)D has a long half-life (about 3 weeks)(9).

The currently used 500 IU per day is sufficient to maintain the optimal level of metabolism of Ca and P, but is not sufficient to implement the non-calcemic 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, remodeling and repair; inhibition of the renin-angiotensin system; anti-inflammatory, regulation of cell growth and differentiation, angiogenesis; regulation of neuromuscular conduction (13). 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)D<sub>2</sub> and D<sub>3</sub>] in blood serum was determined using an enzyme immunoassay method (7). The results of 25(OH)D levels were assessed in accordance with European recommendations. At a vitamin D level <20 ng/ml, its deficiency was diagnosed; at a concentration of 20–30 ng/ml – deficiency (suboptimal status); 30–100 ng/ml was accepted as the optimal level. To prevent vitamin D deficiency, pregnant and lactating women need to receive at least 800-1,200 IU daily. 90 pregnant women were observed, women received 5,000 units of vitamin D daily until 26 weeks of pregnancy, and the control group (44 patients) received placebo. As a result, women taking placebo had a statistically higher rate of development than those in the study group (35.9% vs. 10.9 P <0.005), indicating the effectiveness of vitamin D supplementation in preventing preterm birth in the first and second trimesters of pregnancy (8,12,22). Summarizing the available data, it can be assumed that women at risk of preeclampsia, gestational diabetes mellitus, recurrent miscarriage, placental insufficiency and IUI should take at least 4000 IU of vitamin D at the preconception stage and from early pregnancy (14). For healthy women with a vitamin D level of 25-30 ng/ml, 2000 IU may be used; above 30 ng/ml, the currently recommended dose is 1000 IU (17,21). Preventing prematurity is a global priority; thus, in the future, women at risk of vitamin D deficiency may be assessed and vitamin D supplements prescribed.

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