

EFFECT OF VITAMIN D ON THE HEALTH STATUS IN THE PERINATAL PERIOD

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There is evidence that vitamin D deficiency may be a risk factor in the development of many chronic diseases, such as osteomalacia, rickets, multiple sclerosis, schizophrenia, cardiovascular diseases, Type I diabetes, and cancer. Increased susceptibility to such diseases can originate early in life, during the development of tissue structure and function. Insufficient vitamin D during perinatal development can form the basis that will continue to threaten the health of that individual. This article refers to the risks of vitamin D deficiency on human health and offers updated recommendations for vitamin D supplementation to mothers and their newborns.

Keywords: vitamin D, perinatal period, children, rickets.

Introduction

The purpose of this article is to demonstrate that an insufficient vitamin D level during perinatal development poses a threat to health and to provide updated recommendations for preventing vitamin D deficiency.

In the past, people obtained most of the required vitamin D from exposure to sunlight, which results in synthesis of the vitamin from its provitamin forms. However, because of the association between sun exposure and skin cancer, views have changed, and avoidance of sunlight exposure or use of sunscreen is now actively recommended. Hence, additional dietary intake of vitamin D is required to maintain a normal level in the body. However, only certain natural foods contain vitamin D, the best sources being fish (salmon, tuna, and mackerel) and fish oil. A small amount of vitamin D is found in beef liver, cheese, egg yolk, and some mushrooms [1]. For most people, given the lack of vitamin D production by sun exposure and its insufficient content in food, additional supplementation with vitamin D is required. This need is most significant during the critical stages of fetal and neonatal development.

The period from the beginning of pregnancy to 24 months of a child's life is important because nutrition affects the structural and functional development of the organism [2]. Inadequate

nutrition during this period can have life-long effects on health [3]. Vitamin D plays an important role in the normal developmental process. A fat-soluble molecule acquired from exposure to sunlight or diet, vitamin D is a steroid hormone precursor that regulates long-term programming of human health. Insufficient intake of vitamin D during perinatal development is generally recognized to be associated with disorders of calcium-phosphorus-mineral metabolism and skeletal deformities. However, based on recent studies, researchers are beginning to understand that vitamin D deficiency during the perinatal period is a risk factor for a wide spectrum of diseases, including multiple sclerosis, schizophrenia, cardiovascular diseases, type I diabetes, and cancer.

Vitamin D metabolism

Vitamin D refers to a group of sterols, of which the two most important forms are vitamin D₂ and vitamin D₃. The main difference between the two is the route of entry into the body. When skin is exposed to ultraviolet radiation, it synthesizes vitamin D₃, which is the most available form [1]. However, the skin's ability to synthesize vitamin D₃ is adversely affected by factors that reduce sun exposure intensity, including poor air quality, extreme latitudes, and the winter season. Other factors limiting absorption of solar radiation include

increased skin pigmentation, sunscreen application, and old age, which may also limit vitamin D₃ synthesis [4]. In addition to skin production of vitamin D₃, this form of the vitamin can also be obtained from oily fish. Vegetable sources, on the other hand, provide vitamin D₂. However, the amount of vitamin D supplied by food is generally low and may be limited by malabsorption. For this reason, many people consume vitamin D-enriched food and dietary supplements to meet the vitamin D requirements, particularly when sun exposure is insufficient. Biochemical studies have demonstrated that consumption of vitamin D₃ may be more effective than vitamin D₂ in elevating serum levels of 25-hydroxyvitamin D (25(OH)D) [5]. This is probably due to the fact that vitamin D₃ has a greater affinity for the vitamin D-binding protein, a transporter mediating vitamin D delivery to muscle and fat cells for storage or to liver and kidney cells for bioactivation.

Both vitamin D₂ and D₃ are biologically inert and have to pass through two metabolic stages to become physiologically active molecules. The first stage occurs in the liver, which converts vitamin D to 25(OH)D, a major form in the circulation that is commonly measured to determine the vitamin D level in the body. This conversion stage is disturbed in the presence of liver diseases. According to recent studies, 92% of patients with chronic liver disease have vitamin D deficiency.

The second metabolic stage occurs in the kidneys and other tissues (heart, brain, skin, reproductive system, skeletal muscles, spinal cord, and placenta), which produce the physiologically active hormone, 1,25-dihydroxyvitamin D (1,25(OH)₂D). This hormone is released into the circulation through autocrine and paracrine pathways and stimulates target cells [6]. It binds to vitamin D receptors and regulates various cellular and immune processes [7]. Vitamin D receptors are present in most organs and on some types of leukocytes. This distribution indicates that vitamin D is essential for the development and maintenance of the structure and function of many tissues.

Vitamin D metabolism during pregnancy and lactation

The placenta is formed by the fourth week of gestation and provides transport of nutrients from

the mother to the fetus. Starting from the fourth week of gestation until the onset of labor, 25(OH)D readily crosses the placenta, so that 25(OH)D concentration in the bloodstream of the fetus reaches 87% of the 25(OH)D concentration in the mother's bloodstream. The physiologically active metabolite 1,25(OH)₂D does not penetrate the placenta [8]. However, the placenta and fetal kidneys synthesize 1 α -hydroxylase, the enzyme that converts 25(OH)D to 1,25(OH)₂D. Since the first trimester of pregnancy, the overall level of 1,25(OH)₂D in the mother and fetus increases from 100% to 200%, but a large proportion is bound to vitamin D-binding protein. The free, unbound hormone is widely believed to be a more biologically active form of vitamin D. The concentration of free 1,25(OH)₂D has been found to increase only in the third trimester, perhaps related to stimulation by the onset of labor [9]. Recent studies have demonstrated that 1,25(OH)₂D regulates secretion of placental hormones (estradiol and progesterone) and prevents induction of inflammatory cytokines that cause preeclampsia and stimulate preterm labor [10]. After birth, the mother's levels of 25(OH)D and 1,25(OH)₂D decrease significantly. For this reason, the breastfed baby may require additional vitamin D.

Effect of vitamin D on bone health

Skeletal growth is a dynamic process. The robust formation of fetal bone tissue requires 25–30 g of calcium, which is transferred from the mother during pregnancy [11]. Maternal calcium is provided by increased intestinal absorption, which increases from 33–36% before pregnancy to 54–62% in the third trimester. Vitamin D promotes intestinal absorption of calcium up to a calcium level of 32 ng/mL, after which absorption is not further increased [12]. Vitamin D deficiency impairs physiological control of calcium transport through the mucosa. Secondary hyperparathyroidism or osteomalacia may develop in cases of severe vitamin D deficiency [9, 13].

In pregnancy, the mother's body puts the needs of the fetus before her own. For example, if secondary hyperparathyroidism develops in a mother with vitamin D deficiency, the required substances will be washed out of her bones and transferred to the fetus. This adversely affects the mother's bone metabolism

but will ensure maintenance of pregnancy. The total amount of vitamin D transferred from the mother to the fetus will decrease, which may disturb mineralization and growth of fetal bones [14]. A baby who has vitamin D deficiency during prenatal development will likely be born with a normal serum calcium level and normal bone morphology but will be at increased risk of osteomalacia and rickets in the first weeks and months of life [9]. In addition, these babies may develop severe muscle weakness leading to impaired lung function. If there is a weakness or deformity of the lower limbs, the baby may have problems learning to walk.

Rickets occurs in all countries, but it is particularly common among northern populations who live under conditions of insufficient sunlight. Rickets is more common and severe in children born in autumn and winter. In the early 20th century, rickets occurred in approximately 50–80% of children in Austria and the United Kingdom. In Russia, rickets was diagnosed in 46–68% of children in the first two years of life in the first half of the 20th century; in recent years, the incidence of rickets among young children has ranged from 54% to 66%. In Bulgaria, which has many sunny days throughout the year, the incidence of rickets among children under one year of age is only about 20% [15, 16].

Additional risk factors for rickets have been identified in recent years. Studies have shown that 27% of children with mild to moderate rickets were born of the 3rd to 5th pregnancy. In 73% of cases, there had been rapid delivery with induction or an operative delivery. A combination of complications during pregnancy and labor had occurred in 63% of the mothers. At onset of labor, 8% of the mothers were aged 17–18 years. Rickets was diagnosed in 10% of babies who were born prematurely at 32 to 34 weeks of gestation, with a mean weight of 2323 g (range: 1880–3110) [15].

The need for cesarean section is four times higher in females with a blood plasma 25(OH)D level below 15 ng/mL compared with those with a level above 15 ng/mL [17]. Vitamin D deficiency leads to significantly weakened muscles and may cause myopathy even before bone lesions appear [18]. Myopathy caused by vitamin D deficiency may therefore be asymptomatic until labor, at which point there is inadequate muscle strength for contractions, increasing the incidence of caesarean births. Vitamin D supplementation during pregnancy may prevent

development of bone disease and myopathies, thus improving reproductive function [19].

Effect of vitamin D on other organs and tissues

Brain

Vitamin D receptors and 1 α -hydroxylase are found in human brain cells [20]. 25(OH)D and 1,25(OH)₂D are capable of penetrating the blood-brain barrier, binding to vitamin D receptors, and stimulating a wide range of genomic and nongenomic responses [21]. Low concentrations of 25(OH)D during critical developmental stages can lead to impaired development of the structure and function of brain tissue. At birth, the brains of rats born to vitamin D-deficient females contain a large number of mitotic cells and a smaller number of apoptotic cells. This suggests that a low 25(OH)D level leads to disruption of cellular transcription, which might facilitate tumor growth and brain cancer [22].

Another study conducted in rats demonstrated that maternal vitamin D deficiency is associated with decreased production of neurotrophins and growth factors in fetal brain tissue. Neurotrophins and growth factors regulate myelination, cell growth, and formation of synaptic connections. A decrease in these substances may cause the development of neurological diseases, e.g., multiple sclerosis. The development of multiple sclerosis is associated with disruption of the blood-brain barrier, enabling T lymphocytes to reach brain cells and to destroy myelin sheaths in the central nervous system [23]. Because T cells have vitamin D receptors, biologically active 1,25(OH)₂D has been found to reduce T-cell activity. Thus, vitamin D may prevent demyelination [24].

Enlarged lateral ventricles and thinning of the brain cortex have been found in rats born to females with vitamin D deficiency. These changes were combined with psychological disorders. Thinning of the neocortex and enlarged cerebral ventricles are commonly found in children with schizophrenia. On this basis, it may be supposed that vitamin D deficiency is a risk factor for schizophrenia [25].

Cardiovascular system

According to *National Health and Nutrition Examination Survey (1988–1994)* data, serum

25(OH)D concentration is inversely related to the incidence of cardiovascular diseases such as hypertension, myocardial infarction, congestive heart failure, and stroke [26]. The mechanism of development of these diseases remains unknown. According to one hypothesis, vitamin D deficiency reduces intestinal calcium absorption, which leads to activation of the parathyroid hormone. The parathyroid hormone not only affects calcium reabsorption but also enhances insulin resistance and inflammatory processes and activates the renin-angiotensin-aldosterone system. Over time, these processes contribute to the development of atherosclerosis [27].

A study conducted in rodents demonstrated that rats deficient in vitamin D during perinatal development had reduced synthesis of contractile proteins and retarded cardiac growth, which might significantly affect cardiac function [28].

Development of type I diabetes

Type I diabetes is an autoimmune process that begins in childhood and leads to the destruction of pancreatic insulin-producing β -cells. According to one study, children who receive a daily dose of 2,000 IU of vitamin D beginning at birth have a lower risk of type I diabetes [29]. The exact mechanism of vitamin D action in this case is unknown. However, given the presence of vitamin D receptors on the surface of both immune cells and pancreatic β -cells, it may be supposed that vitamin D supplements will prevent the destruction of β -cells and thus the development of type I diabetes [30].

Current vitamin D recommendations and target serum levels of 25(OH)D

Determination of the serum 25(OH)D concentration enables detection of vitamin D deficiency in pregnancy. A level of less than 10 ng/mL (<25 nM/L) is considered to be severe vitamin D deficiency that can lead to rickets or adversely affect general health [31]. Concentrations between 10 and 20 ng/mL (25–50 nM/L) indicate vitamin D insufficiency and often occur in people living in northern regions with low solar exposure. Concentrations above 32 ng/mL (>80 nM/L) are sufficient for preventing disease. Excessively high 25(OH)D concentrations, greater than 200 ng/mL

(>500 nM/L), are potentially toxic, although data on these concentrations in humans are absent. Vitamin D toxicity may lead to non-specific symptoms such as nausea, vomiting, decreased appetite, constipation, weakness, or weight loss as well as to more serious conditions, including hypercalcemia and hyperphosphatemia.

A risk assessment study, which included 21 clinical trials of vitamin D supplementation, revealed that a daily dose of 10,000 IU may be the most appropriate upper limit for vitamin D intake [32]. A clinical trial conducted in females of childbearing age showed that daily intake of vitamin D by the mother at a dose of 6,400 IU for 6 months ensured adequate 25(OH)D levels in both the mother and baby [6].

A high incidence of vitamin D deficiency in mothers affected their newborns, among whom 10% of white and 46% of black infants had 25(OH)D concentrations below 15 ng/mL [33]. In lactating mothers consuming 200–400 IU of vitamin D per day, the vitamin D content in milk is about 20–70 IU. As this amount is not sufficient for normal infant development the baby should also receive at least 200 IU (5 μ g) of vitamin D per day to achieve adequate 25(OH)D levels. Although the Institute of Medicine's Food and Nutrition Board considers this amount to be sufficient to reduce the risk of disease, the American Academy of Pediatrics recommends that healthy breastfed babies receive 400 IU (10 μ g) of vitamin D per day [34]. Formula-fed babies are given baby food and milk formulas enriched with vitamin D at a dose of 400 IU/L. However, babies who do not ingest at least 1 L of baby food per day need additional vitamin D. Supplementation should begin at birth and continue until the baby is getting at least 400 IU (10 μ g) of dietary vitamin D per day [35].

To prevent rickets, Russian researchers recommended that pregnant females at risk (for example, those with nephropathy, diabetes, hypertension, or rheumatism) should take vitamin D supplements at a dose of 500–1,000 IU for 8 weeks starting from the 28th to the 32nd week of pregnancy, regardless of the time of year. They further advised a minimum dose of vitamin D of 400–500 IU per day for healthy full-term infants to prevent rickets. This dose was to be supplemented starting in the 4th to 5th week of life in autumn through spring, depending on the infant's living conditions and disease risk factors [15].

Conclusion

The period from the beginning of pregnancy to 24 months of a child's life is an important developmental period in which vitamin D has a significant impact on health. An insufficient amount of 25(OH)D during perinatal development adversely affects bone health and brain development and can lead to cardiovascular disease, type I diabetes, and cancer. To lay the basis for good health in adulthood, pregnant mothers and their newborns should receive sufficient amounts of vitamin D during critical developmental stages. The current vitamin D recommendations for pregnant and lactating females are essentially the same as for non-pregnant adult women. This does not take into account the extra needs of the mother and developing baby. There is an urgent need to determine optimal (recommended) doses of vitamin D supplements for pregnant and lactating females. Screening of all mothers and newborns for 25(OH)D levels is impractical and uneconomical. Therefore, recommendations for vitamin D supplementation specific for mothers and newborns are required.

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ВЛИЯНИЕ УРОВНЯ ВИТАМИНА D В ПЕРИНАТАЛЬНОМ ПЕРИОДЕ НА СОСТОЯНИЕ ЗДОРОВЬЯ

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Существуют данные, согласно которым дефицит витамина D может являться фактором риска в развитии многих хронических заболеваний, таких как остеопороз, рахит, рассеянный склероз, шизофрения, сердечно-сосудистые заболевания, диабет I типа и рак. Повышенная подверженность подобным заболеваниям может брать начало на ранних этапах жизни в ходе развития структуры и функции тканей. Недостаточное содержание витамина D в период перинатального развития может заложить основу, которая в течение длительного времени будет представлять угрозу для здоровья человека. В данной статье говорится о рисках дефицита витамина D для здоровья человека и предлагаются современные рекомендации по использованию витамина D у матерей и их новорожденных детей.

Ключевые слова: витамин D, перинатальный период, дети, рахит.

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