The effects of vitamin D in pregnancy

Abstract

The birth, growth, development, reproduction and senescence under physiological conditions can be achieved without diminishing the role of the other important aspects that influence them, only with the support of an optimal diet which is a fundamental requirement nowadays, considering that health and nutritional status are in a permanent interdependence. The effects of inadequate nutrition reflect on the expression of genes, influencing the development of certain diseases in childhood and adulthood. Knowing the phases of the gestation period, in which the needs of certain nutrients are increased and their absence has the most serious impact on fetal growth and development, allows for the adoption in due time of concrete preventive rules. Disorders associated with lipid malabsorption, such as celiac disease, Crohn's disease, pancreatic insufficiency, cystic fibrosis and cholestatic disease, are associated with low serum levels of 5-hydroxyvitamin D. Vitamin D deficiency in the newborn can express as deficient skeletal homeostasis, congenital rickets, and fractures in the early days of life. A low level of vitamin D during pregnancy seems to increase the risk of preeclampsia, intrauterine growth restriction and gestational diabetes, and in the longer term it seems to affect the bone, immune system and general status. The prevalence of hypovitaminosis D is increasing globally, and the effects on pregnancy and neonatal outcome of the vitamin D deficiency and supplementation are a topical issue, which is currently under investigation.

Keywords: *vitamin D, pregnancy, deficiency*

Rezumat

Naşterea, creşterea, dezvoltarea, reproducerea şi îmbătrânirea în condiţii fiziologice pot fi realizate fără a diminua rolul celorlalte aspecte importante care le influenţează, numai cu ajutorul unei diete optime, aceasta fiind o cerinţă fundamentală în era actuală, având în vedere că sănătatea şi starea nutriţională se află într-o permanentă interdependenţă. Efectele nutriţiei necorespunzătoare reflectă expresia genelor, influenţând dezvoltarea anumitor boli în copilărie şi la adulţi. Cunoscând fazele perioadei de gestaţie, în care nevoile anumitor substanţe nutritive sunt crescute, iar absenţa lor are un impact grav asupra creşterii şi dezvoltării fetale, permite adoptarea în timp util a unor reguli concrete de prevenire. Tulburările asociate cu malabsorbţia lipidică, cum ar fi boala celiacă, boala Crohn, insuficienţa pancreatică, fibroza chistică şi boala colestatică, sunt asociate cu niveluri scăzute ale 5-hidroxivitaminei D. Deficitul de vitamină D la nou-născut se poate exprima prin homeostază scheletică deficitară, rahitism congenital şi fracturi în primele zile ale vieţii. Un nivel scăzut de vitamină D în timpul sarcinii pare să crească riscul de preeclampsie, de restricţie de creştere intrauterină şi diabet gestational şi, pe termen lung, pare să afecteze osul, sistemul imunitar şi starea generală. Prevalenţa hipovitaminozei D creşte pe plan global, iar efectele asupra sarcinii şi rezultatului neonatal al deficienţei şi suplimentelor de vitamină D sunt o problemă de actualitate, în curs de investigare.

Cuvinte-cheie: *vitamină D, sarcină, deficienţă*

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Submission date: 17.01.2019
Acceptance date: 24.03.2019

Efectele vitaminei D în sarcină

Suggested citation for this article: Bohîlţea R, Zugravu CA, Ţurcan N, Ioniţă D, Teodor O, Cîrstoiu M. The effects of vitamin D in pregnancy. Ginecologia.ro. 2019;24(2):15-20.

Introduction

Appropriate nutrition is an essential condition for health. The birth, growth, development, reproduction and senescence under physiological conditions can be achieved without diminishing the role of other important aspects that influence them, only with the support of an optimal diet which is a fundamental requirement nowadays, considering that health and nutritional status are in a permanent interdependence.

A particular physiological situation through the impact on the individual, the family, but also on society is the gestation state, the current concepts and orientations referring both to the preconception nutrition of the woman in the fertile period and to the nutritional intake during the pregnancy, targeting its effects on the conception product. The gestational state is a period of intense fetal growth and development, and of major adaptive changes in the maternal body. Malnutrition, both in the sense of deficit and excess, is associated with unfavorable results of pregnancy evolution, which is why it is of particular importance to evaluate, monitor and permanently improve the nutritional status of women, both during preconception period and during pregnancy and lactation.

The effects of inadequate nutrition reflect on the expression of genes, influencing the development of certain diseases in childhood and adulthood[1].

Ideally, the woman's nutritional status should be initially assessed during preconception period so that

diet changes optimize maternal and fetal health before conception. Nutritional supervision and counseling should be continued during pregnancy and lactation. Optimally, this can be done through a team approach that includes obstetrician physician, specialized prenatal nutrition counseling, and dietitian specialized in perinatal nutrition. In the context of the clinical specialties of the Romanian healthcare network, the perinatal nutrition approach could be achieved through the collaboration of the obstetrician and the specialists in diabetes and nutrition (graduate of the master studies in nutrition and food safety), because university studies and the development of dietetics will bring an essential plus of competence to this team.

Knowing the phases of the gestation period, in which the needs of certain nutrients are increased and their absence has a serious impact on fetal growth and development, allows for the adoption in due time of concrete preventive rules. The beneficial effect of preventive therapy is at the present time a certainty and a method of primary prophylaxis.

The effects of food deficiencies on the function of reproductive organs are of particular importance from the point of view of the late disorders they cause and their persistence for a long time after the normalization of food intake. Malnutrition is considered a risk factor for amenorrhea and infertility. Late ovulation and menstrual cycle disorders are the main effects of inadequate intake, which is also associated with an increased risk of recurrent miscarriage, intrauterine growth restriction and congenital malformations. Cranial circumference, length and weight at birth are strongly correlated with the mother's preconception nutritional status, the weight gain during pregnancy and the dietary supplementation. Variation in the child's growth parameter is mainly determined before the end of the first trimester. In the second half of pregnancy, a serious food deficiency of the mother can cause spontaneous abortion. Moderate food deficiencies cause premature delivery and fetal hypotrophy. Inadequate nutrition in the first part of pregnancy may cause, depending on the severity of the deficiency, either abortion, or alteration of embryonic structures. The imbalance of the enzymatic components exerts the most obvious teratogenic effect.

Vitamin D – or calciferol – is a generic term comprising a group of liposoluble compounds having a skeleton composed of four cholesterol molecules. The 25-hydroxyvitamin D is the major circulating form of vitamin D. The half-life is 2-3 weeks compared to 24 hours of the inactive vitamin D form. The 25(OH)D activates in the bone and intestine, but it represents below 1% of the potency of 1,25-dihydroxyvitamin D, representing the highest activity form of this vitamin, whose half-life is 4-6 hours. The 1,25-dihydroxyvitamin D binds to intracellular receptors present in target tissues and regulates gene transcription, a mechanism that is realized with a single receptor (VDR), universally expressed in nucleated cells.

Vitamin D is obtained from dairy products, vegetables, fish oil and dietary supplements. The endogen vitamin D is produced by direct exposure to the sun.

Previtamin D is synthesized non-enzymatically in skin from 7-dehydrocholesterol during exposure to ultraviolet light in sunlight. Previtamin D is subsequently subjected to temperature-dependent conformational rearrangement, forming vitamin D3 (colecalciferol). This system is excessively effective, with the estimated occasional exposure of only arms and face to the sun being equivalent to the ingestion of 200 international units (IU) per day. However, it is difficult to assess the duration of daily exposure required to obtain the equivalent of oral vitamin D supplementation, as there are many variables represented by skin type, latitude, season and time of the day[7,8]. Prolonged exposure of the skin to sunlight cannot produce toxic amounts of vitamin D3 due to the photoconversion of previtamin D3 and vitamin D3 in inactive metabolites (lumisterol, tahisterol, 5,6-transvitamin D and suprasterol 1 and 2)[9,10]. In addition, sunlight induces melanin production that reduces vitamin D3 production in the skin. Children, people with disabilities and the elderly may experience inadequate sun exposure and the dermis of people over the age of 70 years old is no longer able to efficiently convert vitamin D. At Nordic latitudes, there is not enough radiation for this conversion, especially in the cold season. For these reasons, in the United States of America, milk, instant milk for infants, breakfast cereals, and some other foods are fortified with vitamin D3 or synthetic vitamin D2 (ergocalciferol), which is derived from the effect of radiation on ergosterol found in plants, in plankton, or in molds. In other countries, cereals and bakery products are often also fortified with vitamin D.

Vitamin D present in the diet is incorporated into the mycelium, absorbed by enterocytes, and then stored in kilomicrons. Disorders associated with lipid malabsorption, such as celiac disease, Crohn's disease, pancreatic insufficiency, cystic fibrosis and cholestatic disease, are associated with low serum levels of 5-hydroxyvitamin D.

Biochemical mechanisms

Vitamin D from diet or dermal synthesis is biologically inactive and requires enzyme, liver and kidney conversion to generate active metabolites. Dietary vitamin D is directed to the liver linked to the vitamin D binding protein, associated permanently with kilomicrons and lipoproteins. Along with endogenously synthesized vitamin D3, exogenous vitamin D is metabolized into the liver, where the hepatic 25-hydroxylase enzyme places a hydroxy group at the 25-position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D (25[OH]D – calcidiol); 25-hydroxyvitamin D2 has a lower affinity compared to 25-hydroxyvitamin D3 for the vitamin D binding protein. Therefore, 25-hydroxyvitamin D2 has a half-life shorter than 25-hydroxyvitamin D3. In this context, vitamin D2 treatment is not

able to grow total serum level of 25(OH)D as effective as vitamin D3.

The 25-hydroxyvitamin D2 and D3 produced in the liver enter the circulation and cross the kidneys, linked to the specific protein that has a single binding site for all the D vitamins and all their metabolites. Normally, only 3-5% of the circulating binding sites should be occupied, which explains why this protein is not limiting to vitamin D metabolism in terms of filtration rate, except for its urinary large loss as a consequence of nephrotic syndrome[11]. In the renal tubules, the entry of the 25(OH)D-protein (binding protein of vitamin D) into the cells is facilitated by receptor-mediated endocytosis[12]. At least two proteins working in tandem are involved in this process: cubilin and megalina[12,13]. Cubilin and megaline expressed in the proximal renal tubule have multiple binding receptors that facilitate extracellular ligand uptake. The deficiency of any of these proteins results in increased urinary excretion of 25(OH)D and, consequently, on experimental models, resulting in 1,25-dihydroxyvitamin D deficiency and bone damage[12-14]. Within the renal tubule cell, 25(OH)D is released from the complex that it forms with the binding protein. Renal tubular cells contain two enzymes, 1-alpha-hydroxylase and 24-alpha-hydroxylase, which can further hydroxylate 25(OH)D, yielding 1,25-dihydroxyvitamin D, the most active form of vitamin, or 24,25-dihydroxyvitamin D, an inactive metabolite. Both enzymes are members of the P450 system[15].

The plasma concentration of 1,25-dihydroxyvitamin D is dependent both on the availability of (OH)D and on the activity of renal enzymes 1-alphahydroxylase and 24-alphahydroxylase. The first enzyme is under the control of parathyroid hormone (PTH), serum calcium, phosphorus concentrations, and also fibroblastic growth factor 23 (FGF 23). Increased PTH secretion, often due to decreased plasmatic calcium levels, respectively hypophosphatemia, stimulates the enzyme and increases the production of 1,25-dihydroxyvitamin D, which in turn inhibits the synthesis and secretion of PTH, by making a negative feedback on its own production.

The synthesis of 1,25-dihydroxyvitamin D may also be modulated by vitamin D receptors (VDR) present on the cell surface. Down regulation of these receptors may play an important role in regulating vitamin D activation[16]. FGF 23 inhibits renal production of 1,25-dihydroxyvitamin D by limiting 1-alpha-hydroxylase activity in the proximal renal tubule and by simultaneously increasing the expression of 24-alphahydroxylase and, implicitly, the production of 24-25-dihydroxyvitamin D, the inactive metabolite. The 1,25-dihydroxyvitamin D stimulates FGF 23, a phosphate hormone, which creates a feedback loop. Experimental data suggest that FGF 23 reduces renal phosphate reabsorption and counteracts the increased gastrointestinal reabsorption induced by 1,25-dihydroxyvitamin D, thereby maintaining phosphate homeostasis[17]. Both 1,25-dihydroxyvitamin D and 25(OH)D are partially degraded by hydroxylation by 24-hydroxylase. The activity of the gene encoding 24-hydroxylase is increased by 1,25-dihydroxyvitamin D, which thus performs its own inactivation and is lowered by PTH, which allows the synthesis of the high activity hormone[18].

Its active form, 1,25-dihydroxyvitamin D, plays an essential role in promoting enterocyte differentiation and in intestinal calcium absorption, in normal skeletal mineralization, respectively in growth process. Other effects include less important stimulation of intestinal phosphorus absorption, direct suppression of parathyroid hormone (PTH) release from the parathyroid gland, regulation of osteoblastic function and permissiveness of PTH-induced osteoclast activation and bone resorption.

Pregnancy status

According to the American College of Obstetricians and Gynecologists (ACOG), vitamin D deficiency is defined as a serum level of circulating 25(OH)D less than 32 ng/ml (80 mmol/L). Vitamin D deficiency in the newborn can express as deficient skeletal homeostasis, congenital rickets and fractures in the early days of life. Recent studies have shown that vitamin D deficiency is common during pregnancy, especially among the populations at risk. Most experts agree that the screening of 25-hydroxyvitamin D level in the general population or during pregnancy is not necessary, excepting for cases of pregnant women who are obese, have minimal sun exposure, have a history of malabsorption (celiac disease, intestinal inflammatory disease) or other risk factors for vitamin D deficiency (e.g., they live at northern latitudes, have a vegan diet or dark skin). Observational studies report an association between low vitamin D levels (<10/<20 ng/ml) and muscle weakness in children or elderly[20]. *In vitro* studies have shown that the active hormone or its analogs can decrease cellular proliferation by coherently activating or inactivating a large number of genes capable of inducing this effect[21]. Animal studies have shown that vitamin D receptor (VDR) deficiency predisposes to precancerous breast or intestinal lesions[22], while observational studies in humans have highlighted the link between poor vitamin D status and the risk for almost any cancer[23,24]. A review conducted by World Health Organization (WHO) identified colon cancer as the main risk associated with vitamin D deficiency[25]. This result was supported by the results of a meta-analysis of nine control case studies[26] showing that for each increase by 4 ng/ml of serum 25(OH)D level, there is a 6% decrease in the risk of colorectal cancer. In the endocrine system, VDR can modulate most aspects of inborn or acquired immunity, both by exposure to high doses of 1,25-dihydroxivitamine and by extreme deficiency. In some studies, vitamin D deficiency in pregnancy, childhood or adolescence was associated with both the increased

and decreased incidence of allergic diseases like asthma or eczema[28,29]. Randomized trials, analyzing the effect of vitamin D supplementation on asthma, continue to be inconclusive, unable to demonstrate an improved response to corticosteroids, reduced treatment failure or improved ventilator parameters. Two trials analyzing the effect of supplementation with vitamin D during pregnancy revealed a reduction of wheezing in children, an association that did not reach the threshold of statistical significance. In one study, 623 pregnant women received 2800 or 400 IU of vitamin D starting by 24 weeks of gestation[30]. The persistence of wheezing at the age of 3 years old of the children was recorded in 16% and 20% of cases, respectively. Another randomized controlled trial, including 876 pregnant women, analyzed the outcome of 4400 or 400 IU vitamin D supplementation starting from 10-18 weeks of gestation[31]. Their 3-year-old children developed recurrent asthma or wheezing in 24.3% and 30.4% of cases, respectively. A meta-analysis published in 2015, comprising 46 interventional studies, stated that there was no benefit of vitamin D supplementation on systolic or diastolic blood pressure[32]. Another meta-analysis of 19 prospective studies (with 65,994 patients) revealed an inverse relationship between serum levels of 25(OH)D, ranging from 8 to 24 ng/ml, and the risk of cardiovascular disease[33]. The results of the studies evaluating the effect of vitamin D supplementation on the rate of myocardial infarction and stroke do not support any benefit[34]. In this meta-analysis, one of the broadest studies concluded that there was no beneficial effect of vitamin D on cardiovascular and metabolic risk following a rise in basal levels of 25(OH)D from 23 to over 40 ng/ml. In almost all human studies, obesity is associated with a reduced serum concentration of 25(OH)D[35]. A control case study of 720 children with type 1 diabetes and 2610 healthy children of the same age supports the association between type 1 diabetes and a genetic polymorphism with a key role in vitamin D deficiency and responsible for variations in serum concentrations of 25(OH)D[27]. Vitamin D status is low in individuals with obesity and type 2 diabetes, but the causal relationship of this association remains unknown. In a meta-analysis with individual data from 27,000 participants in eight European prospective studies, individuals with average serum levels in standardized measurements below 21 ng/ml (54 nmol/l) showed an increase in mortality of all causes compared to those whose serum concentration was above 30-40 ng/ml, with the maximum risk among severely deficient (less than 12 ng/ml)[36].

The optimal serum level of 25(OH) vitamin D in pregnancy is considered to be around 30 ng/L, with a minimum acceptable value of 20 ng/ml. The US Institute of Medicine (IOM) recommended in 2010 a 600 IU/day dose of vitamin D supplementation for all women of reproductive age, including during pregnancy and lactation[2]. ACOG recommended in 2011 and then in 2017 a vitamin D supplementation during pregnancy with the usual dose until a significant decrease justifies supplementing this dose[3]. Recommended Dietary Allowance (RDA) of vitamin D for children between 1 and 18 years old and for adults up to 70 years of age is 600 IU (15 mcg/day) and 800 IU (20 mcg/day) after 71 years. For pregnant and lactating women, RDA is 600 UI (15 mcg/day)[19].

According to the studies, the administration of up to 2000 IU of vitamin D in pregnancy would be safe, and it would be necessary to maintain the level of 25(OH)D above 30 ng/ml[4]. The administration of a sufficiently high dose to cover the vitamin D deficiency and to maintain a proper serum level throughout pregnancy has not been fully studied, but the administration of 600-800 IU vitamin D3/day is suggested to be adequate and safe. One of the factors that lead to vitamin D depletion during pregnancy is the increased urinary excretion, a parameter mandatory to be monitored for pregnant women at high risk for this deficiency.

Yu et al.[5] analyzed vitamin D supplementation with 800 IU/day or the single oral dose of 200,000 IU in women with pregnancy in the third trimester and vitamin D deficiency, and achieved a significant but insufficient improvement in the level of 25(OH)D. The study conducted by Dawodu[6] aimed to determine the effectiveness and safety of prenatal administration of 2000 IU/day, 4,000 IU/day and 400 IU/day of vitamin D among endemic deficient pregnant women; the onset of administration was between 12 and 16 weeks of gestation, randomized, and measurements at the end of the study showed that supplementation with 4000 IU was the most effective and safe.

Regarding the results of the meta-analyses, they attest that the number of studies is too low to standardize a conclusion on the optimal dosing time and the optimal safe and effective dose during pregnancy to supplement and prevent vitamin D deficiency. Preconceptual initiation of vitamin D supplementation has not been studied[6]. A large, prospective, long-term study (Avon Longitudinal Study of Parents and Children) involving 3,960 mother-child pairs of European origin correlated serum concentrations of 25(OH)D measured in pregnancy with the osteodensitometry results for children at the age of 9-10 years old[42]; this study demonstrates that there is no significant association between maternal vitamin D status during pregnancy and bone mineral content of the offspring in late childhood. In contrast, a smaller cohort study comprising 341 mother-child pairs associates the deficiency of vitamin D during pregnancy with low bone mass in offspring by the age of 20 years old[43]. Several observational studies suggest the association between poor vitamin status and complications of pregnancy[38-41]. As an example, a meta-analysis of 31 studies led by Aghajafari F et al., published in 2013, revealed the association between insufficient vitamin D concentration and increased

risk of gestational diabetes, preeclampsia and intrauterine growth restriction[37]; this meta-analysis lacked a dose-response relationship between serum concentrations of 25(OH)D and the reported complications, and it included studies based on laboratory methods with variable accuracy. A meta-analysis published in 2015, comprising 13 trials comparing vitamin D administration, with or without calcium, with placebo during pregnancy, revealed increased vitamin plasma levels in the supportive group in the absence of preeclampsia or gestational diabetes[44]. There were also no differences in the incidence of low birth gestation, premature birth, vitamin D determination and interventional debut being variable among the trials analyzed. Data from two trials involving 219 women suggest a similar risk of gestational diabetes among patients supplemented with vitamin D, uncompensated and placebo[46]. A meta-analysis conducted by Song Y et al. published in 2013, based on 21 prospective studies, demonstrated the existence of the inverse relationship between serum concentrations of 25(OH)D and the risk of type 2 diabetes (RR: 0.62; 95% CI; 0.54-0.70)[48]. Still, interventional studies continue to remain negative or minimally positive with regard to the beneficial effect of vitamin D on the incidence of diabetes. Data from three trials involving 477 women conclude that supplementation with vitamin D during pregnancy reduces the risk of premature birth compared to no supplementation or placebo (3.3% vs. 9.9%; RR: 0.36; 95% CI; 0.14-0.93; moderate)[47].

Three other trials involving 493 women also suggest that vitamin D supplementation during pregnancy is associated with a decrease in the birth rate of children below 2500 g compared to no supplementation or placebo (RR: 0.40; 95% CI; 0.24-0.67; moderate risk). On the contrary, concomitant supplementation with vitamin D and calcium seems to significantly reduce the risk of preeclampsia(5% vs. 9%; RR: 0.51; 95% CI; 0.32-0.80), but it certainly increases the risk of premature delivery. In 2016, De-Regil LM et al. published in *Cochrane Database Syst Rev*. the review "Vitamin D supplementation for women during pregnancy". The 15 trials included 2,833 women, with the majority having multiple confounding factors present. The integrated outcome of these studies asserts the normalization of serum levels of 25(OH)D under continuous daily and non-supplemental calcium supplementation and reduction of preeclampsia risk (without achieving statistical significance) compared to uncompensated or placebo (8.9% vs. 15.5%; RR: 0.52; 95% CI; 0.25-1.05; low quality)[45]. The Cochrane review concludes with a cautionary recommendation to review these results, given the absence of adverse reactions from all studies included, and the need to carry out rigorous trials confirming these effects for the purpose of administering vitamin D to the antenatal routine and to improve maternal and fetal prognosis.

Discussion and conclusions

A sufficient level of vitamin D during pregnancy ensures an optimal level of vitamin D in the fetus, a fact reflected by a normal bone status at birth due to the passage of the placental barrier by vitamin D and the formation of fetal reserves especially during the third trimester. A low level of vitamin D during pregnancy seems to increase the risk of preeclampsia, intrauterine growth restriction and gestational diabetes, and in the longer term it seems to affect the bone, immune system and general status. However, an optimal dose level during pregnancy has not been established.

The obstetrical impact of vitamin D supplementation has been poorly studied; in 2014, a systematic review of vitamin D supplementation studies during pregnancy concluded that the number of studies was too low and the overall quality of the data was too weak to draw conclusions about safety and efficacy of vitamin D supplements and their protective role in pregnancy prognosis. In this context, there is little data on the appropriate time to supplement vitamin D during pregnancy. Most studies in this direction propose the onset of supplementation by the end of the first trimester of pregnancy, while the initiation of this supplementation and its impact before pregnancy were not evaluated.

In addition, further studies are needed to confirm the safety and efficacy of high-dose vitamin D supplementation in pregnant women with severe vitamin D deficiency.

Currently, most prenatal vitamins contain 400 IU of vitamin D, but this dose is still considered to be insufficient, especially in patients who already have a low vitamin D at onset of pregnancy.

The prevalence of hypovitaminosis D is increasing globally, and the effects on pregnancy and neonatal outcome of the vitamin D deficiency and supplementation are a topical issue, which is currently under investigation. Vitamin D deficiency is significantly present in pregnancy among infertile patients, with a prevalence in Romania two times higher than that of the United States. Subsequent studies are needed to determine the optimal dose for diet supplementation in women of fertile age. Future trials should determine the optimal serum level of vitamin D in pregnancy and how the supplementation achieved particularly early in pregnancy manages to influence or not maternal and fetal prognosis. Also, more data are needed to confirm the safety and efficacy of high vitamin D supplementation in severely debilitated women.

With new clinical research results, we propose the determination of vitamin D in all pregnant and infertile women and also the correction of the deficiency with at least 1000 IU per day. ■

Conflict of interests: The authors declare no conflict of interests.

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