VITAMIN D DEFICIENCY DURING PREGNANCY

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ABSTRACT

Vitamin D plays a crucial role during pregnancy. Its active form calcitriol is of utmost importance for placental physiology, for the synthesis of estradiol, progesterone, human chorionic gonadotropin, embryogenesis, and normal progression of pregnancy. Taking in mind the beneficial role of calcitriol on pregnancy, it could be supposed that its inadequacy may lead to deleterious consequences for the mother and fetus. Several studies reveal a correlation between low vitamin D levels during pregnancy and the development of unfavorable consequences for the mother as well as for the fetus: risk of preterm birth, preeclampsia, gestational diabetes mellitus, low birth weight, and postpartum complications.

Evaluation of vitamin D status during pregnancy is of utmost importance to overcome the adverse outcomes for the mother and newborn. To achieve maximum protection from pregnancy complications, a serum levels of at least 40 ng/mL for the circulating 25-hydroxy vitamin D3 during the earliest time points of pregnancy are recommended.

Control of vitamin D status during pregnancy would present an opportunity for initiating timely and thorough supplementation with harmless and inexpensive vitamin D pharmaceuticals, which in turn would decrease the risk of adverse pregnancy outcomes.

Keywords: *vitamin D, calcitriol, deficiency, pregnancy, outcomes*

INTRODUCTION

In the last two decades, increased attention is being given to vitamin D deficiency, which is ubiquitous and widespread, in connection to lifestyle-changing and dietary habits. Vitamin D deficiency is linked to a number of health problems. The classical concept concerning the role of vitamin D is focused mainly on musculoskeletal and mineral bone health. After the discovery that vitamin D receptor (VDR) and 1-alfa hydroxylase are expressed in numerous extrarenal tissues, the biologic role of vitamin D was expanded to its pleiotropic effects on various tissues. A number of studies show that aside from its role in bone health, vitamin D also has protective role against various infectious, autoimmune, malignant and cardiovascular diseases.

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AIM

The aim of the present review is to summarize and critically analyze the recent findings on the influence of vitamin D deficiency during pregnancy on maternal and newborn health.

Vitamin D Metabolism and Status

The two natural forms of vitamin D—vitamin D3 (cholecalciferol) and vitamin D2 (ergocal-

ciferol) are lipid soluble compounds. In the human body both cholecalciferol and ergocalciferol can be provided by the food and only cholecalciferol is produced endogenously in the skin after UVB irradiation. Few foods are a good source of vitamin D3 and the traditional European diet does not provide sufficient quantities for the organism. Additional factors of the contemporary way of living such as a sedentary lifestyle, environmental pollution and irrational eating contribute to the global spread of vitamin D deficiency or insufficiency. Both forms of vitamin D are metabolized to 25-hydroxy vitamin D (calcidiol) and 1,25-dihydroxy vitamin D (calcitriol).

Calcidiol is synthesized in the liver by the action of the enzyme 25-hydroxylase and is the circulating form of vitamin D3 in the blood. The active form of vitamin D3 is the hormone calcitriol, synthesized primarily in the kidneys through the action of 1-alpha-hydroxylase. After exerting its effect on the target tissues, calcitriol is degraded by the enzyme 24-hydroxylase.

The main metabolically active form is calcitriol acting by endocrine and autocrine manner. The biological effects of calcitriol are mediated through a specific VDR receptor, which is expressed in almost every cell type.

A good indicator for the vitamin D status in the body is the circulating form 25-hydroxy vitamin D3 (25(OH)D3) for its long plasma half-life. There is no consensus on the 25(OH)D3 cut-off determining vitamin D deficiency or insufficiency. Serum levels below 25 nmol/L are defined as severe vitamin D deficiency, linked to bone disease. 25(OH)D3 levels between 25 and 50 nmol/L are related to vitamin D deficiency, without any effect on the bones. Plasma levels between 50 and 80 nmol/L are considered as vitamin D insufficiency; values above 80 nmol/L, referred to as saturation or sufficiency, are required for maintaining the pleiotropic effects of the vitamin D (1,2,3). Most experts agree that 25(OH)D3 values <50 nmol/L are suboptimal for a healthy lifestyle and that the optimal concentration of 25(OH)D3 is in the range of 75–100 nmol/L.

Vitamin D and Pregnancy

Vitamin D deficiency in pregnancy is widespread on a global scale. Sufficient data exist on vitamin D deficiency in women due to limited sun exposure, lack of outdoor activity or decreased dietary intake of vitamin D. There are controversial data regarding vitamin D supplementation during pregnancy. Some guidelines recommend vitamin D supplementation with 1500–2000 IU/day from the beginning of the second trimester of pregnancy in women with vitamin D insufficiency (25(OH)D3 plasma levels <75 nmol/L) (4). Alternatively, according to World Health Organization guidelines oral vitamin D supplementation is not recommended for all pregnant women (5).

Several studies reveal a correlation between low vitamin D levels during pregnancy and the development of unfavorable consequences for the mother as well as for the fetus: risk of preterm birth, preeclampsia, gestational diabetes mellitus, low birth weight and postpartum complications (6,7). During pregnancy the regulatory enzyme of vitamin D metabolism, 1-alfa hydroxylase, is expressed by the decidua and placenta. Interesting to note is the fact that calcitriol produced by maternal tissues cannot cross the placenta and is inaccessible to the fetus, but maternal 25(OH)D3 crosses the placenta and is a primary source of calcitriol for the fetus (6,8,9). There are data revealing that by the end of the third trimester of pregnancy the maternal calcitriol levels double. This observation can be explained not only by the action of the renal 1-alpha-hydroxylase but also by the increasing expression of the placental isoform stimulated by prolactin and placental lactogen (10).

Other factors contributing to the elevated levels of calcitriol in the maternal blood during pregnancy are related to decreased degradation of 1,25OHD by placenta-specific methylation of 24-hydroxylase gene (11) and to 1-alfa hydroxylase induction by elevated calcitonin under normocalcemic conditions (12).

Vitamin D plays an important role in embryogenesis during pregnancy (13). Calcitriol is of utmost importance for placental physiology due to its stimulatory effect on endometrial decidualization and placental hormone genesis-synthesis of estradiol, progesterone, human chorionic gonadotropin and human placental lactogen (10). Calcitriol takes part in the immunological processes and plays an important role in the modulation of the bacterial infection by suppression of the synthesis of proinflammatory factors (IL-6, TNF-alpha and IFN-gamma) stimulating

the release of antimicrobial cathelicidins from the placenta (10). The immune modulating function of vitamin D is of great importance for the normal progression of pregnancy. Taking in mind the beneficial role of calcitriol on pregnancy, it can be supposed that its inadequacy may lead to deleterious consequences for the mother and fetus.

Recommendable Vitamin D Levels During Pregnancy

Data from observational and interventional studies reveal that a concentration of at least 40 ng/mL 25(OH)D3 will ensure maximum protection from pregnancy complications, including adverse outcomes for mother and newborn. It is still a matter of debate the vitamin D dosage for supplementation and the initial start point to achieve the recommendable 25(OH)D3 serum levels (14).

Vitamin D Deficiency and Its Adverse Outcomes During Pregnancy

Preeclampsia

A series of studies have determined a significant connection between low 25(OH)D3 levels and the elevated risk of preeclampsia during pregnancy. Pregnant women between the 15th and 20th gestational week (g.w.) with proved vitamin D3 deficiency (45.4 nmol/L) have developed severe preeclampsia (6,15,16,17). Preeclampsia is defined as a newly diagnosed hypertension (systolic blood pressure >140mmHg, diastolic blood pressure >90 mmHg) after the 20th gestational week in combination with proteinuria (>300 mg/day) and dysfunction of other organs including liver involvement, hematological disorders, neurological or renal complications (18). The protective role of vitamin D3 in preeclampsia can be explained by several mechanisms. One of them is the immune modulating role of calcitriol in regulating the immune response. Vitamin D aids in maintaining the immune homeostasis and prevents placental vasoconstriction and ultimately preeclampsia (19). It regulates the proliferation of endothelial and vascular smooth muscle cells and thus plays an important role in regulating blood pressure through the renin-angiotensin-aldosterone system (RAAS) (19). Calcitriol also preventions cholesterol absorption by macrophages and vascular smooth muscle cells in arterial walls, a phenomenon observed in uterine-placental vessels of patients with preeclampsia (19). A possible explanation of the protective effect of vitamin D3 against preeclampsia is its stimulatory role regarding the synthesis of IL-10 by decidual cells. This leads to a decreased Th response, increased production of Treg Th2 cells and promoted immune tolerance of the mother to the fetus. Furthermore, IL-10 plays a role in placental angiogenesis, growth and remodeling (20,21). Despite all these assertions, other studies exist that have not determined a causal link between vitamin D supplementation and preeclampsia improvement or prophylaxis. Several observational studies have been conducted for researching the link between vitamin D deficiency and development of preeclampsia, but the conclusions are contradictory or without causative relations (6,22,23).

Preterm Birth

Vitamin D deficiency and the immune function suppression related to it can impact the pathophysiology of preterm birth (earlier than 35th g.w.) and can be a cause for its development. Results from recent studies are contradictory. Baker et al. (2011) compared the levels of 25(OH)D3 in ethnically mixed groups of women who gave full-term birth with women who gave birth between the 23rd and 35th g.w. (24), and found no differences in their 25(OH)D3 levels. Others have determined a proportional correlation between maternal 25(OH)D3 levels and the probability of preterm birth. Bodnar et al. (2014) determined that 49.4% of preterm births occurred in women with 25(OH)D3 levels <75 nmol/L. Other studies on women with 25(OH)D3 levels over 100 nmol/L showed a 60% decreased risk of preterm birth (13,25). This promising evidence from recent interventional studies needs confirmation in upcoming randomized controlled trials. Addition of vitamin D as a supplement could be recommended to decrease the risk of preterm birth.

Bacterial Vaginosis

Vitamin D deficiency in pregnant women is linked to the possibility of more frequent bacterial vaginosis. A reason for this could be the decreased capability for producing antibacterial proteins, which play a role in non-specific immune protection (6), because vitamin D induces the expression of these proteins and increases the destruction of bacteria in var-

ious tissues. An American study involving pregnant women of mixed ethnicity established significantly decreased 25(OH)D3 concentrations in patients with bacterial vaginosis (26). Nevertheless, two randomized studies found no positive effect of addition of vitamin D in preventing bacterial vaginosis or its recurrence during pregnancy (27,28).

Labor

Vitamin D3 deficiency is also considered to be responsible for the decreased tone and strength of pelvic musculature contractions, which in turn causes prolonged labor, impossibility for normal childbirth and recourse to Cesarean section (29). This question is debatable because some studies show a significantly increased risk of Cesarean section in pregnant women with 25(OH)D3 levels <37.5 nmol/L (30) or 25(OH)D3 levels <30 nmol/L (29), while others do not establish such a correlation (31). Currently vitamin D3 supplementation of pregnant women for decreasing the frequency of Cesarean section is not recommended (32).

Insulin Resistance and Gestational Diabetes

Normal pregnancy is associated with changes in food intake, body mass, energy expenditure and insulin resistance. Pregnancy is characterized with varying degrees of progressing insulin resistance. The homeostatic model assessment for insulin resistance (HOMA-IR) is a simple and non-invasive method using fasting plasma glucose and serum insulin (33). Adiponectin and leptin are adipokines, which are proven to be related to insulin resistance (34). Adiponectin exerts insulin-sensitizing, anti-inflammatory and anti-atherogenic properties (35). Leptin plays an important role in glucose metabolism and acts as a metabolic and neuroendocrine hormone (36). Decreased adiponectin and increased leptin concentrations are related to insulin resistance (37). Several studies report associations between the ratio adiponectin/leptin and conditions with increased insulin resistance—obesity, type 2 diabetes mellitus, polycystic ovary syndrome, metabolic syndrome, and pregnancy (38). Skvarca et al. (2013) determined that the adiponectin/leptin ratio correlates inversely with the pre-pregnancy body mass index (BMI) and with the HOMA-IR during pregnancy.

An unfavorable complication in pregnant women associated with insulin resistance is the development of gestational diabetes mellitus (GDM). Gestational diabetes mellitus is defined as a glucose intolerance, first diagnosed during pregnancy. The frequency of this type of diabetes in Europe is 2–6% (39) and around 14% in the USA (40). A large number of studies show a consistent and strong correlation between vitamin D deficiency and the risk of GDM.

The regulatory role of calcitriol in glucose metabolism is thoroughly studied—it takes place in insulin production and secretion, protects pancreatic beta cells against immune attack (41), and improves the insulin sensitivity of adipose, muscle, and liver tissue (42). Different research groups have examined the relationship between 25(OH)D3 deficiency and the incidence of GDM. Some observational studies revealed an increased risk of GDM in pregnant women with decreased 25(OH)D3 levels (43–50), while others did not found such relationship (51,52,53,54). Most likely 25(OH)D3 levels influence the development of GDM in the beginning of pregnancy, as it is most frequently diagnosed during second and third trimester of pregnancy (55). Women with GDM are generally older, with a family history of diabetes mellitus or hypertension and with a higher BMI (before pregnancy and during 18–22 gestational week). Women who are both vitamin D deficient and overweight reveal statistically higher risk of developing GDM in comparison to those who have sufficient 25(OH)D3 levels and are with normal weight (56). An increase in 25(OH)D3 levels by 5 ng/mL is associated with lowering the risk of GDM by 14% (45,50). It could be assumed that 25(OH)D3 deficiency is an important factor contributing to the increased risk of GDM. The effect of vitamin D supplementation during pregnancy on the frequency of GDM and on the development of impaired glucose tolerance is thoroughly studied (57,58,59). Vitamin D supplementation during pregnancy may have a beneficial effect due to its safety and proven potential for decreasing GDM frequency (6).

Miscarriages

Frequent miscarriages are a severe and unwanted outcome of pregnancy. A possible reason may be the dysregulation of immune function and the altered immune response. It has been found that calcitriol inhibits the Th1-cell response, the production of IFN-gamma, IL-2 and TNF-alpha, and stimulates

Th2-cell proliferation and release of IL-4, 5, 6, 9 and 13 (60). It is hypothesized that calcitriol considerably impacts the immune regulation during the implantation period. This hypothesis is supported by a study on pregnant women who have had three or more abortions before the 20th gestational week. 25(OH)D3 levels <30 ng/mL (<75 nmol/L) were encountered in 47.4% of cases. In the studied cohort 25(OH)D3 deficiency was accompanied by a significant increase in different types of autoantibodies—antiphospholipid, antinuclear (ANA), anti-single-stranded-DNA (anti-ssDNA), and thyroid-specific-peroxidase (anti-TPO) antibodies (13).

Postpartum Depression

Another unwanted complication of pregnancy is the postpartum depression, one of the most frequent psychological conditions in the postpartum period (61). As a neurosteroid vitamin D takes place in the regulation of numerous brain processes related to the pathophysiology of depression. It may be hypothesized that 25(OH)D3 deficiency contributes to the development of depressive conditions (62). Several mechanisms link vitamin D deficiency to postpartum depression—neurotransmission, neuroprotection, and neuromodulation (63). In addition, low vitamin D levels suppress the degradation of catecholamines by catechol-O-methyl-transferase (COMT) in forebrain and contributes to the reduction of homovanillic acid levels associated with poor working memory in schizophrenia. Vitamin D maintains the levels of the antioxidant glutathione in the brain and thus, contributes to neuroprotection from oxidative stress. Moreover, VDR are expressed in the brain areas responsible for the processes involved in action planning and decision making. (64). A prospective cohort study determined an increased risk of postpartum depression in women with 25(OH)D3 levels <10.2 ng/mL (25.5 nmol/L) (63). A significant negative correlation between 25(OH)D3 levels and postpartum depression has been also established by others (65). In contrast, there are studies which do not confirm the relationship between low vitamin D and depression (66,67).

Fetal Growth and Calcium Homeostasis

Vitamin D plays an important role in fetal growth by regulating calcium homeostasis and parathyroid hormone levels (1). Several studies found a positive correlation between maternal 25(OH)D3 serum levels in the course of pregnancy and the weight of the newborn at birth (68). Zhu's study (2015) determined that for every 10 nmol/mL of 25(OH)D3 in the umbilical cord the weight of the newborn increased by 61 grams. Other studies did not establish such correlation (69, 70). Since vitamin D plays a fundamental role in bone remodeling, calcium homeostasis and skeletal muscle function, its deficiency during pregnancy is linked to impaired bone development, fetal growth and other deleterious effects on the musculoskeletal system of the offspring (71). Adverse effects from a decreased maternal 25(OH)D3 are also found in the anthropometric measurements of the children. In a study of Morales et al (2015) serum 25(OH)D3, the femoral bone length, the biparietal diameter, and the abdominal circumference of the fetus were measured at the 12th, 20th and 34th g.w. A negative correlation was found only for maternal 25(OH)D3 serum levels and fetal biparietal diameter at the 34th g.w. A study conducted in India (72) reported that women on vitamin D supplementation had offspring with higher weight and corona-heel length at birth compared to the offspring of pregnant women without supplementation. Other authors also confirmed the positive effects of vitamin D supplementation during pregnancy on the anthropometric indicators of newborns (head circumference, weight and body length) (73,74).

Respiratory Infections in Newborns

Vitamin D deficiency is also linked to frequent respiratory infections in newborns (75). Vitamin D receptors (VDR) are present in almost all immune cells and their activation plays a crucial role in both the adaptive and innate immunity, together with the regulation of the inflammatory response (76). There are numerous mechanisms through which vitamin D can regulate the inflammatory response—by inducing the expression of antimicrobial peptides such as cathelicidin and beta-defensin playing a vital role in innate immunity, by inhibiting dendrite cell maturation and IL-12 and IL-23 production, and by regulating macrophages activity (76). Calcidiol levels <30 nmol/L are linked to increased frequency and severity of respiratory infections in newborns (75,77). A study involving preterm newborns established a positive correlation between decreased serum 25(OH) D3 levels and increased oxygen needs, duration of

intermittent positive pressure ventilation and necessity of assisted ventilation (75). A statistically significant link between umbilical cord 25(OH)D3 levels and susceptibility to lower respiratory tract infections in newborns was also established (77). Vitamin D deficiency may also be linked to more frequent allergic and asthmatic conditions in newborns and infants. A study on the association between vitamin D levels of mothers with a history of atopy and the immune response of their offspring found that higher maternal 25(OH)D3 serum levels are related to lower risk of developing allergies in their newborns (78,79).

A number of factors play a role in the pathogenesis of autism in children—impaired immune function, oxidative stress, and disbalance of biogenic amines (80). Vitamin D deficiency could change the activation profile of T-cells and thus could influence the adaptive immunity leading to autistic disorders (81). Moreover, vitamin D could prevent the development of autism by increasing the cellular levels of glutathione. It is well known that glutathione is one of the main cellular antioxidants and its increased levels inhibit the generation of different reactive oxygen and nitrogen species and their neurotoxic effect on the brain. (82). Serotonin plays a significant role in emotional control. In patients with autism reduced serotonin concentrations in the brain and elevated blood levels were established. Vitamin D activates serotonin synthesis in the brain and suppresses it in peripheral tissues (83). It can be concluded that keeping optimal 25(OH)D3 levels may have beneficial effect on brain development and prevention of autistic disorders (80).

CONCLUSION

Sufficient research revealed that vitamin D insufficiency is widespread not only in the general population but also in pregnant women. Vitamin D insufficiency/deficiency during pregnancy is related to various adverse complications for both the mother (miscarriages, bacterial vaginosis, preeclampsia, gestational diabetes mellitus, and postpartum depression) and for the newborn (preterm birth, small for gestational age, susceptibility to respiratory infections, allergic and asthmatic conditions later on). Detection of early-onset and mild vitamin D deficiencies would present an opportunity for initiating timely and thorough supplementation with harmless and inexpensive vitamin D pharmaceuticals, which in turn would decrease the risk of adverse pregnancy outcomes.

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