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REVIEW ARTICLE

CURRENT VIEW OF VITAMIN D IN PREGNANT WOMEN: A REVIEW

VISÃO ATUAL DA VITAMINA D EM GESTANTES: UMA REVISÃO

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ABSTRACT

Hypovitaminosis D is a global health problem that affects all age groups. Pregnant women are considered a high-risk group and the condition has potentially associated maternal and fetal complications. The goal of the present review is to analyze the magnitude and consequences of hypovitaminosis D in pregnant women and the safety of vitamin D supplementation. Prevalence of hypovitaminosis D during pregnancy is very high, even in sunny countries. Maternal vitamin D deficiency has been associated with increased risk of specific hypertensive disease of pregnancy, bacterial vaginosis, prematurity, gestational diabetes mellitus, osteomalacia, and muscle weakness. It has also been linked to prematurity, low birth weight, and fetal infectious complications.

Due to potential maternal and fetal complications, it is extremely important to achieve adequate vitamin D levels prior to pregnancy. During pregnancy, it would be prudent to monitor serum vitamin D levels and implement preventive measures to reduce maternal and fetal morbidity. No consensus exists in the medical literature regarding vitamin D supplementation in pregnant women.

Keywords: deficiency; pregnancy; insufficiency; vitamin D

RESUMO

A hipovitaminose D é um problema de saúde universal que atinge todas faixas etárias. As gestantes constituem um grupo de alto risco, com possíveis complicações materno-fetais. Esta revisão visa avaliar a magnitude e consequências da hipovitaminose D na gestação e a segurança da suplementação de vitamina D. Os resultados obtidos sugerem que a prevalência de hipovitaminose D na gestação é muito elevada, mesmo em países com elevada disponibilidade de sol. Potenciais complicações maternas da hipovitaminose D incluem aumento do risco de doença hipertensiva específica da gravidez, diabetes gestacional, vaginose bacteriana, osteomalacia e fraqueza muscular. A condição associa-se ainda a prematuridade, baixo peso ao nascimento e complicações infecciosas no feto. Devido às potenciais complicações materno-fetais associadas à hipovitaminose D, é extremamente importante atingir níveis adequados de vitamina D na fase pré-gestacional. Durante a gestação, seria prudente monitorizar os níveis séricos de vitamina D e adotar medidas preventivas para reduzir a morbilidade materno-fetal. Não há consenso na literatura médica sobre suplementação de vitamina D durante a gestação.

Palavras-chave: deficiência; gestação; insuficiência; vitamina D

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INTRODUCTION

Hypovitaminosis D is a significant health problem, which affects individuals of all ages.[1] Several groups are at increased risk, such as pregnant women, who have a reported 20–40% prevalence of hypovitaminosis D.[1] Vitamin D (Vit. D) is one of the most extensively studied molecules in the human body. Its action on skeletal health, preventing growth retardation, osteopenia, osteoporosis and increasing fracture risk is well documented.[2] Several other non-skeletal actions have been further assigned to this vitamin, and its deficiency has been linked to development of infectious, autoimmune, and even neoplastic diseases.[2] A growing interest in Vit. D deficiency during pregnancy and its repercussions in maternal and fetal health has recently emerged. Herein, some of the main aspects of hypovitaminosis D in pregnant women are reviewed.

A-VIT.D METABOLISM

Vit. D is a fat-soluble substance, endogenously produced in the skin upon sun exposure.[3] Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, inducing its transformation to pre-vitamin D3, which is rapidly transformed to vitamin D3.[3] Cutaneous Vit. D production is influenced by skin pigmentation, sunscreen use, aging, season, latitude, time of day, air pollution, obesity, and protection with glass during sun exposure.[3] This vitamin is also naturally found in some foods, such as fish liver oil, fatty fish, mushrooms, egg yolk, and liver.[2] Once formed, the metabolically inactive vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 (25 [OH] D), or calcidiol, which is the form of Vit. D usually measured in biochemical assays.[3] As production of this molecule in the liver is fast and undergoes little regulation, plasma levels reflect Vit. D stores in the body. To become active, 25-hidroxyvitamin D3 requires one additional hydroxylation occurring in the kidneys under the action of 1-alpha-hydroxylase, hence becoming 1,25-dihydroxyvitamin D (1,25-[OH]2-Vit.D), or calcitriol. This is the most biologically active form of Vit. D.[2,3]

Parathyroid hormone (PTH) and phosphate serum levels regulate the process of calcitriol formation in the kidneys. Calcitriol is considered an important pre-hormone, with active metabolites responsible for bone integrity and calcium homeostasis.[4] The main sites of Vit. D action are the skin, bowel, bones, parathyroid glands, pancreas, small intestine, and human fetal colon[5] Vit. D helps to maintain normal blood glucose levels by binding and activating Vit. D receptor in pancreatic beta-cells and regulating insulin release in response to glucose levels.[6-9]

A unique association exists between Vit. D and calcium. PTH is responsible for increasing calcium concentrations in blood through bone resorption. Calcitriol inhibits PTH, increasing calcium concentrations from sources other than bone, namely through increased absorption and reduced renal excretion.[4]

Vit. D metabolism in pregnant women has some peculiarities, since the mother must supply the fetus' calcium requirements. Levels of calcitriol (1-25 [OH]2 Vit. D) raise early in pregnancy when compared to pre-pregnancy values, reach maximum values in the third trimester, and return to normal in the puerperium.[10] Vit. D carrier also raises in pregnancy, but there is some controversy as to whether calcidiol (25[OH] Vit.D) levels raise during gestational period.[10]

Calcidiol is able to cross the placenta and reach fetal circulation, but little is known about 1,25[OH]2 Vit. D in this setting.[10]

B- VIT.D SERUM LEVELS AND EPIDEMIOLOGY OF HYPOVITAMINOSIS D IN PREGNANCY

Following Endocrine Society criteria, most authors have accepted the following Vit. D reference values: sufficiency ≥30 ng/mL or ≥75 nmol/L; insufficiency 20 to <30 ng/mL or 50 to <75 ng/mL; and deficiency <20 ng/mL or <50 nmol/L.[11]

Approximately one billion individuals are estimated to have Vit. D deficiency or insufficiency worldwide, and this number seems to be globally increasing.[12] A recent review found a high prevalence of hypovitaminosis D in infants, children, adolescents, adults, and older adults, even in sunny countries throughout the year.[13] The highest prevalence was found in the Middle East, particularly in girls and women, due to sociocultural factors such as excessive clothing.[13] There is a lack of data from most South American and African countries.

Prevalence of hypovitaminosis D in the pregnant population varies according to geographical area. A large review by Mulligan *et al* reported values of 18–84% depending on the country of residence and local customs.[1] A recent review included seventeen studies (two in America, six in Europe, one in Africa, seven in Asia, and one in Oceania) that assessed pregnant and breastfeeding women.[13] In this study, Vit. D insufficiency (defined as concentrations <30 ng/mL) was found in 33% of pregnant women in the United States, 24% in Canada, 45% in Belgium, 35% in the United Kingdom, 44% in the Netherlands, 20% in Spain, and 77% in Germany. In addition, prevalence of Vit. D deficiency (defined as <20 ng/mL) was 12% in Belgium, 4% in England, and 23% in the Netherlands. The only study conducted in Africa reported a very low hypovitaminosis D prevalence (1%). In Asia, Vit. D insufficiency in pregnant women was as high as 90% in Turkey, 67% in Iran, 72% in Pakistan, 70–83% in Kuwait, 96% in India, and 69% in China. Vit. D deficiency had a prevalence of 50% in Turkey,

45% in Pakistan, 38–41% in Kuwait, and 60% in India. In Australia, Vit. D insufficiency and deficiency in pregnant women is 48 and 15%, respectively.[13]

Seasonal variation increases the risk of hypovitaminosis D in pregnant women, with higher prevalence of this deficiency during winter months compared to summer months.[14,15] Latitude differences also influence Vit. D concentrations in most pregnant women.[16] In Brazil, a study in 520 pregnant women from the South region showed that only 20% had normal Vit. D levels, and vitamin deficiency was more pronounced in winter and in high-risk populations.[17]

C-MATERNAL CONSEQUENCES OF VIT. D DEFICIENCY

Maternal Vit. D deficiency during pregnancy has been associated with increased risk of specific hypertensive disease of pregnancy (SHDP), bacterial vaginosis, prematurity, gestational diabetes mellitus, osteomalacia, and muscle weakness in the mother.[18-20]

C.1- Specific hypertensive disease of pregnancy

A recent meta-analysis including eight studies found a significant association between Vit. D deficiency and risk of SHDP, a condition associated with increased maternal, fetal, and perinatal morbidity and mortality.[2,21-25] It is believed that low levels of urinary calcium (hypocalciuria) in women with SHDP may be caused by decreased intestinal calcium absorption, secondary to low Vit. D levels.[26,27] In addition, SHDP and Vit. D deficiency are directly and indirectly associated with biological mechanisms associated with immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, and hypertension.[22]

C.2- Diabetes mellitus

Maternal Vit. D deficiency at the beginning of pregnancy has also been associated with increased risk of gestational diabetes mellitus (GDM).[28,29] This increased risk of GDM increases by 49% in women with low Vit. D, according to a recent meta-analysis of 31 observational studies.[30]

Similar results were found in another meta-analysis including 24 observational studies.[31] Zhang *et al* reported that inadequate control of maternal diabetes at the beginning of pregnancy was associated with maternal hypovitaminosis D and low bone mineral content in newborns.[29] A randomized, double-blind, placebo-controlled trial by Shahgheibi *et al* including 90 pregnant women showed that supplementation with 5000 units of vitamin D daily during the first and second trimesters of pregnancy was effective in reducing GDM risk and controlling glucose tolerance and challenge tests.[32]

C.3-Bacterial vaginosis

Bacterial vaginosis develops as the result of a reduction in vaginal lactobacilli and overgrowth of anaerobic microorganisms, and affects almost one in every three women worldwide.[33] It is a very important determinant of women's health, as it is associated with increased HIV transmission, spontaneous abortion, premature delivery, and other reproductive morbidities.[34-37] Teens with 25(OH) Vit. D concentrations <30 ng/mL are more likely to test positive for candida and bacterial vaginosis during pregnancy, according to Akoh *et al*.[38] However, studies in this area are contradictory.[38,39]

The possible association of Vit. D with infections is supported by the fact that innate immunity cells, as macrophages, have Vit. D receptors (VDRs).40 In vitro, Vit. D has been shown to modulate levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and to induce expression of cathelicidin, an endogenous antimicrobial peptide effective against several microorganisms.[40,41]

C.4- Osteomalacia and weakness

As previously mentioned, the main function of Vit. D is to regulate bone mineral physiology. In addition to stimulating duodenal calcium absorption and renal calcium reabsorption, Vit. D regulates phosphatemia and phosphaturia, thus promoting an ideal medium for proper bone mineralization.[42,43]

Persistently low levels of vitamin D may lead to a mineralization defect (osteomalacia) and a compensatory PTH increase (secondary hyperparathyroidism).[44] In patients with osteomalacia, the osteocyte overestimates mechanical loads and the trabecular volume increases, due to increased strain in cortical undermineralized bone that, on the other hand, goes with a low volume. In other words, osteomalacia is associated with reduced cortical versus trabecular volume bone mass.[44] A Saudi Arabian study examined the relationship between spine and femur bone mineral density and Vit. D status, pregnancy, and lactation and found that the number of pregnancies and total lactation duration correlated with weight-matched Z scores of the bone mass density at spine.[45]

Severe symmetrical musculoskeletal pain in the lower back and lower extremities and muscular weakness are associated with osteomalacia.[44] Additionally, VDRs are present on skeletal muscle fibers, and genetic variations in these receptors have been shown to correlate with muscle strength.[44] A Swedish study found that musculoskeletal pain in pregnant women could be associated with hypovitaminosis D.[46]

D-VITAMIN D AND PREMATURITY, LOW BIRTH WEIGHT, AND NEONATAL COMPLICATIONS

Fetuses are fully dependent on the mother as a source of vitamin D.[47] Plasma levels of 25-hydroxyvitamin D (25[OH] Vit. D) in the newborn average 60–70% of the mother's.[47] Studies have shown that low maternal 25(OH) Vit. D levels are linked to reduced birth weight and that Vit. D deficiency is associated with a higher risk of small-for-gestational-age neonates.[18,47,48]

Reduced intrauterine long bone growth, poor skeletal mineralization, and lower bone mineral content occur in children of Vit. D-deficient mothers.[31] A recent meta-analysis of 24 observational studies confirmed the association between low Vit. D levels (<30 ng/mL) and increased risk of premature birth.[31] In addition, two other meta-analyses found a significant association between low Vit. D levels and small-for-gestational-age infants.[31,48] A large multi-ethnic cohort in the Netherlands that studied 3730 relatively healthy women with Vit. D measurements in early pregnancy found that deficient Vit. D levels resulted in a 2.4 (95% CI 1.9–3.2) odds ratio (OR) for small-for-gestational-age babies.[49] A recent Cochrane review which investigated infant outcomes highlighted that Vit. D supplementation without calcium decreases rates of preterm birth and birthweight below 2500 g.[50]

The mechanisms of reduced fetal growth associated with hypovitaminosis D are not completely understood. One possible explanation states that low calcium levels in the cord blood, as a consequence of maternal abnormal calcium metabolism, results in low birth length.[49] Other explanation proposes that Vit. D affects glucose metabolism, which in turn influences fetal mass.[49] A third possible explanation suggests that calcitriol may control human chorionic gonadotropin and sex steroid secretion.[49,51,52]

Intrauterine growth restriction is associated with perinatal morbidity and mortality.[49] Some observations suggest that these children are at risk of coronary heart disease and related disorders in adulthood.[53]

Other childhood complications possibly associated with Vit. D deficiency in pregnancy include respiratory tract infections, type 1 diabetes, and central nervous system and psychiatric disorders. However, these observations are contradictory and require further evidence support.[54-57]

E- VIT D SUPPLEMENTATION DURING PREGNANCY

Some health organizations recommend Vit. D supplementation during pregnancy.[58,59] The American Academy of Pediatrics suggests that health professionals should monitor serum Vit. D concentrations during pregnancy. However, there are controversies regarding ideal levels. The National Academy of Medicine of the United States considers 20 ng/mL as the adequate level. Although most researchers believe that optimal levels are ≥30 ng/mL, they suggest supplementation between 1.000 and 1.600 IU/day.[60]

The required Vit. D dose to prevent or treat Vit. D deficiency has not been established yet. Some researchers suggest 1.000 IU/day and others 5.000 IU/week, or a single dose of 200.000 IU.61-63 The Brazilian Society of Endocrinology and Metabolism recommends daily oral Vit. D supplementation. The recommended doses are 600 IU/day for the general pregnant population, 600 to 1.000 IU/day for pregnant women at risk aged between 14 and 18 years, and 1.500 to 2.000 IU/day for pregnant women at risk aged over 18 years.[64] In addition, weekly or monthly supplementation should be avoided.[64]

Vit. D intoxication is a rare event. Toxicity in adults occurs in those receiving doses that exceed 10.000 IU/day for an extended period of time, or single doses of 300.000 IU or more, achieving serum 25 (OH) D concentrations greater than 150 ng/mL or 200 ng/mL.[65-67] The most important reported side effect is hypercalcemia, which suggests intoxication when observed in the laboratory.[68]

Studies in animals have suggested potential teratogenic effects induced by Vit. D, such as ossification delay and craniofacial hypoplasia.[69-72] However, assessment of these results in humans has limitations. In general, studies show that no fetal complications should arise with normal maternal Vit. D levels.[65]

CONCLUSION

There is no consensus on Vit. D supplementation or optimal administration doses during pregnancy.

In Brazil, assessment of serum Vit. D concentrations is not part of routine prenatal tests, due to cost-benefit issues. However, in regions with high prevalence of hypovitaminosis D in the general population, it would be prudent to carry out Vit. D supplementation in pregnant women. Guidelines regarding sun exposure and adequate nutrition should be emphasized and, if necessary, pregnant women should receive the required minimum dose, in order to prevent hypovitaminosis D and avoid possible diseases affecting the maternal-fetal dyad.

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