



Revisión

Relationship between vitamin D deficiency and both gestational and postpartum depression

Relación entre el déficit de vitamina D y la depresión tanto gestacional como posparto

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Abstract

Introduction: vitamin D deficiency (VDD) has been associated with depressive symptoms in pregnancy and postpartum, which can result in increased adverse outcomes in the maternal-infant segment. A possible explanation in the literature is VDD relationship with genetic and neurological mechanisms.

Objective: to evaluate VDD relationship with gestational and postpartum depression.

Methods: this review followed the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Research was conducted in electronic databases, PubMed and LILACS, including studies of the analytical type (cross-sectional and longitudinal), systematic reviews, meta-analyses, and controlled clinical trials carried out in humans; inclusion and exclusion criteria were applied.

Results and conclusions: in this systematic review, eight articles were analyzed comprising 8,583 women from seven different countries. Among the selected articles, six found an association between VDD and gestational and postpartum depression. Considering the data collection, it was possible to conclude that there is a probable relationship between VDD and a higher predisposition to gestational and postpartum depression. Also, we concluded that vitamin D supplementation has proven to be a promising strategy for reducing the risk of depressive symptoms.

Keywords:

Postpartum depression.
Depression.
Pregnancy. Vitamin D.
Polymorphism.

Resumen

Introducción: la deficiencia de vitamina D (VDD) se ha asociado a síntomas depresivos en el embarazo y el posparto, lo que puede resultar en un aumento de los resultados adversos en el segmento materno-infantil. Una posible explicación en la literatura es la relación de la VDD con mecanismos genéticos y neurológicos.

Objetivo: evaluar la relación de la VDD con la depresión gestacional y posparto.

Métodos: esta revisión siguió las recomendaciones propuestas por los Elementos de Informes Preferidos para revisiones sistemáticas y metaanálisis. La investigación se llevó a cabo en bases de datos electrónicas, PubMed y LILACS, incluyendo estudios de tipo analítico (sección transversal y longitudinal), revisiones sistemáticas, metaanálisis y ensayos clínicos controlados realizados en seres humanos; se aplicaron criterios de inclusión y exclusión.

Resultados y conclusiones: en esta revisión sistemática se analizaron ocho artículos que comprenden a 8716 mujeres de siete países diferentes. Entre los artículos seleccionados, seis encontraron asociación entre la VDD y la depresión gestacional y posparto. Teniendo en cuenta la recopilación de datos, fue posible concluir que existe una relación probable entre la VDD y una mayor predisposición a la depresión gestacional y posparto. También llegamos a la conclusión de que la suplementación con vitamina D ha demostrado ser una estrategia prometedora para reducir el riesgo de síntomas depresivos.

Palabras clave:

Depresión posparto.
Depresión. Embarazo.
Vitamina D.
Polimorfismo.

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INTRODUCTION

Gestational depression affects about 10 % to 15 % of women (1), and postpartum depression ranges from 5 % to 20 % worldwide, while in Brazil it varies from 12 % to 25 % (2). Symptoms of both gestational and postpartum depression range from lack of appetite to thoughts of death or suicide (1,2).

During the gestational and postpartum periods depression is associated with an increase in morbidity, maternal-infant impairment, and adverse outcomes such as premature child-birth, low birth weight, and intrauterine growth restriction (3,4), in addition to an increased risk of preeclampsia and cesarean section (5).

Studies also have shown that low serum concentrations of vitamin D (25(OH)D) were associated with depression (6), and that there is a positive relationship between serum concentrations of 25(OH)D and mental health indicators (7,8).

The literature has shown that vitamin D deficiency (VDD) during pregnancy may affect about 84 % of the maternal-infant segment, and that there is an association between VDD and depressive symptoms (9). Increased nutritional demands to meet the needs of the conceptus makes pregnant women more prone to VDD and consequently to associated depressive symptoms (10,11).

There is evidence linking the metabolically active form of vitamin D (1,25(OH)₂D) to the activation of gene expression for tyrosine hydroxylase, an enzyme regulating the production of various neurotransmitters such as dopamine, adrenaline, and norepinephrine, all involved in the pathophysiology of mood and its disorders. Such findings suggest that vitamin D can minimize depressive symptoms by stimulating the genes that produce neurotransmitters (12).

In view of the above, this systematic review aims to evaluate the relationship between VDD and the triggering of gestational and postpartum depression, as well as the role of vitamin D supplementation in the reduction of depressive symptoms, considering the lack of studies with this joint approach.

METHODS

This review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and consists of evaluating the relationship between VDD and the occurrence of gestational and postpartum depression. Articles were selected through research into the PubMed and LILACS electronic databases, and included analytical (cross-sectional and longitudinal), prospective, case-control, cohort, descriptive, and exploratory studies in addition to controlled clinical trials carried out in humans. It excluded animal studies, studies with poorly-defined methodology, studies that evaluated the supplementation of other micronutrients besides vitamin D, and studies that evaluated vitamin D only from dietary sources.

The terms used for the bibliographic search were proposed by Health Descriptors for terms in Portuguese and Medical Subject Headings for terms in English (Table I). The search expressions

were elaborated by combining the descriptors or using them in isolation. The bibliographical research took place from October 28, 2017 to February 26, 2018 without delimitation per year of study or language.

The data collection process was initially carried out by reading the titles and abstracts of the available studies. The articles selected (Fig. 1) in this first stage after reading their abstracts were separated for full analysis so that relevant publications could be identified in accordance with the inclusion/exclusion criteria. Additionally, the lists of references for each article included in the review were consulted (Fig. 1).

For this study, VDD was defined as serum concentrations of 25(OH)D below 20 ng/mL, insufficiency as 25(OH)D levels from 21 to 29 ng/mL, and sufficiency as serum 25(OH)D levels greater than or equal to 30 ng/mL, according to the proposal by Holick et al. (13).

Table I. Keywords used to search databases

Descritores em saúde	Gestação	Vitamina D OR 25(OH)D	Depressão
	Gestação		Depressão
	Gestação	Vitamina D	Depressão
Medical Subject Headings	Pregnancy	Vitamin D OR 25(OH)D	Depression
	Pregnancy		Depression
	Pregnancy	Vitamin D	Depression

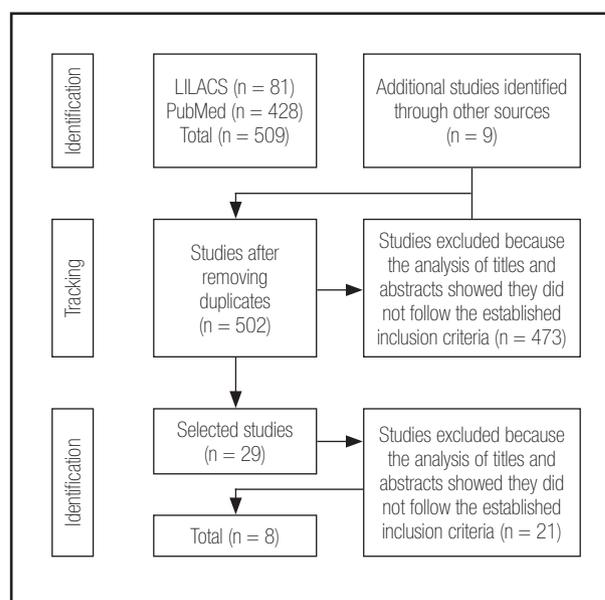


Figure 1.

Diagram of the selection process and review of articles.

RESULTS

In this systematic review, after establishing the inclusion and exclusion criteria, eight studies were included (Fig. 1), with two studies dealing with pregnancy and six with postpartum. Among them, only two studies evaluated the effect of supplementation. The selected articles comprised different types of studies, such as prospective (14), case-control (15), cross-sectional (16), cohort (17,18,19), randomized clinical trial (20), and descriptive exploratory (21) studies. They amounted to a total of 8,716 women from seven different countries.

These studies evaluated the impact of VDD on the gestational and postpartum periods, and their results are shown in table II.

DISCUSSION

BRAIN MECHANISMS, VITAMIN D AND DEPRESSION

There has been an increasing number of studies reporting an association between vitamin D and depression (7,22-32), as well as existing correlations between the adequacy of serum 25(OH)D concentrations and better scores in mental health indicators (33).

The active metabolite 1,25(OH)2D is present in different tissues, originating from 25(OH)D (22). Subsequently to its formation, 1,25(OH)2D binds vitamin D receptors (VDRs) in target tissues to regulate gene transcription and structures inside cellular membranes, thus mediating a series of non-genomic responses. VDRs are present in most tissues and cells in the body, and in the brain area they have some specificity in the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra, with many of these areas being involved in the pathophysiology of depression (34).

Most of these brain areas also showed important immunoreactivity for the enzyme 1-alpha-hydroxylase, capable of metabolizing 25(OH)D into 1,25(OH)2D (12,15), thus suggesting that 1,25(OH)2D probably has autocrine and/or paracrine activity in these areas (12).

One of the functions of vitamin D is to control the formation of serotonin, a neurotransmitter strongly associated with social behavior, which is another feature of the association between VDD and depression. Cerebral serotonin is synthesized from tryptophan by the action of tryptophan hydroxylase-2 gene expression. In this context, vitamin D plays an important role in the activation of tryptophan hydroxylase-2, which raises the hypothesis that vitamin D may prevent depression while maintaining serotonin at adequate levels (35-37).

Another important function of vitamin D is to prevent hypermethylation of gene promoters, some of which play an important role in the function of GABAergic neurons (38), a fact that may explain the decline in the size and number of GABAergic neurons occurring in depression (39,40). Such epigenetic alterations can lead to a decline in the expression of primary signaling proteins, which is characteristic of many neural disorders, including depression (38,41,42).

Another evidence of the above association relates to the onset and progression of depression, which seems to depend on an increase in Ca^{2+} in neuronal cells. These high levels would act by reducing protein synthesis, which possibly explains the decline in function and number of GABA neurons, to be described later (39).

Evidence has shown that vitamin D acts by maintaining Ca^{2+} homeostasis. One of its primary functions is the regulation of the expression of Ca^{2+} signaling components, which function by keeping low cytosolic calcium concentrations in the resting state (22). This has been corroborated by studies showing that vitamin D can increase the expression of plasma membrane-bound calcium-ATPase (PMCA) and sodium-calcium exchanger (NCX1), two mechanisms responsible for eliminating Ca^{2+} , and calbindin D-9k, calbindin D-28k, and parvalbumin, important Ca^{2+} buffers in the cytoplasm of neurons (43-46).

In VDD, the expression of CaV1.2 and CaV1.3 channels is increased, and Ca^{2+} pumps and buffers are reduced, these being changes that can contribute to high Ca^{2+} levels, a characteristic of depression (47).

Based on these findings, evidence has suggested that vitamin D can prevent depression by reducing neural levels of Ca^{2+} . Considering that in VDD an elevation of Ca^{2+} levels in neuronal cells has been reported, such aspects may explain its connection with depression (22).

GENETICS, VITAMIN D AND DEPRESSION

The analysis of polymorphisms has shown different results for each population studied. For this reason, it is appropriate to calculate the genotype frequencies of VDR for each population. A study has found that polymorphism in exon 2 is the only VDR polymorphism that alters the structure of the receptor, and the FokI restriction enzyme is used for its determination (48). However, studies performed by Can et al. (49) did not confirm the hypothesis that vitamin D levels and the FokI polymorphism of the VDR gene play any role in the etiology of depressive disorder.

Glocke, Melanie, et al. (50), when analyzing the VDR FokI polymorphism (rs2228570), found a significantly lower prevalence of depression in AA and GA allele carriers when compared to GG allele carriers, among whom up to 40 % of male and female GG carriers and 15 % of female GG carriers had developed depression.

Monticelio (51) has pointed out that the ff genotype was associated with the highest serum concentrations of 25(OH)D when compared to the FF genotype. In Turkey, a study carried out by Dayangaç D, et al. (2002) with 100 healthy individuals reported that the prevalence of the VDR FF genotype accounted to 55 % of individuals, and Ahmadi et al. (2012) (53) has noted the association of bipolar disorder with reduced gene expression of dopamine receptor D1 in patients with the FF genotype. Can et al. (2017) found similar results; however, no difference was observed in genotypical distribution between patients and controls (49).

Furthermore, there is a hypothesis that single nucleotide polymorphisms (SNPs) may impair the conversion of 25(OH)D to 1,25(OH)2D in some populations.

Table II. Description and main results of the studies included in the systematic review

Study	Type of study	Location of clinical trial	Supplementation period	Vitamin D dosage	Supplementation results	No of participants	25 (OH) D dosage method	Results
Varizi et al. (20)	Randomized clinical trial	Shiraz, Iran	From 26th to 28th PW through to delivery	2000 IU D3	Vitamin D group (12.84 ± 7.9) versus control group (1.89 ± 6.40) at baseline (p = 0.63). Vitamin D group (17.46 ± 10.0) versus control group (12.07 ± 5.98) at delivery (p = 0.001)	169	CLIA	The vitamin D group had a greater reduction in depression scores as compared to the control group at the 38 th -40 th PW (p = 0.01); also at 4 and 8 weeks after delivery (p < 0.001)
Brandenburg et al. (16)	Cross-sectional	Amsterdam, The Netherlands	Without supplementation	Without supplementation		4,101	Enzyme immunoassay method (OCTEIA AC-57F1; IDS Ltd, Boldon, UK)	Higher prevalence of depressive symptoms during pregnancy in women with VDD (OR, 1.48; 95 % CI, 1.13-1.95) and VD insufficiency (OR, 1.44; 95 % CI, 1.12-1.85) when compared with women with adequate concentrations. Additional analyses revealed a linear trend, with an OR of 1.05 (95 % CI, 1.02-1.08) for each 10-nM decrease in vitamin D status
Murphy et al. (21)	Descriptive exploratory	South Carolina, Charleston, USA	4-6 weeks after delivery	400 (G1); 2000 (G2); 6000 (G3)	G1 35,7 % Insufficient G2 35,7 % Insufficient G3 28,6 % Insufficient	97	RIA	Reduced risk of postpartum depression in women supplemented in G3 (D = 0.8 ± 0.3, t (388) = 2.3, p = 0.02). Mothers with lower levels of vitamin D had higher EPDS sum scores over time than mothers with higher vitamin D levels (p = 0.02)
Gur et al. (14)	Prospective	Izmir, Turkey	Without supplementation	Without supplementation		687	ELISA	VDD can be associated with increased risk of depressive symptoms in the 1 st week, 6th week, and 6th month PP (p = 0.003, 0.004, < 0.001, respectively)
Robinson et al. (18)	Cohort	Perth, Australia	Without supplementation	Without supplementation		929	Enzyme immunoassay kit from Immunodiagnostic Systems Ltd	Inverse association between 25(OH)-VD and depression symptoms (p < 0.05) for women in the lowest quartile for vitamin D status (p = 0.93, 95 % CI = 0.27, 1.58). Women who were in the lowest quartile for VD status at the 18 th PW were significantly more likely to report six or more depressive symptoms in the PPD (OR = 2.19, 95% CI = 1.26, 3.78) when compared with women in the highest quartile for VD

(Continuation in the next page)

Table II (Cont). Description and main results of the studies included in the systematic review

Study	Type of study	Location of clinical trial	Supplementation period	Vitamin D dosage	Supplementation results	N° of participants	25 (OH) D dosage method	Results
Nielsen et al. (15)	Case-control	Denmark	Without supplementation	Without supplementation		1,480	LC-MSMS	There was no significant association between VDD and risk of PPD ($p = 0.08$)
Gould et al. (19)	Cohort	Australia	Without supplementation	Without supplementation		1,040	HPLC-MS	There was no significant association between VDD and risk of PPD after six weeks (ARR: 0.92, 95 % CI: 0.84-1.02; $p = 0.11$) and six months (ARR 0.96; 95 % CI: 0.88-1.05; $p = 0.41$) after delivery
Fu et al. (17)	Cohort	Beijing, China	Without supplementation	Without supplementation		213	E601 modular analyser (Roche Diagnostics, Mannheim, Germany)	Increased risk of high EPDS scores in women with serum 25(OH)D deficiency during pregnancy (OR: 7.17; 95 % CI: 3.81-12.94; $p < 0.0001$)

PW: pregnancy week; PP: postpartum; VD: vitamin D; VDD: vitamin D deficiency; G1: group 1; G2: group 2; G3: group 3; PPD: postpartum depression; EPDS: Edinburgh Postnatal Depression Scale; ARR: adjusted risk ratio; CI: confidence interval; OR: odds ratio; D: delta; CLIA: chemiluminescence immunoassay; LC-MSMS: liquid chromatography-tandem mass spectrometry; ELISA: enzyme-linked immunosorbent assay; RIA: rapid direct radioimmunoassay; HPLC-MS: high-performance liquid chromatography- mass spectroscopy.

As a consequence, despite high serum concentrations of 25(OH)D in these populations, 1,25(OH)2D levels remained below the recommended range, resulting in an increased risk of developing postpartum depression (54).

In the face of the current scenario, there is a need for further investigation on the role of polymorphisms and genetic alterations in VDD and depression.

VITAMIN D DEFICIENCY AND GESTATIONAL DEPRESSION

During pregnancy and childhood, VDD can cause growth delay and skeletal deformities, as well as an increased risk of hip fracture in adulthood (34). In addition, studies have reported that there are receptors for 1,25(OH)2D and enzymes related to its hydroxylation, in the central nervous system, showing an effective role of vitamin D in the brain (20). Another study has pointed out that VDD may be associated with pathological, neurodegenerative, or psychiatric conditions such as depression (16).

Additionally, the third National Health and Nutrition Examination Survey analyzed 7,970 non-institutionalized US residents aged 15 to 39 years, and confirmed that people with VDD are at a significantly higher risk of showing depression than individuals with adequate serum levels of vitamin D (60). Reinforcing this association, a large cohort study suggested the possibility that VDD indicates an underlying biological susceptibility for depression, and this can be explained by the association between low vitamin D levels and presence and severity of depression that was observed in the study (61).

During pregnancy, due to increased demands to meet the needs of the fetus, VDD occurs most frequently. Thus, many studies have related depressive symptoms during pregnancy and postpartum with VDD (15-19). A recent study conducted in Iran showed that more than 80 % of women with gestational age between 26 and 28 weeks had VDD (20).

During pregnancy, vitamin D is transported to the fetus through the placenta in the form of 25(OH)D. At birth, there is a high correlation between the nutritional status of the mother for vitamin D and the infant's, as the concentration found in umbilical blood is about 80 % of that in maternal blood. This means that if vitamin D inadequacy occurred during pregnancy, the offspring would probably be deficient as well (56). In this context, a randomized, controlled, double-blind study of vitamin D supplementation in pregnant women with up to 16 weeks' gestation reported that neonatal 25(OH)D correlated significantly with maternal 25(OH)D, mainly 1 month before and in the postpartum (r^2 1/4 0.6; OR 1/4 0.50). In short, the authors of the aforementioned study suggested that vitamin D supplementation during pregnancy should be 4,000 IU in order to achieve vitamin D sufficiency in both women and newborns (58). The prevalence of postpartum depression varies across the world. A systematic review conducted by Halbreich & Karkun (2006) reported a prevalence of up to 60 % due to the use of different scales and cutoff points to describe this psychological disorder (55).

Worldwide, the predictors of postpartum depression vary. Maternal-social support, family history, demographic aspects, depression during or before pregnancy, and socioeconomic status are some of these factors (16). Additionally, studies have suggested that depression during or before pregnancy may be seen as a predictor of postpartum depression (56,16).

SUPPLEMENTATION OF VITAMIN D AND GESTATIONAL AND POSTPARTUM DEPRESSION

A cross-sectional study in 4,101 Dutch women reported that women with VDD showed a significantly higher prevalence and increased depressive symptoms during pregnancy when compared to women with adequate concentrations of vitamin D (OR = 1.48; 95 % CI, 1.13-1.95) (16).

In relation to supplementation during pregnancy, Varizi et al. (20) conducted a randomized study in Iran with pregnant women who received daily supplementation with 2,000 IU of vitamin D3 from the 26th to the 28th week of pregnancy until delivery. Initially, no correlation was observed between 25(OH)D concentrations and depression scores (Edinburgh-EPDS); however, after the 38th and the 40th week of pregnancy and in the postpartum period, significant differences in depression grade were observed in women who received supplementation when compared to the control group ($p = 0.01$). The study concluded that daily supplementation with 2,000 IU of vitamin D3 throughout the entire pregnancy was effective in reducing the levels of perinatal depression. Nonetheless, more studies are needed to assess the risk of depression in women during the postpartum period.

The findings on the relationship between serum vitamin D levels and postpartum depression (PPD) are conflicting. It has been speculated that the serum concentrations of 25(OH)D have an inverse association with PPD (15).

Murphy et al. (21) have evaluated the serum concentrations of vitamin D in 97 women during the postpartum period. It was observed that low serum vitamin D concentrations during pregnancy are related to high EPDS scores. Gur et al. (14) have studied women in the first pregnancy week, and in the first and sixth month postpartum, making also use of the EPDS, and found that serum vitamin D deficiency may be associated with the highest risk for depressive symptoms in the postpartum. In agreement with this, Robinson et al. (18) have evaluated women in the first three days of the postpartum period, and found that serum vitamin D deficiency in the second trimester of pregnancy was related to an increased risk of depression (OR = 2.19, 95 % CI = 1.26, 3.78).

On the other hand, Nielsen et al. (15) have not found a significant association between vitamin D deficiency and PPD risk. Another finding concerns the study of Gould et al. (2015), which evaluated the relationship between 25(OH)D concentration in the umbilical cord at birth and PPD after six weeks and six months postpartum, and found no significant association (19).

As far as supplementation is concerned, Fu et al. (17) have evaluated women between 24 and 48 hours postpartum, and

observed an increased risk of high EPDS scores among women with serum 25(OH)D deficiency during pregnancy (OR = 7.17; 95 % CI: 3.81-12.94; $p < 0.0001$). Based on that finding, they suggest that the use of vitamin supplementation during pregnancy may reduce the occurrence of PPD. In agreement with the above, Murphy et al. (21) have used supplementation in three different protocols: 400, 2,000, and 6,000 IU, reporting a lower risk of postpartum depression among the women supplemented with the higher concentrations of vitamin D.

These findings suggest that an association between serum vitamin D concentrations during pregnancy and the occurrence of postpartum depression has not been positively established yet, and that more studies are needed for understanding the mechanisms that may mediate it. Regarding mental health, albeit there is no universal consensus about a treatment cutoff point, supplementation is recommended during pregnancy to maintain concentrations within a range of > 30-50 ng/mL, which is seemingly sufficient to avoid the adverse effects of deficiency (18,59). In addition, the amount of information available to date suggests that the use of vitamin D supplementation during pregnancy has proven a promising strategy for reducing postpartum depression.

CONCLUSION

The present study found a possible relationship between VDD and a greater predisposition to the occurrence of depression during pregnancy and postpartum. Additionally, it was possible to observe that supplementation with vitamin D has been reported to be a promising strategy for reducing the risk of depressive symptoms during these biological periods.

However, more studies are needed to determine whether vitamin D deficiency is one of the risk factors for gestational and postpartum depression, or if it is more an effect than a cause of these. We emphasize the importance of having more randomized controlled trials evaluating vitamin D supplementation throughout gestational trimesters and its impact on both gestational and postpartum depression, in addition to assessing the recommended and safe dosage of vitamin D required to maintain serum vitamin D concentrations and prevent these symptoms during this period.

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