



Evidence of the functions of vitamin D in pregnant women in COVID-19: a systematic review

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Abstract

Introduction: In the world, about 1 million people suffer from vitamin D deficiency. Vitamin D deficiency in pregnant women increases maternal mortality and morbidity rates. In the scenario of COVID-19, it is known that the immune response, inflammation, and coagulation are modulated by vitamin D activity.

Objective: It was to analyze the main considerations of the effects of vitamin D on pregnant women and fetuses in the scenario of COVID-19, presenting the mechanisms of inflammatory and immunological processes in an attempt to mitigate the worsening of comorbidities and deaths. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from September to October 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 210 articles were found, 82 articles were evaluated and 32 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $I^2 = 98.9\% > 50\%$. There is a relationship between vitamin D status and the severity of COVID-19 in pregnant women. Vitamin D levels are low in pregnant women with COVID-19. Furthermore, there is a significant difference regarding the level of vitamin D and the severity of COVID-19 in pregnant women. Maintaining adequate vitamin D levels may be useful as an approach to preventing an aggressive course of inflammation induced by this novel coronavirus in pregnant women.

Keywords: Vitamin D. Hypovitaminosis D. Pregnant women. COVID-19.

Introduction

Around 1 million people worldwide suffer from vitamin D deficiency (serum 25hydroxyvitamin D [25(OH)D] <20 ng/mL, referring to vitamin D2 and/or D3) [1]. Due to the increased physiological demand for vitamin D during pregnancy, pregnant women are considered a high-risk group for developing vitamin D deficiency, with prevalence ranging from 51.3% [2] to 100% [3]. Vitamin D deficiency in pregnant women increases maternal mortality and morbidity rates. Worldwide, the highest prevalence (>80%) of disability in pregnancy was seen among Chinese women (100%) [3] and Turkish pregnant women (95.6%) [4]. In Middle Eastern countries, vitamin D deficiency among pregnant women is estimated at 60-80% [5,6]. Among Iranian pregnant women, studies have reported prevalence rates of 78%, 76%, 70.4%, and 69.2% [7]. The estimated prevalence of pregnant women in the US and Canada was 42 to 72% [8]. In Sweden, a longitudinal study reported that 37% of pregnant women in the first trimester had 25(OH)D concentrations < 20 ng/mL [9], compared with 23% of Canadian women [10]. In Mexico, a previous cross-sectional study reported vitamin D deficiency among 61% of women in the third trimester, and 98% of their newborns were vitamin D deficient [11].

In this sense, vitamin D is a critical fat-soluble vitamin within the body for many functions, including cell proliferation, differentiation, apoptosis, and immune modulation [12]. Vitamin D is transmitted from mother to fetus through the placenta and is critical at all stages of embryonic and fetal development, from implantation to overall growth, including skeletal

maturation and placental function [13-15].

In the scenario of COVID-19, it is known that the immune response, inflammation, and coagulation are modulated by vitamin D activity [16,17]. In particular, vitamin D induces the conversion of monocytes into macrophages and influences the activity of dendritic, T, and B cells. It also enhances cellular immunity by reducing the cytokine storm induced by the innate immune system, which generates pro-inflammatory and anti-inflammatory cytokines. Inflammation in response to viral infections, as seen in patients with COVID-19 [18]. Furthermore, vitamin D may alter the development of inflammatory T helper 17 (Th17) cell mass towards anti-inflammatory regulatory T cell populations (T-reg cells), reducing levels of pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α , simultaneously increasing the level of the anti-inflammatory IL-10 [19,20].

The role of vitamin D in pregnant women with COVID-19 has been poorly investigated to date. During pregnancy, vitamin D alters anti-Müllerian hormone signaling, follicle-stimulating hormone sensitivity, and progesterone production and release in human granulosa cells, indicating a possible physiological role for vitamin D in ovarian follicular development and luteinization. In detail, 25-hydroxyvitamin D is positively correlated with anti-Müllerian hormone concentrations: consequently, vitamin D supplementation can reduce seasonal changes in anti-Müllerian levels [21].

In this context, the concern is that there is a high worldwide prevalence of vitamin D deficiency and the spotlight is on potential adverse effects on human health, including pregnant women and their children. In addition to its classic role as a regulator of calcium and phosphate metabolism, along with its key role in bone health at all stages of life, its deficiency has been associated with multiple adverse health effects, particularly vulnerability to viruses [22].

Still, there is controversy regarding the optimal levels of 25(OH)D [23,24]. 25(OH)D levels <20 ng/mL are considered an indication of vitamin D deficiency, although the Endocrine Society and other expert groups consider insufficiency with levels between 25(OH)D 20–29 ng/mL and \geq 30 ng/mL as sufficient levels; for non-classical actions, some authors propose reaching levels >40 ng/mL.

Given the above, this study analyzed the main considerations of the effects of vitamin D on pregnant women and fetuses in the context of the COVID-19 pandemic, presenting the mechanisms of inflammatory and immunological processes in an attempt to mitigate the worsening of comorbidities and deaths.

Methods

Study Design

This study followed the concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and meta-analysis).

Search Strategy and Search Sources

The literary search process was carried out from September to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: “Vitamin D. Hypovitaminosis D. Pregnant women. COVID-19” (Vitamin D. Hypovitaminosis D. Pregnant women. COVID-19), and using the Boolean “and” between MeSH terms and “or” between historical findings.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and discussion

Summary of Findings

As a corollary of the literary search system, a total of 210 articles were found that were submitted to the eligibility analysis, then, 32 of the 82 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $I^2=98.9\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 72 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

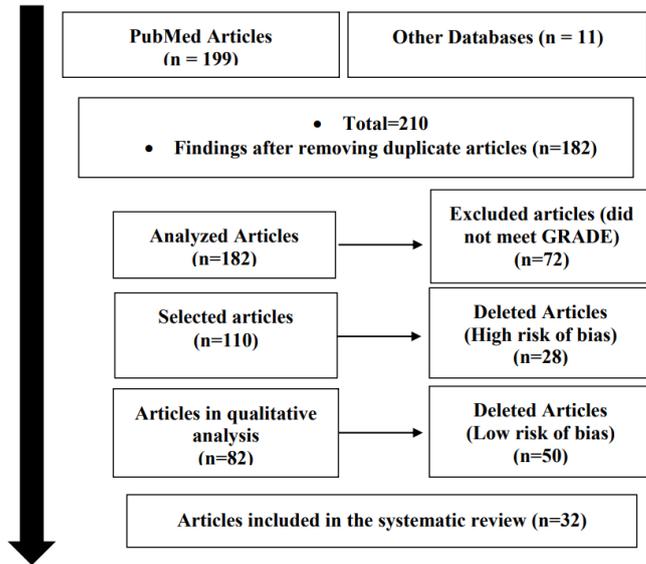
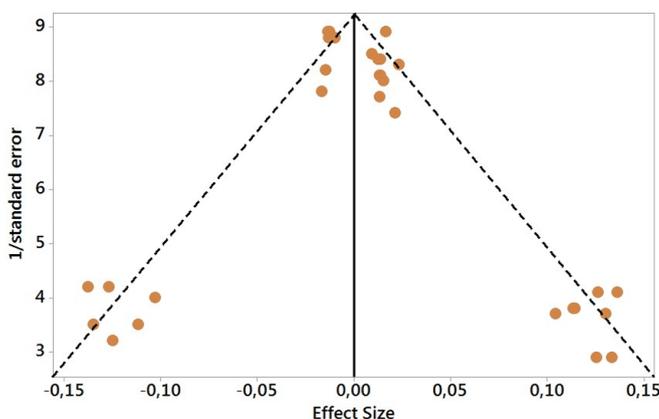


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph (studies shown in red color) and in studies with large sample sizes that are presented at the top (studies shown in blue color).

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=32 studies).



Source: Own authorship.

Main Results

Vitamin D insufficiency is highly prevalent in children and adults, including pregnant women. During pregnancy, maternal vitamin D insufficiency can increase the risks of various pregnancy complications and adverse birth outcomes. The FEPED study was designed to assess the effects of maternal vitamin D status in the first trimester during pregnancy on the risks of preeclampsia, gestational diabetes mellitus (GDM), and premature delivery for gestational age (SGA) at birth. A prospective observational study included 3129 women with a singleton pregnancy between April 2012 and July 2014 in six maternity hospitals in France and Belgium. In the first trimester, the mean 25(OH)D concentration was 21.9 ± 10.4 ng/mL, and 25(OH)D concentration was <20 ng/mL in 46.5% of patients. After comparing 83 preeclampsia cases with 319 controls, a significant decrease in the risk of preeclampsia was associated with maternal vitamin D levels ≥ 30 ng/mL in the third trimester (OR = 0.34; 95% CI: 0.13-0.86, $p=0.023$). In the first trimester, the risk of preeclampsia decreased in these patients but did not reach statistical significance (OR = 0.57 95% CI, 0.30-1.01; $p = 0.09$). For the 250 GDM cases matched with 941 controls, no linear relationship was found between GDM and 25OHD levels in the first trimester of pregnancy. Finally, 2,813 pregnant women were included in the risk analyses for preterm birth and SGA. No association was found between low maternal vitamin D levels in the first trimester and the risk of preterm birth (aOR = 1.53; 95% CI: 0.97-2.43) or SGA (aOR = 1.07; CI 95 %: 0.75-1.54). More investigations are needed to understand the mechanisms behind the association between vitamin D and birth outcomes [25].

In this regard and the context of the COVID-19 pandemic, it should be noted that vitamin D deficiency has been associated with the severity of COVID-19. The role of vitamin D in pregnant women with COVID-19 has been poorly investigated to date. Thus, a study evaluated the influence of vitamin D in affecting some clinical characteristics in pregnancy among positive and negative SARS-CoV-2 patients. Polymorphisms related to the vitamin D pathway and 25-hydroxyvitamin D levels were quantified in pregnant women followed from the first to the third trimester of pregnancy. Vitamin D deficiency was considered with values ≤ 30 ng/mL. In total, 160 women were enrolled: 23 tested positive for at least one SARS-CoV-2-related test (molecular swab or antibody tests). Vitamin D associated polymorphisms were able to affect vitamin D levels in SARS-CoV-2-negative and positive

individuals, notably, all patients with VDR TaqICC genotype were negative for SARS-CoV-2. In one subpopulation (118 patients), vitamin D levels correlated with pregnancy-related factors such as alpha-fetoprotein levels. Vitamin D levels in the third trimester were lower in preterm births compared to pregnancy [26].

Still, Schmitt et al., 2022 [27], recently measured vitamin D levels and tried to correlate them with the severity of COVID-19. They found that both positive and negative women had low levels of vitamin D in the third trimester. However, the deficiency was greater in women with mild COVID-19.

To better understand this process, SARS-CoV-2 enters target cells through the ACE2 receptor and downregulates it. ACE2 has a high catalytic activity to produce Angiotensin 17 (Ang-1-7), which has a vasodilator effect and also inactivates the vasoconstrictor Angiotensin II. In normal pregnancy, ACE2 expression increases in the uterus and placenta. Plasma Ang-1-7 levels are significantly higher in third-trimester pregnant women compared to non-pregnant women. This may be contributing to systemic vasodilation and blood pressure reduction and hemodynamic modulation during pregnancy. Interestingly, plasma levels of Ang-1-7 are lower in pregnancies complicated by preeclampsia than in normal pregnancies. COVID-19 infection increased inflammatory cytokines and reduced ACE2 levels. This can lead to pre-eclampsia or hypertensive pregnancies, increasing perinatal and maternal mortality and morbidity. Vitamin D increased ACE2 expression and plasma levels of Ang-1-7 and also decreased plasma Ang II levels. Furthermore, vitamin D reduced the inflammatory cytokine storm. Thus, vitamin D supplementation may prevent the risk of preeclampsia or hypertension in pregnant women with COVID-19 [28].

A clinical study developed by the authors Sinaci et al, 2021 [29], evaluated the vitamin D status of pregnant women with COVID-19 and the association between vitamin D levels and the severity of COVID-19. A total of 159 women with a single pregnancy and a positive result for SARS-CoV-2 were included, and 332 healthy pregnant women with similar gestational ages were randomly selected. Patients with COVID-19 were classified as mild, moderate, and severe. Vitamin D deficiency was defined as 25-hydroxycholecalciferol <20 ng/mL (50 nmol/L), and vitamin 25-OH D <10 ng/mL was defined as severe vitamin D deficiency, also vitamin 25- H D between 20-29 ng/mL (525-725 nmol/L) was defined as vitamin D insufficiency. Vitamin D levels of pregnant women in the COVID-19 group

(12.46) were lower than those in the control group (18.76). Vitamin 25-OH D levels of those in the mild COVID-19 category (13.69) were significantly higher than those in the moderate/severe category (9.06). Regarding vitamin D supplementation, there was no statistically significant difference between the groups. However, it was observed that all who had severe COVID-19 were patients who did not take vitamin D supplementation.

In addition, a 2022 meta-analysis study looked at the association between vitamin D, pregnancy, and COVID-19. Among 259 registries, 7 and 6 studies were included in the metaanalysis, respectively. All included studies were of acceptable quality. The results demonstrated an insignificant difference between infected women and uninfected controls (MD = -2.55 ng/ml, 95% CI: -6.85 - 1.74). But serum vitamin D levels in severe/moderate versus mild cases (MD = -2.71 ng/ml, 95% CI: -4.18 to -1.24) are significantly lower. Therefore, serum vitamin D level is not associated with the risk of SARS-CoV-2 infection among pregnant women, but there is a significant association with disease severity [30].

Authors Seven et al., 2022 [31], evaluated the relationship between 25hydroxyvitamin D (25(OH)D) levels and disease severity in pregnant women hospitalized with positive COVID-19. Pregnant women with COVID-19 (+) (confirmed by PCR test) were classified as asymptomatic, mildly symptomatic, and severely ill according to their symptoms and laboratory results. Patients were divided into two groups; the asymptomatic or mildly symptomatic group (Group 1) and the severe disease and/or poor prognostic factor group (Group 2). 25(OH)D levels were compared between groups. ROC curve analysis was used to analyze the cut-off value of vitamin D to predict COVID-19 severity. 25(OH)D levels were statistically significantly lower in Group 2 (15.5 (10.25) ng/mL in Group 1, 13 (12) ng/mL in Group 2, p=0.010). A 25(OH)D level below 14.5 ng/mL was associated with severe COVID-19 and/or poor prognostic factors (p=0.010). The risk of severe COVID-19 and/or poor prognostic factors was 1.87 times higher among pregnant women who had 25(OH)D levels below 14.5 ng/mL. This value was found to have a sensitivity of 54.1% and a specificity of 61.3% in predicting severe COVID-19 and/or poor prognostic laboratory findings in pregnant women. There is a relationship between vitamin D status and the severity of COVID-19 in pregnant women. During the pandemic period, vitamin D supplementation for pregnant women should gain more importance.

Finally, to corroborate all the other findings above

on physiological changes during pregnancy that may increase the risk of complications in pregnant women with COVID-19, a study prepared by Ferrer-Sánchez et al., 2022 [32], analyzed a relationship between serum 25-hydroxyvitamin D (25(OH)D) levels in pregnant women and COVID-19. A comparative case-control study was performed with a study population of 256 pregnant women (82 pregnant women with infection and 174 women in the control group). Serum 25(OH)D levels were significantly lower in pregnant women with COVID-19 infection than in those without infection. In addition, 89% of pregnant women with positive COVID-19 had 25(OH)D deficiency, while in the control group, the percentage was 75.30%, finding statistically significant differences (ORa = 2.68; CI 95% 1, 19-6.06; $p = 0.01$). Therefore, the results revealed a relationship between vitamin D deficiency in pregnant women and COVID-19 infection.

Conclusion

There is a relationship between vitamin D status and the severity of COVID-19 in pregnant women. Vitamin D levels are low in pregnant women with COVID-19. Furthermore, there is a significant difference regarding the level of vitamin D and the severity of COVID-19 in pregnant women. Maintaining adequate vitamin D levels may be useful as an approach to preventing an aggressive course of inflammation induced by this novel coronavirus in pregnant women.

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Ethics approval

Not applicable.

Informed consent

Not applicable.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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