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Systematic Review and Meta-Analysis

Risk Factor of Vitamin-D Deficiency in Pregnant Women with COVID-19 Infection: Comprehensive Meta-Analysis and Systematic Review

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ABSTRACT

Introduction: It has been suggested that coronavirus infection (COVID-19) in pregnant women may be influenced by vitamin D deficiency (VDD). The physiological changes brought on by pregnancy, and the body's partial immune suppression make pregnant women more susceptible to vitamin D deficiency and viral infections. Therefore, this review aims to synthesize the current information on the link between vitamin D levels and the risk of COVID-19 in pregnant women.

Material and Methods: A systematic search is conducted in PubMed, ScienceDirect, and Google Scholar. Articles retrieved were screened based on the PRISMA 2020 guidelines. Studies that assessed the effect of vitamin D levels on pregnant women with COVID-19 infection were considered for the review. Odds ratios with their 95 percent confidence intervals (CI) from a meta-analysis using a random-effects model were reported.

Results: Three eligible studies were relevant to the relationship between vitamin D deficiency and COVID-19 infection in pregnant women (n=1005). The metanalysis showed that vitamin D deficiency in pregnant women was 1.8 times (95% confidence interval, OR 1.72 to 1.88; p=0.0005) more likely to be infected with COVID-19.

Conclusion: According to our results, vitamin D deficiency in pregnant women may increase the risk of COVID-19 infection. Therefore, we recommend adequate vitamin D levels to prevent COVID-19 and its severity.

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INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is currently one of the most challenging worldwide concerns facing public health. In Wuhan, Hubei Province, China, COVID-19 infection first appeared in December 2019 [1]. The WHO declared a worldwide pandemic on March 11, 2020 [2]. The COVID-19 illness is very infectious and spreads quickly around the globe. As of June 28th, 2022, it has infected over 541 million individuals worldwide, including the general public and pregnant women.

Because of the physiological changes brought on by pregnancy and the body's partial immune suppression, pregnant women are more prone to viral infections. These changes could increase the likelihood of conception and expose the woman to pregnancy complications brought on by viral infections of the respiratory system [3]. They have a particular immune response that keeps the fetal semi-allograft tolerable. Pregnant women are more vulnerable to viral infections due to the temporarily reduced immunity caused by a decrease in T cell activation. The physiological changes in the respiratory and circulatory systems during pregnancy may also worsen clinical outcomes when a virus is infected. Serious Acute Respiratory Syndrome SARS-CoV-2 agents cause unfavorable pregnancy outcomes [4].

During pregnancy, a physiological change takes place. It is stated that the blood's 25(OH)D vitamin D concentrations are low during pregnancy. A high-risk group for vitamin D deficiency (VDD), which affects

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pregnant women at a rate of 18 to 84 percent, has been found. VDD is acknowledged as a regional and local public health concern [5].

Vitamin D is also essential to maintain a balance in immune responses. According to epidemiological statistics, there is a direct link between vitamin D deficiency and a higher risk of developing several infectious diseases, such as the flu and viral respiratory tract infections. Academics, health planners, and treating clinicians must prioritize research on the level of vitamin D serum and pregnant women with COVID-19 infection because recent epidemiologic studies found a significant correlation between the blood vitamin D serum and the number of COVID-19 fatalities per million [6]. The results of studies on vitamin D deficiency in pregnant women with COVID-19 infection provide evidence-based risk factors [6–14]. This study aimed to examine vitamin D deficiency in pregnant women with COVID-19 infection and determine whether it may be involved in the etiology or pathogenesis of the disease.

MATERIAL AND METHODS

Protocol and Registration

The International Perspective Registry for Systematic Reviews, PROSPERO, has this review protocol registered with no. You can access the whole protocol at https://www.crd.york.ac.uk/prospero.

Literature Searching

This systematic review and meta-analysis were carried out to ascertain the relationship. The following databases were searched using Google Scholar, ScienceDirect, and PubMed. The following Medical Subject Heading (MeSH) terms were entered individually or in combination in the search: "("Vitamin-D deficiency" OR "25(OH)D deficiency" OR "25-hydroxyvitamin D deficiency" OR "calcitriol deficiency") AND ("serum" OR "blood") AND ("pregnant women" OR "pregnancy") AND ("COVID-19" OR "Coronavirus disease 2019" OR " For this evaluation, all publications up through June 30th, 2022, were located and evaluated. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

The following were the study's inclusion criteria:

1. Observational study
2. Studies within the last ten years
3. Subjects were pregnant women whose PCR test was positive for COVID-19 as the case group dan healthy non-comorbid pregnant women as the control group.
4. The blood sample was venous blood drawn at a period
5. Having the same unit of measurement. If the units are different, it is equated with a standardized calculation.

However, the exclusion criteria include:

1. Experimental study, such as supplementation during the study.
2. Review articles/case series, letter in response, and conference abstract
3. Study with irrelevant titles/abstract
4. No full text available
5. Language other than English
6. The unit of measurement is not mentioned/ incomplete data.

Study selection and screening

Revman v. 5.4 exported all citations found by our search approach, and duplicate articles were removed. Two independent reviewers then evaluated the titles and abstracts of the chosen papers, and relevant research was incorporated for further analysis. Before data extraction, the whole texts of the selected papers were collected and carefully reviewed to guarantee their eligibility. If the two reviewers were unable to agree, a consensus-building meeting was organized, and the third reviewer was consulted.

Study Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to judge the caliber of the research for cross-sectional and case-control studies. Good was deemed to be six points, Fair was four to five points, and Poor was three points. To maintain the caliber of this study's meta-analysis, we did not use articles of low caliber. The NOS mean value was provided by the two reviewers who separately assessed the NOS of each research.

Data Extraction

The following data were taken from the RevMan v. 5.4 files: first author name, publication year, and country.

The following data were taken from the methodology section:

1. COVID-19 Status

   Clinical signs, radiographic criteria, and laboratory confirmation utilizing SARS-CoV-2 RT-PCR testing were used to diagnose COVID-19, an asymptomatic disease that causes severe acute respiratory distress syndrome (ARDS) [3].
2. Maternal vitamin-D serum level was presented as mean $\pm$ standard deviation.

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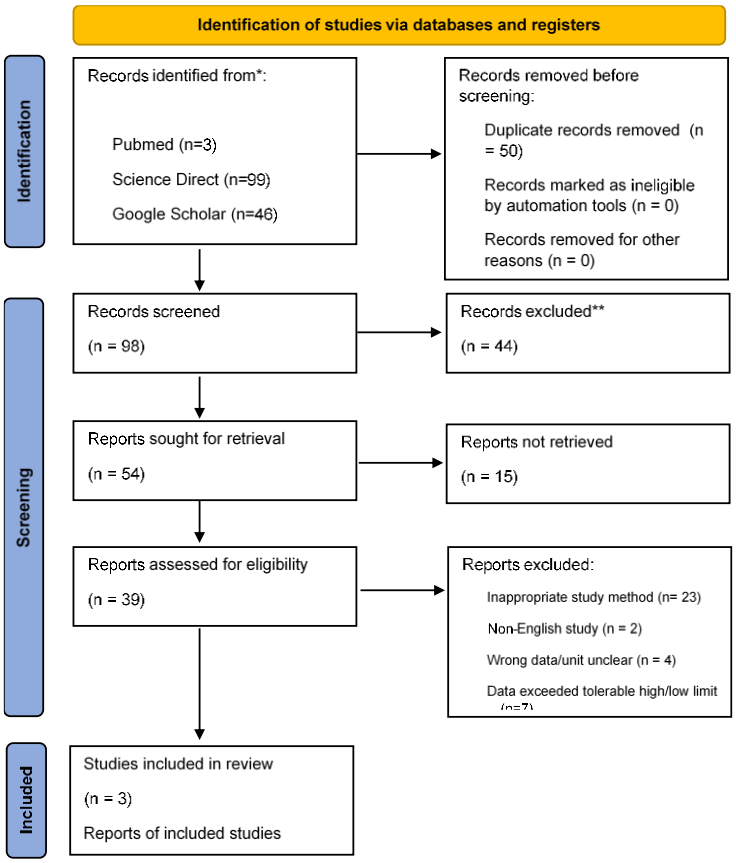


Fig. 1. PRISMA Flowchart of the Literature Selection

Venous blood samples were used to analyse serum 25(OH)D concentrations. Vitamin D deficiency was indicated by serum 25(OH)D levels below 50 nmol/L (20 ng/mL) [15].

3. Study Design. Eligible studies can be in the form of case-control, retrospective or prospective cohort, or cross-sectional studies.
4. Subject age range.
5. Gestational age range.
6. Biochemical method used.

Statistical Analysis

We compile the relevant research for each trace element in Microsoft Excel. The strength of the association between vitamin D deficiency and pregnant women with COVID-19 infection was evaluated statistically using Review Manager (RevMan) v.5.4 and standardized mean difference (SMD) with a 95% confidence interval (CI). To measure heterogeneity, I2 was utilized. Low heterogeneity was defined as an I2 of less than 25%, moderate heterogeneity as an I2 of between 25% and 75%, and high heterogeneity as an I2 more significant than 75%. A random-effects model was used in the research population was highly diverse. Significant P values are those with a value less than 0.05. Additionally, a subgroup analysis based on race was conducted to look at potential variables that may significantly affect between-study heterogeneity if sufficient studies were available.

RESULTS

Overview of Literature Searching

Through searching databases from PubMed, ScienceDirect, and Google Scholar, 148 studies were found. After deleting duplicate titles and abstracts from 98 submissions, we evaluated the remaining 39 studies, which we then chose and examined for qualitative synthesis. Three trials for vitamin D deficiency and pregnant women with COVID-19 infection underwent quantitative synthesis (**Fig. 1**).

Study Characteristics

In this review, 3 case-control studies were included. A total of 256 [16], 258 [17], and 491 [15] participants were enrolled in the study of vitamin D deficiency for pregnant women with COVID-19 infection respectively (**Table 1**).

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Summary SMD for Vitamin D Deficiency and Subgroup Results

In this study, pregnant women with COVID-19 infection and healthy pregnant women controls were compared for vitamin-D serum deficit. The difference in vitamin D deficiency between the two groups was statistically significant (P<0.05) (**Fig. 2**).

According to our data, those who are vitamin D deficient are more likely than those who are not to contract COVID-19 during pregnancy. According to this review, the risk or susceptibility to COVID-19 is increased by decreased serum 25(OH)D levels. Low blood 25(OH)D levels were found in both groups by Ferrer-Sánchez et al. [16] but were significantly higher in the control group, where they averaged 13.80 [11.45] ng/mL versus 10.15 [9.45] ng/mL in the COVID-19 group (p=0.005), with SMDs of -0.34 (95 percent CI -0.6, 00.07). There was a significant difference in 25-OH D vitamin levels between COVID-19 and the control group, with values of 12.46 [6.46] ng/mL vs. 18.76 [13.74] ng/m(p = 0.000), SMDs of -0.53 (95 percent CI -0.72, -0.34), according to study Sinaci, et al. [15]. According to research by Tekin et al. [17], pregnant women with COVID-19 infection had somewhat higher blood 25(OH)D concentrations than the control group (14.64 [10.72] ng/mL vs. 12.52 [8.28] ng/mL, respectively; p = 0.001) and SMDs of 0.23. (95 percent CI 0.03, 0.43) (**Fig. 2**).

The chosen papers discussed the effects of vitamin D deficiency on pregnant COVID-19-infected women. In conclusion, vitamin D deficiency was linked to a higher risk of COVID-19 infection in pregnant women, according to the pooled OR in the random-effect model (OR = 1.47, 95 percent CI: 0.64, 3.36). The forest plot displayed significant variability with an I^2 of 87% (**Fig. 3** and **Fig. 4**).

DISCUSSION

In this study, we discovered a strong link between low vitamin D levels and the likelihood that pregnant women will contract COVID-19. Pregnancy is considered a unique biological or immunological situation that increases susceptibility to illnesses with much higher severity. COVID-19. With its anti-inflammatory, antiviral, and antioxidant effects, vitamin D is essential for the immune system and many physiological functions [3]. Pregnant women frequently experience vitamin D deficiency, which can negatively impact pregnancy outcomes by raising the risk of pre-eclampsia, gestational diabetes, and premature birth, among other conditions. That was corroborated by earlier research showing vitamin D preventive benefits against acute respiratory infections [18].

The regulation of innate and acquired immunity by vitamin D makes it possible to affect infectious diseases like COVID-19. Vitamin D may also help in the treatment of COVID-19 by lowering the cytokine storm and the subsequent ARDS, which is frequently the cause of mortality in the illness [19]. That discovered that a higher prevalence of vitamin D deficiency was strongly correlated with mortality attributable to COVID-19. Due to decreased exposure (people prefer the shade in the intense sun) and partly because skin pigmentation

Table 1. Characteristics of The Included Study

Country	Authors	Year	Study Design	Method	Age Subjects (Interquartile Range)	Gestational Age (Interquartile Range)
Spain	Ferrer-Sánchez, Nazaret et al. [16]	2022	Case-control	Immunoassay	31 [8]	40 [3]
Turkey	Sinaci, Selcan et al. [15]	2021	Case-control	Immunoassay	29.6 [5.72]	34 [6-41]
Turkey	Tekin, Arzu Bilge et al. [17]	2018	Case-control	Immunoassay	27.98 [5.14]	27.6 [9.18]

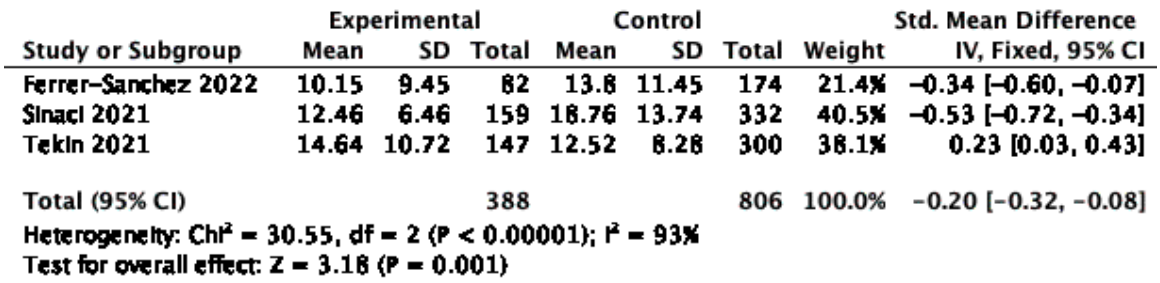


Fig. 2. Summary SMD for Vitamin D Deficiency in Both Group

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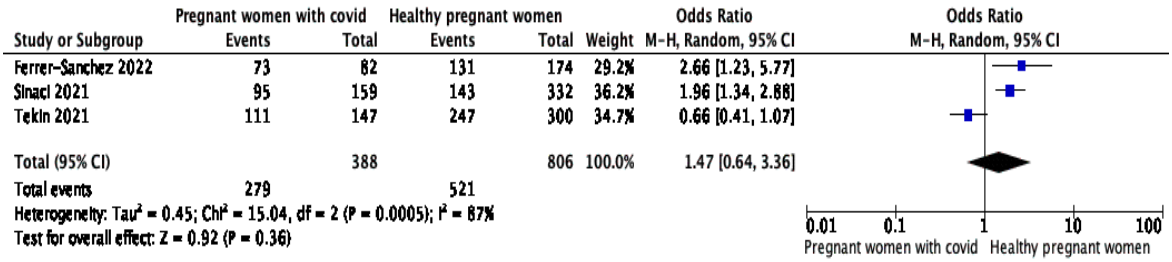


Fig. 3. Forest Plot Pooled SMD for Vitamin D deficiency and pregnant women with COVID-19 Infection

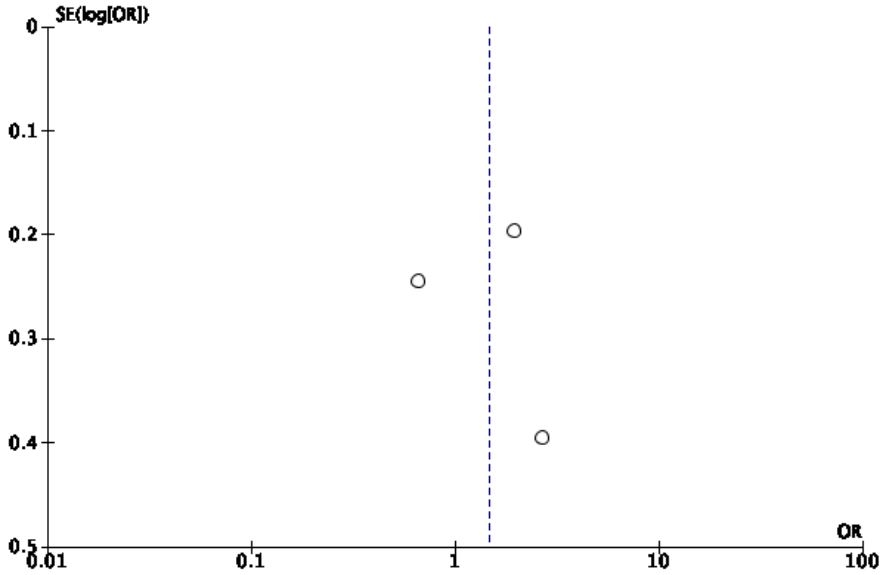


Fig. 4. Funnel Plot Vitamin D Deficiency and Pregnant Women with COVID-19 Infection

reduces vitamin D synthesis [20], the southern European countries have higher levels of vitamin D because vitamin D status is influenced by dietary intake; for instance, samples with low levels of 25(OH) D were accepted, indicating improved resistance to the coronavirus by providing them with suitable supplements and raising the proper concentration [21].

The pooled estimate confirmed that persons with vitamin D deficiency were at an elevated risk of COVID-19 infection (OR = 1.47, 95 percent CI: 0.64, 3.36) and that this risk was higher in the previous meta-analysis (OR = 1.80; 95% CI: 1.72, 1.88) [22]. Additionally, Ilie et al. established a negative association between mean vitamin D levels and COVID-19 infection and revealed that vitamin D levels are extremely low in COVID-19-positive people [6].

Vitamin D significantly contributes to cellular immunity strengthening through a decrease in cytokine production brought on by the innate immune system. In patients with COVID-19, the innate immune system generates pro and anti-inflammatory cytokines in response to viral and bacterial infections [22]. Vitamin D can considerably lower and limit the production of Th1 cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma). Macrophages can express more anti-inflammatory cytokines and fewer primary inflammatory cytokines as a result of vitamin D [23]. This might lessen or perhaps stop the hyperinflammatory response in COVID-19 individuals. Natural killer (NK) cell reduction in vitamin D deprivation hinders the development of the cell barrier during early viral infection [22].

Since vitamin D has immune-stimulating and anti-inflammatory properties, adequate serum levels in vulnerable populations, such as pregnancy, may reduce the transmission of COVID-19 [8]. This is because vitamin D has immune-stimulating and anti-inflammatory properties. Thus, effective prophylactic programs for the condition are essential to avoid vitamin D deficiency and to accompany obstetric consequences

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in pregnant women, particularly during the winter. However, vitamin D management's curative and preventive effects in pregnant women with COVID-19 infection require more study and clinical studies.

According to the currently available literature, it is conceivable to assume that an adequate level of vitamin D serum in pregnant women may be particularly significant for preventing the developing course of COVID-19 [24]. Our study offers a number of strengths as a meta-analysis of published studies. The results showed that high-quality original papers were regularly published. However, we had some limitations. The differences between multiple research projects could be due to various study designs, clinical approaches, and biochemical methodologies. Additional research has to confirm the correlations between vitamin D serum levels and COVID-19 severity in pregnant women.

CONCLUSION

A vitamin D deficiency is one of the many things that alter the course of COVID-19. Lack of vitamin D is a severe problem that could influence how COVID-19 in pregnant individuals develops. This study's primary goal was to synthesize evidence on the potential impact of vitamin D deficiency on pregnant women with COVID-19 infection. Our findings suggest that low vitamin D levels may enhance the probability of COVID-19 disease. Physicians should therefore concentrate on establishing optimal vitamin D levels during pregnancy.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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