

The impact of vitamin D deficiency on gestational COVID-19 infection

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Abstract

Background: A worldwide pandemic infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020 caused an outbreak of the disease called COVID-19 infection. Multiple researchers investigated the effect of serum Vitamin D levels in preventing and treating infectious respiratory syndromes. Vitamin D is a steroid hormone and fat-soluble vitamin which helps preserve a strong immune system and is frequently taken as supplements for the prevention of viral and bacterial illnesses. The serum Vitamin D levels in pregnant women have led to discussions on the severity of the clinical outcomes and its possible role in preventing a COVID-19 infection by treating Vitamin D deficiency with supplements. The purpose of this study is to describe the most recent studies on the impact of vitamin D levels on pregnant women with COVID-19 infection.

Methods: This is a narrative literature review in which PubMed, Medline, ScienceDirect, Cochrane and Google Scholar database were used to select the most relevant research published in English before December 2022 and available to the authors.

Results and Conclusion: Although lower serum vitamin D levels are associated with a higher chance of contracting a serious disease caused by several respiratory viruses like SARS-CoV-2, they are not associated with a higher possibility of COVID-19 occurring in expecting women.

Key words: COVID-19, SARS-CoV-2, Vitamin D, Vitamin D deficiency, pregnant women

Introduction

In March 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the coronavirus disease 2019 (COVID-19) outbreak was classified as a pandemic (1). Despite intense international attempts, the spread of COVID-19 infection has caused more than 700 million confirmed illnesses and more than 6.5 million fatalities globally as of January 2023 (2).

Compared to SARS-CoV-1 and the Middle East Respiratory Syndrome (MERS), SARS-CoV-2 has increased transmissibility and infectivity, but had a lower fatality rate (3).

SARS-CoV-2 is mainly transmitted through respiratory droplets and binds to pulmonary epithelial cells via membrane-bound angiotensin-converting enzyme 2 (ACE-2), resulting in its down-regulation (4). Based on current knowledge, the host immune system plays a significant role in the elimination of SARS-CoV-2. Consequently, alterations in the immunological state during conditions like pregnancy could substantially impact the course of COVID-19 and its clinical outcomes (5).

Discussions about the advantages of normal serum vitamin D levels in preventing and treating infectious respiratory syndromes have been sparked by COVID-19. Numerous researchers have investigated how vitamin D supplementation and serum levels relate to the likelihood and severity of respiratory virus infection (6, 7). There is currently insufficient evidence to conclusively link vitamin D concentration to COVID-19 risk and consequences.

COVID-19 infection symptoms in pregnant women are comparable to those in the general population. However, compared to non-pregnant women, pregnant women are more likely to need treatment in the intensive care unit (ICU) when they exhibit clinical signs of cough, chills, headache, malaise, and shortness of breath (8). The availability of studies on vitamin D's function in expectant mothers who have COVID-19 is limited.

The aim of this narrative literature review is to present the current state of knowledge on the influence of vitamin D levels in pregnant women with COVID-19.

Methods and Search Strategy

We performed electronic searches using PubMed, Medline, ScienceDirect, Cochrane and Google Scholar databases for literature published in English before December 2022. The keywords used for the literature search were: COVID-19, SARS-CoV-2, pregnant women, Vitamin D, and Vitamin D deficiency. The results were further screened by heading and abstract. Finally, the screened full-text articles were evaluated by both authors and included in this review.

Results and Discussion

1. Covid-19 and vitamin D

Micronutrients, which include vitamins and minerals, are important for preserving a strong immune system and are frequently taken as supplements for the prevention of viral and bacterial illnesses. Anti-infective, anti-inflammatory, and immunomodulatory properties are properties of vitamin D. Vitamin D is a steroid hormone and fat-soluble vitamin that is created on the skin as a result of UV radiation. It can also be acquired exogenously through food sources or dietary supplements.

It helps to maintain the integrity of the physical barrier of the cell and boosts the activity of T cells, macrophages, and monocytes, which are part of the innate immune system (13).

Tekin et al. have suggested that vitamin D's immunomodulatory and anti-inflammatory properties are the potential mechanisms for the vitamin's positive effects on the treatment of a SARS-CoV-2 infection. It is thought that vitamin D can diminish inflammatory responses connected to a cytokine storm in COVID-19 and slow down the SARS-CoV-2 replication (14).

Low vitamin D levels (i.e., deficiency) were found to be significantly linked with worse patient outcomes and prognoses in a meta-analysis involving a total of 1,368 COVID-19-positive patients (15). Vitamin D deficiency plays an independent causal role in the expression of illness severity, remaining untouched by potential "confounders" like age, gender, or concomitant disorders. Notable was the marginally evident variation in vitamin D levels between individuals who survived versus not survived as a result of COVID-19 (15).

The COVID-19 pandemic has sparked debates over vitamin D's potential for both preventing and treating the illness. This is due to the fact that adequate blood vitamin D levels enable the immune system to work well, which can aid in a positive cellular response and defend against the severity of infections brought on by microorganisms (16).

2. COVID-19 and pregnant women

There is currently little information on the impact of SARS-CoV-2 infection on the mother or fetus in pregnant women. However, pregnant women are known to be more prone to experiencing severe symptoms when they contract viral respiratory disease due to the physiological changes typical during pregnancy, especially in the immune system (immunosuppression) and the cardiopulmonary system. Studies of other viruses conducted in the past have contributed to the knowledge regarding the effects of SARS-CoV-2 infection on pregnant women and the fetus. For example, only 1% of women who contracted influenza A H1N1 in 2009 were pregnant, but they were responsible for 5% of infection-related mortality (9).

In a very small study of 12 patients during the SARS-CoV pandemic in 2002 and 2003, women infected during their first trimester had a high miscarriage rate (57%). Women who were in their second and third trimesters developed intrauterine growth restriction (40%), and preterm delivery (80% [one spontaneous and 3 induced by maternal condition]) and 3 women died during pregnancy (25%) (10).

Another study found that of 11 MERS-CoV-infected pregnant patients, nine (91%) had adverse outcomes, six (55%) were admitted to the neonatal intensive care unit, and three (27%) died (11).

According to data so far from the Wuhan SARS-CoV-2 outbreak, the infection seems to affect pregnant women less severely than it did during earlier SARS-CoV and MERS-CoV outbreaks (9). It is essential to mention the small sample sizes of these studies, which could raise the risk of bias and low power.

There were very few cases of confirmed SARS-Cov-2 pneumonia in the first and second trimesters and a lot of cases in the third trimester (31). As a result, more data should be gathered from a bigger group of pregnant women who are infected with the virus.

To understand the effects of the novel coronavirus infection on the expectant mother, the fetus, and the course of pregnancy, follow-up studies of infected pregnant women with coronavirus during the first and second trimesters should be encouraged (12).

3. Vitamin D and Pregnancy

The serum calcifediol concentrations of many pregnant women around the world are relatively low, and this has been linked to an elevated risk for the mother's health, the health of the fetus or neonate, and even on later health events of the progeny. More than 10% of pregnant women in the majority of Mediterranean nations had mean serum Vitamin D levels < 10 ng/mL (17).

Another cohort study (18) indicated that pregnant women from various ethnic groups frequently have vitamin D deficiency: 26% in Sub-Saharan Africa, 40% in the Middle East, and 45% in South Asia

Numerous other cross-sectional investigations also produced similar findings. A review of 54 observational studies from around the world found that mothers with serum 25OHD concentrations below 12 ng/mL had a higher risk of having babies who were small for gestational age (OR 1.59) and a lower birth weight (mean difference—88 g) (19). This risk persisted (OR 1.43) in mothers with serum 25OHD concentrations below 20 ng/mL compared to mothers with higher serum calcifediol levels.

In a Cochrane review, Palacios et al. analysed 22 RCT's involving 3,725 women and reached similar findings. According to the result of this meta-analysis vitamin D supplements lower the risk of pre-eclampsia (RR 0.48), gestational diabetes mellitus (RR 0.51), and low birth weight (RR 0.55)—all statistically significant (20).

Another meta-analysis evaluated 24 RCTs which included 5,405 participants, and it concluded that vitamin D supplementation decreased the risk of being small-for-gestational-age (OR significant at 0.72) but not for perinatal mortality. Vitamin D supplementation slightly increased the mean birth weight by 75g (21).

A large RCT in Bangladesh involving primarily mothers with severe vitamin D deficiency (mean blood 25OHD of 10ng/ml) did not discover any positive effects of vitamin D supplementation (starting at 20 weeks of gestation) on their offspring either at birth or at age 1 (no effects of body length, weight, or head circumference) (22).

However, pregnancy-related problems and rates of caesarean sections decreased, according to the evaluation of the effects of high doses of vitamin D beginning before 16 weeks of gestation (23,24).

According to a study conducted in India, where the majority of pregnant women had mild vitamin D insufficiency, taking vitamin D supplements reduced the risk of preterm labour, pre-eclampsia, and gestational diabetes by almost 50% (25).

A meta-analysis studied 11,082 participants who received vitamin D supplementation during their pregnancy in doses ranging from 800 IU daily to 50,000 IU weekly (Liu et al. 2022). The risk of fetal death was considerably decreased by supplementation, as shown by the RR of 0.690 (95% CI, 0.482-0.985; P =.04). Preterm delivery, small for gestational age, and low birth weight were not significantly linked with the vitamin D supplementation intervention. The regulation of immunomodulation at the maternal-fetal interface, lung development, and vitamin D's effects on the genome are thought to be the mechanisms underlying its effects (26,27).

4. Vitamin D deficiency in COVID-19-positive pregnant women

Most recently a systematic review and a meta-analysis were conducted by Mazaheri-Tehrani et al. A case-control approach was employed in five of the seven studies that were included (13,14,28,29, 30) a retrospective cohort analysis was used in one study (31) and a cross-sectional design was used in another study (32).

The included studies included a total of 1799 pregnant women, 886 of whom were healthy, and 913 of whom had been diagnosed with COVID-19. A retrospective cohort research with 34 participants had the smallest sample size, while a case-control study with 491 people had the largest sample size. While several research studies accepted participants regardless of gestational age, three solely evaluated pregnant women in the third trimester. All studies considered quantities above 30 ng/ml of vitamin D to be within the normal range, with the exception of one conducted in Turkey by Tekin et al., who deemed levels above 50 ng/ml to be an ideal blood level.

Serum vitamin D levels were shown to be considerably lower in SARS-CoV-2-infected pregnant women compared to healthy subjects in five studies (13,28,29,31,32).

Tekin et al. discovered that pregnant women diagnosed with COVID-19 had no difference in serum vitamin D levels than controls (12.52 ± 8.28 ng/ml vs. 14.64 ± 10.72 ng/ml). Additionally, the blood vitamin D status of cases (21.28 ± 9.52 ng/ml) and controls (18.54 ± 8.04 ng/ml) in a case-control research conducted in Spain did not show any discernible differences (30).

Even though the mean serum vitamin D level was 2.55 ng/ml lower in the COVID-19 group compared to the healthy group (WMD = 2.55 ng/ml, 95% CI: 6.85 - 1.74), the combined results of five studies (14,28,29,30,31) did not demonstrate a significant difference between infected women and the non-infected group.

In December 2022 Vásquez-Procopio et al. published a retrospective study that involved 165 pregnant women in the third trimester.

By RT-qPCR, 86 people (52%) tested positive for SARS-CoV-2, while 79 people (48%) tested negative. 32 (19%) of the positives had no symptoms, 44 (27%) had just minor symptoms, and 10 (6%) had severe COVID-19 symptoms. The serum vitamin D levels were lower in SARS-CoV-2-infected women than in healthy, pregnant controls. Women who had severe symptoms also had considerably lower levels, which is consistent with the progression of the condition.

Three observational studies found a link between vitamin D deficiency and the severity/mortality of COVID-19 (16,34,35,36) however, four other studies did not find a link (37,38,39,40).

It is important to keep in mind that vitamin D status varies significantly depending on factors including age, ethnicity, place of residence, and sun exposure. Therefore, the association between low vitamin D status and severe COVID-19 is still debatable.

Conclusion

Most of the studies indicate a connection between the severity of COVID-19 infection and vitamin D deficiency in pregnant women. Moreover low serum vitamin D levels are a risk factor for the development of severe COVID-19 in pregnant women which supports the use of Vitamin D supplements to prevent worse COVID-19 outcomes during pregnancy. According to the available data, vitamin D has a critical function in immune regulation and has a connection to the prevention of respiratory infections and local inflammation at the pulmonary level. Vitamin D helps to prevent illnesses and reduces the severity of illness caused by several respiratory viruses, such as influenza and respiratory syncytial virus.

Although lower serum vitamin D levels are linked to a greater risk of developing a serious illness, serum vitamin D levels are not linked to the likelihood of COVID-19 occurrence in expectant women. The relationship between vitamin D levels and COVID-19 in pregnant women should be better researched by additional studies, comparing participants with adequate vitamin D status to those with vitamin D deficiency. These discoveries might be useful for newly discovered viral illnesses in the future.

Declaration of Competing Interest

The authors declare that they have no relationships or financial conflicts that could have seemed to affect the results presented in this study.

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