



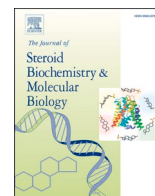
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Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Impact of vitamin D on the course of COVID-19 during pregnancy: A case control study

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ARTICLE INFO

Keywords:

COVID-19
Pregnancy
Vitamin D deficiency
Immune system
Cytokine storm

ABSTRACT

Objective: We aimed to evaluate the vitamin D status of pregnant women with COVID-19, and the association between vitamin D level and severity of COVID-19.

Methods: In this case control study, 159 women with a single pregnancy and tested positive for SARS-CoV-2, and randomly selected 332 healthy pregnant women with similar gestational ages were included. COVID-19 patients were classified as mild, moderate, and severe. Vitamin D deficiency was defined as 25-hydroxycholecalciferol <20 ng/mL (50 nmol/L), and 25-OH D vitamin <10 ng/mL was defined as severe vitamin D deficiency, also 25-OH D vitamin level between 20–29 ng/mL (525–725 nmol/L) was defined as vitamin D insufficiency.

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

Conclusion: The vitamin D levels are low in pregnant women with COVID-19. Also, there is a significant difference regarding to vitamin D level and COVID-19 severity in pregnant women. Maintenance of adequate vitamin D level can be useful as an approach for the prevention of an aggressive course of the inflammation induced by this novel coronavirus in pregnant women.

1. Introduction

The novel Severe Acute Respiratory Syndrome-coronavirus-2 (SARS-CoV-2) originated in Wuhan, Hubei, China in December 2019 [1]. Since it was declared a pandemic by the World Health Organization on March 11, 2020, millions of people around the world have been affected [2,3].

Although COVID-19 is characterized by high infectivity, the majority of those affected are asymptomatic. While most of the cases show mild symptoms, severe illness develops only in less than 15% [4,5]. Pregnant women with novel coronavirus 2019 (COVID-19) and their newborns remain in the substantially unknown part of the issue. Comparing to nonpregnant women, pregnancy may worsen the course of COVID-19 infection. In the literature, it has been indicated that COVID-19 may cause an increase in obstetric complications such as preterm labor and

fetal distress [6–8].

1.1. Vitamin D and pregnancy

Vitamin D is a fat-soluble vitamin and steroid hormone produced on the skin with the effect of ultraviolet radiation and also can be obtained from exogenous food sources or dietary supplements. Maternal vitamin D deficiency is an important worldwide public health problem that may worsen pregnancy outcomes [9]. Vitamin D deficiency is common among pregnant women. In a recent study, the prevalence of vitamin D deficiency in pregnant women in our country was reported as 81.4–86%. [10,11]. Vitamin D has various effects during pregnancy such as placental implantation, angiogenesis, immune function, oxidative stress, endothelial function, inflammatory response, and glucose homeostasis

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<https://doi.org/10.1016/j.jsbmb.2021.105964>

Received 11 May 2021; Received in revised form 4 August 2021; Accepted 9 August 2021

Available online 11 August 2021

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[12,13]. A meta-analysis of observational studies has shown a positive association between low vitamin D levels and adverse pregnancy outcomes such as preeclampsia, gestational diabetes mellitus, preterm birth, and SGA (small-for-gestational age) [14].

1.2. Vitamin D and COVID-19

Vitamin D supplementation has been shown to reduce the incidence of viral respiratory infections [15–17]. It is thought that vitamin D supplementation could be a useful method to reduce the risk of influenza and COVID-19 [15–18]. The role of vitamin D in the response to COVID-19 is twofold. First, vitamin D increases the production of antimicrobial peptides in the respiratory epithelium and reduces viral replication rates, making viral infection and symptoms milder. Second, Vitamin D reduces the inflammatory response to SARS CoV-2 by increasing anti-inflammatory cytokine concentrations and decreasing the concentrations of pro-inflammatory cytokines which increase lung damage [16].

Recently, a range of studies reported that low vitamin D levels are associated with an increased risk of COVID-19 positivity [17,19–21]. Additionally, many studies in the literature show a strong association between vitamin D deficiency and COVID-19 hospitalisation, severity and mortality [15,17,21–24]. ARDS (acute respiratory distress syndrome) caused by COVID-19 and its damage to other organs is secondary to cytokine storm and related oxidative stress. Active hydroxyl forms of vitamin D are anti-inflammatory, inducing anti-oxidative responses and inducing innate immunity against infectious agents [24–26]. Lower vitamin D levels in winter are facilitating viral outbreaks, and vitamin D supplementation may reduce the incidence, severity, and risk of viral diseases [24–27]. On the other hand, the association between the incidence of severe COVID-19 and 25-OH D vitamin level is controversial, as some studies do not show a benefit when it is administered in critical cases [15,28–33].

In our study, for the first time, we aimed to evaluate 25-OH D vitamin levels of pregnant women with and without COVID-19 infection, which is a sensitive group, and also whether the vitamin D level are associated with the severity of COVID-19.

2. Material and methods

2.1. Procedure and patient selection

This case control study was carried out between July–December 2020 at the Ministry of Health Ankara City Hospital, the main public maternity hospital which handles approximately 15,000 deliveries yearly and covers all surgical and medical disciplines.

159 women with a single pregnancy, from all trimesters and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-

CoV-2) using quantitative RT PCR (qRT-PCR) from nasopharyngeal and oropharyngeal samples were included in the study. According to the Chinese management guideline for COVID-19 (version 6.0), patients were classified as mild, moderate, and severe [34]. Those who had maternal systemic diseases (diabetes, cardiovascular diseases, hypertensive diseases of pregnancy, asthma, thromboembolic disorders, inflammatory bowel diseases, autoimmune connective tissue diseases, other infectious diseases) and multifetal pregnancy were excluded. Randomly selected 332 singleton pregnant women with similar gestational ages were designed as the control group for the same period. The following information was recorded by the researchers: maternal age; gravidity; parity; the number of living children; previous miscarriages; pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters; BMI \geq 30 was defined as obese); gestational age at diagnosis; minimum oxygen saturation; disease severity; maternal mortality; mode of delivery; obstetric and neonatal outcomes; taking vitamin D supplementation; and the following laboratory parameters at the time of admission: 25-OH D vitamin (ng/mL), D-dimer (mg/L), CRP, IL-6. According to the National Institute's prophylaxis recommendations for pregnant women, whether taking vitamin D supplementation was noted. Blood samples were taken from the antecubital vein and serum 25-OH D vitamin levels (which is the most reliable biomarker of functional vitamin D status) were measured using enzyme-linked immunosorbent assay (ELISA). 25-hydroxycholecalciferol level $<$ 20 ng/mL (50 nmol/L) was defined as vitamin D deficiency, $<$ 10 ng/mL was defined as severe vitamin D deficiency, and 25-OH D vitamin level between 20–29 ng/mL (525–725 nmol/L) was defined as vitamin D insufficiency, according to the Endocrine Society Guidelines [35].

2.2. Statistical analyses

SPSS for Microsoft Windows 24.0 (SPSS Inc., Armonk, NY, USA) was used for statistical analyses. Frequency tables and descriptive statistics were used in the interpretation of the findings.

The relationship between two qualitative variables, the expected value levels were analyzed by the Fisher-Exact and Pearson- χ^2 test. The Mann-Whitney *U* test (*Z*-table value) was used to compare the measurement values of two independent groups. $p < 0.05$ indicates a statistically significant correlation.

3. Results

The patients of COVID-19 and the normal pregnancy group did not differ in terms of maternal age, gestational week, gravidity, parity, pre-pregnancy BMI, and vitamin D supplementation, as seen in Table 1. A statistically significant difference was found between the groups in terms of Apgar 5th min value. Apgar 5th min scores were significantly

Table 1
Characteristics of the patients.

Group	COVID-19 (n = 159)		Control (n = 332)		P**
	Median	[Min-Max]	Median	[Min-Max]	
Age (year)	29.6 \pm 5.72*		27.48 \pm 5.14*		p = 0.055
Gravidity	2.0 [1.0–7.0]		2.0 [0.0–7.0]		p = 0.174
Parity	1.0 [0.0–5.0]		1.0 [0.0–5.0]		p = 0.279
Abortion	0.0 [0.0–3.0]		0.0 [0.0–4.0]		p = 0.064
Living child	1.0 [0.0–5.0]		1.0 [0.0–5.0]		p = 0.312
Gestational week	34.0 [6.0–41.0]		31.0 [5.0–41.0]		p = 0.166
Pre-pregnancy BMI (kg/m ²)	27.08 \pm 2.98*		26.60 \pm 4.51*		p = 0.064
Birth weight	3202.48 \pm 683.57*		3384.41 \pm 400.30*		p = 0.161
Apgar 1st min	8.0 [0.0–9.0]		8.0 [5.0–8.0]		p = 0.386
Apgar 5st min	9.0 [0.0–10.0]		10.0 [7.0–10.0]		p = 0.000
25-OH D vitamin (ng/mL)	12.46 \pm 6.46*		18.76 \pm 13.74*		p = 0.004

* Mean \pm SD (SD=Standard Deviation).

** Mann-Whitney *U* test.

lower in the COVID-19 group than the control group ($p < 0.05$).

As presented in Table 1, the Vitamin D levels of the patients in the COVID-19 group (12.46) were statistically significant lower than the control group (18.76) ($p = 0.004$). 11 newborns were admitted to NICU in COVID-19 group, and indication was low birth weight in 8 cases, transient tachypnea of newborn in 3 cases. The mothers of the 7 newborns were in mild, 3 were in moderate, 1 was in severe COVID-19

Table 2
Distribution of the patients according to vitamin D levels.

	COVID-19 (n = 159)	Control (n = 332)	
25-OH D vitamin (ng/mL)	n [%]	n [%]	p*
<10: severe deficiency	59 [37.1]	35 [10.5]	p = 0.000
10–19: deficiency	36 [22.6]	108 [32.5]	
20–29: insufficiency	31 [19.5]	128 [38.6]	
≥30: normal	33 [20.8]	61 [18.4]	

* Pearson- χ^2 test.

Table 3
Demographic and clinical features of the severe COVID-19 cases.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (year)	35	24	27	31	30	36	41
Gravidity	2	2	1	4	1	3	6
Gestational week	31	33	38	34	28	32	12
Pre-pregnancy BMI (kg/m ²)	20	28	31	26	25	30	28
25-OH D vitamin (ng/mL)	6	4.5	10.9	8	12	9.1	10.6
D vitamin supplementation	–	–	–	–	–	–	–
Calcium (mg/dL)	8	7.5	7.4	8	8.30	7.8	7.6
Alkaline phosphatase (U/L)	150	103	61	42	96	214	32
Total protein (g/L)	56	51	54	48	55	47	48
D-dimer	1.46	1.65	15.4	2.1	0.92	3.86	0.9
CRP	127.9	38	167.7	181.5	100.5	186.8	87.1
IL-6	101	8.6	75.5	701	33.3	135	146
ICU admission	+	+	+	+	+	+	+
High flow oxygen	+	+	+	+	+	+	+
Mechanical ventilation	–	–	+	+	+	+	+
Maternal outcome	Discharged healthily at 30 weeks		Maternal ex	Maternal ex	Maternal ex	Maternal ex	Maternal ex
Birth weight (g)	NA	1870	NA	NA	1720	2050	–
APGAR 1st and 5th min	NA	7/9	NA	NA	5/7	7/9	–
NICU	NA	+	+	NA	+	+	–
Neonatal complication	NA	LBW	LBW, RDS	NA	LBW, RDS	LBW	abortion
Nasopharyngeal PCR of the newborn	NA	–	–	NA	–	–	–
Neonatal outcome	NA	Discharged healthily on 18 days of life	Discharged healthily on 12 days of life	NA	Discharged healthily on the 88 days of life	Discharged healthily on the 24 days of life	abortion

ICU: intensive care unit.

NICU: neonatal intensive care unit admission.

LBW: low birth weight.

RDS: Respiratory distress syndrome.

NA: Not applicable.

Table 4
25-OH D vitamin level in patients according to COVID-19 severity.

	n	COVID-19 Severity		p**
		Mild	Moderate + Severe	
25-OH D vitamin	Mean \pm SD	128 13.69 \pm 9.72	31 9.06 \pm 8.82	p = 0.041

* Standard Deviation.

** Mann-Whitney U test.

category. One fetus died in utero at 25 gestational weeks, whose mother was in mild COVID-19 category and on the 4th day of the SARS-CoV-2 PCR positivity. Also, nasopharyngeal PCR of the newborn was negative for SARS-CoV-2.

As presented in Table 2, there was a significant difference in 25-OH D vitamin levels between COVID-19 and control group ($p = 0.000$). While the majority of the patients in the control group had vitamin D insufficiency and deficiency, severe 25-OH D vitamin deficiency had the highest rate in the COVID-19 patients.

As presented in Table 3, five mothers died in severe COVID-19 category. While one mother was at 12 gestational week, four of them were in mid-late third trimester of the pregnancy. 25-OH D vitamin level of those were ranging between 4.5 and 12.

The distribution of vitamin D levels according to COVID-19 categories was given in Table 4. There was a statistically significant relationship between groups in terms of COVID-19 severity and 25-OH D vitamin level ($p < 0.05$). Although 25-OH D vitamin levels were low in both groups, 25-OH D vitamin levels of those in the mild COVID-19 group (13.69) were significantly higher than those in the moderate or severe COVID-19 group (9.06) ($p < 0.05$).

There was a significant relationship between groups in terms of 25-OH D vitamin deficiency and COVID-19 severity ($p = 0.000$). In both mild and moderate + severe COVID-19 groups, the majority of the patients had severe 25-OH D vitamin deficiency (Table 5).

There was no statistically significant relationship between vitamin D supplementation and COVID-19 severity ($p > 0.05$). However, it was observed that all of those who had severe COVID-19 were the patients who did not take vitamin D supplementation. In those taking vitamin D supplementation, the mild COVID-19 rate was 77.8 %; while moderate and severe was 22.2 %, as seen in Table 6.

Table 5
Distribution of the COVID-19 patients according to vitamin D levels.

25-OH D vitamin (ng/mL)	COVID-19 Group		p*
	Mild n [%]	Moderate + Severe n [%]	
<10: severe deficiency	36 [28.1]	23 [74.2]	p = 0.000
10–19: deficiency	33 [25.8]	3 [9.7]	
20–29: insufficiency	28 [21.9]	3 [9.7]	
≥30: normal	31 [24.2]	2 [6.4]	

* Pearson- χ^2 test.

Table 6
Relationship between Vitamin D supplementation and COVID-19 severity.

		COVID-19 Severity		p*	
		Mild	Moderate + Severe		
Vitamin D supplementation	Yes (n = 36)	n 28 % 77.8	n 8 % 22.2	p = 0.818	
	No (n = 123)	n 100 % 81.3	n 23 % 18.7		

* Pearson- χ^2 test.

4. Discussion

There are several reports from different countries mentioning that vitamin D deficiency is associated with the incidence and severity of COVID-19. The ongoing debate is focusing on the idea that vitamin D supplementation may reduce the viral infection risk and the majority of the risk groups for severe COVID-19 tend to have vitamin D deficiency.

It is known that SARS-CoV-2 causes an excessively increased production of proinflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-8 (IL-8), interleukin-12 (IL-12), and especially interleukin-6 [IL-6] [36]. Hyperactivation of immune cells results in hypercytokinemia with excessive innate immune response and infiltration of inflammatory cytokines in lung cells [37, 38]. Extensive tissue damage with dysfunctional coagulation results in acute lung injury called acute respiratory distress syndrome (ARDS) related to COVID-19. An unrestricted immune reaction in the host leads to the situation called cytokine storm which is associated with the severity of COVID-19.

Apart from its effects on bone health and calcium-phosphor metabolism, vitamin D also plays an essential role in the immune system. T regulatory lymphocytes (Tregs) generally provide a basic defense against viral infection and prevent uncontrolled inflammation which has been reported to be low in COVID-19 patients, furthermore significantly lower in severe cases [39]. It suggests that supplementation of vitamin D, which is effective in raising Tregs levels, may be beneficial in reducing the severity of COVID-19 [40]. Vitamin D inhibits T cell proliferation and activation and acts on most immune system cells such as macrophages, neutrophils, and dendritic cells. Also, vitamin D has a regulatory role on the immune system, downregulating the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines [41,42]. In some recent studies, it was reported that vitamin D deficiency is related to increased levels of pro-inflammatory cytokines such as TNF- α and IL-6 and it was claimed that adequate levels of vitamin D may reduce the incidence of cytokine storm, which can occur in severe COVID-19 cases [42–44]. Vitamin D stabilizes the immune response supporting the innate immune system that provides an anti-inflammatory response [42,43]. Due to its effects on the immune system, vitamin D may reduce the course of severe COVID-19 [15,17,21–24].

In the literature, the majority of the studies reported a significant association between vitamin D deficiency and COVID-19 incidence, while some others claimed the opposite by showing that there is no such

association [15,18–24,43,44]. In this study, we observed a prominent association between vitamin D deficiency and the incidence of COVID-19 in pregnant women. Additionally, 25-OH D vitamin levels were low (<20 ng/mL) on both COVID-19 (12.46) and control (18.76) groups. Considering the fact that vitamin D deficiency is common among pregnant women, we think it is not surprising that 25-OH vitamin D levels were also low in healthy pregnant women in control group [9–11]. Besides the incidence of COVID-19, our findings showed a significant correlation between 25-OH D vitamin level and the COVID-19 severity in pregnant women, and this is in line with the majority of the related literature [15,18–23,31–33,42,43].

Through several mechanisms, vitamin D is likely to reduce acute respiratory tract infection risk [15–17]. For prevention of the infection, 25-OH D vitamin level is recommended to be between 40–60 ng/mL [24]. A meta-analysis of 15 randomized controlled trials that investigated the effectiveness of vitamin D supplementation in reducing the risk of developing respiratory tract infections indicated no significant risk reduction among healthy individuals [45]. However, supplementation is required especially in the case of vitamin D deficiency. In 2011, the Endocrine Society recommended 1000–4000 IU/day (up to 10,000 IU/day particularly for obese individuals) vitamin D supplementation to reach serum 25-OH D vitamin levels above 30 ng/mL, especially in winter [35]. The upper limit of supplementation for pregnant women is reported to be 5000 IU/day in the literature [46]. In our study population, the majority of the patients were not on vitamin D supplementation. Also, the patients taking vitamin D supplements were using it at the prophylaxis dose. Although our results showed no statistically significant correlation between vitamin D supplementation and COVID-19 severity, similar to the literature, we observed that none of the severe cases were using vitamin D supplementation [15,19,21].

If a good nutritional status and vitamin D supplementation provided in vulnerable populations such as pregnancy, it may be conceivable that the spread of COVID-19 will decrease due to the immune-enhancing and anti-inflammatory effects of vitamin D [47]. Therefore, effective prophylaxis programs for vitamin D deficiency are essential to prevent vitamin D deficiency and its obstetric outcomes in pregnant women, especially in the winter season [48]. However, further research and clinical trials are needed on both the therapeutic and preventive roles of vitamin D supplementation in pregnant women with COVID-19 infection. Based on the available literature, a plausible presumption is that the pre-infectious level of vitamin D in pregnant women might be of particular importance for the resistance to the progressing course of COVID-19.

A potential limitation of this study is the relatively low number of moderate and severe COVID-19 cases, which was probably related to the course of COVID-19 being mild in most of the pregnant patients. However, although the numbers were low since the population size is high, the small numbers were considered sufficient to present early results about COVID-19 and its relationship with vitamin D level during pregnancy.

To the best of our knowledge, this is the first study analyzing the 25-OH D vitamin levels in pregnant COVID-19 patients. Moreover, the high number of patients in the study population recruited in a single-center is another fundamental strength of our study.

5. Conclusion

Vitamin D deficiency is just one of the many factors that affect the course of COVID-19. Vitamin D deficiency can be thought of as a risk factor for severe COVID-19. Vitamin D deficiency is an important issue that may affect the course of COVID-19 in pregnant patients. Vitamin D supplementation and maintenance of adequate vitamin D levels can be useful as an approach for the prevention of an aggressive course of the inflammation induced by this novel coronavirus in pregnant women.

Funding

No funding was received for conducting this study.

Author contributions

SS: conceptualization, methodology, data collection, investigation, visualization and writing the article; DFO: reviewing and editing; FDYY, DUH, GBU, SGA: data collection; AT, SOE: formal analysis, visualization; OMT: supervision; DS: conceptualization, methodology, reviewing, and editing, project administration.

Ethics approval

This study was approved by the Ethics Committee of the Ankara City Hospital on December 23, 2020, with the number E1-20-1192.

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors report no declarations of interest.

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