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SERUM VITAMIN D CONCENTRATIONS AND COVID-19 IN PREGNANT WOMEN, DOES VITAMIN D SUPPLEMENTATION IMPACT RESULTS? A COMPREHENSIVE STUDY

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Abstract

Aim: Low vitamin D levels were related to an increased risk of upper respiratory tract infection and pneumonia. Vitamin D might therefore protect against symptoms of the Covid 19. The present study aims to evaluate the relationship between the acquisition and course of Covid 19 and serum vitamin D levels and investigate the prophylactic efficacy of vitamin D supplementation in pregnant women.

Methods: This case-control study was conducted on 318 pregnant women admitted to our tertiary clinic to give birth between March 2020 and December 2021. All cases were tested for Covid 19 via nasopharyngeal swab. Fifty-four patients with positive PCR for SARS-CoV-2 (Group 1) were matched with 264 consecutive healthy controls (Group 2). 25 OH D Vitamin levels were measured and compared between the two groups, along with the frequency of vitamin D supplementation.

Results: Group 1 showed significantly low mean 25 OH D levels, compared to Group 2 (10,22 ± 7,10 (3-37) ng/ml vs. 16,63 ± 10,80 (3,40-48,90) ng/ml, p = 0,000). Sixteen point seven % of controls and 3,7% of cases had normal Vitamin D levels (>30 ng/mL); the difference was also statistically significant (p=0,005). The frequency of vitamin D supplementation was also detected higher in controls than those with positive SARS-CoV-2 (35,6% vs. 14,8%, p=0,003).

Conclusions: Sustaining adequate levels of Vitamin D may positively impact protection against Covid 19 during pregnancy. In this context, Vitamin D supplementation should be considered for the pregnant population, particularly in settings where profound vitamin D deficiency is common.

Keywords: *Vitamin D deficiency; COVID-19; pregnancy; vitamin D supplementation*

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Introduction

The World Health Organization declared an acute respiratory syndrome-Coronavirus-2 pandemic in March 2020 as it spreads worldwide[1]. Although most infected individuals are asymptomatic or mildly symptomatic, among elderly patients or those with concomitant comorbid conditions (cardiovascular disease, diabetes, chronic respiratory disease, and hypertension), it tends to be severe[2].On the other hand, physiological changes in the cardiopulmonary system during pregnancy may influence the Covid 19. Increased heart rate reduced pulmonary residual capacity, and hyperventilation during pregnancy facilitate progression and bring the additional risk of a severe form of infection[3].

Growing evidence suggests that maternal Covid 19 increases risks of neonatal morbidities and mortality, preterm delivery, and small for gestational age (SGA) along with maternal morbidity and mortality[4]. Di Mascio et al. also reported a strong relationship between Covid 19 and early pregnancy loss, preterm delivery, preeclampsia, operative labor, and perinatal mortality[5]. The balance between T helper-1 and T helper-2 cells is crucial for a successful pregnancy, and it could be disturbed by a severe form of Covid 19[6].

Low vitamin D levels were related to an increased risk of upper respiratory tract infection and pneumonia[7]. A meta-analysis evaluating 25 randomized controlled trials showed that Vitamin D supplementation avoids acute respiratory tract infections, and people who were very deficient in vitamin D (< 10 ng/mL) experienced particular benefits[8]. Vitamin D induces antimicrobial peptides, defensins, and cathelicidin and plays a pivotal immunomodulatory role[9]. Vitamin D may also protect against symptoms of the Covid 19, primarily by increasing the level of angiotensin-converting enzyme 2 in the lungs[10].

Less is known about Covid 19 prophylaxis. Thus, risk-reducing strategies and preventive measures for the acquisition and course of the disease are warranted. Vitamin D3 supplementation before or during Covid 19 may benefit the results of the recent studies[11]. When considering the increased rate of receive to the intensive care unit and the risk of thromboembolic complications, need for supplemental oxygen, ventilation, and mortality, pregnant women would be a major target population for prophylaxis. Herein, we also investigated the prophylactic efficacy of vitamin D supplementation on the course of infection in pregnant women.

Materials and Methods

This case-control study was carried out between March 2020 and December 2021 at Izmir Katip Celebi University Ataturk Training and Research Hospital, where 1500 deliveries were managed annually. An informed consent form in accordance with the principles of the Declaration of Helsinki was taken from all pregnant women, both for themselves and their newborns. The study protocol was approved by the institutional ethics committee and the Turkish Ministry of Health (0408).

All single pregnant women from the third trimester were tested for SARS CoV 2 infection using quantitative RT PCR (qRT-PCR) from nasopharyngeal and oropharyngeal swabs before admission to give birth in our tertiary clinic and included in the study. Those with maternal systemic diseases (hypertension, diabetes mellitus, systemic lupus erythematosus, chronic kidney failure) and multifetal pregnancies were excluded. Patients were divided into two groups according to PCR positivity; 54 pregnancies with positive PCR were matched with 264 health controls and described as Group 1 and 2, respectively. 25-OH D vitamin (ng/mL) was recorded at the time of approval for delivery. The matched controls matched closely regarding the 25(OH)D concentration measurement date. Patients in Group 1 were evaluated according to WHO Covid-19 guidelines; SARS-CoV-2 seropositive all patients were asymptomatic ex-

cept two patients who had severe disease[12]. Newborns of group 1 were also tested for SARS CoV 2 using quantitative RT PCR (qRT-PCR) from nasopharyngeal and oropharyngeal swabs.

Blood samples of the entire patient's serum 25-OH D vitamin levels were measured using enzyme-linked immunosorbent assay (ELISA) via DxI 800Beckman, Coulter (California) with interassay variation and intraassay variation of 7%. Maternal age; gravidity; parity; disease severity; maternal mortality; mode of delivery; gestational age; obstetric and neonatal outcomes; total hospitalization length; vitamin D supplementation status; and 25-OH D vitamin (ng/mL) at the time of approval for delivery were recorded.

We use Endocrine Society Guidelines criteria for the description of vitamin D deficiency levels such as<10 ng/mL: severe vitamin D deficiency;10-20 ng/mL (50 nmol/L): vitamin D deficiency; 20−29 ng/mL (50−74 nmol/L): vitamin D insufficiency[13].

Table 1. Comparison of demographic features and clinical characteristics according to study groups

Variables	Study Groups		Test Statistics	p-value
	Covid 19 Group (n=54)	Control Group (n=264)		
p-val	27.92 ± 6.17 (17-43)	27.98 ± 5.81 (18-44)	7123.5	0.994
Gravidity				
1	16 (29.6)	76 (28.8)	8.462	0.076
2	19 (35.2)	87 (33.0)		
3	19 (35.2)	38 (14.4)		
4	2 (3.7)	36 (13.6)		
5+	3 (5.6)	27 (10.2)		
Parity				
0	15 (27.8)	81 (30.7)	1.653**	0.899
1	21 (38.9)	94 (35.6)		
2	13 (24.1)	49 (79.0)		
3	3 (11.5)	23 (8.7)		
4	2 (3.7)	14 (5.3)		
5+	0 (0.0)	3 (1.1)		
Birth Weight†	3141.76 ± 668.76 (621.0-4330.0)	3265.76 ± 484.32 (2000.0-4900.0)	6529.0	0.330
1.st minute APGAR				
0-6	6 (11.1)	15 (5.7)	-**	0.142
7-10	48 (88.9)	249 (94.3)		
5.th minute APGAR				
0-6	6 (11.1)	15 (5.7)	-**	0.142
7-10	48 (88.9)	249 (94.3)		
Maternal hospitalization length†	2.37 ± 3.06 (1-20)	2.00 ± 1.52 (1-12)	6319.5	0.147
25-OH D vitamin (ng/mL) †	10.22 ± 7.10 (3-37)	16.63 ± 10.80 (3.40-48.90)	4556.0	0.000*
Vajinal Labor	14 (25.9)	130 (49.2)	26.723	0.000*
Sectio Cesarea	35 (64.8)	126 (47.7)	5.237	0.025*

**p<0.05 and **Fisher's Exact test, †mean ± standard deviation (minimum-maximum).*
Other variables are presented with frequency and percentage based on columns.
APGAR: Appearance, Pulse, Grimace, Activity, Respiration

As the first step of analyzing the data, the conformity to the normal distribution was examined with the Shapiro Wilk test. The Mann-Whitney Y test was used to compare the means of two independent groups that did not have a normal distribution. In cases where the sample size assumption of the relationships between the categorical data is met (n>5), with the Pearson Chi-Square test; In cases where it was not met, it was applied with Fisher's Exact test. Analyzes were performed in IBM SPSS 25 program.

Results

The demographic features and clinical characteristics of the two groups are shown in table 1. The median age of the control group was higher than those with Covid 19, but the difference was not statistically significant (p=0.994). Gravidity, parity, birth weight, APGAR scores, and total hospitalization length were also similar.

Mode of delivery varied significantly different between groups, namely cesarean section rates were 64.8% vs. 47.79% among Group 1 and 2, respectively (p=0.025). The maternal mortality rate was found to be 3.7% (n=2) in the case group, and this rate was statistically significantly higher than the control group (3.7% vs. %0 p= 0.028). Both cases had a severe form of Covid 19 and a history of mitral valve replacement. Gestational ages of the patients at the time of labor were 35 and 25 weeks, while mortality happened at postpartum 20th and 15th days, respectively.

Table 2. Distribution of fetal and maternal mortality rates between the two groups

	Study Groups			
Variables	Covid 19 Group (n=54)	Control Group (n=264)	Test Statistics	p-value
Intrauterine fetal death	2 (3.7)	14 (5.3)	-**	1.000
Maternal mortality	2 (3.7)	0 (0.0)	-**	0.028*

**p<0.05 and **Fisher's Exact test*

†mean ± standard deviation (minimum-maximum). Other variables are presented with frequency and percentage based on columns.

Table 3. Relationship between study groups and vitamin D levels.

	Study Groups			
25-OH D vitamin (ng/mL)	Covid 19 Group (n=54)	Control Group (n=264)	Test Statistic	p-value
Severe vitamin D deficiency	33 (61.1)	110 (41.7)	12.944	0.005*
Vitamin D deficiency	14 (25.9)	54 (20.5)		
Vitamin D insufficiency	5 (9.3)	56 (21.2)		
Normal	2 (3.7)	44 (16.7)		

*p<0.05

Table 4. Relationship between study groups and Vitamin D supplementation.

	Study Groups			
	Covid 19 Group (n=54)	Control Group (n=264)	Test Statistic	p-value
Vitamin D supplementation	8 (14.8)	94 (35.6)	8.895	0.003*

*p<0.05

The first case also had severe vitamin D deficiency with a 25 OH D level of 4 ng/mL. (Table 2). That value could have been lower than before COVID-19 due to COVID-19[14]. Intrauterine fetal death was present at the time of admission in 16 patients. Among them, 2 cases were in controls, and 14 were in the Covid-19 group, while their 25-OH D vitamin levels varied between 5-16 ng/mL. All fetuses had negative PCR test results for SARS-CoV-2. As shown in Table 2, there was no relationship between Covid 19 and fetal death (p =1.000).

The patient with severe vitamin D deficiency (<10 ng/mL) rate in Covid 19 group was significantly lower than in the control group (41.7% vs. 61.1%; p=0.005). Normal vitamin D levels (>30 ng/mL) were detected significantly higher in the control group than those with Covid 19 (16.7 % vs. 3.7%; p=0.005). The categorical distribution of vitamin D levels between groups is shown in table 3. Concerning vitamin D supplementation, we found that it was higher in the control group, and the difference was statistically significant (35.6% vs. 14.8%; p =0.003) (Table 4).

Discussion

In recent years, the effect of vitamin D on the immune system has gained importance, and experimental studies have shown that vitamin D exerts immunologic activities on various components of the native and adaptive immune system, as well as endothelial membrane stability. Some trials demonstrated protective efficacy on infection, especially those of viral origin[15].

Covid-19, which has extended worldwide like a pandemic since March 2020, has led to severe morbidities and even mortality in the immunocompromised and pregnant population. Accordingly, several clinical studies have been conducted to determine vitamin D's effectiveness in preventing and treating disease[15-16]. Thus, our study focused on whether adequate vitamin D level during pregnancy affects the protection against transmission and severity of the disease, and vitamin D supplementation during pregnancy could be an eligible method for this purpose.

Our study found severe vitamin D deficiency (<10 ng/mL) was higher in the Covid-19 + group. This finding suggests that low vitamin D levels may impair local immune system barriers and facilitate the transmission of infection. In their study, Seven et al. also found a relationship between vitamin D status and the severity of Covid 19 in pregnant women. Interestingly, the entire study cohort showed inadequate serum vitamin D concentrations regardless of the severity of the disease. They further reported that a 25(OH)D level under 14.5 ng/ml is associated with severe Covid 19 and/or poor prognostic factors[17]. Similar to our study, In the study of Ferrer-Sánchez et al. [18] in which the vitamin D levels of pregnant women with Covid 19 were compared with the healthy control group, although the levels were low in both groups, 89% of pregnant women with Covid 19 had 25(OH)D deficiency (<20 ng/mL); it was present in 75.30% of Covid 19 negative pregnant women, the results were statistically significant; also they reported that pregnant women with 25(OH)D deficiency was 2.68 times more likely to contract COVID-19.

As a result, adequate vitamin D levels could be protective against both transmission and severity of the disease.

In addition to the relationship between vitamin D levels and the risk of contracting Covid 19, in another study of 159 Turkish patients with Covid 19 and 332 healthy controls, serum 25(OH)D levels were significantly lower in patients with Covid 19[19]. The relationship between vitamin D deficiency and symptomatology of Covid 19 in pregnancy is reported in a recent study[20].

Nonetheless, a cohort study of 447 Turkish pregnant women with positive and negative Covid 19 tests showed no association between vitamin D levels and severity of Covid 19 even when serum 25(OH)D levels

were found to be 37 ± 27 and 31 ± 21 nmol/L in Covid 19 group and control group, respectively (p = 0.001)[21]. This contradictive finding is likely because the entire cohort of the study had normal (>30ng/mL) vitamin D levels; in other words, there were no cases of vitamin D deficiency, and the severity of the disease may be influenced by clinical factors rather than vitamin D levels. In our study, however, the proportion of patients with normal vitamin D levels was significantly higher in the control group (%16.7% (n= 44) vs. 3.7% (n=2)) (p =0.005).

Another study of 50 hospitalized pregnant with Covid 19 showed that the mean serum 25(OH)D level of the study population was 10-59, significantly lower than the accepted cut-off values (p < 0.001). This value was within the limits of severe vitamin deficiency according to the classification in our study, which was found to be higher in the Covid-19 group. The authors concluded that low vitamin D levels might contribute to a deficiency in immune response, and supplementing Vitamin D during the pandemic could be beneficial during pregnancy for prevention[22].

In our study, we found that vitamin D supplementation was significantly higher in the control group compared to the SARS-CoV-2 group, and we found the difference statistically significant (p =0,003). In line with our finding, a case-control study showed that none of the pregnant with severe diseases were supplemented with vitamin D, even though there was no statistically significant difference in taking supplementation between cases and controls19. The major handicap of our study is the relatively low number of Covid 19 + cases because it was conducted in a single center. Another limitation is the retrospective nature of the study. The relationship between vitamin D levels and the severity of Covid-19 couldn't be statistically related due to the limited number of the group with severe disease.

There is a need for other prospective studies to evaluate the relation to vitamin D‘s effect on Covid 19 in pregnancy. Our study will supply additional knowledge to the cumulative data concerning Covid 19 pandemic.

Conclusion

Sustaining adequate levels of Vitamin D may positively impact protection against Covid 19 during pregnancy. Vitamin D supplementation to maintain serum 25(OH)D at a level of at least 30 ng/mL and above may benefit protection or decrease the risk of Covid 19 and its severity. However, there is a need for new studies comparing the severity of the disease with the level of vitamin D to reach a definitive conclusion. In this context, Vitamin D supplementation should be considered for the pregnant population, particularly in settings where profound vitamin D deficiency is common.

Author contributions
All authors read and approved the final manuscript.
M. Sengül: Project development, Data Collection, data analyzing Manuscript writing
H. Sen Selim: Data collection, data analyzing, manuscript writing
S. Sen: Data analyzing, manuscript writing
H.Erbak Yılmaz: Data Collection
K.Kurt: Project development

Conflict of interest
The authors declare that they have no conflict of interest.

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Ethical approval
Informed consent was obtained from pregnant women both for herself and the newborn. This study was approved by the ethical committee with date 21.09.2021 and number 408 of Izmir Katip Celebi Univesity, Faculty of Medicine and the Turkish Ministry of Health.

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