



Vitamin D status is not associated with clinical severity of COVID-19 in pregnant women

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Abstract

Purpose To investigate the association between vitamin D status and the clinical severity of COVID-19 in pregnant women.

Methods This prospective case–control study included 147 pregnant women with COVID-19 and 300 matched controls. Serum 25-hydroxyvitamin (25(OH)D) concentrations were measured on admission. Patients with mild-to-moderate disease ($n = 114$, 77.6%) and severe-to-critical disease ($n = 33$, 22.4%) were classified as symptomatic patients who did not require oxygen support and those who received oxygen support, respectively. SARS-CoV-2 positivity rates, clinical severity of COVID-19, and pulmonary involvement were compared according to vitamin D status.

Results Serum 25(OH)D concentrations were found to be 36.6 ± 26.8 and 31.3 ± 20.7 nmol/L in pregnant women infected with SARS-CoV-2 and healthy controls, respectively ($p = 0.001$). The clinical severity of pregnant women with COVID-19 did not differ concerning vitamin D deficiency (RR = 0.568, 95% CI [0.311–1.036]; $p = 0.065$), even after excluding patients on vitamin supplementation (RR = 0.625, 95% CI [0.275–1.419]; $p = 0.261$). Testing positive for SARS-CoV-2 was not related to vitamin D status in the overall cohort of pregnant women (RR = 0.767, 95% CI [0.570–1.030]; $p = 0.078$). Pulmonary involvement of COVID-19 was found to be similar between patients with vitamin D deficiency and adequate vitamin D levels (RR = 0.954; 95% CI [0.863–1.055]; $p = 0.357$).

Conclusion The clinical severity and pulmonary involvement of COVID-19 may not be associated with vitamin D status in pregnant women. Vitamin D deficiency/adequacy rates were comparable in pregnant women infected with SARS-CoV-2 and healthy pregnant women.

Keywords COVID-19 · Disease severity · Pregnancy · SARS-COV-2 · Vitamin D

Introduction

The clinical severity of Severe Acute Respiratory syndrome coronavirus-2 (SARS-CoV-2) infection varies from asymptomatic to critical disease and mostly depends on age, comorbidities, and viral load [1]. Currently, there is still no

definite treatment for coronavirus disease-2019 (COVID-19); therefore, studies are seeking prevention and supportive measures to modulate the immune system [2]. Amid the recent controversies, the relationship between vitamin D status and COVID-19 has been widely discussed [3–5].

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The immunomodulatory and anti-inflammatory characteristics of vitamin D have been proposed as possible pathways for its beneficial effects on SARS-CoV-2 infection in the literature [2, 4]. It is believed that vitamin D can slow down the replication of coronaviruses and reduce the inflammatory responses related to cytokine storm in COVID-19 [2, 4].

The number of SARS-CoV-2 cases was shown to be associated with serum vitamin D concentrations derived from 62 data sets from 20 European countries; however, reliable proof of the link between vitamin D deficiency and COVID-19 severity and mortality is still needed [4, 6]. The current evidence supports the positive role of vitamin D adequacy during the SARS-CoV-2 pandemic in the non-pregnant population [5, 7–9]. Vitamin D deficiency was proposed as a risk factor for COVID-19, particularly for severe and critical cases [10].

Low vitamin D levels were previously associated with an increased risk of developing several important gestational complications including preeclampsia, fetal growth restriction, gestational diabetes, gestational hypertension, preterm birth, and bacterial vaginosis, as well as increased susceptibility of newborns to respiratory illness, autoimmune diseases and autism spectrum disorder [11–14]. Pregnancy makes women vulnerable to having more severe COVID-19 [15], and robust data about the possible relationship with vitamin D are scarce. This study aimed to investigate the association between vitamin D status and the clinical severity of COVID-19 in pregnant women.

Materials and methods

This prospective cohort study was conducted at the maternal unit of a pandemic hospital in a referral tertiary center from September 2020 to December 2020 (latitude 41). Symptomatic pregnant women aged over 18 years with COVID-19 were included. There was a minimum of 1509 to a maximum of 6903 daily cases of diagnosed SARS-CoV-2 infection with a stable mortality rate of 1% during the study period. Approval from the local administration board, regional ethical committee, and national scientific research platform (E-46059653-000-696) was obtained. Written informed consent was obtained from all participants.

Data were prospectively collected from electronic health records using a standardized data collection form. Clinical, obstetric, and laboratory outcomes were regularly updated until December 25th, 2020. Patients who reported having medical treatment that could modulate 25-hydroxyvitamin (25(OH)D) concentrations (e.g., steroids, antiepileptics) and those with disorders known to affect vitamin D metabolism/absorption were excluded from the study.

We hypothesized that there would be a significant relationship between the clinical severity of COVID-19 and

vitamin D status in pregnant women with COVID-19. A further case–control study was conducted to compare pregnant women with COVID-19 and healthy low-risk pregnant women at a 1:2 ratio, respectively. Healthy controls were recruited during the study period from pregnant women who presented to outpatient clinics for their routine follow-up. Primary outcome measures were the comparison of the clinical severity of the COVID-19 infection with serum 25(OH)D concentrations. Secondary outcome measures were to assess the effects of serum 25(OH)D concentrations on pulmonary involvement and hospitalization duration. Vitamin D status was defined as severe deficiency (serum 25(OH)D < 30 nmol/L), deficiency/suboptimal (30–50 nmol/L), and adequacy/optimal (\geq 50 nmol/L) according to the recent update on the current status worldwide [16]. Patients were initially stratified into two categories as vitamin D deficiency (< 50 nmol/L) and adequate vitamin D (\geq 50 nmol/L) for statistical purposes [16]. Later, patients were stratified into three categories regarding vitamin D status. Use of multivitamin, calcium or vitamin D supplements during the pregnancy was noted.

Serum 25(OH)D concentrations were analyzed from venous blood samples that were collected at the time of diagnosis between 08:00 a.m. and 10:00 a.m. using competitive chemiluminescence immunoassays using an Elecsys Vitamin D total II and COBAS 6000 Core devices (Roche Diagnostics, IN, USA). The intraassay and interassay coefficients of variation were 8.7–6.6% and 8.9–7.4% at low (< 30 nmol/L) low serum 25(OH)D concentrations, respectively. The lower detection limit of the assay was 7.5 nmol/L.

The diagnosis of COVID-19 infection was made either using reverse transcription real-time polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 or imaging studies including chest computed tomography, lung ultrasound or chest X-ray. The clinical severity of COVID-19 was classified according to the World Health Organization (WHO) [1]. Patients with mild-to-moderate disease and severe-to-critical disease were classified as symptomatic patients who did not require oxygen support and those who received oxygen support, respectively. All patients were managed according to the current national treatment protocols. The first trimester of pregnancy was defined as < 14 weeks, the second trimester between 14 and 27 weeks and 6 days, and the third trimester as \geq 28 weeks until birth.

The collected data were analyzed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of demographic data was assessed using the Shapiro–Wilk test. Demographic data are summarized as the median \pm interquartile range for non-normally distributed data and as mean \pm standard deviation for normally distributed data. Pearson's Chi-square test was used to assess whether the adequacy of vitamin D and the clinical severity of COVID-19 were related. Student's *t* test and the

Chi-square test were used to compare the means and rates of independent groups as indicated. Binary logistic regression was performed to assess the impact of patients' characteristics and serum 25(OH)D concentrations on testing positive for SARS-CoV-2. The first block of variables entered consisted of potential risk factors including age, body mass index (BMI), parity, gestational week, co-morbidity, serum 25(OH)D concentrations, and vitamin D deficiency status. Nagelkerke R^2 was used to measure the overall model performance and the Hosmer–Lemeshow test for the goodness-of-fit test. A p value of <0.05 was considered to indicate a significant difference.

Results

The study cohort comprised 147 symptomatic pregnant women aged over 18 years with COVID-19 and 300 healthy pregnant women. The demographic characteristics of the infected and healthy pregnant women are presented in Table 1. Serum 25(OH)D concentrations were slightly increased in women infected with SARS-CoV-2 when compared with non-infected subjects (36.6 ± 26.8 nmol/L vs. 31.3 ± 20.7 nmol/L, respectively; $p = 0.001$, independent samples t test).

Following further stratification concerning the adequacy of vitamin D (deficiency vs. adequate), vitamin D status was found to be similar in both groups ($p = 0.090$, Table 1). The mean serum 25(OH)D concentrations were 23.6 ± 10.7 and 70.8 ± 20.7 nmol/L in patients with deficient and adequate vitamin D levels, respectively (mean difference:

-47.1 nmol/L, $p < 0.001$, independent t test). The relative risk (RR) of testing positive for SARS-CoV-2 in vitamin D deficiency (< 50 nmol/L) was found to be 0.767 (95% CI [0.570–1.030]; $p = 0.078$). The clinical severity of infected patients did not differ with regard to vitamin D deficiency (RR = 0.568, 95% CI [0.311–1.036]; $p = 0.065$), even after excluding patients on vitamin supplementation (RR = 0.625, 95% CI [0.275–1.419]; $p = 0.261$).

When patients were categorized by serum 25(OH)D concentrations as severe deficiency (< 30 nmol/L), deficiency/suboptimal (30–50 nmol/L), and adequacy/optimal (> 50 nmol/L); 57.3% ($n = 256$) of the patients were diagnosed as having severe deficiency, 22.8% ($n = 102$) as deficiency/suboptimal, and 19.9% ($n = 89$) as adequacy/optimal. The categorized vitamin D status did not differ between infected and healthy pregnant women ($p = 0.223$, $\chi^2 = 2.998$, Pearson's Chi-square test). Among pregnant women infected with SARS-CoV-2, the clinical severity (mild, moderate, severe, and critical) did not differ regarding vitamin D deficiency ($p = 0.538$, $\chi^2 = 5.049$, Pearson's Chi-square test). This non-significant trend between the vitamin D status and the clinical severity of SARS-CoV-2 infection was also similar with the dichotomous classification as mild to moderate and severe to critical ($p = 0.184$, $\chi^2 = 3.386$, Pearson's Chi-square test).

The binary logistic regression analysis showed that parity (Wald = 8.045, $\text{Exp}(B) = 1.415$, 95% CI for $\text{Exp}(B)$ [1.113–1.799]; $p = 0.005$) and gestational week (Wald = 4.032, $\text{Exp}(B) = 1.066$, 95% CI for $\text{Exp}(B)$ [1.002–1.135]; $p = 0.045$) significantly predicted SARS-CoV-2 positivity. The Omnibus test of model coefficients

Table 1 Demographic characteristics and vitamin D status of the overall cohort

	SARS-CoV-2 positive		SARS-CoV-2 negative		p
	Mean	SD	Mean	SD	
Age (years)	27.98	5.14	27.99	5.49	0.530 ^a
BMI (kg/m ²)	28.44	4.84	26.26	4.79	0.554 ^a
Gestational week	27.60	9.18	17.49	10.42	0.006 ^a
Serum 25OH(D) concentration (nmol/L)	36.6	26.8	31.3	20.7	0.001 ^a
	Median	IQR	Median	IQR	
Parity	1	2	1	1	
	Exist (n (%))	Absent (n (%))	Exist (n (%))	Absent (n (%))	p (χ^2)
Comorbidity	16 (10.9)	131 (89.1)	40 (13.3)	260 (86.7)	0.462 ^b (0.540)
	Deficiency	Adequate	Deficiency	Adequate	p (χ^2)
Vit D status	111 (75.5%)	36 (24.5%)	247 (82.3%)	53 (17.7%)	0.090 ^b (2.880)

25OH(D) 25-hydroxyvitamin, SD standard deviation, IQR interquartile range, BMI body mass index

^aIndependent samples T test

^bPearson Chi-square test

was significant ($p < 0.001$) and Nagelkerke R^2 was adequate with 0.290. The Hosmer–Lemeshow test showed a good fit for the model ($p = 0.150$) and the model explained 73.2% of the variance.

In the present cohort, 12.53% ($n = 56/447$) of pregnant women had underlying health conditions or co-morbidities. The co-morbidities of all pregnant women were hypothyroidism 4.5%, diabetes mellitus 2.5%, asthma 2.5%, hypertension 1.6%, rheumatoid disease 1.3%, and cardiovascular conditions 0.5%. The co-morbidities did not differ between pregnant women who were diagnosed as positive and negative for SARS-CoV-2 ($p = 0.462$).

Out of 147 patients infected with SARS-CoV-2, 3.4% ($n = 5$) were diagnosed through imaging studies. The duration of hospitalization was 9.97 ± 4.70 and 10.05 ± 3.73 days in patients with vitamin D deficiency and adequate vitamin D levels, respectively ($p = 0.924$, independent samples t test). The rate of admission to the intensive care unit (ICU) was 1.36% ($n = 2$) and there was no mortality.

Patient characteristics were comparable in patients with vitamin D deficiency and adequate vitamin D levels (Table 2). Pulmonary involvement was present in 91.16% ($n = 134$) of all pregnant women with COVID-19 and did not show a significant relation with the vitamin D status

($p = 0.424$, Table 2). The rate of patients who refused computed tomography (CT) for diagnostic purposes was 71% in patients infected with SARS-CoV-2. COVID-19 pulmonary involvement found with CT, lung ultrasound (LUS) or chest X-ray was found to be similar between patients with vitamin D deficiency and adequate vitamin D levels (RR = 0.954; 95% CI [0.863–1.055]; $p = 0.357$).

Discussion

Our findings showed that vitamin D status did not affect the clinical severity of COVID-19 in pregnant women, even when patients on vitamin supplementation were excluded. Pulmonary involvement of COVID-19 disease did not differ between pregnant women with vitamin D deficiency and adequacy. Furthermore, having vitamin D deficiency/adequacy was similar in pregnant women infected with SARS-CoV-2 and healthy pregnant women. To the best of our knowledge, this is the first study in the literature to compare the effect of vitamin D status in pregnant women regarding the risk of SARS-CoV-2 infection and clinical severity of COVID-19 disease.

Patients with vitamin D deficiency were proposed to be at increased risk of severe SARS-CoV-2 infection [17]. The

Table 2 The characteristics of pregnant women with COVID-19 and primary outcomes according to vitamin D status

	Vitamin D deficiency (< 50 nmol/L) ($n = 111$)			Adequate vitamin D (≥ 50 nmol/L) ($n = 36$)			p		
	Mean	SD		Mean	SD				
Age (year)	27.81	5.32		28.50	4.57		0.487 ^a		
BMI (kg/m ²)	28.18	4.84		29.27	4.78		0.237 ^a		
Gestational week	27.32	9.49		28.47	8.20		0.513 ^a		
Hospitalization (days)	9.97	4.70		10.05	3.73		0.924 ^a		
	Exist ($n(\%)$)		Absent ($n(\%)$)		Exist ($n(\%)$)		Absent ($n(\%)$)		$p(\chi^2)$
Comorbidity	11 (9.9)		100 (90.1)		5 (13.9)		31 (86.1)		0.505 ^b (0.444)
	1st	2nd	3rd	1st	2nd	3rd	$p(\chi^2)$		
Trimesters	15 (13.5%)	35 (31.5%)	61 (55%)	2 (5.6%)	11 (30.6%)	23 (63.9%)	0.391 ^b (1.877)		
	Exist ($n(\%)$)		Absent ($n(\%)$)		Exist ($n(\%)$)		Absent ($n(\%)$)		$p(\chi^2)$
Pulmonary involvement	100 (90.1%)		11 (9.9%)		34 (94.4%)		2 (5.6%)		0.424 ^b (0.639)
	O ₂ not required (mild to moderate)		Received O ₂ (severe to critical)		O ₂ not required (mild to moderate)		Received O ₂ (severe to critical)		$p(\chi^2)$
Clinical severity	90 (81.1%)		21 (18.9%)		24 (66.7%)		12 (33.3%)		0.072 ^b (3.244)
Clinical severity (excluding those with supplementation, $n = 90$)	50 (83.3%)		10 (16.7%)		22 (73.3%)		8 (26.7%)		0.264 ^b (1.250)

SD standard deviation, IQR interquartile range, BMI body mass index

^aIndependent samples T test

^bPearson Chi-square test

potential mechanisms of vitamin D action on SARS-CoV-2 infection include the direct anti-inflammatory properties of vitamin D in the lungs with the local inhibition of nuclear factor-KB and mitogen-activated protein kinase activity by reducing inflammatory cytokines. In addition, vitamin D plays role in the regulation of the tissue remodeling pathway, proliferation of monocytes to macrophages, and the anti-infectious process with the upregulation of cathelicidin [16]. In a recent systematic review and meta-analysis, a higher risk of SARS-CoV-2 infection and greater severity of COVID-19 disease was concluded in a cohort consisting of mostly adults [8].

Vitamin D deficiency on admission was also linked with mortality in adults with COVID-19 pneumonia. A recent observational, cohort study observed higher rates of COVID-19 mortality in an older population with vitamin D deficiency [5]. De Smet et al. found that the radiologic stage was correlated with vitamin D status in patients with pulmonary involvement independent of co-morbidities in male patients only [10]. It should be noted that their cohort only included patients with severe infection; therefore, the observed significant relation between vitamin D status and stage of pulmonary involvement cannot be generalized.

In our study, pulmonary involvement was present in 91.16% of all pregnant women with COVID-19 and showed no significant relation to vitamin D status ($p=0.424$). It was interesting to obtain a high refusal rate of CT (71%) among pregnant women in our cohort; LUS was helpful to overcome this obstacle because it was considered to be safe, rapid, and easy to use in pregnant women [18].

A recent systematic review and meta-analysis reported a significant association between serum vitamin D status and COVID-19 infection risk [19]. Another systematic review and meta-analysis that included more studies within a similar period revealed no clear and strong relation for a cause–effect relationship of vitamin D status (< 50 nmol/L) on COVID-19 health-related outcomes including the risk of mortality, ICU admission, invasive ventilation, non-invasive ventilation, and SARS-CoV-2 positivity [20]. Hernandez et al. found significantly lower serum 25(OH) D concentrations at admission in patients with COVID-19 compared with those of healthy controls, although the severity of infection did not differ between the groups [21]. In our study, a significant difference was found in favor of infection (36.6 ± 26.8 nmol/L vs. 31.3 ± 20.7 nmol/L); however, we believe this finding was not clinically relevant because both means were lower than the pre-defined cutoff of 50 nmol/L and the vast majority of the entire cohort (80.1%) had vitamin D deficiency. In their large retrospective study, Meltzer et al. observed adults with deficient vitamin D concentrations measured within 1 year before testing COVID-19 were found at higher risk of SARS-CoV-2 infection [9]. Pugach and Pugach compared the prevalence of vitamin D

deficiency in recently published data with the death rate per million of the population of COVID-19. They found that mortality related to COVID-19 was positively associated with a higher prevalence of severe vitamin D deficiency [7]. Although these studies proposed a significant possible relationship between the vitamin D levels with SARS-CoV-2 infection prevalence and mortality, the lack of testing at the time of diagnosis for SARS-CoV-2 might cause the results to be difficult to generalize. The design of the current study including concurrent testing for SARS-CoV-2 and serum 25(OH)D concentrations may lower this possible bias. Contrary to the latest evidence, Hastie et al. observed a lack of association between serum 25(OH)D concentrations and the risk of contracting COVID-19, regardless of ethnicity [22].

The prevalence of vitamin D deficiency (< 50 nmol/L) is very high in up to every four in five pregnant women [11, 23, 24]. Low serum 25(OH)D concentrations are known to be associated with adverse pregnancy outcomes including preeclampsia, gestational diabetes, preterm birth, and low birth weight [12–14, 25]. Although routine screening is not suggested, vitamin D supplementation is recommended during the antenatal period [26]. In the current study, the prevalence of vitamin D deficiency was found to be consistent with the existing literature at 80.1% [11, 23, 24]. Seasonality effect, ethnicity, and increased vitamin D-binding protein concentrations against the haemodilution gradient may play an important role in decreased concentrations of free 25(OH)D in the maternal circulation and therefore can cause suboptimal vitamin D status in pregnant women despite supplement use [27, 28]. However, the vitamin D status of the healthy controls in this study was also rather poor, which may cause a potential bias considering the inadequate number of patients with sufficient vitamin D status. Thus, the evaluation of the impact of vitamin D deficiency on SARS-CoV-2 infection should not be generalized.

There is a dearth of evidence on the effect of vitamin D status in pregnant women with COVID-19. To date, only one study in the literature has investigated serum 25(OH) D concentrations in pregnant women infected with SARS-CoV-2 [29]. The mean serum 25(OH)D concentration was found low, however, the major limitations of that study were the lack of a control group and that clinical severity was not assessed.

The number of subjects in our study was too small to rigorously evaluate the major outcomes, thus, this was the main limitation of the current study. The clinical severity of pregnant women with COVID-19 was found unrelated to vitamin D status in this study. This finding can be explained by viral load and possible non-controlled confounders. It is known that a higher viral load is possibly associated with more severe clinical outcomes [30]. It was impossible to measure the viral load in patients at the time of the study. Except for the controlled confounders,

the seasonal effect can be another limitation of the current study. However, this effect might have been minimal because the study was conducted between September and December. The major strengths of our study were its prospective, cohort design, and the limited potential for confounding variables including similar population composition, age, BMI, gestational week, and comorbidity.

There is still debate as to whether vitamin D deficiency causes worse COVID-19 outcomes or if low vitamin D is a consequence of the infection itself [6]. Future studies should focus on assessing the cause-effect relationship between vitamin D status and the clinical severity of COVID-19 in pregnant women. The findings of the current study should be considered carefully because the results do not oppose vitamin D supplementation in pregnant women, but only question the association between vitamin D status and the susceptibility to and clinical severity of COVID-19.

In conclusion, clinical severity and pulmonary involvement of COVID-19 may not be associated with vitamin D status in pregnant women. Vitamin D deficiency/adequacy rates were comparable in pregnant women infected with SARS-CoV-2 and healthy pregnant women. Given the overall high vitamin D deficiency rate, physicians should focus on establishing adequate vitamin D levels in pregnancy. Further well-designed studies with larger sample sizes and optimal vitamin D status are required.

Author contributions NT, PB and ABT designed the study. SNU, TS, AMB and EA collected the data. MY, ABT and PB participated in data analysis, reviewed and edited the manuscript. SNU, TS, AMB and EA contributed to the writing of the manuscript. ABT, PB wrote the initial manuscript. SNU, TS, AMB and EA agreed with manuscript results and conclusions. NT and MY supervised the project. All authors reviewed and approved the final manuscript.

Declarations

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

Ethical approval The local Institutional Ethics Committee has approved the study (E-46059653-000-696).

Consent for publication The corresponding author and co-authors agree with the publication of the manuscript.

References

- World Health Organization (WHO) (2020) Clinical management of COVID-19: interim guidance, 27 May 2020. World Health Organization. <https://apps.who.int/iris/handle/10665/332196>. Accessed 25 Mar 2021
- Cena H, Chieppa M (2020) Coronavirus disease (COVID-19–SARS-CoV-2) and nutrition: is infection in Italy suggesting a connection? *Front Immunol* 11:944. <https://doi.org/10.3389/fimmu.2020.00944>
- Boulkrane MS, Ilina V, Melchakov R et al (2020) COVID-19 disease and vitamin D: a mini-review. *Front Pharmacol* 11:2107. <https://doi.org/10.3389/fphar.2020.604579>
- Ali N (2020) Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health* 13(10):1373–1380. <https://doi.org/10.1016/j.jiph.2020.06.021>
- Angelidi AM, Belanger MJ, Lorinsky MK et al (2021) Vitamin D status is associated with in-hospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. *Mayo Clin Proc* 96(4):875–886. <https://doi.org/10.1016/j.mayocp.2021.01.001>
- Smolders J, van den Ouweland J, Geven C, Pickkers P, Kox M (2021) Letter to the editor: Vitamin D deficiency in COVID-19: mixing up cause and consequence. *Metabolism*. <https://doi.org/10.1016/j.metabol.2020.154434>
- Pugach IZ, Pugach S (2021) Strong correlation between prevalence of severe vitamin D deficiency and population mortality rate from COVID-19 in Europe. *Wien Klin Wochenschr*. <https://doi.org/10.1007/s00508-021-01833-y>
- Kazemi A, Mohammadi V, Aghababae SK, Golzarand M, Clark CC, Babajafari S (2021) Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. *Adv Nutr*. <https://doi.org/10.1093/advances/nmab012>
- Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J (2020) Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw Open* 3(9):e2019722. <https://doi.org/10.1001/jamanetworkopen.2020.19722>
- De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA (2021) Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. *Am J Clin Pathol* 155(3):381–388. <https://doi.org/10.1093/ajcp/aqaa252>
- Christoph P, Challande P, Raio L, Surbek D (2020) High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. *Swiss Med Wkly*. <https://doi.org/10.4414/smw.2020.20238>
- Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM (2013) Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. *BMJ*. <https://doi.org/10.1136/bmj.f1169>
- Fogacci S, Fogacci F, Banach M et al (2020) Vitamin D supplementation and incident preeclampsia: a systematic review and meta-analysis of randomized clinical trials. *Clin Nutr* 39(6):1742–1752. <https://doi.org/10.1016/j.clnu.2019.08.015>
- Zhang Y, Gong Y, Xue H, Xiong J, Cheng G (2018) Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. *BJOG Int J Gynaecol Obstet* 125(7):784–793. <https://doi.org/10.1111/1471-0528.15060>
- Tug N, Yassa M, Köle E et al (2020) Pregnancy worsens the morbidity of COVID-19 and this effect becomes more prominent as pregnancy advances. *Turk J Obstet Gynecol* 17(3):149. <https://doi.org/10.4274/tjod.galenos.2020.38924>
- Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Berisha AT et al (2020) Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr* 74(11):1498–1513. <https://doi.org/10.1038/s41430-020-0558-y>
- Tian Y, Rong L (2020) Does vitamin D have a potential role against COVID-19? Authors' reply. *Aliment Pharmacol Ther* 52(2):410–411. <https://doi.org/10.1111/apt.15817>
- Yassa M, Mutlu MA, Kalafat E et al (2020) How to perform and interpret the lung ultrasound by the obstetricians in pregnant

- women during the SARS-CoV-2 pandemic. *Turk J Obstet Gynecol* 17(3):225. <https://doi.org/10.4274/tjod.galenos.2020.93902>
19. Teshome A, Adane A, Girma B, Mekonnen ZA (2021) The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. *Front Public Health* 9:169. <https://doi.org/10.3389/fpubh.2021.624559>
 20. Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M, Fuleihan GEH (2021) The link between COVID-19 and Vitamin D (VIVID): a systematic review and meta-analysis. *Metabolism*. <https://doi.org/10.1016/j.metabol.2021.154753>
 21. Hernández JL, Nan D, Fernandez-Ayala M et al (2021) Vitamin D status in hospitalized patients with SARS-CoV-2 infection. *J Clin Endocrinol Metab* 106(3):e1343–e1353. <https://doi.org/10.1210/clinem/dgaa733>
 22. Hastie CE, Mackay DF, Ho F et al (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr* 14(4):561–565. <https://doi.org/10.1016/j.dsx.2020.04.050>
 23. Gellert S, Ströhle A, Bitterlich N, Hahn A (2017) Higher prevalence of vitamin D deficiency in German pregnant women compared to non-pregnant women. *Arch Gynecol Obstet* 296(1):43–51. <https://doi.org/10.1007/s00404-017-4398-5>
 24. Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW (2011) Vitamin D deficiency and insufficiency is common during pregnancy. *Am J Perinatol* 28(01):007–012. <https://doi.org/10.1055/s-0030-1262505>
 25. Royal College of Obstetricians and Gynaecologists (2014) Vitamin D in pregnancy. Scientific Impact Paper no. 43
 26. Health NICE, Excellence C (2017) Vitamin D: supplement use in specific population groups. National Institute for Health and Care Excellence (NICE). <https://www.nice.org.uk/guidance/ph56>. Accessed 1 Oct 2021
 27. Zhang JY, Lucey AJ, Horgan R, Kenny LC, Kiely M (2014) Impact of pregnancy on vitamin D status: a longitudinal study. *Br J Nutr* 112(7):1081–1087. <https://doi.org/10.1017/S0007114514001883>
 28. Li W, Green TJ, Innis SM, Barr SI, Whiting SJ, Shand A, von Dadelszen P (2011) Suboptimal vitamin D levels in pregnant women despite supplement use. *Can J Public Health* 102(4):308–312. <https://doi.org/10.1007/BF03404056>
 29. Bahat PY, Talmac MA, Bestel A, Selcuki NFT, Aydın Z, Polat İ (2020) Micronutrients in COVID-19 positive pregnancies. *Cureus*. <https://doi.org/10.7759/cureus.10609>
 30. Liu Y, Yan L-M, Wan L et al (2020) Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 20(6):656–657. [https://doi.org/10.1016/s1473-3099\(20\)30232-2](https://doi.org/10.1016/s1473-3099(20)30232-2)