The Importance of Optimal Vitamin D Serum Levels in Pregnancy During the Covid-19 Pandemic

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Introduction

Covid-19 pandemic, pregnancy and vitamin D deficiency

The COVID-19 pandemic has strongly affected global healthcare systems. Since early spring of 2020, a severe acute respiratory syndrome coronavirus 2 (SARS CoV2) caused many critical cases and deaths, particularly in high-risk groups, also pregnant women. Factors that have been shown to contribute to higher risk for complications and death include older age, higher body mass index (BMI) and obesity, dark skin, the presence of chronic illnesses, such as diabetes, malignant disease, high blood pressure, and many other conditions such as pregnancy [1,2]. Most people with these risk factors for higher severity and mortality from COVID-19 have been shown to be also at increased risk for vitamin D deficiency and vice versa. And this might not be only a coincidence [1]. There are some data showing that pregnant women group is also at higher risk for COVID-19 morbidity and mortality. It is also known that this group of women is also known to be at higher risk for vitamin D deficiency [3].

Covid-19 and pregnant women

Few systematic reviews and meta-analyses have focused on morbidity and mortality in pregnant women with COVID-19 [2,4,5]. One such systematic review and meta-analysis concluded that pregnancy is associated with an increased risk of ICU admission and ventilation in pregnant women with COVID-19 [2]. Pregnant and newly pregnant women with COVID-19 had higher odds of being admitted to the ICU compared with fertile non-pregnant women with COVID-19 (OR=2.13, 95% CI=1.53-2.95). In addition, retrospective cohort studies have also found that women with COVID-19 at delivery have higher rates of intubation, ICU admission, and preterm birth compared with pregnant women without COVID-19. Although no statistical association was found between pregnancy and death in patients with COVID-19, mortality was higher in pregnant women with COVID-19 than in non-pregnant women with COVID-19 (0.90% vs.0.55 [2].

One of the systematic reviews showed that most women (73.9%) were in their third trimester; 52.4% gave birth and half babies were delivered by caesarean section (48.3%). Percentage belonging to black, Asian or minority ethnic groups (50.8%); obesity (38.2%) and chronic comorbidities (32.5%) were high. The most common clinical symptoms were fever (63.3%), cough (71.4%) and dyspnea (34.4%). The most common laboratory abnormalities were elevated CRP or procalcitonin (54.0%), lymphopenia (34.2%), and elevated transaminases (16.0%). Preterm birth before the 37th week of pregnancy was common (21.8%) and mostly medically indicated (18.4%). 7.0% required maternal intensive care and 3.4% required intubation. Maternal mortality was uncommon (~1%). Maternal ICU care was higher in the cohort with higher rates of comorbidities (β=0.007, p<0.05) and maternal age over 35 years (β=0.007, p<0.01). Higher maternal mortality was in cohorts with higher rates of antiviral drug use (beta=0.03, p<0.001), likely due to residual confounding.

Neonatal nasopharyngeal swab RT-PCR was positive in 1.4%, suggesting that vertical transmission of the virus probably occurs,

albeit in a small proportion of cases [4]. Another systematic review concluded that pregnant and recently pregnant women with Covid-19 who presented or were admitted to hospital for any reason were less likely to have symptoms such as fever, cough, shortness of breath and myalgias, but were more likely to be hospitalized in an intensive care unit. There was also a higher risk for invasive ventilation in pregnant women than in non-pregnant women. Pre-existing comorbidities, non-white ethnicity, chronic hypertension, pre-existing diabetes, advanced maternal age, and high body mass index were risk factors for severe Covid-19 outcomes in pregnancy. Pregnant women with Covid-19 were more likely to give birth prematurely and had an increased risk of maternal death and ICU admission, compared with pregnant women without Covid-19 [5].

Vitamin D and Covid-19

According to the reported data, there are seasonal fluctuations of COVID-19 disease severity. It has been known for decades that seasonal changes cause significant immunity variation, including fluctuations in lymphocyte response and circulating levels of lymphocytes and neutrophils. Epidemiological studies have shown also a strong reverse correlation between serum vitamin D (25-hydroxyvitamin D, 25(OH)D) levels, which are normally higher during the summer season, and the incidence of certain infectious diseases. Vitamin D induces cathelicidin and beta defensin transcription and synthesis in macrophages and a favorable anti-inflammatory Th1 to Th2 phenotype ratio. Additionally, vitamin D exhibits a mitigating effect on the pathogenesis of the cytokine storm, which is one of the main contributing factors to fatality in COVID-19 patients. Vitamin D showed also potent activity against SARS CoV 2 in vitro [1,6].

Many observational studies showed a correlation between vitamin D serum levels and inverse risk for COVID-19 infection and risk for disease severity. A new double-blind, parallel, randomized trial determined the efficacy and safety of vitamin D supplementation in the prevention of SARS-CoV-2 infection in highly exposed frontline healthcare workers from four hospitals in Mexico City. Participants were randomly assigned to receive 4,000 IU vitamin D or placebo daily for 30 days. SARS-CoV-2 infection rate was lower in vitamin D group than in placebo group (6.4 vs. 24.5%, p<0.001). The risk of acquiring SARS-CoV-2 infection was lower in the vitamin D group than in the placebo group (RR: 0.23; 95% CI: 0.09-0.55) and was associated with an increment in serum levels of 25-hydroxyvitamin D3 (RR: 0.87; 95% CI: 0.82-0.93), independently of vitamin D deficiency. These results suggest that vitamin D supplementation in highly exposed individuals prevents SARS-CoV-2 infection [7].

Vitamin D deficiency and pregnant women

Pregnant women are known to be at increased risk of vitamin D deficiency. According to a systematic review from 2016, the prevalence of vitamin D deficiency in women was at 57% in the United States, 46% in Eastern Europe, 87 % in Southeast Asia and 83% in Western Pacific. The high prevalence of maternal vitamin D deficiency may be related to changes in lifestyle (sun exposure and food intake) rather than increased physiological needs. In addition, women with higher skin melanin levels, immigrant women (especially women who have migrated from sunny climates), and women who wear veils or coverings are thought to be particularly vulnerable to the deficiency because of endogenous effects from UV exposure. Vitamin D is limited. Because the fetus is dependent on the mother's vitamin D, vitamin D deficiency can have an impact on the health of the mother and the growth and development of the fetus and baby.

Globally, vitamin D deficiency has a high incidence and is a potential public health problem. There is considerable debate about the circulating levels of 25(OH)D associated with deficiency, adequacy, and optimal health. The Endocrine Society recommends a threshold of >30ng/mL (75nmol/L) and recommends that pregnant women need 1,500 to 2,000IU per day to achieve these levels. Because vitamin D status is influenced by multiple factors, including maternal baseline vitamin D status, pre-pregnancy weight, UV exposure, sunscreen use, skin pigmentation, seasonality and latitude, and genetics. Because sun exposure is not considered a safe or sustainable source of vitamin D, vitamin D should be obtained from exogenous sources during pregnancy.

Natural dietary sources of vitamin D are limited in the United States, so most North American populations rely on fortified sources of vitamin D, such as milk and dairy products, to meet their needs. However, vitamin fortification is mandatory D is not common in all countries, including Europe. As a result, many pregnant women rely primarily on prenatal vitamin D supplementation as their primary source of vitamin D. Although adherence to daily prenatal supplementation is high (72% to 80% reported), many commercially available supplements contain as little as 400IU of vitamin D per day, which some experts say may be less than ideal. Appropriate vitamin D requirements for healthy pregnancies, including perinatal outcomes, need to be addressed to facilitate the development of clinical practice guidelines. Study shows link between vitamin D status and pregnancy [7]. Some data shows the importance of optimal vitamin D level during the pregnancy to prevent or mitigate the infections during the pregnancy [8].

Vitamin D, covid-19 severity and pregnancy

It is well known that pregnancy alters the immune system and its response to viral infection, and infection with coronavirus, in theory, could lead to more severe symptoms, especially in the third trimester [2]. There are rare studies related to vitamin D status, COVID-19 and pregnant women [9-11]. One of the case control studies included 159 women with a single gravidity with a positive SARS-CoV-2 test, 332 healthy pregnant women were included as controls. COVID-19 patients were classified as mild, moderate, and severe. Vitamin D deficiency was defined as 25-hydroxycholecalciferol <20ng/mL (50nmol/L), and 25-OH D

vitamin <10ng/mL was defined as severe vitamin D deficiency, also 25-OH D vitamin level between 20-29ng/mL (52,5-72,5nmol/L) was defined as vitamin D insufficiency.

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). It was observed that all of those who had severe COVID-19 were the patients who did not take vitamin D supplementation, so there was a significant difference regarding to vitamin D level and COVID-19 severity in pregnant women [7]. Another comparative case-control study from Spain studied 256 pregnant women (82 infected and 174 control women). Pregnant women infected with COVID-19 had significantly lower serum 25(OH)D levels than uninfected pregnant women. In addition, 89% of COVID-19-positive pregnant women had 25(OH)D deficiency compared with 75.30% of the control group, showing a statistically significant difference (OR = 2.68; 95% CI 1.19-6.06; p= 0.06). 0.01). These results suggest an association between vitamin D deficiency in pregnant women and COVID-19 infection [8].

The third study assessed the relationship between 25-hydroxyvitamin D (25(OH)D) levels and disease severity in hospitalized COVID-19-positive patients and determined the relationship between maternal vitamin D status and COVID-19 severity Relationship. Patients were divided into two groups: asymptomatic or mildly symptomatic (Group 1) and those with severe disease and/or poor prognostic factors (Group 2). 25(OH)D levels were compared between groups. ROC curve analysis was used to determine cut off values for vitamin D to predict the severity of COVID-19. 25(OH)D levels were statistically significantly lower in group 2 (15.5 (10.25)ng/mL in group 1 and 13 (12)ng/mL in group 2, p=0.010). 25(OH)D levels below 14.5 ng/ml were associated with severe COVID-19 and/or poor prognostic factors (p = 0.010). Pregnant women with 25(OH)D levels below 14.5ng/mL had a 1.87-fold increased risk of severe COVID-19 disease and/or poor prognostic factors. This value was found to have 54.1% sensitivity and 61.3% specificity in predicting severe COVID-19 and/or poor prognostic laboratory findings in pregnant women [9]. The data regarding COVID-19 infection risk, disease severity course risk during the pregnancy in correlation to vitamins D are scarce, more studies are needed.

Possible mechanisms lowering the risk of complications in pregnant women in COVID-19 pandemic with vitamin D

The current evidence supports the positive role of vitamin D adequacy during the SARS-CoV-2 pandemic in the non-pregnant population [1]. Vitamin D deficiency was proposed as a risk factor for COVID-19, particularly for severe and critical cases [1]. 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 [12]. Pregnancy is a physiological state that has multiple effects on the body. Pregnant women maintain immunosuppression by inhibiting the activity of T cells during pregnancy, which makes them vulnerable to viral infection.

Throughout pregnancy, a woman's body is in a state of high immunosuppression, when infected with the virus during pregnancy, especially respiratory infectious virus, immune changes may impair pathogen clearance, and other changes may also worsen clinical outcomes and increase the severity of infection, especially in the third trimester [2]. The pathogen clearance is known to be increased with optimal vitamin D serum levels, via the innate immunity pathway [1]. Pregnant women are more susceptible to infection by respiratory pathogens, which, once contracted, can develop into a more severe course of disease, where SARS-CoV-2-induced cytokine storms may induce more severe inflammation, and vitamin D can also have a role in mitigating the cytokine storm [1,2].

One of possible mechanisms of vitamin D in pregnancy is also impacting the RAAS system. Estrogen and progesterone during the pregnancy raise angiotensinogen and renin levels. The mechanism behind this response instructed to the accompanied increment in the ACE2 during pregnancy. COVID-19 infection increased the inflammatory cytokines and reduced ACE2 level. This may lead to pre-eclampsia or hypertensive pregnancies, then increasing the perinatal and maternal mortality and morbidity. Vitamin D increased ACE2 expression and Ang-1-7 plasma levels and decreased Ang II level in plasma. Moreover, Vitamin D reduced the inflammatory cytokine storm. So, Vitamin D supplementation might prevent the risk of preeclampsia or hypertension in pregnant women with COVID-19 [13].

How to avoid COVID-19 complications in pregnancy?

To minimize the chance of infection with COVID-19, pregnant women should be educated about the risks of COVID-19 virus and the signs of severe symptoms of COVID-19 infection. They should be educated about the importance of avoiding the contact with people who may have been exposed to or are infected with COVID-19, educated about masks, a safe social distance, and sanitizing their hands. Nevertheless, pregnant women should also keep up with their scheduled influenza vaccination and prenatal care check-ups. Ideally, pregnant women and their caregivers should be immunized against COVID-19. Additionally, it is of great importance that pregnant women receive adequate nutritional support, including vitamin D supplementation in cases of vitamin D deficiency in order to maintain homeostasis [2]. Maintenance of adequate vitamin D level can be useful as an approach for the prevention of an aggressive course of the inflammation induced with SARS-Cov-2 in pregnant women.

Conclusion

The COVID-19 pandemic caused many critical cases and deaths also among pregnant women. There is known high risk for pregnancy complications with SARS-CoV-2 infection, with an increased risk of ICU admission and ventilation of pregnant women and even with increased risk for preterm birth. The vitamin D deficiency is known to be highly prevalent in pregnant woman, and this brings additional risks for some complications during the pregnancy also regarding the higher risk for infections. There are already known strong data supporting the protective role of vitamin D in COVID-19 infection in non-pregnant population and now there are some new data also stressing the importance of optimal serum levels of vitamin D in pregnant women in COVID-19 pandemic. To conclude, in the pandemic period, vitamin D supplementation for pregnant women should gain more importance.

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