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Letter to Editors

Vitamin D may prevent COVID-19 induced pregnancy complication

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ABSTRACT

SARS-CoV-2 enters target cells via the ACE2 receptor and downregulates it. ACE2 exhibits high catalytic activity to produce Angiotensin 1–7 (Ang-1–7), which has a vasodilator effect and also inactivates the vasoconstrictor Angiotensin II. In normal pregnancy ACE2 expression is raising in the uterus and placenta. Ang-1–7 levels in plasma are significantly higher in third-trimester pregnant women when compared to non-pregnant women. This may be contributing to systemic vasodilation and reduced blood pressure and modulating hemodynamics during pregnancy. Interestingly, Ang-1–7 plasma levels are lower in pregnancies complicated by pre-eclampsia than normal pregnancies. 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 also decreased Ang II level in plasma. Moreover, Vitamin D reduced the inflammatory cytokine storm. So, Vitamin D supplementation can prevent the risk of preeclampsia or hypertension in pregnant women with COVID-19.

To the editor;

The pregnancy is considered a physiological condition, that accompanied by hypervolemia, increased cardiac output, and a diminished total peripheral resistance, still, the pregnant are normotensive, and blood pressure even tends to decrease in the second trimeste. Estrogen and progesterone raise angiotensinogen and renin levels, which in turn leads to increased angiotensin II levels, the increased concentration of angiotensinogen, angiotensin II, indicate the increased activity of RAAS, but instead, there is a decrease in systemic vascular resistance characterizes the hemodynamics of the normal pregnancy [1]. The mechanism behind this response instructed to the accompanied increment in the ACE2 during pregnancy, ACE2 is producing Ang-1–7 which may reach 20-fold higher compared with non-pregnant women [1], contributing to the systemic vasodilation, reduced blood pressure and modulating hemodynamics during pregnancy.

Di Mascio et al. stated that the high miscarriage rate, preterm delivery, pre-eclampsia, cesarean section and perinatal mortality were associated with COVID-19 [2]. Most of these complications could be resulted from increased maternal vascular resistance and increase arterial blood pressure. Neves et al. [3] demonstrated that in the late pregnancy, Ang I and Ang II levels are increased [3], this may lead to a compromise in the quantity of the active ACE2 and could cause an increase in the activity of RAAS, and eventually increase maternal vascular resistance.

It has been known that SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2) receptor. ACE is a part of the renin-angiotensin system (RAS), which converts the angiotensin I (Ang) I to the vasoconstrictor Ang II. ACE2 converts the Ang II to vasodilator Ang-1–7. COVID-19 infection downregulates ACE2, leading to increased accumulation of Ang II [4]. Moreover, Ang-1–7 plasma levels are shown to be higher in normal pregnancies than pregnancies complicated by pre-eclampsia [5]. In the case of COVID-19 pregnant women, complex formation of virus-ACE2 can lead to more inactivation of ACE2. ACE2 reduction leads to an inevitable decrease in Ang 1–7 level results in pre-eclampsia.

Lin et al. [6] showed that the administration of Vit.D increased the ACE2 levels, decreased the ACE, and reduced the ACE1/ACE2 ratio and provides a renoprotective effect [6]. In an experimental study, Vit.D supplementation prevents acute lung injury by increased ACE2 level expression and inhibiting renin, ACE, and Ang II level [7]. It can prevent the development of preeclampsia and protect maternal and fetal health by increasing the ACE2 level in pregnant women infected with COVID-19 (Fig. 1).

Preeclampsia is associated with the immune system [8,9]. Failure of the immune system in pregnant women causes insufficiency of blood supply to the fetus and result in preeclampsia. Todros et al. indicated that preeclampsia is also concerned with the exaggerated inflammation that causes endothelial damage [9]. This immune response is a favorable scenario for predisposing COVID-19 infection, and increases the susceptibility to develop preeclampsia or increase arterial resistance in pregnant women, then may increase the maternal and fetal complications.

Vit D has been exhibits as an anti-inflammatory effect, as it reduces the T cells, so inflammation progression can be repressed indirectly by reducing inflammatory cytokines (IL-2, IL-6, IL-8, IL-12, IL-17, TNFα), and directly inhibits IFN-γ [4]. A meta-analysis and systematic reviews reported that Vit.D deficiency is an increased risk of the preeclampsia in nearly all pregnancies. Pregnant women with a Vit.D deficiency at a level lower than 20 ng/ml are more at the risk of preeclampsia [10]. Vit. D could have some protective properties against COVID-19 infection by enhancing cellular innate immunity through inducing the production of antimicrobial peptides, including defensins and cathelicidin, which reduce the survival and replication of viruses [4].

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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 1. The effect of Vit.D on RAAS and ACE2 levels. The inflammatory cytokines storm induced by the immune response to COVID-19 can cause severe organ damage and compromise the patient life, and in the pregnant patient could be a predisposing factor to develop preeclampsia. Vit.D supplement can decrease cytokines storm and prevent preeclampsia. Vit.D supplement can increase ACE2 levels and restore ACE2 levels in the late pregnancy, then prevent the concomitant complications of preeclampsia or increased maternal blood pressure caused by decreased ACE2 in late pregnancy and accompanied COVID-19 infection. Consequently, decrease fetal and maternal morbidity and mortality.
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