Review Article

Pregnancy, Preeclampsia, and COVID-19: Susceptibility and Mechanisms: A Review Study

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters cells through angiotensin converting enzyme 2 (ACE2), which expression of its gene increases during pregnancy that is resulted in an enhanced level of the ACE2 enzyme. It might enhance the risk of SARS-CoV-2 infection and its complications in the pregnant women. Although, pregnancy hypertensive disorders and severe infection with SARS-CoV-2 are correlated with high comorbidity, these two entities should be discriminated from each other. Also, there is a concern about the risk of preeclampsia and consequently severe coronavirus disease 2019 (COVID-19) development in the pregnant women. So, to answer these questions, in the present review the literature was surveyed. It seems there is higher severity of COVID-19 among pregnant women than non-pregnant women and more adverse pregnancy outcomes among pregnant women infected with SARS-CoV-2. In addition, an association between COVID-19 with preeclampsia and the role of preeclampsia and gestational hypertension as risk factors for SARS-CoV-2 infection and its complications is suggested. However, infection of the placenta and the SARS-CoV-2 vertical transmission is rare. Various mechanisms could explain the role of COVID-19 in the risk of preeclampsia and association between preeclampsia and COVID-19. Suggested mechanisms are included decreased ACE2 activity and imbalance between Ang II and Ang-(1-7) in preeclampsia, association of both of severe forms of COVID-19 and pregnancy hypertensive disorders with comorbidity, and interaction between immune system, inflammatory cytokines and the renin angiotensin aldosterone system and its contribution to the hypertension pathogenesis. It is concluded that preeclampsia and gestational hypertension might be risk factors for SARS-CoV-2 infection and its complications.

Keywords: Comorbidity, COVID-19, Preeclampsia, Pregnancy, Renin Angiotensin Aldosterone System

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Introduction

Severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). The virus binding to angiotensin converting enzyme 2 (ACE2), a renin angiotensin aldosterone system (RAAS) counter-regulator, leads to its entrance to the cells and consequently, cells infection (1). Although, the ACE2 has 60% homology with the ACE1 enzyme, its different active site leads to its inhibition prevention by ACE inhibitors (2). ACE2 is the SARS-CoV-2 spike protein receptor (3). The cellular entry of SARS-CoV-2 through ACE2 that its expression increases during pregnancy might increase susceptibility to SARS-CoV-2 infection in the pregnant women and the risk of pregnancy complications including preeclampsia (4).

Pregnant women are at high risk of viral pneumonia compared to the general population, especially in the absence of antiviral therapy (5). The unfavorable impact of SARS-CoV-2 infection during pregnancy might be due to the RAAS dysregulation (4). The most common COVID-19 related adverse outcomes in the pregnant women include maternal sepsis, preeclampsia, premature rupture of membrane and post-partum hemorrhage (6). Also, hypertension is known as a strong risk factor for complicated COVID-19 (7).

Preeclampsia is presented with hypertension, proteinuria, edema, and a coagulation cascade activation (8). The RAAS dysregulation is involved in the pathogenesis of preeclampsia. Angiotensin (Ang)-(1-7) is produced through the action of ACE2 on angiotensin (Ang) I and the imbalance between angiotensin (Ang) II and Ang-(1-7) might be involved in the etiology of the preeclampsia (9).

There are two questions to be answered; whether pregnant women infected with SARS-CoV-2 are at greater

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risk of preeclampsia; and whether preeclampsia could be a risk factor for developing severe COVID-19. Therefore, the aims of this retrospective study were to review: i. The susceptibility of pregnant women to COVID-19, ii. The outcome of SARS-CoV-2 infection in pregnancy and preeclampsia as a pregnancy complication, and iii. The role of preeclampsia as a risk factor for infection with SARS-CoV-2 and its complications and its possible mechanisms.

The RAAS pathway

The RAAS pathway consists of renin, angiotensinogen (AGT), ACE/ACE1, ACE2, angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R) components. All these components exist in both systemic and local/tissue RAAS; however, the regulation of local RAAS is independent from the systemic RAAS that is found in many tissues such as kidneys, heart, lungs and blood vessels (10). This enzyme, renin, degrades AGT to inactive Ang I decapeptide. The ACE catalyzes the conversion of Ang I, a decapeptide, to Ang II, an active vasoconstrictor octapeptide. The Ang II elevates the aldosterone secretion and consequently increases blood pressure and inhibits the renin secretion. The ACE2 degrades Ang I into angiotensin (Ang)-(1-9) and also, Ang II to Ang-(1-7) peptides. The Ang-(1-7) exerts its vasodilatory, apoptotic and antiproliferative effects by binding to a G-protein coupled receptor, Mass receptor (11).

Preeclampsia

Preeclampsia, a complication of pregnancy with unknown etiology, is defined as the presence of hypertension and proteinuria after 20 weeks of gestation in a woman that has previously been normotensive. The preeclampsia diagnosis is a challenge, since non-specific signs detection basement. However, some biomolecules such as anti-angiogenic markers, renin angiotensin system related markers, immunological markers, metabolic markers, and endocrine markers have been suggested for early preeclampsia diagnosis (12). Dysfunction of the maternal vascular endothelium and abnormal placentation are risk factors for susceptibility to preeclampsia (13). Hypertension is the most serious clinical symptom of preeclampsia that affects mothers and fetus health. Thrombocytopenia, disseminated intravascular coagulation (DIC), and platelet aggregation are known to be associated with preeclampsia (14).

The criteria of preeclampsia diagnosis include high systolic and diastolic blood pressure (≥140 mmHg, and ≥90 mmHg, respectively), the protein excretion > 300 mg in 24 hours, the ratio of urine protein: creatinine of more than 0.3 and the presence of ≥30 mg/dl protein in a randomly provided urine sample (1+ reaction on a standard urine dipstick). Severe preeclampsia is defined as a blood pressure higher than 160/110 mmHg, more than 3+ urine protein, visual disturbances, headache, upper abdominal pain, increased serum creatinine and transaminases, thrombocytopenia and restriction of fetal-growth. Preeclampsia <34 weeks, gestation is defined as early-onset preeclampsia (8).

The RAAS dysregulation and preeclampsia

In a normal pregnancy the RAAS stimulation results in the increased plasma levels of renin and aldosterone. During pregnancy, pregnant women remain normotensive even in the presence of a two times increase in the Ang II level that could be due to the resistance to the Ang II presser effects and the AT1R down-regulation (15). The angiotensin peptides of Ang II and Ang IV act through the AT2R and angiotensin type 4 receptor (AT4R), respectively. The high expression of both AT2R and AT4R in the early stage of pregnancy contributes to normal placenta formation (16).

The renin angiotensin aldosterone system in the preeclamptic women is suppressed and vascular resistance increases, so, the hypervolemia, a physiologic condition in pregnancy, could not develop. In this pregnancy complication, the RAAS perturbation is correlated with an enhanced vascular responsiveness to Ang II (15). According to a hypothesis the presence of hypertension and proteinuria in the preeclampsia can be attributed to the imbalance in the RAAS and increased abdominal pressure, which may lead to functional or structural renal injuries (17).

The levels of Ang I, Ang II, and Ang-(1-7) peptides are increased during a normal pregnancy. In physiological pregnancy, increased activity of the RAAS is accompanied by reduced hypertensive Ang II function. So, in a normal pregnancy, the reduced hypertensive effect of Ang II along with increased aldosterone secretion allows the proper blood volume circulation in the vascular bed. The main mechanisms that maintain proper organ perfusion for the placenta during pregnancy are the enhanced circulating blood volume and cardiac output. However, in gestational hypertension, decreased the RAAS activity and enhanced sensitivity to Ang II effects have been detected. In preeclampsia, low activity of the RAAS results in the decrease of circulating blood volume and cardiac output reduction. Consequently, these alterations lead to the blood flow decrease in the kidney and placenta that will accompany with an abnormal placental development and followed by impaired intrauterine fetal growth (18).

In an advanced and severe form of preeclampsia, some clinical symptoms such as cerebral edema, hemolysis, renal failure, low platelets count, and elevated liver enzymes, are observed. The profile of RAAS components in the preeclamptic women is greatly different from healthy pregnant women; for example, the vasodilator Ang-(1-7) peptide is significantly decreased in the preeclampsia. The Ang-

(1-7) vasodilator peptide plays a significant role in human pregnancy and along with effect on the renal vascular resistance and renal function, might contribute in the physiologic vasodilation occurring during the pregnancy. The imbalance between levels of Ang II and Ang-(1-7) might be involved in the preeclampsia etiology. Although, dysregulated RAAS contributes to the preeclampsia risk, the triggering factor of RAAS imbalance is still unknown (9, 19).

Systemic inflammation activates the immune response in the brain. There is an interaction between the immune system and the RAAS in the central nervous system which is a contributing factor in the pathogenesis of hypertension. The RAAS and inflammatory factors act synergistically in blood pressure regulation in the brain (20).

Preeclampsia and COVID-19

A survey of 42 consecutive pregnancies indicated 34 cases with non-severe and 8 with severe COVID-19 (Table 1). A preeclampsia-like syndrome in the 6 out of 8 ICU admitted pregnant patients were reported of SARS-CoV-2 affected (21). Moreover, the symptoms of patients with severe COVID-19 were similar to those of preeclampsia. However, no preeclampsia-like symptoms were detected among 34 mildly COVID-19 pregnancies affected. Due to the small sample size and the possible effect of confounding factors, data interpretation needs more caution (22). Furthermore, in a population of 23 UK pregnant women, preeclampsia occurred in 10.5% of patients in the third trimester, one of which even developed liver dysfunction, HELLP and DIC (23). These patients that were included multi ethnic suffered from confirmed COVID-19 with mild symptoms. Since, proteinuria could be associated with severe COVID-19 infection, false positive diagnoses of preeclampsia, might be possible (24). In a report of 2184 pregnant women that 33.2% of them diagnosed with COVID-19 and among them there were 123 women with preeclampsia of which 8.1% had COVID-19, a strong association between COVID-19 with preeclampsia, especially in nulliparous women was detected. This study suggested preeclampsia and gestational hypertension are strong risk factors for SARS-CoV-2 infection and its complications (25). In a meta-analysis among pregnant women with SARS-CoV-2 infection, preeclampsia was one of the risk factors that were correlated with the severe COVID-19 complications such as admission to the intensive care unit (ICU), invasive ventilation and maternal death (26). A case of severe hypertension and heart failure in a woman whose delivery was complicated with both preeclampsia and SARS-CoV-2 was reported to occur after delivery and discharge from the hospital (27). Furthermore, a maternal death occurred in a delivery complicated by preeclampsia and the concomitant presence of postpartum COVID-19. Although, during the delivery patient was asymptomatic for COVID-19, she rapidly developed a severe respiratory distress and coagulopathy very soon after postpartum (28). Also, a pregnant patient concomitantly diagnosed with COVID-19 and preeclampsia has been reported with severe features and preterm birth (29). However, in a report of 9 pregnant women with COVID-19 from Wuhan, China, these women did not show a severe clinical characteristic of COVID-19 pneumonia and were similar to non-pregnant women with COVID-19 pneumonia and only one patient developed preeclampsia (30). Among 20 pregnant women from Peru with confirmed SARS-CoV-2 infection who developed preeclampsia, the severe respiratory symptoms of COVID-19 were absent and 80 % of patients were asymptomatic (31).

Table 1: Characteristics of studies reported pregnant women with and without preeclampsia infected with confirmed COVID-19

Reference	Pregnant women (n)	Pregnant women with COVID-19 (n)	Severity of COVID-19 in pregnant women (n)			Preeclamptic women with COVID-19 (n)	Severity of COVID-19 in preeclamptic women (n)		
			Non-severe	Severe	Death		Non-severe	Severe	Death
21	42	42	34	8	0	6	0	6	0
23	6779	23	15	8	1	2	0	2	0
25	2184	725	292[#]	NA	NA	59	22[##]	NA	NA
26	67,271	41,664	NA	NA	339	316	NA	316	NA
28	1	1	0	1	1	1	0	1	1
29	1	1	0	1	0	1	0	1	0
30	9	9	9	0	0	1	1	0	0
31	20	20	20	0	0	20	20	0	0
36	1	1	0	1	0	1	0	1[*]	0
37	1	1	0	1	0	1	0	1[*]	0

Reference number 26 was a meta-analysis. Severe disease includes Intensive Care Unit admission. *; Complicated with acute fatty liver of pregnancy and acute kidney injury, [#]; 433 women were symptomatic, [##]; 37 women were symptomatic, and NA; Not available.

In general, older age and the presence of greater number of comorbidities were associated with the COVID-19 severity (32). Gestational hypertension as a comorbidity factor is correlated to the severity of COVID-19. SARS-CoV-2 infection reduces the ACE2 availability on the surface of cells through targeted degradation of ACE2 via the clathrin-mediated endocytic pathway. In addition, SARS-CoV-2 affects other components of the RAAS including ADAM metallopeptidase domain 17, ADAM17. This enzyme cleaves the membrane-bound ACE2 receptors and downregulates them. On the other hand, RAAS dysregulation is associated with adverse pregnancy outcomes, especially preeclampsia and restriction of fetal growth. It has been suggested that the unfavorable impact of infection with SARS-CoV-2 on the pregnancy might be due the RAAS pathway disruption, which is the results of degradation and decreased availability of ACE2 by virus binding. Since, the SARS-CoV-2 enters the cells by binding to the ACE2, whose expression is enhanced during pregnancy; ACE2 might contribute to the increased susceptibility of pregnant women to SARS-CoV-2 infection. Moreover, COVID-19 could increase the risk of pregnancy adverse outcomes (4).

Association of preeclampsia with COVID-19 and its severity might be interpreted by the significantly lower levels of Ang-(1-7) peptide during complicated pregnancy, preeclampsia, and dysregulation of placental ACE2 by SARS-CoV-2 (33). Excess amount of ACE2 is expressed in the syncytiotrophoblast, the cytotrophoblast, the endothelium and the villi vascular smooth muscle, which mainly regulates blood pressure and fetus development. It has been suggested that intrauterine SARS-CoV-2 infection might alter the ACE2 expression and increased the Ang II level in the placental villi that lead to preeclampsia. COVID-19 is correlated with cytokine storm and hypercoagulability (34). Also, pro-inflammatory cytokines have been elevated in the both COVID-19 and preeclamptic patients. Furthermore, the hyperinflammatory state in preeclamptic women has been confirmed with maternal high serum ferritin levels (35).

Acute fatty liver of pregnancy (AFLP) is a rare variant of preeclampsia with an incidence rate of 1 in 13000 that could result in the mother and fetus mortality. There are two case reports of pregnant women in the late pregnancy who simultaneously had severe preeclampsia complicated by AFLP and acute kidney injury following infection with SARS-CoV-2. The women recovered and discharged from hospital. In pregnant women the SARS-CoV-2 infection can predispose them to hepatic dysfunction. The necessity of health care and awareness of complex synergistic interaction between COVID-19 and hypertensive disorders of pregnancy are considerable that in the patient with AFLP and multi-organ dysfunction are remarkable and more important (36, 37).

Pregnancy and the severity of COVID-19

Pregnant patients infected with SARS-CoV, and Middle East Respiratory Syndrome (MERS)- CoV had more adverse outcomes of pregnancy, including intrauterine growth restriction, spontaneous miscarriage, and premature delivery. And also, the rate of mortality among infected pregnant patients was more than the general infected population (25 vs. 10%, respectively) (23). Among French pregnant women, mostly symptomatic it was revealed that COVID-19 can be serious and acute in pregnant women. Although, the most serious COVID-19 was observed in women with the highest rates of comorbidities such as obesity, diabetes mellitus, hypertension, and advanced age (33). A retrospective study was conducted to compare clinical outcomes and the results of laboratory tests of COVID-19 infected pregnant women of $\geq$ 20 weeks gestational age with non-pregnant women from four large hospitals of France and Belgium. This study found a significant high risk of ICU admission among pregnant women in comparison with non- pregnant women. Also, they did not report mortality in the groups (38). This study along with a report from Iran with 7 out of 9 deaths due to severe COVID-19 in their pregnant women (39) and one study from Sweden with higher risk of ICU admission in the pregnant and postpartum women with COVID-19 in comparison with non-pregnant women (40) indicated more severe outcomes of COVID-19 in pregnant women than their non-pregnant women. However, Blitz et al. (41) evaluated the data from a large hospital system in the New York State, USA among hospitalized women with COVID-19 and reported that the risk of ICU admission in the pregnant women was not higher than the non-pregnant women. In a retrospective study of Wuhan, China patients (n=82), an increase in the COVID-19 susceptibility and its severity were not observed in the pregnant women (n=28) in comparison with the non-pregnant women (n=54) (42).

Maternal COVID-19 and placental infection

The infection of the placenta and SARS-CoV-2 vertical transmission is rare. In a meta-analysis including 1316 pregnant women infected with SARS-CoV, MARS-CoV, and SARS-CoV-2, no transmission of CoVs from the mother to the fetus was detected (43). In the Di Mascio et al. study, analysis of a small number of cases (n=41) suggested that COVID-19 was associated with a higher preterm birth rate, preeclampsia, cesarean delivery, and prenatal death, with no clinical evidence of vertical transmission (27). Also, no evidence of vertical transmission through intrauterine infection in the COVID-19 pneumonia affected woman in the late pregnancy was found (30). However, significant abnormalities in the placenta morphology have been detected among COVID-19 infected patients (44). Examination of 16 placentas from mothers with COVID-19, including 15 live births and one intrauterine fetal death that demonstrated an increased prevalence of maternal vascular malperfusion in the COVID-19 patients, placentas compared with controls, a pattern indicative of injury of the placenta that is associated with adverse perinatal outcomes (45). Although, one COVID-19 infected pregnant woman in the

second trimester was reported that placental infection and severe early-onset preeclampsia were detected. This study suggested that COVID-19 might contribute to placental inflammation and consequently result in early-onset preeclampsia. Both infections with SARS-CoV-2 and hypertensive disorders of pregnancy decrease the ACE2 activity which leads to enhanced tissue levels of Ang II. It seems that RAAS dysregulation in the COVID-19 patients might contribute to hypertensive complications of pregnancy such as preeclampsia; and COVID-19 may increase the severity of these complications by infecting the placenta (46). The ACE2 is involved in the placentation and also plays a role in the multiple pregnancy adverse outcomes, including miscarriage, ectopic pregnancy, and preeclampsia. Regarding its presence in the placenta, it is likely SARS-CoV-2 might bind to ACE2, which leads to infection and affecting placental function and fetal development; this entity should be elucidated (44).

Diagnostic and therapeutic roles of exosomes in COVID-19 and preeclampsia

Exosomes are nano-sized extracellular vesicles that are secreted by all cell types and have structural similarities with viruses. Exosomes are secreted by cells infected with viruses and mediated in communication between infected and un-infected cells. Also, the contents of exosomes induce the inflammation through activation of the receptors of the cells. So, it seems exosomes be involved in the propagation of the SARS-CoV-2 and inflammation induction contributing to organ dysfunction in the severe COVID-19. Also, theses extracellular vesicles are involved in the pathogenesis of pregnancy complications such as preeclampsia. Due to modulation of the production and composition of exosomes by SARS-CoV-2, they can be used for COVID-19 diagnosis and also could have therapeutic benefits in the COVID-19. The engineered exosomes can be used as a therapeutic tool for different, diseases (47, 48). The exosomal contents can be released into the circulation. This various content can be acted as potential diagnostic biomarkers. Exosomes can be used in the early detection of complications of pregnancy including preeclampsia. In preeclampsia, exosomes contain specific miRNA, DNA and proteins that secreted by trophoblasts and could help in the preeclampsia onset prediction much earlier than blood protein markers (48). Also, the engineered exosomes can be used as different antiviral therapeutics types including COVID-19 treatment.

Conclusion

According to the literature, many studies reported higher severity of COVID-19 among pregnant women in comparison with non-pregnant women. And also, there are more adverse pregnancy outcomes such as intrauterine growth restriction, premature delivery, and spontaneous miscarriage in the pregnant women infected with SARS-CoV, and MERS-CoV. Also, an association between COVID-19 with preeclampsia and the role of preeclampsia and gestational hypertension as risk factors for infection with SARS-CoV-2 and its complications is suggested. There were rare reports of placenta infection and SARS-CoV-2 vertical transmission. Although, many studies reported contribution of COVID-19 to placental inflammation and pregnancy complications such as preeclampsia, there are still some studies that indicated no increased in the COVID-19 severity among pregnant women. Discrepancies in the studies could be due to differences in the characteristics and prevalence of risk factors among populations or ICU admission threshold. More studies are necessary to confirm the greater COVID-19 severity in the pregnant women and its role in development of pregnancy complications. However, until then, COVID-19 is supposed to influence the pregnancy outcomes or susceptibility of pregnant women to severe forms of COVID-19 by the following mechanisms: i. In both SARS-CoV-2 infection and hypertensive disorders of pregnancy, including preeclampsia, the activity of ACE2 decreases, which results in increased Ang II, decreased Ang-(1-7) and imbalance between the levels of Ang II and Ang-(1-7). Therefore, COVID-19 might contribute to the pathogenesis of hypertensive disorders of pregnancy such as preeclampsia through RAAS dysregulation, which is itself a major mechanism of pregnancy hypertension. Ii. Severe forms of COVID-19 are associated with the presence of comorbidities; furthermore, hypertensive disorders of pregnancy are also related to comorbidities, which might explain the severity of COVID-19 in these patients. Iii. There is an interaction among the immune system, inflammatory cytokines and the RAAS and its contribution to the pathogenesis of hypertension. Among patients with COVID-19 and also in preeclamptic patients, there are increased pro-inflammatory cytokines and hyper-inflammatory state that could be considered in the evaluation of the disease severity in these patients.

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Authors' Contributions

B.S., Z.R.: Contributed to study conception and design, preparation of final manuscript, and writing of the manuscript. M.S., Z.M.A., F.M., M.Sh., R.M., S.R.; Contributed to the design, and writing the initial draft. Z.R., Z.M.A.; Editing and revising. All authors read and approved the final manuscript.

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