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Review article

Is highly expressed ACE 2 in pregnant women “a curse” in times of COVID-19 pandemic?

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ABSTRACT

Angiotensin-converting enzyme 2 (ACE 2) is a membrane-bound enzyme that cleaves angiotensin II (Ang II) into angiotensin (1–7). It also serves as an important binding site for SARS-CoV-2, thereby, facilitating viral entry into target host cells. ACE 2 is abundantly present in the intestine, kidney, heart, lungs, and fetal tissues. Fetal ACE 2 is involved in myocardium growth, lungs and brain development. ACE 2 is highly expressed in pregnant women to compensate preeclampsia by modulating angiotensin (1–7) which binds to the Mas receptor, having vasodilator action and maintain fluid homeostasis. There are reports available on Zika, H1N1 and SARS-CoV where these viruses have shown to produce fetal defects but very little is known about SARS-CoV-2 involvement in pregnancy, but it might have the potential to interact with fetal ACE 2 and enhance COVID-19 transmission to the fetus, leading to fetal morbidity and mortality. This review sheds light on a path of SARS-CoV-2 transmission risk in pregnancy and its possible link with fetal ACE 2.

1. Introduction

Angiotensin-converting enzyme (ACE) is an ectoenzyme with a molecular weight of 195 kDa, which plays a crucial role in the renin-angiotensin system (RAS) pathway. The ACE enzyme converts angiotensin I (Ang I), a decapetide to angiotensin II (Ang II), an octapeptide that binds to the AT1 receptor to induce vasoconstrictor response, which is a well-known target for the treatment of cardiovascular complications [1,2]. ACE 2 is a type I transmembrane metalloproteinase, composed of a single HEXXH zinc-binding domain and is a homologue of ACE with 40% similarity. ACE 2 is able to hydrolyze angiotensin I (Ang I) to produce angiotensin (1–9) and inactivates potent vasoconstrictor Ang II to produce angiotensin-(1–7) (Ang I-7). The enzyme is able to cleave several peptides from other systems such as the kinin metabolites, neurotensin 1–13, apelin 13, dynorphin 1–13 [3]. The enzyme has vasodilator property as an endogenous ligand for the G protein-coupled receptor Mas, stimulates prostaglandin synthesis and inhibits proliferation of vascular smooth muscles [4–6]. ACE 2 is a membrane-bound enzyme and is most abundantly present in the intestine, kidney and heart compared to other organs such as lungs and arteries [7,8]. Several reports from the literature, have indicated that ACE 2 is highly expressed in the reproductive organs, placenta, uterus and, maternal-fetal interface during pregnancy; which is important for normal fetal growth and also for regulation of the Ang II level. Besides, renal ACE 2 is also upregulated in pregnant women, further in comparison; the placenta shows the highest expression of renal ACE 2 mRNA, followed by kidney...
and, then the uterus; whereas, the ACE 2 activity is higher in kidney in comparison to placenta and uterus (Table 1) [11–14]. Recently, it is documented that transmembrane ACE 2 also serves as an entry point into cells for human pathogenic human coronavirus NL63 (HCoV-NL63), severe acute respiratory syndrome-related coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [15–18]. The RAAS inhibitors in the pathogenesis of Covid-19 are overly complex and controversial. Recently, Saavedra et al. reported that treatment with AT1 receptor blocker protects the lungs from the viral infection including coronavirus through the modulation of inflammation and ACE 2 upregulation. Hence, the AT1 receptor blocker can be used in comorbid conditions including diabetes, hypertension and renal diseases among COVID-19 patients. Contrary, the expression of ACE 2 is upregulated in patients with heart failure, arterial hypertension and diabetes mellitus when treating with ACE inhibitors & AT1R blockers and thereby, increased chances of COVID-19 disease [19,20]. In addition, higher expression of ACE 2 in fetal tissues such as heart, liver and lung but not in the kidney, may also increase the risk to neonates in pregnant women, infected with COVID-19, could facilitate the disease transmission to developing fetus and may affect different organ systems which have high expression of ACE 2 [12,21,22].

Preeclampsia is a pregnancy complication characterized by high blood pressure and proteinuria and usually begins after 20 weeks of gestation. It is one of the foremost reasons for maternal and fetal morbidity and mortality [23]. Reports suggest that the levels of angiotensinogen, Ang II, and mineralocorticoids are increased in pregnancy and lead to preeclampsia [11,24]. Further, to regulate this increased blood pressure, a compensatory increase in ACE 2 activity leads to the production of Ang (1–7) which causes vasodilation, reduces the production of aldosterone by acting on adrenal glomerulosa cells [23,25–28]. ACE 2 has an antihypertrophic activity that plays a pivotal role in cardiac tissue during the gestational period and may modulate myocardial tissue growth [29,30]. Additionally, a report shows that ACE 2 is also involved in fetal brain and lung development in the gestation period [29]. Experimental evidence shows that Murine coronavirus

Table 1

| Expression | Tissue | Reference |
|-----------|--------|-----------|
| mRNA expression of ACE 2 in tissue | Small intestine > Colon > Duodenum > Kidney > Testis > Gall bladder > Heart muscle > Thyroid gland > Adipose tissue > Epididymis (Consensus data set) | [9], [10] |
| Protein expression of ACE 2 in tissue | Duodenum > Gall bladder > Kidney > Small intestine > Testis > Adrenal gland > Colon > Rectum > Seminal vesicle | [10] |
| ACE 2 mRNA in the pregnancy | placenta > kidneys > or = uterus | [11] |
| ACE 2 activity in the pregnancy | kidney > placenta > uterus | [11] |
| ACE 2 expression in fetal tissues | Heart, liver and lung, but not in fetal kidney | [12] |
| High expression of ACE 2 | At maternal-fetal interface cells, stromal cells, perivascular cells of decidua, cytotrophoblast and syncytiotrophoblast in placenta | [12] |

Fig. 1. Structure of the ACE 2 N-Terminal which contains peptidase domain (red) and C-Terminal domain contains collectrin like a domain that includes intracellular domain (yellow) with chain (pink) and transmembrane helix (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
infects placenta and uterus in pregnancy/challenge of susceptible BALB/cByJ mice. In addition, a porcine Betaarterivirus suid infection induces fetal death in pigs at early stage of pregnancy [31]. Moreover, MERS CoV and SARS-CoV infection during pregnancy is also linked with maternal illness, abortion, maternal deaths and preterm birth but little is known about SARS-CoV-2 transmission in pregnancy and its impact on the fetus [31–33]. The lacuna in the availability of reports in literature regarding the vertical transmission of SARS-CoV-2 infection from mother to fetus has raised the concern for the potential interaction of ACE 2 with SARS-CoV-2 virus. In this review, we focus on the importance of the ACE 2 receptor in SARS-CoV-2 transmission from pregnant women to fetuses and neonates.

2. SARS-CoV-2 and ACE 2

SARS-CoV-2 is a positive-sense single-stranded RNA virus and causes respiratory illness. SARS-CoV-2 genome is identical to SARS-CoV (80%) and BatCoV RaTG13 (96%) [18]. There are four major proteins in the structure of SARS-CoV; namely N protein (nucleocapsid), M protein (membrane), E protein (envelope), and S protein (spikes that lead to virus entry) [34–38]. N protein functions largely to bind to the CoV RNA genome and the nucleocapsid formation. In endoplasmic reticulum (ER)-Golgi, it helps in assembling and budding of SARS-CoV [39]. M Protein is an ample structural protein that maintains the shape of the viral envelope [40,41]. E protein is the smallest of all the proteins available and is abundantly produced during viral infection and then incorporated in the viral envelope to mediate membrane fusion [42–44]. Cleavage of S protein (Trimer) leads to the formation of S1 and S2 subunits. S1 subunit is primarily composed of the receptor-binding domain and is liberated during the phase of post-transfusion conformation [44–47]. It has a tendency to bind directly to the angiotensin-converting enzyme 2 (ACE 2) at its peptidase domain (PD) site [48,49]. Whereas the S2 subunit facilitates membrane fusion which is a paramount step for viral infection. S2 comprises a cleavage site for host proteases [45,50,51]. The ectodomain of the SARS-CoV-2 S protein binds to the peptidase domain (PD) of ACE 2 [52,53].

ACE 2 consists of the N-terminal peptidase domain (PD) and a C-terminal collectrin-like domain (CLD) which is comprised of 40 intracellular residue segments; including chain and the single transmembrane helix at the end of C-Terminal [54,55]. PD of ACE 2 cleaves Ang I, resulting in the formation of Ang (1–9), which are then further converted to Ang (1–7). However, ACE 2 performs the direct cleavage of Ang II to produce Ang (1–7) [54,56,57]. The dimer structure of the ACE 2 domain structure is shown in Fig. 1 [58].

ACE 2 seats the receptor-binding domain (S Protein of SARS-CoV-2) in its peptidase domain (Fig. 2). The presence of polar interactions between the ACE 2 and SARS-CoV-2 enabled the binding efficacy [47,49,59–61]. An arch-shaped helix of the peptidase domain of ACE 2 interacts with the loop region of the Receptor Binding Domain of the S protein. The other helix and loops connect the antiparallel strands and co-ordinate the peptidase domain to the receptor-binding domain.

Based on data and analysis published by Statistical Research Department for Italy, there can be inferences that men may be more at risk than women (53.1% vs. 46.9% among total COVID-19 cases) [62]. Further, growing evidence shows that there is an increased mortality rate in male COVID-19 patients as compared to females underlying with chronic illness such as hypertension, which is the foremost reason for the comorbidity and mortality followed by diabetes mellitus, renal disorder, chronic obstructive pulmonary disease and cancer [63–65]. The infection and fatality rate is less in females, possibly due to strong immune response; less susceptibility to viral infections; high level of the protective hormone estrogen, progesterone and, presence of ACE 2 which is X-linked [66–69].

However, in an article by World Economic Forum, it is suggested that COVID-19 fallout may be worse in women compared to men since i) women are on the front lines of the fight against SARS-CoV-2 infection as...
they form the majority of health and social care workers (Fig. 3) [70] ii) women are specifically affected by mass school closures as they still bear most of the responsibility for childcare iii) Women already do three-times as much unpaid care work than men [71].

Globally, we have analyzed the last five years data of Women of reproductive age (15–49 years) population made available by UN Population Division and found that each year there are around 1.9 billion women of childbearing age (Fig. 4) [72].

Furthermore, these numbers were segregated based on Income groups (High, Low, Low middle and Upper middle). According to the article published by the Center on Society and Health, income is a leading force behind the striking health disparities and low-income adults are approximately five folds more likely to report being in poor health [73]. Therefore, especially women belonging to low and lower-middle-income groups (approximately 1.1 billion; Fig. 4) are much more susceptible to these COVID-19 infections.

3. Current cases of COVID-19 in pregnancy and fetal risk

Due to the presence of limited data, COVID-19 transmission in pregnancy and its effect on the fetus is still not so clear. ACE2 is extensively expressed in human placenta and chiefly in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi. In the maternal stroma, ACE2 is expressed in the invading and intravascular trophoblast and decidual cells. ACE2 is also found in arterial and venous endothelium and smooth

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Fig. 3. Distribution of physicians and nurses by gender.

Fig. 4. Women of reproductive age (15–49 years) by UN population division.
catalyze the formation of octapeptide angiotensin II. Renin is an enzyme that acts on angiotensinogen to produce decapeptide angiotensin I. Further, the high levels of Ang II, ACE2 and Ang-(1–7) expression may be involved in hypertension of pregnancy, preeclampsia and eclampsia. In addition, preeclamptic women presented plasma Ang-(1–7) suppressed levels when compared with normal pregnancy subjects [76].

Recently, Chen et al. reported that nine women in the third trimester of pregnancy are infected with SARS-CoV-2 and all had pneumonia. Women underwent cesarean delivery and all infants are born with good health, having Apgar scores “between” 8–10 [77]. In addition, a report also shows that a 30-week pregnant woman infected with SARS-CoV-2 gave birth to a baby without any symptoms of COVID-19 and after testing the neonate swab, the results were negative [78]. A study also reports eleven pregnant women with the disease gave birth without neonatal respiratory illness, abortion and deaths [79]. Schwartz et al. analyzed the thirty-eight pregnant women infected with SARS-CoV-2 in China and reported that there is no evidence of intrauterine transmission of the virus, no maternal deaths and all neonates found negative for COVID-19 test [80]. In support of these reports, Fan, C et al. show that newborns are safe and there are no abnormalities observed in babies of SARS-CoV-2 infected mothers [81].

Contrary to these reports, Wang, S et al. reveal that pregnant women infected with SARS-CoV-2 delivered a COVID-19 positive baby in China. This was confirmed in the neonatal pharyngeal swabs which were tested positive with SARS-CoV-2 after 36 h; this shows the still unexplored vertical transmission of the virus from mother to fetus [82]. Zhu H et al. reported that prenatal SARS-CoV-2 exposure might have adverse effects on neonates such as fetal distress, premature labor, respiratory distress, thrombocytopenia associated with abnormal liver function, and death. However, swab testing reports of infants were negative, thus challenging the intrauterine COVID-19 transmission to the fetus.

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Note: Green dotted arrow indicates proposed/hypothetical pathway.
nasopharyngeal and anal swabs were taken and confirmed with COVID-19 on day 2 and 4, after birth. However, later one infant was tested negative for the disease on day 7, whose mother underwent cesarean delivery at 31 weeks of the gestational period [87]. In addition, the mother underwent a Cesarean section with all infection control measures, in a negative pressure isolation room. She gave birth to neonate presenting positive serum IgM, high level of cytokine level after 2 h of birth, indicating the possibility of vertical transmission of the virus from mother to fetus [31,88]. Zambrano et al. reported that 31 weeks pregnant woman suffering from gestational hypertension and hypothyroidism with symptoms of fever, dry cough, headache and myalgias admitted to the hospital. An obstetric ultrasonography report shows dysplastic and multicystic right kidney in fetuses. However, these defects are not confirmed due to COVID-19 [33].

Here, we hypothesized that high expression of ACE 2 might be responsible for the fetal defects, as there are chances of binding of SARS-CoV-2 with fetal ACE 2. However, further research is required to clarify any information. The report shows that pregnancy leads to immunosuppressive state and may increase susceptibility to respiratory pathogens [33,89,90]. Na Li, MD et al. compare the effect of SARS-CoV-2 infection in maternal and neonatal outcomes in pregnant women with and without COVID-19 pneumonia. Nine pregnant women infected with SARS-CoV-2 went under the cesarean section and two pregnant women had a normal delivery with a higher risk of premature delivery (33.3%) but none was due to severe maternal respiratory failure. [91]. A mother infected with SARS-CoV-2 during the third trimester of pregnancy experienced decreased fetal movement, anemia, dyspnea, and newborns infected with SARS-CoV-2 [92]. In total, SARS-CoV-2, induced fetal abnormalities reported are miscarriage (2%), intrauterine growth restriction (10%) and pre-term birth (39%). However, there is no evidence of vertical transmission of SARS-CoV-2 from mother to fetus and as well under cesarean section and vaginal delivery [77,91,93].

Recent report shows that both S-protein and N-protein of SARS-CoV-2 presented positive to immunostains in the cytoplasm of the syncytiotrophoblast and the presence of N protein in rare intervillous macrophages and Hofbauer cells however, SARS-CoV-2 proteins were not detected in villous capillaries. In addition, in situ hybridization technique showed intense signal positivity for SARS-CoV-2 in syncytiotrophoblast lining with a distribution similar to that detected for the S-protein immunohistochemistry. Further, nucleic acid analysis, ultrastructural examination studies revealed the presence of coronavirus-like particles within the cytoplasm of syncytiotrophoblast and within chorionic villous fibroblasts and fetal capillary endothelial cells. Therefore, this could be the possible mechanism of SARS-CoV-2 may enter the placenta and passed to the fetus prior to delivery [94–96]. However, presently the data suggest that there is little evidence of vertical transmission to the newborn; hence, more studies will require to prove vertical transmission from the pregnant woman to the fetus.

4. Conclusion

The literature studies and data support that there is no clear information regarding the infection and its intrauterine transmission of COVID-19 to the fetus. However, a wide range of trials needs to be conducted to warrant fetuses’ safety from COVID-19 disease in pregnancy. There is no clear evidence, it might be due to the small population size of pregnant women infected with the disease and thus, further prospective studies need to be carried out worldwide. However, we hypothesize that fetal ACE 2 may interact with SARS-CoV-2 and increase the potential for fetal morbidity and mortality. Further, there is a lack of evidence about whether SARS-CoV-2 can cross the placenta and causes intrauterine infection through vertical transmission. If it crosses the placenta, it might interact with the fetal ACE 2, which is abundantly present in fetal tissues such as lungs, heart, liver, brain and may induce fetal death and abortion (Fig. 5). The incidence of SARS-CoV-2 infection to the fetus is really debated therefore careful monitoring of pregnant women is warranted to prevent neonatal infection.

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Declaration of competing interest

All authors declare that they have no conflicts of interest.

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