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Highly expressed ACE-2 receptors during pregnancy: A protective factor for SARS-COV-2 infection?

Ernesto Antonio Figueiro-Filho *, Sebastian R. Hobson, Dan Farine, Mark H. Yudin

Mount Sinai Hospital, Maternal Fetal Medicine Division, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Canada

Saint Michael’s Hospital, Maternal Fetal Medicine Division, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Canada

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SUMMARY

While previous viral pandemics showed that pregnancy was a risk factor for susceptibility and adverse outcomes, current evidence is conflicting whether SARS-CoV-2 infection during pregnancy is more severe than in the general population, with relatively low maternal and fetal/neonatal mortality rates. SARS-CoV-2 is known to enter host cells via the ACE-2 receptors, competitively occupying their binding sites. In theory, viral invasion can lead to a reduction in available ACE-2 receptors and consequently an unbalanced regulation between the ACE-AngII-AT1 axis and the ACE-2-Ang-(1-7)-MAS axis, thus enhancing pathological vasoconstriction, fibrosis, inflammation and thrombotic processes. We hypothesize that the normal pregnant state of highly expressed ACE-2 receptors leads to higher Ang-(1-7) levels and consequently more vasodilation and anti-inflammatory response to SARS-COV-2 infection. We suggest that this up-regulation of ACE-2 receptors in human gestation may actually be clinically protective and propose a potential research line to investigate this hypothesis, which may lead to future novel therapeutics.

Key points

- SARS-CoV-2 is known to enter host cells via the ACE-2 receptors, competitively occupying their binding sites. In theory, viral invasion can lead to a reduction in available ACE-2 receptors and consequently an unbalanced regulation between the ACE-AngII-AT1 axis and the ACE-2-Ang-(1-7)-MAS axis, thus enhancing pathological vasoconstriction, fibrosis, inflammation and thrombotic processes.
- We hypothesize that the normal healthy pregnant state of highly expressed ACE-2 receptors leads to higher Ang-(1-7) levels and consequently more vasodilation and anti-inflammatory response to SARS-COV-2 infection.
- We suggest that this up-regulation of ACE-2 receptors in human gestation may actually be clinically protective and propose a potential research line to investigate this hypothesis, which may lead to future novel therapeutics.

Introduction

Initial reports of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had suggested that pregnancy negatively impacted on the clinical course of infection [1–3]. Conversely, current evidence is conflicting whether SARS-CoV-2 infection during pregnancy is more severe than in the general population [3–5], with relatively low maternal and fetal/neonatal mortality rates [3–5].

Previous viral outbreaks [1,6] demonstrated detrimental effects on perinatal and maternal outcomes. Rejection of fetal tissues is mitigated by elevation of humoral responses and suppression of cell-mediated immunity throughout pregnancy [7]. These changes are referred to as the T-helper lymphocyte type-1-type-2-type17 (Th1/Th2/Th17) and regulatory T cell (Treg) paradigm [8], and impact directly on the response to viral infections [7,9]. Curiously, SARS-CoV-2 has not, thus far, demonstrated the same pregnancy related adverse effects [4,10,11], rather than those associated to preterm deliveries [12].

Both the immune system and the renin-angiotensin system (RAS) play particularly important roles in mediating SARS-CoV-2 virus entry into human cells [13]. The efficient binding of the SARS-CoV-2 spike (S) viral envelope protein to the angiotensin converting enzyme-2 (ACE-2) receptor, and the transmembrane protease serine 2 (TMPRSS2) for S protein priming, are necessary steps to facilitate the successful viral entry to host cell [14,15].
It was described that, in individuals with COVID-19, severe multi-organ involvement is related to pathobiological immune alterations, rather than to direct viral response [16]. Inflammatory changes were extensively observed in post-mortem organs of patients that succumbed to severe COVID-19 illness [16]. These organ tissues share common local RAS-autocrine pathways that may have been affected by the immune-inflammatory interaction between SARS-CoV-2 and ACE-2 receptors [13,16].

ACE-2 and Ang-(1-7) expression during pregnancy

The most important role of the ACE-2 membrane-bound enzyme, is the cleavage of angiotensin I or II (Ang I or Ang II) to angiotensin1-7 (Ang-(1-7)) [13,17]. This branch of the RAS cascade has an important counter-regulatory effect on the vasoconstrictor, pro-inflammatory and pro-thrombotic activity of the ACE-AngII-AT1 axis. Ultimately, the ACE-2-Ang-(1-7)-MAS axis results in vasodilatation, natriuresis, anti-inflammatory and anti-thrombotic effects [13,18–21] (Fig. 1).

Animal and human studies before the SARS-CoV-2 pandemic have demonstrated that ACE-2 and Ang-(1-7) expression are enhanced during normal pregnancy [18,19,22,23], resulting in increased vasodilation, and a reduction in fibrosis, inflammation, thrombosis and pulmonary damage [13,20,21]. In theory, SARS-CoV-2 viral invasion can induce a relative reduction in unbound ACE-2 receptors and subsequent unbalanced dysregulation between the ACE-AngII-AT1 axis and the ACE-2-Ang-(1-7)-MAS axis, thus contributing to an environment of progressive vasoconstriction, fibrosis, inflammation and thrombo-embolic processes [13], (Fig. 1).

Comorbidities that are known to be associated with ACE-2 deficiency include older age, diabetes, cardiovascular disease and hypertension [13]. Individuals with these conditions also represent those that are more likely to be infected with SARS-CoV-2 and develop more severe complications of COVID-19 both in the general population and also during pregnancy [5,24,25]. In pregnancies with preeclampsia (PE), plasma ACE-2, Ang-(1-7) levels and ACE-2 activity are lower compared with normotensive pregnant women [22], resulting in the opposite biological consequences of vasoconstriction, inflammation and pro-thrombotic effects [26]. Others have previously described the similar clinical phenotypes of preeclampsia and severe COVID-19 infection during pregnancy [26].

The relationship between the downregulation of ACE-2 receptors in individuals with a reduced baseline ACE-2 phenotype and its effect on worsening SARS-CoV-2 infection, compared to those individuals with normal baseline or enhanced ACE-2 phenotype was previously explored by Verdecchia et al., at early stages of the COVID-19 pandemic [13]. This proposed physiological pathway [13] was the basis for the rationale hereby presented.

Placental and fetal expression of ACE-2 and Ang-(1-7)

Strong expression of ACE-2 receptors in trophoblastic human cells is demonstrated throughout pregnancy, supporting a receptor-mediated mechanism leading to SARS-CoV-2 placental infection [27]. Low levels of ACE-2 and TMPRSS2 have been identified in extra villous trophoblast (EVT) cells at 8 weeks gestation, whereas ACE-2 and TMPRSS2 placental expression was significantly increased in EVT at 24 weeks gestation [28]. These results suggest that the placental expression of ACE-2 and TMPRSS2 at the maternal-fetal interface may increase as pregnancy advances [28]. Furthermore, syncytiotrophoblastic ACE-2 expression may regulate Ang-(1-7) release into maternal circulation.
thus promoting maternal vasodilatation [29].

Even before the COVID-19 pandemic, animal studies demonstrated that ACE-2 and Ang-(1-7) are highly expressed on the fetal side of the placenta [30], whereas human and animal studies demonstrated that the maternal side has low expression of ACE-2 and Ang-(1-7) [30,31]. While a recent study reported that ACE-2 receptor expression is negligible on the chorioamniotic membranes in the human placenta [32], other authors described intense signal positivity for SARS-CoV-2 in syncytiotrophoblast lining the chorionic villi (with RNA in situ hybridization) [33]. Moreover, fetal vascular malperfusion, interstitial space inflammatory infiltrates, increased villous stromal macrophages and increased inflammatory platelet aggregates were observed on the fetal sides of the same human placentas [33].

Irregular expression of ACE-2 and TMPRSS2 have been described in 19 SARS-CoV-2 infected placentas [34]. The authors concluded that the human placenta is capable of being infected, although the polarized expression of ACE-2 towards the fetal compartment and the scarce expression of TMPRSS2 in trophoblast, remote from maternal blood, may justify the rarity of vertical transmission of COVID-19 [34]. ACE-2 is abundantly present in the heart, lungs, intestine, kidneys, and fetal tissues [35]. In live fetuses, ACE-2 receptors are involved in myocardium growth, lung and brain development [35]. These findings suggest that a potential Placental Barrier against COVID-19 is possible [36].

ACE-2 receptors in Pregnancy: Protective against COVID-19?

Contrary to what was previously inferred [35], and based on the physiological interactions between SARS-CoV-2 and ACE-2 receptors [13,15], along with previous evidence that ACE-2 and Ang-(1-7) levels are enhanced during pregnancy [18,19,22], it is possible to hypothesize that:

1) in normal healthy pregnancies, highly expressed ACE-2 receptors [23] lead to higher Ang-(1-7) levels [19] and consequently more vasodilatation and anti-inflammatory response to SARS-CoV-2 infection. We suggest that the up-regulation of ACE-2 receptors in pregnancy may be protective against severe COVID-19 disease.

2) the gestational Th1-Th2 immune shift [7], known as a potential contributor to the severity of viral infections during pregnancy [9], are counter-regulated by the enhanced pregnancy-induced ACE-2-Ang-(1-7) expression [18,22], which may explain the observed improved outcomes of COVID-19 during pregnancy, when compared to previous viral outbreaks in pregnant women.

3) the irregular and unbalanced expression of ACE-2/TMPRSS2 in human placentas [29–34], mostly expressed to the fetal [27,29,30] side but negligible to maternal side [32,34] also play a protective role on vertical transmission of SARS-CoV-2.

4) down-regulation of ACE-2 receptors induced by SARS-CoV-2 cell entry may be detrimental to those with pre-existing ACE-2 deficiencies in pregnancy, explaining the poor outcomes of pregnancies with co-morbidities [25].

Conclusion

We propose to test the hypothesis described above with a case-control design using: a) Non-COVID-19 Control Group (normal, low-risk pregnant women, non-COVID-19 infected, with term deliveries); b) COVID-19 Case Group – Asymptomatic/Symptomatic (pregnant women, COVID-19 infected, without preeclampsia, with term deliveries). Optionally, the investigation could be extended with these groups: c) Non-COVID-19 with Preeclampsia Control Group (pregnant women with preeclampsia, non-COVID-19 infected, with term deliveries); d) COVID-19 with Preeclampsia Case Group – Asymptomatic/Symptomatic (pregnant women, COVID-19 infected, with preeclampsia, with term deliveries).

Table 1 describes the potential maternal, placental, fetal and neonatal investigations to explore the hypothesis. Each of these tests have been previously described [22,32,33,37], attesting to feasibility. The idea of performing these tests upon the different proposed groups, would allow the comparison of ACE-2/TMPRSS2 and Ang-(1-7) expression along the different compartments of the gravid cycle. The dichotomy of the exposed groups in symptomatic and asymptomatic is extremely important to confirm/rule-out the hypothesis described. Additionally, the investigations could be extended to preeclamptic women to test the confounding factor of overlapping clinical phenotypes in COVID-19 and preeclampsia [26].

It has already been demonstrated that, in vitro, recombinant human soluble ACE-2 significantly blocks SARS-CoV-2 in the early stages of cellular infection [38]. If the proposed hypotheses are confirmed, a future potential therapeutic use of soluble recombinant ACE-2, angiotensin1-7 and angiotensin II type 1 receptor blockers might be beneficial in treating severe COVID-19 infections [39].

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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