

## SPECIAL ISSUE ARTICLE

# Is pregnancy an immunological contributor to severe or controlled COVID-19 disease?

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**Abstract**

Since its emergence in Wuhan as a novel coronavirus disease, it has taken only a few months since January 2020 for it to be recognized as a widespread COVID-19 pandemic which has contributed to global health devastation. As pointed out by health experts, it is a once in a century pandemic of our times. Clinical observations so far indicate that the older population and immune compromised individuals, particularly in African American and Hispanic/Latino communities, are at much higher risk for infection with this novel coronavirus. In this regard, pregnancy offers an altered immunity scenario which may allow severe COVID-19 disease. The literature is so far highly conflicting on this issue. This review will offer a conceptual basis for severe or controlled disease and address trepidations for pregnant women associated with COVID-19 pandemic, particularly in the comparative context of clinical consequences of other coronaviruses such as SARS and MERS. We will highlight the possible consequences of COVID-19 on the general health of pregnant women as well as its possible effects at the maternal-fetal interface. For the placenta-related pathology, we will focus our discussion on the temporal expression of ACE2 throughout gestation for possible propagation of SARS-CoV-2 in the placenta in infected women and ensuing consequences.

**KEYWORDS**

angiotensin-converting enzyme-related carboxypeptidase 2, coronavirus disease, extravillous trophoblasts, middle east respiratory syndrome, severe acute respiratory syndrome, severe acute respiratory syndrome coronavirus-, syncytiotrophoblasts

## 1 | INTRODUCTION

It is for the first time in almost a century that the severity of COVID-19, combined with its pandemic spread, has placed unparalleled pressure on our healthcare system and global economy in a span of only a few months.<sup>1,2</sup> This warrants that treatment strategies should be urgently available either in the form of an efficacious vaccine or a drug. A very recent press release from the University of Oxford in England puts dexamethasone, a common steroid, at the center of

treatment modalities, which still needs to be validated for its efficacious use at least in severe COVID-19 cases. Nevertheless, overall lack of a well-defined drug or vaccine leaves the global population at the mercy of social distancing, face covering, and almost complete avoidance of mass gatherings and travel. Along with the older population and immune compromised individuals at much higher risk for infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2),<sup>3-5</sup> it was thought that pregnant women would also fall in the clinical category of severe COVID-19 cases.<sup>6,7,8</sup> This notion

manifested from the known observations of altered immunity and hormonal influx during pregnancy.<sup>9-11</sup> However, data so far do not support significant detrimental effects of SARS-CoV-2 on the general health of pregnant women. On the other hand, the placenta expresses angiotensin-converting enzyme-related carboxypeptidase 2 (ACE2), a cognate receptor for SARS-CoV-2,<sup>12-14</sup> and presents itself as a possible site for infection. Since the maternal-fetal interface maintains anti-inflammatory pregnancy-compatible immunity during gestation,<sup>9-11</sup> it was presumed that there will be an active propagation of the novel virus in the placenta. This scenario could change the highly choreographed cross talk between the placenta and the maternal immune system that could impart vertical transmission of the virus and affect neonatal health, in particular the neurological development.<sup>15,16</sup> Although it is too early in the pandemic to foretell long-term health consequences in children born to COVID-19-positive mothers, other clinical suppositions have not turned out to be on the serious side of the spectrum,<sup>17,18</sup> and it may be related to anti-viral and/or anti-inflammation salient features of the maternal-fetal interface or temporal expression of ACE2. This review will provide insights to the question whether pregnancy is an immunological contributor to severe and controlled COVID-19 disease.

## 2 | CURRENT KNOWLEDGE OF INNATE AND ADAPTIVE IMMUNE RESPONSES DURING COVID-19 ASYMPTOMATIC AND SEVERE INFECTIONS

One major finding related to COVID-19 infection is that many patients remain asymptomatic<sup>19,20</sup> and yet are fully capable of transmitting virus, suggesting that the virus is actively propagating in these individuals.<sup>21,22</sup> It is possible that strong anti-COVID immune responses protect these individuals from developing severe disease. Appearance of symptoms of symptomatic dyspnea (shortness of breath) is seen, in most cases, almost a week after infection.<sup>21,22</sup> This may provide a window of transmission in the absence of severe disease with acute respiratory distress syndrome (ARDS) triggered by a cytokine storm.<sup>23,24</sup> Recent articles have provided a detailed overview of the innate and adaptive immune hyperactivity that may act as a double edged sword for combating the severe consequences of COVID-19 infection.<sup>25-28</sup> For innate immune hyper-activation in response to COVID-19 infection, the focus has been placed on macrophages and neutrophils.<sup>25,27,28</sup> While data on COVID-19 patients continue to rapidly emerge, the research on innate immune dysfunction programmed by macrophages, neutrophils, and other myeloid cells in SARS-CoV-1 and MERS may provide some clues. One key finding is that pathogenic CoVs have mounted multifold strategies to escape immune detection. In particular, CoVs failed to elicit the type 1 interferon (IFN-1) immune response.<sup>29,30</sup> This may also be the case with COVID-19.<sup>31</sup> This lack of response is not related to non-engagement of pattern-recognition receptors (PRRs) and/or danger-associated molecular patterns (DAMPs). Pathogenic (sterile) inflammation in COVID-19 patients is most likely induced by activation of PRRs

and DAMPS, culminating in production of cytokines such as IL-1 $\beta$ , IL-6, and IL-18.<sup>28,32-34</sup> IL-1 $\beta$  and IL-6 can then promote recruitment of neutrophils and cytotoxic T cells.<sup>27,32</sup> Indeed, COVID-19 patients harbor an expanded population of circulating monocytes that secrete IL-1 $\beta$  and IL-6. COVID-19 patients also show higher content of circulating lactate dehydrogenase (LDH),<sup>33</sup> a marker of sterile inflammation (pyroptosis). These studies could be further strengthened by studying pyroptosis markers such as cleaved gasdermin D and caspase-1.<sup>35</sup> For neutrophil recruitment, an autopsy specimen from a patient who succumbed to COVID-19 showed extensive infiltration. Neutrophil infiltration may give rise to formation of neutrophil extracellular traps (NETs) and to pneumonitis and/or ARDS-related mortality in COVID-19 patients.<sup>27,36</sup>

It is evident that a single cytokine or dysregulated innate immunity cannot be assigned a sole pathological inducer in severe COVID-19 infections. For example, blocking of IL-6 receptor signaling by tocilizumab has only given mixed results with even poor results in severely ill patients.<sup>37,38</sup> It is possible that primary activation of macrophages and IL-6 production, unlike secondary production in the case of chimeric antigen receptor (CAR) T-cell therapy, is quite overwhelming and may overcome blockade and cause severe pathology.<sup>34,39</sup> It is expected that IL- $\beta$  and IL-6 production in COVID-19 patients should promote activation of adaptive immunity. The question that remains unanswered is uninhibited viral dissemination. As mentioned earlier, dysregulated IFN-type 1 response may be associated with poor innate immune response to COVID-19. Is T cell-mediated immune response intact in COVID-19 patients? Is an adaptive immune response hyper-activated or suppressed? Unlike H1N1 influenza virus incubation period (24-48 hours), the incubation time for COVID-19 is at least 5-7 days and it takes another few days for a patient to be admitted to the intensive care unit.<sup>21,40</sup> It is then possible that T-cell responses are curtailed as a result of possible T-cell loss or exhaustion (PD-1-PD-1L expression) which may contribute to slow, subacute propagation of COVID-19. In patients with COVID-19, progressive lymphopenia has been noticed,<sup>33,41,42</sup> supporting the concept of poor T-cell responses. These observations suggest that immune responses occur in a non-synchronized manner with production of innate cytokines with poor T-cell responses in the general population and raise an important question of how these immune responses are elicited in COVID-19 infected pregnant women in the context of specialized immunity at the maternal-fetal interface and production of pregnancy hormones.

## 3 | CURRENT KNOWLEDGE OF PREGNANCY COMPLICATIONS WITH COVID-19 INFECTION

Respiratory infections during pregnancy are associated with increased infectious morbidity and high maternal mortality rates.<sup>43</sup> However, it is currently uncertain if pregnant women will have a more severe disease as a result of COVID-19 infection. Some studies suggest that pregnant women with COVID-19 are not at a higher risk of

developing critical pneumonia compared to non-pregnant women.<sup>17</sup> On the other hand, recent data from the Centers for Disease Control and Prevention (CDC) analyzing 8207 pregnant women with confirmed COVID-19 suggest that pregnant women may have increased risk for severe illness compared to non-pregnant women.<sup>44-46</sup>

These data indicate an increased risk of ICU admissions and mechanical ventilation in a very limited number of cases.<sup>45,46</sup> However, there was no increase in mortality rate (1 in 513 of pregnant versus 1 in 400 of non-pregnant women, crude risk ratio 0.8, 95% CI 0.5-1.3).<sup>45,46</sup> Furthermore, the CDC data analysis suggests that pregnant patients who are black or Hispanic may be disproportionately affected by SARS-CoV-2 infection.<sup>45,46</sup> According to the American College of Obstetricians and Gynecologists (ACOG),<sup>46</sup> although there is an increase in the risk of severe outcomes in pregnant women with SARS-CoV-2 infection, the overall risk to pregnant women is substantially lower compared to risks from other upper respiratory illnesses of pandemic H1N1 influenza infection during pregnancy. During the H1N1 influenza pandemic, pregnant women made up 5% of deaths, despite only making up 1% of the population and pregnancy risk of ICU admission was reported as high as a 7-fold increase.<sup>47,48</sup> It was also demonstrated that pregnant patients with comorbidities such as obesity had increased risk for severe illness consistent with the general population with similar comorbidities.<sup>44</sup> These results suggest that the pregnancy immune alteration that was expected to cause detrimental effects on the general health of pregnant women with COVID-19 infection was somehow balanced unlike other respiratory illnesses during pregnancy.

#### 4 | IMMUNE RESPONSES IN PREGNANT WOMEN AND SEVERITY OF DISEASE

Chen et al<sup>49</sup> published a report from Wuhan covering the information on 118 SARS-CoV-2 infected pregnant women stating that the rate of severe maternal disease was 7.6%. Some other studies have reported even lower prevalence of infection in pregnant women.<sup>50</sup> A study with severe disease rate was from New York City, presumably including African American and Hispanic patients.<sup>18</sup> These studies and others have not demonstrated that COVID-19 puts pregnant women at relatively much higher risk of complications than those seen in non-infected pregnant women. At this point, there is simply a precautionary warning from CDC and ACOG but solid information is not yet available.

Importantly, according to the CDC Morbidity and Mortality Weekly Report (MMWR), black non-Hispanic and white non-Hispanic pregnant women exhibit similar COVID-19 infection rates unlike in the general older population. On the other hand, Hispanic or Latino pregnant women show significantly higher infection rates with minimal severe disease. It is presumed that since women experience immunologic, hormonal, and metabolic changes, these could increase their risk of severe illness from respiratory complications. However, this is simply a presumption and no solid information is available to support this notion. Moreover, extended incubation

period and asymptomatic status of SARS-CoV-2 infection may make this virus behave differently than other coronaviruses.

Does the protective immunity at the maternal-fetal interface take advantage of asymptomatic period and is responsible for lack of the expected severe disease or vertical transmission in COVID-19 infected pregnant women? Besides placental immunity including anti-inflammatory cytokines and hormones, recent evidence also suggests that active trophoblast autophagy can induce resistance to viruses.<sup>51-53</sup> On the other hand, some viruses can exploit autophagy for their survival.<sup>54</sup> Whether the placenta mounts such a response against SARS-CoV-2 is not known. During normal pregnancy, anti-inflammatory cytokines enrich the intrauterine milieu and the decidual immunity is pregnancy-compatible involving M2 macrophages, regulatory T cells, non-cytotoxic NK cells, and tolerized T cells.<sup>9,10</sup> In the case of SARS-CoV-2 infections, increased T-helper 2 (Th2)-associated anti-inflammatory cytokines are detected.<sup>21,55</sup> This suggests that this novel virus does not dampen the pregnancy-associated anti-inflammatory milieu. We do not know whether COVID-19 infection has any effect on placental hormone production. As discussed earlier, sterile inflammation (pyroptosis) dominated by IL- $\beta$  and IL-6 has been thought to be induced during COVID-19 infection. It is possible that elevated Th2 responses during pregnancy blunt sterile inflammation and suppress the severity of the COVID-19 disease. A thorough study on hormone production, immune changes, and cytokine production is warranted to better understand the effect of SARS-CoV-2 infection in pregnant women.

#### 5 | COMMENTS ON LYMPHOPENIA IN COVID-19 INFECTED PREGNANT WOMEN

Signature features of COVID-19-related severe illness include the presence of elevated levels of pro-inflammatory cytokines, coagulopathy, and lymphopenia.<sup>41-43,56,57</sup> Lymphopenia signifies severe reduction in lymphocytes and is used as a consistent predictor of COVID-19-associated mortality.<sup>33</sup> Pregnancy is intrinsically associated with moderate reduction in lymphocytes.<sup>58,59</sup> Although representing a small sample size, laboratory results did show marked lymphocyte decrease in five out of 9 women with pneumonia between 36 weeks and 39 weeks of pregnancy, suggesting that severe COVID-19 disease can further contribute to loss of lymphocytes.<sup>33</sup> However, no deaths were reported, dissociating lymphopenia in these patients from mortality. On the other hand, a report from affiliated New York hospitals tested over 200 pregnant women and found 43 women positive for COVID-19.<sup>60</sup> Fourteen patients initially presented without any COVID-19 symptoms. Of these, 10/14 developed symptoms or signs of COVID-19 infection over the course of their delivery admission. Of the other 29 patients presented symptomatic COVID-19 infection, three women required admission and one required oxygen supplementation post-partum. This report suggested that disease percentage was similar to non-pregnant women and did not describe any abnormal immune abnormalities, suggesting that lymphopenia may vary between patient populations depending

on comorbidities and communities. There have not been consistent reports of mortality in COVID-19-positive pregnant women, suggesting that pregnancy-compatible immunity may decelerate severity of the COVID-19 disease. Thus, the question of whether pregnancy is an immunological contributor to severe or controlled COVID-19 disease should be extensively debated.

## 6 | POSSIBLE EFFECT(S) OF COVID-19 INFECTION IN THE PREGNANT UTERUS

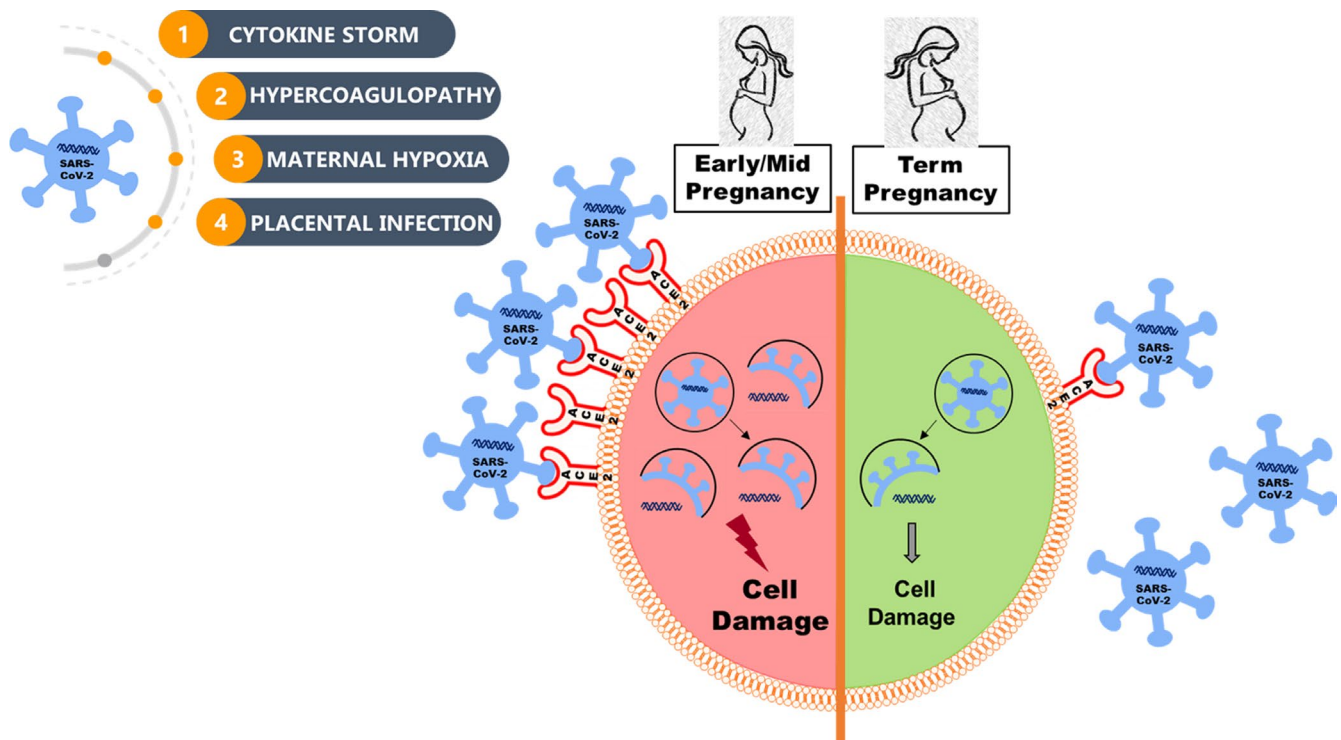
The CDC recently warned against an increased risk of preterm birth among pregnant people with COVID-19.<sup>44</sup> In a study that included women with COVID 19 infections in the second trimester, the pregnant women had higher rates of preterm birth due to preterm labor, PPRM, stillbirth, and fetal distress.<sup>61</sup> A recent study analyzed the clinical characteristics of symptomatic mothers with SARS-CoV-2 pneumonia (total 18 cases) in the third trimester (from 31 to 40 weeks of gestation).<sup>33</sup> Ten out of the eighteen pregnant women who were admitted before 37 weeks of gestation delivered prematurely, suggesting an increased risk for preterm delivery with SARS-CoV-2 infection.<sup>15</sup>

At the NYU Winthrop Hospital, data were analyzed from a cohort of 155 COVID-19 positive mothers and their neonates. There was no evidence of vertical transmission from mothers

with SARS-CoV-2 infection to their newborns which agrees with the published observations. Forty-one percent of these mothers were asymptomatic but tested positive during universal screening upon admission. However, preterm delivery was significantly increased in symptomatic compared to asymptomatic mothers ( $P = .006$ ).<sup>62</sup>

As discussed earlier, there is growing recognition that cytokines play a pivotal role in the maintenance of a healthy pregnancy.<sup>63,64</sup> A pro-inflammatory production of these immune modulators due to infections (bacterial/viral) can lead to pathologic pregnancy, including preterm labor, abortion, preeclampsia, and intrauterine growth restriction.<sup>65,66</sup> It is possible that the systemic pro-inflammatory cytokine storm often seen with severe SARS-CoV-2 infection will compromise the delicate balance of cytokines at the maternal-fetal interface inducing preterm births.

Another study described histopathologic findings in the placentas of women with COVID-19 infection.<sup>67</sup> Placental tissues from COVID-19 pregnancies showed an increased prevalence of decidual arteriopathy and other features of maternal vascular malperfusion. This pathology is often seen with placental injury reflecting oxygenation abnormalities and is associated with adverse perinatal outcomes. These changes may indicate complications related to placental viral infection, systemic inflammation (cytokine storm), maternal hypoxia, or hypercoagulable state (Figure 1).



**FIGURE 1** COVID-19 and placental ACE2 expression and its possible consequences. The SARS-CoV-2 can cause placental dysfunction by inducing systemic inflammation (cytokine storm), oxygenation abnormalities within the intervillous space (COVID 19-associated coagulopathy and maternal pneumonia), or by directly infecting the placenta causing cell damage. Since ACE2 expression is highly expressed in early/mid-pregnancy compared to term placentas, the viral entry and trophoblasts cell damage is more extensive in early/mid-pregnancy compared to term

## 7 | IS THERE A VERTICAL TRANSMISSION OF SARS-COV-2 DURING PREGNANCY?

Vertical transmission from a mother to her fetus has not been observed in either SARS-CoV-1 or in MERS-CoV.<sup>68</sup> However, vertical transmission with COVID-19 remains to be clarified.<sup>69</sup> A recent study reported results of placental/membrane SARS-CoV-2 RNA PCR swabs done within 30 minutes after delivery in 11 COVID-positive symptomatic mothers.<sup>70</sup> Of the 11 placental or membrane swabs sent for testing after delivery, 3 swabs returned with positive results for SARS-CoV-2, from all women with severe to critical COVID-19 infection at the time of delivery. However, there was no reported evidence of vertical transmission.

In a retrospective review of nine Chinese pregnant women with laboratory-confirmed COVID-19 pneumonia who had a cesarean section, amniotic fluid, cord blood, and neonatal throat swabs all tested negative for the virus.<sup>71</sup> The authors suggested that there is currently no evidence for intrauterine infection in women who develop COVID-19 pneumonia in late pregnancy. Zhang et al followed 16 pregnant women with COVID-19 that delivered by cesarean section at a gestational age of 38+ weeks of gestation.<sup>72</sup> All neonates tested by PCR were found to be negative for SARS-CoV-2. Other studies demonstrated similar results.<sup>73</sup>

Interestingly, three independent case reports linked SARS-CoV-2 placental infection to maternal COVID-19 infection in early/mid-pregnancy. The first case report involved a COVID-19-positive symptomatic pregnant woman at 35 weeks of gestation delivering by cesarean section.<sup>74</sup> Placental tissues as well as placental swabs from the maternal and fetal sides were positive for SARS-CoV-2 as detected by RT-PCR. Each of the five random sections of the placenta showed multiple areas of infiltration by inflammatory cells and extensive early infarction. Three neonatal nasopharyngeal swabs done at different dates after birth were also positive for SARS-CoV-2. The second case report involved a 35-year-old pregnant woman at 22 weeks of gestation with symptomatic COVID-19 disease, complicated by severe preeclampsia and placental abruption.<sup>75</sup> Using qRT-PCR assay, the placenta was positive for SARS-CoV-2 RNA. On histological examination, the placenta was remarkable for the presence of diffuse perivillous fibrin and an inflammatory infiltrate composed of macrophages and T lymphocytes. SARS-CoV-2 virus was localized predominantly to the syncytiotrophoblast cells of the placenta, as demonstrated by electron microscopy, immunohistochemistry, and in situ hybridization. The third case report was from our institution at NYU Winthrop Hospital, that involved a 40-year-old pregnant woman at 28 weeks of gestation with symptomatic COVID-19 infection complicated by severe pneumonia requiring intubation.<sup>76</sup> The SARS-CoV-2 virus was also localized predominantly to the cytotrophoblast and syncytiotrophoblast cells of the placenta, as demonstrated by electron microscopy and immunohistochemistry.

Taken together, it appears that placental infection/vertical transmission of COVID-19 in term pregnancy is unlikely. However, there is

evidence of possible placental infection/vertical transmission if SARS-CoV-2 infection occurs in early/mid-pregnancy.

## 8 | DOES SARS-COV-2 INFECT THE PLACENTA IN A GESTATIONAL AGE-DEPENDENT MANNER? A POSSIBLE ROLE OF ACE2

ACE2 is a zinc-containing metalloenzyme located on the cell membranes of endothelial cells as well as cells of various lineages.<sup>77,78</sup> ACE2 protein contains an N-terminal peptidase domain and a C-terminal collectrin amino acid transporter domain.<sup>79</sup> ACE2 counters the activity of the related angiotensin-converting enzyme (ACE) by reducing the amount of angiotensin-II and increasing ANG 1-7.<sup>80</sup> ANG 1-7 is a bioactive peptide with vasodilatory activity and is thought to modulate the effect of the renin-angiotensin system on vascular tension.<sup>81,82</sup> ACE2 also serves as the entry point into cells for some coronaviruses, including SARS-CoV-2.<sup>83-85</sup> Upregulation of ACE2 is likely to increase the susceptibility to SARS-CoV-2 infection.<sup>86,87</sup>

Much of the focus has been on the kidney as the source of ACE2 during pregnancy, but data from the pregnant rat model suggest that the placenta and the uterus are important sources of ACE2,<sup>12,13</sup> leading to an estimated twofold increase in total ACE2 activity during pregnancy.<sup>12</sup> ACE2 deficiency can impact pregnancy by impairing gestational weight gain and restricting fetal growth in mice.<sup>88</sup>

These data are consistent with the hypothesis that transient ACE2 overexpression and increased activity during pregnancy may be important in modulating blood pressure during pregnancy as well as local hemodynamics in the uteroplacental unit.<sup>12,13</sup> However, transient ACE2 overexpression may also indicate increased suitability to SARS-CoV-2 infection during pregnancy.<sup>12</sup> Similar to the mouse model, the human placenta expresses ACE2 enzyme.<sup>89-91</sup> Therefore, it is likely that SARS-CoV-2 can infect the placenta and can lead to adverse pregnancy outcomes. In a study using single-cell RNA sequencing, ACE2 was highly expressed in maternal-fetal interface cells including cytotrophoblasts and syncytiotrophoblasts from first-trimester samples.<sup>14</sup> This ACE2 expression was further increased at 24 weeks of gestation. The high expression of ACE2 in these cells suggests that the placenta has the potential to be infected by SARS-CoV-2 and may cause placental dysfunction and pregnancy complications. However, there were no scRNA-seq data from human placentas in the third trimester.<sup>14</sup>

Recently, our laboratory evaluated ACE2 expression in the human placenta in a gestational age-dependent manner. Total placental RNA from the first- and second-trimester terminations as well as from term delivery (before the onset of labor) was isolated, and ACE2 expression was determined by SYBR Green Primer assay. Our results suggest significant expression of ACE2 in the first- and second-trimester placental samples that was found to be somewhat

decreased in term placenta (six samples per group,  $P < .05$ , by one-way ANOVA followed by Kruskal-Wallis test). The ACE2 expression was localized to cytotrophoblasts and syncytiotrophoblasts in first- and second-trimester placental tissues as visualized by immunohistochemistry.

Taken together, we hypothesize that placental trophoblasts may be susceptible to infection by SARS-CoV-2 infection in early/mid-pregnancy but not that robustly at term due to the differential expression of ACE2 throughout gestation (Figure 1). On the other hand, ACE2 expression may be optimal in most reproductive tissues during labor. However, it is possible that term placenta in labor or otherwise presents a variant form of ACE2 incapable of functioning as a receptor for SARS-CoV-2. This can explain the rarity of placental infection/vertical transmission observed at term pregnancy. Furthermore, it might explain observed pregnancy complications in mid-pregnancy, including preterm birth, abruption, and stillbirth. However, a solid experimental and clinical support for our hypothesis is still awaited.

## 9 | CONCLUSION

Discussion on COVID-19 infection and its consequences changes on daily basis with new insights for general population. For example, it was previously thought that only older population and immune compromised individuals were at risk for severe disease. However, recent data suggest that younger populations including children can be infected and develop severe complications. The fluid situation with COVID-19 further complicates the maternal and fetal clinical care and the management of healthy pregnancy. It is clear that being current with the emerging new data regarding the extent of the disease and treatment modalities is vital, particularly for pregnant women. On a semi-positive note, it appears that pregnant women have not presented with the expected high rate of mortality and severity of the disease as compared to their non-pregnant women. We still do not have clarification on whether African American and Hispanic women are at higher risk of developing severe COVID-19 disease. CDC and ACOG have published directives for pregnant women that they may be at higher risk of severe disease, although several reports suggest that pregnant women may remain asymptomatic. This review has attempted to address the question whether pregnancy is an immunological contributor to severe or controlled COVID-19 disease. We propose that the placenta, fetal membranes, and pregnancy intrauterine milieu may provide a protective environment to SARS-CoV-2 infection and suggest that therapeutic interventions should also include cues from the maternal-fetal interface tissues. We further propose that based on temporal ACE2 expression, COVID-19 placental infection may occur during first and second trimesters with little or no infection during third trimester. This may also explain, in part, the poor vertical transmission of this novel virus at term pregnancy but the possible increased incidence of preterm births in mid-pregnancy. We also support the precautionary notion that

pregnancy may provide an immunological balance to COVID-19-mediated alterations at the maternal-fetal interface.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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