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COVID-19 susceptibility in pregnancy: Immune/inflammatory considerations, the role of placental ACE-2 and research considerations

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ABSTRACT

SARS-CoV-2 is a new virus, to which herd immunity has not yet developed and both molecular and serological testing are not without flaws. The virus evokes a state of severe and widespread inflammation, and stimulates both innate and adaptive immune response. The angiotensin-converting enzyme 2 (ACE2), which acts as the SARS-CoV-2 receptor, is present in endothelial cells and has been noted within the human placenta. There are questions about whether pregnancy would increase the susceptibility of pregnant women to COVID-19 and disease severity within this population. In this report, we highlight physiological and immune/inflammatory considerations that may explain the susceptibility and disease pathology in response to SARS CoV-2 during pregnancy, explore testing considerations in asymptomatic individuals, discuss the potential role and of placental ACE2 receptor in the pathogenesis of COVID-19 in pregnancy and in pregnancy outcomes, and finally share our perspective with respect to an urgently needed change concerning involvement of pregnant women in research addressing COVID-19.

1. Introduction

According to the Centers for Disease Control and Prevention (CDC), 26,364 pregnant women with COVID-19 were identified in the United States from January 22 to October 13 2020. The majority 18,872/26,364 (72 %) were 25–44 years old. Of women for whom data for these specific parameters were available, 6011/22,658 (27 %) were hospitalized, 219/6155 (4 %) were admitted to the Intensive Care Unit (ICU), and 81/5362 (2 %) required mechanical ventilation, with mortality recorded in 45 cases (0.17 %) [1]. Similarly, data from a recent systematic review and meta-analysis of outcomes from 2567 pregnancies affected by SARS-CoV-2, demonstrated that ICU admission is required in 7 % and intubation in 3.4 %; with maternal mortality observed ~1 % and perinatal mortality of <1 % [2].

The pregnant state is a formidable challenge to maternal immunity. Physiological alterations take place in order to adapt to a semi-allogeneic fetus, while maintaining the ability to fight against microbial infections [3]. Local and systemic immune adaptations during pregnancy occur to suit the fetal growth at different phases of gestation. Overall, this involves a switch from a pro-inflammatory state in the first (implantation and placentation) and third (preparation for parturition) trimester, to an anti-inflammatory state (progressive fetal growth) in the second trimester [4]. Alongside these immune changes, physiologic pregnancy adaptations affect multiple other organ systems [5], with the respiratory tract in particular demonstrating significant modifications, influenced by high levels of estrogen and progesterone (alongside altered levels of other steroid hormones), as well as by restricted lung expansion, rendering pregnant women more susceptible to respiratory pathogens as well as to the development of a more severe disease course if infected [6].

Interestingly, expression of the angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor, which has also been shown to have an anti-inflammatory function [8], has been noted within the human placenta. These factors raise questions around susceptibility of pregnant women to COVID-19 and of disease severity in this population. In this report, we highlight immune/inflammatory considerations in the response to SARS CoV-2 during pregnancy, explore testing considerations in asymptomatic individuals, discuss the potential role of placental ACE2 receptor in the

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pathogenesis and implications of COVID-19 in pregnancy, and finally share our perspectives on research involving the pregnant population affected with COVID-19.

2. Immunologic and physiologic perspectives on pregnancy and COVID-19

SARS-CoV-2 is a novel virus, to which herd immunity has not yet developed, thus all populations are susceptible to infection [10]. However, pregnant women in general, are more vulnerable to infection with respiratory pathogens [11], and were feared to be more susceptible to development of clinical complications of SARS-CoV-2 infection than the general population [10]. This susceptibility to more severe morbidity is likely predicated on the basis of anatomic and physiologic pregnancy adaptations, such as hormone-mediated respiratory tract edema [10], escalation in oxygen demand based on a 15 % surge in metabolic rate and 20 % more oxygen consumption [5], as well as restricted lung expansion [10], and lung volume changes in late pregnancy, partly influenced by diaphragmatic elevation secondary to the gravid uterus [5]. These variables, also likely contribute to the rapid deterioration in respiratory condition observed in those pregnant women who progress to severe disease [11]. Furthermore, in pregnant women who do experience the severe spectrum of infection critical care interventions (e.g. airway management, ventilation, proning) can be much more challenging [11].

Susceptibility to viral infection in pregnancy is likely also influenced by the unique immunologic state, the development of which is vital to a successful gestation [10]. This adaptation includes a shift from the typically predominant T-helper 1 (Th1) system (characterized by the presence of microbicidal and pro-inflammatory cytokines including Interferon-γ, Tumor Necrosis Factor-α, and Interleukin (IL)-2), toward Th2 system dominance (characterized by presence of anti-inflammatory cytokines including IL-4, IL-5, IL-10, and IL-13) [3,12]. While this shift occurs in the interest of fetal protection, it does so at the expense of maternal vulnerability to viral infection, which is better contained by the Th1 system [3].

Yet, while previously encountered corona viruses were marked by high rates of maternal morbidity and mortality, the majority of pregnant women with COVID-19 thus far seem to experience a mild course, comparable to the general population [13,14]. Specifically, while ICU admission rates for pregnant women with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) reached 60 % and 64 % respectively; a living systematic review documents ICU admissions for pregnant women with COVID-19 at 4% of cases [15]. Similarly, while the case fatality rate for pregnant women with SARS and MERS was 15 % and 27 % respectively, it has thus far been documented at 0.1 % for COVID-19 [15].

These differences in susceptibility between SARS-CoV, MERS-CoV and SARS-CoV-2 in pregnancy, may be explained in part on the basis of their respective cytokine profiles [3,16]. While SARS-CoV and MERS-CoV preferentially activates the Th1 immune system, with documentation of proliferation of pro-inflammatory cytokines, SARS-CoV-2 has been shown to activate both the Th1 and Th2 components of the immune system, resulting in the relative propagation of IL-4 and IL-10 [3,16]. Expression of anti-inflammatory cytokines, alongside the physiologic shift to Th2 immunity in pregnancy may underlie the generally milder course of COVID-19 in comparison to SARS [3]. Thus, the course of COVID-19 in pregnancy has been found to be severe in 13 %, with 3 % requiring mechanical ventilation and 0.4 % needing extra-corporeal membrane oxygenation [15]. Fever and cough are the most common presenting symptoms, noted in 40 % and 39 % of infected pregnant women respectively, and risk factors for severe disease include maternal age over 39 years, BMI over 30 kg/m2, chronic hypertension, pre-eclampsia, and pre-existing diabetes [15]. Additionally, 28 % of infected pregnant women experienced pneumonia, with abnormalities on computed tomography in 30 % of those for whom imaging findings were reported [15].

3. Testing considerations during pregnancy

The laboratory diagnosis of SARS COV-2 is based either on detection of the virus via RT-PCR or on evidence of an immune response to the virus derived via serological methods identifying IgG or IgM (IgA; mucosal immunity) in patients' serum; neither of which are without flaws [23,24]. While RT-PCR detects virus-specific RNA molecules, it is not useful in distinguishing between highly-infectious viruses and those neutralized by the host, may detect lingering residual RNA from a no longer infectious virus, and cannot asses immunity status [24]. It has also been demonstrated that RT-PCR can have low sensitivity, low stability, and can be affected by external factors, including specimen source (upper/lower respiratory tract) and sampling timing (before or after symptom onset) [24]. Conversely, serological tests are less effective in the early stages of COVID-19 infection, as seroconversion may take place days after viral load has peaked or up to 1 week from symptom onset. Additionally, a relationship between the severity of symptoms and IgG/IgM/IgA levels has been noted, suggesting that serological tests may not be effective in detecting lower levels of antibodies in mild cases. Thus, serologic investigations are better suited for later stages of infection and/or identification of more severe cases [23].

Some guidelines now recommend molecular testing in all pregnant women upon hospital admission at least once, and more often if symptomatic, or with concern over exposure. Some caution would be prudent with respect to interpretation of such evaluation. For instance, positive RT-PCR testing of asymptomatic women presenting for delivery may in fact identify a subset of women who have been infected in an earlier time-frame and who have recovered (or never experienced symptoms), but in whom lingering RNA viral remnants are identified. It is likewise important to appreciate that viral RNA detection is not synonymous with infectiousness; specifically, while the time-frame for viral shedding varies, with potential for isolation of the virus and thus positive RT-PCR testing even months after diagnosis, the viral concentration in such context is typically well-below the threshold of infectivity or transmissibility of the virus [25]. While the literature suggests that COVID-19 infection in pregnancy most often occurs in the third trimester, at times close to delivery [3,13,14,17], this conclusion may be misleading, as it may reflect the fact that women in the third trimester of pregnancy are likely tested more frequently (for instance, some centers test all pregnant women presenting for delivery, regardless of symptoms), while women in the first and second trimester, who are asymptomatic or have mild illness, may not undergo testing, and thus will not be counted and reported. On the other hand, testing would be completed for significant illness leading to hospitalization, yet most reported cases requiring hospitalization were found to be in the third trimester of pregnancy [13].

Serologic testing on the other hand is likely sub-optimal for identification of affected women, as testing in this setting may be too early for detection of relevant antibodies. Similarly, considering current knowledge limitations, presence of antibodies from an earlier infection does not guarantee immunity on re-exposure. Furthermore, a positive RT-PCR or other serological test may in fact indicate a false-positive result, following exposure not to SARS-COV-2, but to another virus from the coronavirus family [23,27]; for instance, those who have been exposed to MERS or SARS-CoV-1 may have already developed antibodies to fight this family of

viruses, leading to cross-reactivity with SARS-CoV-2 testing. This indeed may have implication for the diagnosis and management of CVID-19 in pregnancy. We hope as the pandemic evolves; further pregnancy specific studies will help elucidate the crucial considerations for serological testing in pregnancy.

4. SARs-CoV-2 induced inflammation and pregnancy implications

The origins of SARS-CoV-2 induced inflammation have been linked to varying degrees of cytokine release, the most severe form of which is referred to as a cytokine-storm and characterized by increased plasma levels of interleukins (IL-2, IL-7, IL-10), granulocyte colony stimulating factor, interferon-γ-inducible protein 10, monocyte-chemoattractant-protein-1, macrophage-inflammatory-protein-1-alpha and tumour necrosis factor α (TNF- α) [7]. Pregnant women diagnosed with COVID-19, have been shown in one study to have significantly higher inflammation indices (including white blood cell and neutrophil count, C-reactive protein, procalcitonin and D-dimers), yet significantly lower lymphocyte counts in comparison to non-pregnant women with COVID-19. Interestingly, the pregnant women again on average presented milder symptoms and shorter hospital stays, though they displayed higher rates of asymptomatic infection [28]. Further data exploring these parameters will be helpful to allow extrapolation to the general obstetric population with COVID-19.

Pregnancy is marked by pro-inflammatory periods. Specifically, the stages of implantation and placentation (first trimester) involve the active breakdown and re-structuring of the maternal decidua resembling the process of tissue injury and repair accomplished in the setting of a pro-inflammatory environment. This is followed by fetal growth (second trimester), whereby a symbiotic maternal-fetal relationship is facilitated by a shift to Th2 immunity and an anti-inflammatory environment. With completion of fetal development, a return to a pro-inflammatory environment occurs in preparation for labour and parturition, again marked by tissue injury and repair [4]. Given the pro-inflammatory state characterizing a notable part of the pregnancy, specifically the first and third trimester, the cytokine storm invoked by SARS-CoV-2 may induce even more severe inflammation, which can have deleterious implications for the fetus. Of concern are the potential effects of this inflammatory state on fetal brain development, possibly influencing neuronal or behavioural dysfunction later in life [4]. For instance, an autism spectrum-like phenotype in offspring has previously been linked to increased levels of IL-17 [29]. Further elucidation of these potentially concerning observations as they relate to COVID-19 infection in pregnancy awaits long-term follow-up studies.

Activation of the complement cascade has also been described in COVID-19, with evidence that it mediates microvascular injury syndrome [30]. This is concerning, as a significant increase of complement activation is known to be associated with pregnancy-related pathologies, such as pre-eclampsia, recurrent pregnancy loss, intra-uterine growth restriction, and antiphospholipid syndrome [31].

5. ACE2 and the placenta

ACE2 converts Angiotensin (Ang) II into Ang-(1-7), and Ang I into Ang-(1-9), thereafter transforming it to Ang-(1-7), exerting control over blood pressure [32]. ACE2 in syncytiotrophoblasts is thought to potentially regulate the liberation of Ang 1-7 into the maternal circulation, assisting in vasodilation of the maternal vasculature [32]. In one study, the placentas, uterus, and kidneys were found to be a significant source of ACE2 activity, supporting the hypothesis that transient ACE2 overexpression and enhanced activity during pregnancy may modulate hemodynamics within the uteroplacental unit [33]. Reduction in placental expression of ACE2 and Ang-(1-7) following dexamethasone treatment has been linked with intrauterine growth restriction and potentially disease-programming in adulthood [34]. During pregnancy, ACE2 and Ang-(1-7) may function in the role of an autocrine/paracrine regulator for early pregnancy angiogenesis, apoptosis, and growth, as well as for late pregnancy uteroplacental blood flow events; with late pregnancy models demonstrating elevated ACE2 and reduced uterine perfusion pressure models showing significant ACE2 depletion [35].

Abundant angiotensin-converting enzyme 2 (ACE2); the SARS-CoV-2 receptor expression has been noted within the human placenta; mainly within the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle of the villi [36]. This marked expression of ACE2 in maternal-fetal interface cells, including stromal cells and perivascular cells of decidua, as well as the cytotrophoblast and syncytiotrophoblast within the placenta has been confirmed by Li et al. [37]. The authors suggested that the SARS-CoV-2 receptor was abundant within the maternal-fetal interface and certain fetal organs (including the heart, liver, and lung), underscoring the need for further study of potential vertical transmission and placental dysfunction in affected pregnancies [37].

In contrast, a recently published paper found that co-transcription of ACE2 and TMPRSS2 (transmembrane proteases) in the placenta were negligible, and chorio-amniotic membranes lacked expression of SARS-CoV-2 receptors in the third trimester, surmising that the placenta was an unlikely pathway for vertical transmission [38]. Yet, the authors did not exclude the possibility that SARS-CoV-2 could infect the placenta in using an alternative path and through interaction with other proteins, such as Basigin (also referred to as CD147 or EMMPRIN), a transmembrane glycoprotein that belongs to the immunoglobulin superfamily, with high expression in the placenta and chori-amniotic membranes [38–41].

A recent systematic review has noted pre-eclampsia in 16 % and fetal growth restriction in 12 % of pregnancies affected by coronavirus [43]. On the other hand, another study found that COVID-19 affected pregnancies can be characterized by a 'preeclampsia-like syndrome,' that could be differentiated from true preeclampsia by assessment of sFlt-1/PlGF, LDH and uterine artery flow [44]. This observation is in keeping with yet another report, featuring COVID-19-related coagulopathy with mildly elevated transaminases, ostensibly masquerading as HELLP syndrome [45].

A study of 16 placentas from SARS-Cov-2 infected pregnancies demonstrated increased rates of decidual arteriopathy and other features of maternal vascular malperfusion, placental damage reflective of sub-optimal oxygenation within the intervillous space and associated with adverse pregnancy outcomes [46]. Interestingly, only a single woman in this study was hypertensive [46]. In another study, SARS-CoV-2 RNA was noted in 3/11 placental and membrane samples [47]. Similarly, SARS-CoV-2 was identified in three placenta from two reports in which the infants also tested positive for SARS-CoV-2 infection [26,48]. Both these reports demonstrated similar placental features; the first consistent with chronic histiocytic intervillositis (CHI) confined to the intervillous space (differing from classic CHI by early infarction and the clustering of the inflammatory cells around the chorionic villi) [26], while the second consistent with chronic intervillositis, with presence of macrophages, in the intervillous and the villous space [48]. These disparate findings confirm the need for continued evaluation of the rate of vertical transmission associated with COVID-19.

6. Evidence for vertical transmission

There has been significant debate regarding evidence of vertical/congenital transmission in the setting of maternal COVID-19 infection. Reassuringly, a recent systematic review of 49 studies with 666 neonates from 655 women determined that 8/292 (3 %) of neonates born vaginally and 20/374 (5 %) neonates born by Caesarean section were positive for SARS-CoV-2. The study concluded that congenital infection is rare and often asymptomatic, and that the incidence of infection is similar with vaginal or Caesarean delivery, maintenance of breastfeeding, or preservation of maternal-newborn contact [49].

7. Research involving the pregnant population affected with COVID-19

It must be underscored that the approach to management of pregnant women with COVID-19 is extrapolated from the literature involving the non-pregnant population. Pregnant women remain barred from participation in most trials. A search of *ClinicalTrials.gov* demonstrates that less than 1% of COVID-19-related intervention studies are open to pregnant women.

The Global Forum on Bioethics in Research (GFBR) produced guidance for scientific investigation during states of public health emergency, a context applicable to the current COVID-19 pandemic [50]. Emergency situations often underscore the difficulties inherent in research involvement of pregnant individuals, and the GFBR proposed that, once vetted by a research ethics board, the option to participate should be extended to this group. The GFBR's recommendations were spurred by lessons from the Ebola outbreak, which restricted pregnant individuals from trials with any degree of reproductive toxicity, and outright barred them from vaccine trials (GFBR). At the time of the Ebola outbreak, facing the moral dilemma of potentially delaying trials that may benefit the population as a whole, by the necessity of securing appropriate approvals, "speed won over justice" and pregnant individuals were excluded (GFBR). Following these events the GFBR emphasized the imperative need for a plan to include pregnancy data ahead of the next epidemic (GFBR). Sadly, we find ourselves repeating our errors [51]. Our instinct to protect pregnant women from harm may paradoxically impose more harm by shifting experimentation into the clinical arena [50,51], and robbing pregnant women of the choice to participate in the rigorous, gold-standard approach to establish evidence-based treatment standards, available to the remainder of the population [44]. We must do better!

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] Centers for Disease Control and Prevention (CDC). Data on COVID-19 during pregnancy: weekly COVID-19 pregnancy data. 2020 Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19.html. (Accessed on: 17 October 2020).

[2] Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine 2020.

[3] Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020;222:521–31.

[4] Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol 2017;17:469–82.

[5] Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89–94.

[6] Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol 2012;207:S3–8.

[7] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect 2020;80:607–13.

[8] Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes ESAC. The anti-inflammatory potential of ACE2/angiotensin-(1-7)/Mas receptor axis: evidence from basic and clinical research. Curr Drug Targets 2017;18:1301–13.

[10] Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol 2020;139:103122.

[11] Lapinsky SE. Acute respiratory failure in pregnancy. Obstet Med 2015;8:126–32.

[12] Pandya A, Das M, Rolin J. Role of cytokines in healthy and pathological pregnancies. In: Duttaroy AK, Basak S, editors. Human placental trophoblasts. . p. 311–20.

[13] Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;69:m2107.

[14] Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound Obstet Gynecol 2020;55:586–92.

[15] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320.

[16] Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 2018;104:8–13.

[17] Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet 2020;150:47–52.

[23] Ghaffari A, Meurant R, Ardakani A. COVID-19 serological tests: how well do they actually perform? Diagnostics (Basel) 2020;10:.

[24] Younes N, Al-Sadeq DW, Al-Jighefee H, Younes S, Al-Jamal O, Daas HI, et al. Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. Viruses 2020;12:.

[25] McIntosh K, Hirsch MS, A. B. Coronavirus disease 2019 (COVID-19): epidemiology, virology, and prevention. UpToDate; 2020 Available at: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-and-prevention?sectionName=Viral%20shedding%20and%20period%20of%20infectiousness&topicRef=128404&anchor=H166293483&source=see_link#H166293483 [Accessed on: 17 Oct. 2020].

[26] Kirtsman M, Diambomba Y, Poutanen SM, Malinowski AK, Vlachodimitropoulou E, Parks WT, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ 2020;192:E647–50.

[27] Ma Z, Li P, Ji Y, Ikram A, Pan Q. Cross-reactivity towards SARS-CoV-2: the potential role of low-pathogenic human coronaviruses. Lancet Microbe 2020;1:e151.

[28] Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet 2020.

[29] Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 2016;351:933–9.

[30] Song WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest 2020.

[31] Tincani A, Cavazzana I, Ziglioli T, Lojacono A, De Angelis V, Meroni P. Complement activation and pregnancy failure. Clin Rev Allergy Immunol 2010;39:153–9.

[32] Pringle KG, Tadros MA, Callister RJ, Lumbers ER. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta 2011;32:956–62.

[33] Levy A, Yagil Y, Bursztyn M, Barkalifa R, Scharf S, Yagil C. ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol 2008;295:R1953–61.

[34] Ghadhanfar E, Alsalem A, Al-Kandari S, Naser J, Babiker F, Al-Bader M. The role of ACE2, angiotensin-(1-7) and Mas1 receptor axis in glucocorticoid-induced intrauterine growth restriction. Reprod Biol Endocrinol 2017;15:97.

[35] Neves LA, Stovall K, Joyner J, Valdes G, Gallagher PE, Ferrario CM, et al. ACE2 and ANG-(1-7) in the rat uterus during early and late gestation. Am J Physiol Regul Integr Comp Physiol 2008;294:R151–61.

[36] Valdes G, Neves LA, Anton L, Corthorn J, Chacon C, Germain AM, et al. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathological pregnancies. Placenta 2006;27:200–7.

[37] Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One 2020;15:e0230295.

[38] Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Alazizi A, et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? Elife 2020;9.

[39] Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181:1036–45 e9.
[40] Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep 2020;16:434–40.
[41] Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. 2020 bioRxiv pre-print server Available: https://wwwbiorxivorg/content/101101/20200314988345v1 [Accessed on: 17 October 2020].
[43] Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020100107.
[44] Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, et al. Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study. BJOG 2020.
[45] Koumoutsea EV, Vivanti AJ, Shehata N, Benachi A, Le Gouez A, Desconclois C, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost 2020.
[46] Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol 2020;154:23–32.
[47] Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of SARS-COV-2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM 2020100133.
[48] Patane L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of COVID-19: SARS-CoV-2 RNA on the fetal side of the placenta in pregnancies with COVID-19 positive mothers and neonates at birth. Am J Obstet Gynecol MFM 2020100145.
[49] Walker KF, O'Donoghue K, Grace N, Dorling J, Comeau JL, Li W, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG 2020.
[50] Global Forum on Bioethics Research. Ethics of research in pregnancy: Meeting Report Buenos Aires, Argentina. Available at: http://www.gfbr.global/wp-content/uploads/2017/04/GFBR-2016-report-ethics-of-research-in-pregnancy-FINAL.pdf [Accessed on: 17 October 2020]. 2020.
[51] Malinowski AK, Snelgrove J, Okun N. Excluding pregnancy from COVID-19 trials: protection from harm or the harm of protection? Can Med Assoc J 2020;192: E634-E.