The risk of intrauterine exposure to SARS-CoV-2 in female COVID-19 patients: A comprehensive review

Guo-hua Zhu¹,² | Lu Liu¹,² | Xi-xi Huang¹,² | Da-jin Li¹,² | Yi-zhun Zhu³
Xin Lu² | Mei-rong Du¹,²,³,⁴

¹Laboratory for Reproductive Immunology, NHC Key Lab of Reproduction Regulation (Shanghai Institute of Planned Parenthood Research), Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Hospital of Obstetrics and Gynecology, Shanghai Medical College, Fudan University, Shanghai, China
²Shanghai Key Laboratory of Bioactive Small Molecules, Department of Pharmacology, School of Pharmacy, Fudan University, Shanghai, China
³State Key Laboratory of Quality Research in Chinese Medicine and School of Pharmacy, Macau University of Science and Technology, Macau SAR, China
⁴Department of Obstetrics and Gynecology, Guangzhou First People’s Hospital, School of Medicine, South China University of Technology, Guangzhou, China

Correspondence
Meirong Du, Laboratory for Reproductive Immunology, Hospital of Obstetrics and Gynecology, Fudan University Shanghai Medical College, ZhaoZhou Road 413, Shanghai 200011, China.
Email: mrdu@fudan.edu.cn
Xin Lu, Hospital of Obstetrics and Gynecology, Fudan University Shanghai Medical College, Shenyang Road 218, Shanghai 200011, China.
Email: xinludoc@163.com

Guo-hua Zhu and Lu Liu contributed equally to this work.

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 31970859, 81630036, 82101706, 91542116; the National Basic Research Program of China, Grant/Award Number: 2017YFC1001403; International Cooperation Project between Macau and Shanghai, Grant/Award Number: 2041070300; Strategic Collaborative Research Program of the Ferring Institute of Reproductive Medicine; Ferring Pharmaceuticals and Chinese Academy of Sciences, Grant/Award Number: FIRMA200504; Innovative Research Team of High-level Local Universities in Shanghai; Key Laboratory Program of the Education Commission of Shanghai Municipality, Grant/Award Number: ZDSYS14005; Shanghai Municipal Health and Family Planning Commission, Grant/Award Number: 20204Y0403; Shanghai Sailing Program, Grant/Award Number: 21YF1403700

Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new type of coronavirus that has caused fatal infectious diseases and global spread. This novel coronavirus attacks target cells through the interaction of spike protein and angiotensin-converting enzyme II (ACE2), leading to different clinical symptoms. However, for a successful pregnancy, a well-established in-uterine environment includes a specific immune environment, and multi-interactions between specific cell types are prerequisites. The immune-related changes in patients infected with novel coronavirus could interfere with the immune microenvironment in the uterus, leading to fetal loss. We first reviewed the intrauterine environment in the normal development process and the possible pregnancy outcome in the infection state. Then, we summarized the immune response induced by SARS-CoV-2 in patients and analyzed the changes in ACE2 expression in the female reproductive system. Finally, the present observational evidence of infection in pregnant women was also reviewed.

KEYWORDS
angiotensin-converting enzyme 2, endometrium, fertility, severe acute respiratory syndrome coronavirus 2
It had been more than 1 year since China first reported a few cases of pneumonia of unknown cause. The pathogen was later identified as a new type of coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The coronavirus is spreading rapidly, and there is no sign of ending. SARS-CoV-2 infects and lyses the host cells by binding with angiotensin-converting enzyme II (ACE2), which is widely expressed in the ovary, uterus, vagina, and placenta. However, whether SARS-CoV-2 would cause intrauterine infection or affect female fertility is still a mystery, which should not be neglected.

Researchers mainly pay attention to women in the second or third trimester of pregnancy and paid more attention to the evidence of the vertical transmission of SARS-CoV-2. At present, there is little evidence that SARS-CoV-2 would spread vertically during the third trimester of pregnancy. It was proved that most of the clinical symptoms of pregnant women infected with SARS-CoV-2 were not obvious. However, the effect of SARS-CoV-2 on early pregnancy still lacks clinical evidence. Because the successful blastocyst implantation is closely related to the state of the endometrium and its acceptance time window, the establishment and maintenance of a normal pregnancy require sufficient crosstalk between the implantation and the embryo and the embryo best microenvironment in uterus. In addition, abnormal hormone and inflammatory environments may disturb the dialog of immune-endocrine interaction between the decidua and trophoblast during embryo implantation, leading to pregnancy complications.

In this review, we would like to explain the risk of intrauterine exposure to the SARS-CoV-2 virus in female patients with COVID-19 and whether it could interrupt the development of pregnancy.

2 NORMAL PREGNANCY REQUIRES A WELL-ESTABLISHED INTRAUTERINE ENVIRONMENT

Endometrial epithelial cells express estrogen and progesterone receptors, which can sense hormone changes and send signals to endometrial stromal cells and immune cells. Endometrial stromal cells also express estrogen and progesterone receptors and experience decidualization under the stimulation of hormones. They can secrete cytokines to recruit immune cells from peripheral blood. Decidual immune cells (DICs) participated in the formation of uterine spiral arteries, the directional migration of trophoblast cells, and protection of the fetus from infection. Because the fetus is similar to a semiallograft, maintaining normal pregnancy requires DICs to form an immune tolerance microenvironment in the maternal interface to avoid the fetus’s maternal immune rejection. For example, decidua natural killer Cells (dNK cells) show low-toxicity CD16 dim CD56 high phenotype. Moreover, our previous studies confirmed that the decidual CD8+ T cells highly expressed inhibitory receptors, such as PD-1 and Tim-3, and showed a highly exhausted phenotype, with low cytotoxicity.

In addition, indoleamine-pyrore 2,3-dioxygenase (IDO) derived from monocytes and FasL on the trophoblast surface could inhibit T cells’ activity via different mechanisms. Progesterone, which was sustained at a high plateau during pregnancy, can also inhibit the cytotoxicity of CD8+ T cells. Therefore, immune adaptability is required to adapt to the fetus. The special immune-microenvironment of the fetal-maternal interfaces may relate to the increased risk for acquiring infections, which have demonstrated that certain conditions disproportionately affect pregnant women.

The dysfunction of the endometrium is one of the main causes of decreasing fertility. It was reported that about 60% of pregnancy loss occurs at 3–4 weeks during embryo implantation, and 10% occurs at 4–12 weeks of pregnancy. Abnormal maternal-fetal interaction may cause spontaneous abortion in the first trimester of pregnancy, resulting in fetal growth restriction or eclampsia in the second or third trimester. The study of infection during pregnancy shows that various pathogens such as cytomegalovirus (CMV), dengue fever, acquired immunodeficiency syndrome, and rubella infections in early pregnancy would induce abortion. Infection can lead to abnormal maternal-fetal interactions through various mechanisms. TNF-α is a critical effector to induced pregnancy loss because blockade of TNF-α or TNF-α deficiency is a protective effect against the antiphospholipid syndrome. While pregnant mice were challenged with LPS, a cell wall component from gram-negative bacteria, the decidua can synthesize and secret TNF-α, which results in fetal resorption. Injection of polyinosinic-polycytidylic acid (Poly(I: C)), a viral mimic, can lead to fetal death through NKG2D-dependent manner by uterine NK cells or through IFNAR expression in pregnant mice. Meanwhile, we cannot neglect that pathogens could directly attack the trophoblast leading to fetal death. For example, CMV can target trophoblast cells, induce apoptosis of trophoblast cells, and activate TNF-α, leading to cell death and pregnancy failure.

3 THE TARGET OF SARS-COV-2 AND ITS PATHOGENESIS

SARS-CoV-2 mainly encodes four structural proteins named spike protein (S protein, composed of S1 subunit and S2 subunit), membrane protein, envelope protein, and nucleocapsid, respectively. SARS-CoV-2 initiates the fusion of the viral envelope and cell membrane through the interaction between S protein and ACE2 receptor, and the viral genome is subsequently released to target cells. Subsequently, the virus started to replicate and translate into the host cells. Single-stranded (ss) RNA-sensing Toll-like receptors (TLR), such as TLR3 and TLR7 in the endosome, could recognize SARS-CoV-2 virions. And then, the recognition could activate the interferon regulatory factor (IRF) 3, IRF7, and nuclear factor (NF)-κB, inducing fast production of IFN-I, IFN-III, and proinflammatory cytokine. IFN-signaling plays a critical role in antiviral immune response. However, the function of IFN-
more than a dozen of kinds of proteins encoded by SARS-CoV-2 is to escape immune recognition of host cells and killing.\textsuperscript{46–48} For example, nonstructural protein 1 (NSP1) protein could inhibit host protein, thus inhibiting IFN-\(\beta\) production.\textsuperscript{46} Based on immune escape mechanisms, severe patients usually show a delayed IFN reaction and prolonged virus replication.\textsuperscript{49} Cytokine storm followed with impaired IFN response was another feature in coronavirus disease 2019 (COVID-19) clinical manifestation.\textsuperscript{50,51}

After transcription factors such as NF-\(\kappa\)B, c-Jun, and the downstream of p 38/MAPK (mitogen-activated protein kinase) pathway are activated, the levels of inflammatory cytokines including IL-6 and TNF-\(\alpha\) are rapidly produced, resulting in the recruitment of macrophages, monocytes, DCs, and neutrophils to lung.\textsuperscript{52–54} The pulmonary macrophages might fire the first shot in the process of antiviral immune. Single-cell RNA sequencing (scRNA-seq) from the bronchoalveolar lavage (BAL) of COVID-19 patients shows that macrophages and monocytes take a large proportion from the BAL of severe disease.\textsuperscript{55} These inflammatory monocytes displayed a pro-IFN signature, which expressed chemokines such as CCL2, CCR5, and CXCR3 ligands and genes from IFN-stimulated genes, eventually forming a proinflammation differentiation pattern.\textsuperscript{55}

ACE2 is widely expressed in the lung, cardiovascular system, intestine, kidney, central nervous system, and adipose tissue.\textsuperscript{56} Although SARS-CoV-2 mainly targets alveolar cells, it can also impair organs outside the lungs and cause clinical symptoms whether the virus directly infects it or not.\textsuperscript{57} Systemic inflammatory response syndrome (SIRS), or virus directly transmitting to organs through vascular transport and replicated in organs, is the cause of damage in distal tissues.\textsuperscript{58,59} Clinical tests show that almost 40–80% of patients diagnosed as COVID-19 have elevated troponin-I levels, indicating myocardial injury.\textsuperscript{50,61} Among men infected with SARS-CoV-2, different degrees of inflammatory changes can be found in testicular tissue, which expresses ACE2 in various types of cells with impaired sperm quality (Figure 1, A-B).\textsuperscript{62–64}

Recently, a preprint article revealed that the SARS-CoV-2 viral RNA was detected in 42.5\% of reproductive tissues.\textsuperscript{65} These pieces of evidence suggest that SARS-CoV-2 could target the reproductive system that expresses ACE2. However, there is insufficient research to provide substantial evidence for the harmful effects of this new virus on the reproductive system. Whether SARS-CoV-2 could also impair the female reproductive system was still a puzzle.\textsuperscript{66}

### 4 | THE THEORETICAL BASIS OF INTRAUTERINE SARS-COV-2 INFECTION

It is reported that before pregnancy, the endometrial state of the women of childbearing age will change with the menstrual cycle. Castillo et al. analyzed the published endometrial transcriptome data, describing ACE2, TMPRSS4, CTSL, CTSB, FURIN, MX1, and other primary gene expression levels in the endometrium. They found that the expression levels of TMPRSS4, CTSL, CTSB, FURIN, and MX1 were high, TMPRSS2 was medium, and ACE2 was low.\textsuperscript{57} However, the expression of ACE2, TMPRSS4, CTSB, CTSL, and MX1 increased during the implantation window. In addition, the mRNA levels of ACE2, TMPRSS4, CTSB, CTSL, and MX1 genes increase with age.\textsuperscript{67} It corresponded to the earlier research.\textsuperscript{6} In our unpublished data, the expression level of ACE2 protein in decidua was higher than that in the proliferation stage. In addition, studies found that the RAS system was expressed in large quantities in the uterus, mainly containing target cells that encode ACE2.\textsuperscript{6} A recent multicenter prospective study showed that 46.2\% of women had abdominal or pelvic pain.\textsuperscript{12} It cannot exclude the female reproductive system damaged in COVID-19 patients.

Whether pregnant women are harmed by SARS-CoV-2 infection is of interest to researchers and clinicians, especially in the context of a pandemic. After pregnancy, endogenous decidualization occurs in the maternal endometrial cells. Li et al. utilized the published maternal-fetal interface scRNA-seq to illustrate the dynamic levels of ACE2 at the maternal-fetal interface.\textsuperscript{58} The results showed that ACE2 was highly expressed in the stromal cells, pericellular cells, the placenta cytotrophoblast (CT) and syncytiotrophoblasts (SCT), while it was lower expressed in extravillous trophoblasts (EVT) and gradually increased with the development of embryo.\textsuperscript{66} However, another team analyzed the published single cells data of early pregnancy and concluded that the maternal-fetal interface showed little susceptibility to infections of SARS-CoV-2 because compared to the expression levels of AXL, a receptor of Zika virus (ZIKV) which can be vertically transmitted from an infected mother to the developing fetus in utero, the expression level of ACE2 was lower.\textsuperscript{69} In addition, the expression of ACE2 in placental gradually decreased with pregnancy.\textsuperscript{70} These researches may partly explain why SARS-CoV-2 infections in the third trimester scarcely caused vertical transmission.\textsuperscript{11}

### 5 | GESTATIONAL COMPLICATIONS AFTER SARS-COV-2 INFECTION

In the early period of the epidemic, due to the lack of a clear understanding of the pathogenic mechanism of SARS-CoV-2, most pregnant women chose cesarean section for delivery. By performing nucleic acid tests on the fetus, delivery placenta, and amniotic fluid of women with SARS-CoV-2 infection, researchers found little evidence of virus intrauterine infection.\textsuperscript{10,71} A cohort study in the United Kingdom showed that about 5\% of newborn babies were detected SARS-CoV-2 mRNA positive. Six were found positive for SARS-CoV-2 within 12 h after birth, which could not exclude the possibility of viral transmission.\textsuperscript{11} It is worth noting that compared with nonpregnant women, the proportion of pregnant women suffering from serious diseases is relatively higher.\textsuperscript{71}

According to a case report, a 22-week pregnant woman diagnosed with COVID-19 had aborted, and the placenta was positive for the SARS-CoV-2 test (Figure 1, C-D).\textsuperscript{72} Specifically, the placenta (3 \(\times\) \(10^7\) virus copies/mg) and umbilical cord (2 \(\times\) \(10^3\) virus copies/mg) were tested positive for SARS-CoV-2. The patient had typical symptoms of pre-eclampsia, accompanied by severe hypertension and abnormal coagulation. In addition, placental pathology showed that SARS-CoV-2...
FIGURE 1  Illustrations of SARS-CoV-2 infection in the reproductive system. (A) Hematoxylin-eosin (HE) staining showed several pathological changes in the infected male testes: Sertoli cells grow swelling, vacuolation, and cytoplasmic rarefaction, impaired spermatogenesis. (B) Severe tubular injury shows cytoplasmic vacuolation and detachment of Sertoli cells from the basement membranes. Spermatogenesis is present. Scattered Leydig cells are present (arrow). However, few articles reported whether females’ reproductive systems could be infected. In infected pregnant women, HE staining images show histiocytic intervillositis at the section of the placenta. (C) In situ analysis for the presence of the virus, RNA confirms strong positive staining within the placenta. (D) The puzzles of whether endometrium or decidua could be infected need to be settled. The organ pictures were downloaded from the SERVIER MEDICAL ART (https://smart.servier.com/image-set-download/)

was mainly located in placental SCT, while fibrin deposition and mononuclear cell infiltrations were observed in the interstitial space, similar to lung pathology. Another study reported the same clinical manifestation. So far, more and more researchers have found cases of placental infection. Recently, a multicenter clinical study demonstrated that pulmonary comorbidities, hypertensive disorders and diabetes were several risk factors for pregnant females developing severe complications of SARS-CoV-2 infection. Furthermore, the obstetrical and neonatal outcomes were determined by the maternal disease.

Placenta infection by SARS-CoV-2 may not represent vertical transmission, but the severe placenta infections may hurt the nutrient exchange between fetal and decidua. Cribiù et al. found that more than half of pregnant women diagnosed with COVID-19’s disease tested positive for placenta. However, there was no evidence to show the relationship between the virus, placental pathology, maternal and perinatal outcomes. The Lancet recently published an article reviewing the maternal and perinatal outcomes of the COVID-19 epidemic. They found significant increases in stillbirth and maternal death during verses before the pandemic. However, there was no sig-
significant change in the rate of premature delivery, while the incidence of ectopic pregnancies was increased.\textsuperscript{60} Besides, there was no significant effect on pregnancy complications, such as maternal gestational diabetes, pregnancy-induced hypertension, and premature delivery.\textsuperscript{60} Although there was no vertical transmission, an article reported that IFN-stimulating gene (ISG) and major histocompatibility complex gene were up-regulated in the umbilical blood mononuclear cells of the fetuses whose mothers were diagnosed as COVID-19.\textsuperscript{81} In conclusion, though the transmissibility of SARS-CoV-2 is horrific, the fetal development in the mother’s uterus was relatively secure. It might be owed to the maternal immunologic barriers.

6 | CONCLUSION

In summary, considering the expression of ACE2 and the discovery of virus particles in the placenta, the reproductive system, including the uterus and ovary, is more likely to be infected with SARS-CoV-2. Among the women diagnosed with abdominal pain or pelvic pain, 46.2% have the possibility of a pelvic infection,\textsuperscript{12} which could be a vital signal for reproductive damage. For women infected with SARS-CoV-2, it remains a mystery how the immune system of pregnant women fights the virus and whether the viral infection fatally damages women’s fertility. These questions need to be answered in the background of the COVID-19 epidemic.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 31970859, 81630036, 82101706, and 91542116), the grants from the National Basic Research Program of China (No. 2017YFC1001403), the International Cooperation Project between Macau and Shanghai (No. 20410760300), the Strategic Collaborative Research Program of the Ferring Institute of Reproductive Medicine Supported by Ferring Pharmaceuticals and Chinese Academy of Sciences (No. FIRMA200504), and Innovative Research Team of High-level Local Universities in Shanghai and a Key Laboratory Program of the Education Commission of Shanghai Municipality (No. ZDYSYS14005), Shanghai Municipal Health and Family Planning Commission (20204Y0403), and Shanghai Sailing Program (21YF1403700).

CONFLICT OF INTEREST

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

ORCID

Da-jin Li https://orcid.org/0000-0003-2280-9727
Mei-rong Du https://orcid.org/0000-0001-9998-1379

REFERENCES

1. Ren L, Wang Y, Wu Z, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese Med J-Peking. 2020;133:1015-1024.
2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271-280.
3. Reis FM, Bouissou DR, Pereira VM, Camargos AF, Dos Reis AM, Santos RA, Angiotensin(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. Fertil Steril. 2011;95:176-181.
4. Vaz-Silva J, Carneiro MM, Ferreira MC, et al. The vasoactive peptide angiotensin(1-7), its receptor mas and the angiotensin-converting enzyme type 2 are expressed in the human endometrium. Reprod Sci. 2009;16:247-256.
5. Jing Y, Run-Qian L, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod. 2020;26:367-373.
6. Khalil A, von Dalldolzen P, Draycott T, Uygunumadu A, O Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. JAMA. 2020;324:705.
7. Wadman M. COVID-19 unlikely to cause birth defects, but doctors await fall births. Science. 2020;369:607.
8. Cribiù FM, Erra R, Pugni L, et al. Severe SARS-CoV-2 placenta infection can impact neonatal outcome in the absence of vertical transmission. J Clin Invest. 2021:131.
9. Subbaraman N. Pregnancy and COVID: what the data say. Nature. 2021;591:193-195.
10. Chen S, Huang B, Luo DJ, et al. Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases. Zhonghua Bing Li Xue Za Zhi. 2020;49:418-423.
11. Chen S, Liao E, Cao D, Gao Y, Sun G, Shao Y. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. J Med Virol. 2020;92:1556-1561.
12. Knox N, Lee C, Moon JY, Cohen SP. Pain manifestations of COVID-19 and their association with mortality: a multicenter prospective observational study, Mayo Clin Proc. 2021;96:943-951.
13. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. New Engl J Med. 1999;340:1796-1799.
14. Giacomini E, Scotti GM, Vanni VS, et al. Global transcriptomic changes occur in uterine fluid-derived extracellular vesicles during the endometrial window for embryo implantation. Hum Reprod. 2021;36:2249-2274.
15. Enciso M, Aizpurua J, Rodríguez-Estrada B, et al. The precise determination of the window of implantation significantly improves ART outcomes. Sci Rep-UK. 2021;11:13420.
16. Vannuccini S, Clifton VL, Fraser IS, et al. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. Hum Reprod Update. 2016;22:104-115.
17. Albayrak OG, Azhari F, Colak EN, et al. Endometrial gene expression profiling of recurrent implantation failure after in vitro fertilization. Mol Biol Rep. 2021;48:5075-5082.
18. Fernández L, Grasso E, Soczewski E, et al. Understanding the natural selection of human embryos: blastocyst quality modulates the inflammatory response during the peri-implantation period. Am J Reprod Immunol. 2022;89:e13423.
19. Amjadi F, Zandieh Z, Mehdizadeh M, et al. The uterine immunological changes may be responsible for repeated implantation failure. J Reprod Immunol. 2020;138:103080.
20. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. Nat Med. 2012;18:1754-1767.
21. Okada H, Tszuki T, Murata H. Decidualization of the human endometrium. Reprod Med Biol. 2018;17:220-227.
22. Ruiz-Magaña MJ, Martinez-Aguilar R, Llorca T, Abadia-Molina AC, Ruiz-Ruiz C, Olivares EG. Decidualization modulates the mesenchymal/stem cell and pericyte characteristics of human decidual stromal cells. Effects on antigen expression, chemotactic activity on monocytes and antitumoral activity. J Reprod Immunol. 2021;145:103326.
23. Carlino C, Stabile H, Morrone S, et al. Recruitment of circulating NK cells through decidual tissues: a possible mechanism controlling NK cell accumulation in the uterus during early pregnancy. Blood. 2008;111:3108-3115.

24. Huang Y, Zhu X, Du M, Li D. Human trophoblasts recruited T lymphocytes and monocytes into decidua by secretion of chemokine CXCL16 and interaction with CXCR6 in the first-trimester pregnancy. J Immunol. 2008;180:2367-2375.

25. Hofmann AP, Gerber SA, Croy BA. Uterine natural killer cells pace early development of mouse decidua basalis. Mol Hum Reprod. 2013;20:66-76.

26. Hanna J, Goldman-Wohl D, Hamany Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med. 2006;12:1065-1074.

27. Crespo AC, Mulik S, Dotiwala F, et al. Decidual NK cells transfer granulysin to selectively kill bacteria in trophoblasts. Cell. 2020;182:1125-1139.

28. Ander SE, Diamond MS, Coyne CB. Immune responses at the maternal-fetal interface. Science Immunol. 2019;4.

29. Wang S, Li Y, Piao H, et al. PD-1 and Tim-3 pathways are associated with regulatory CD8+ T-cell function in decidua and maintenance of normal pregnancy. Cell Death Dis. 2015;6:e1738.

30. Vacca P, Cantoni C, Vitale M, et al. Crosstalk between decidual NK and CD14+ myelomonocytic cells results in induction of Tregs and immunosuppression. Proc Natl Acad Sci USA. 2010;107:11918-11923.

31. Baban B, Chandler P, McCool D, Marshall B, Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase expression is restricted to fetal trophoblast giant cells during murine gestation and is maternal genome specific. J Reprod Immunol. 2004;61:67-77.

32. Hunt JS, Vassmer D, Ferguson TA, Miller L. Fas ligand is positioned in mouse uterus and placenta to prevent trafficking of activated leukocytes between the mother and the conceptus. J Immunol. 1997;158:4122-4128.

33. Shah NM, Imami N, Johnson MR. Progesterone Modulation of Pregnancy-Related Immune Responses. Front Immunol. 2018;9:1293.

34. Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC Med. 2013;11:154.

35. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SEM, Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC Med. 2013;11:154.

36. Gutierrez MC, Martin-de Las Heras A, Diaz-Gimeno P. SARS-CoV-2 infection risk assessment in the maternal-fetal environment throughout the human body and brain. In, 2021.

37. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020;369:718-724.

38. Boudewijns R, Thibaut HJ, Kaptein SJF, et al. STAT2 signaling restricts viral dissemination but drives severe pneumonia in SARS-CoV-2 infected hamsters. Nat Commun. 2020;11:5838.

39. Zheng J, Wong LR, Li K, et al. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature. 2021;589: 603-607.

40. Innis BL, Nolan TM, Arulanantham DN, et al. Analysis of placental transcriptome study. PLoS One. 2020;15:e0230295.
69. Zheng Q, Duan T, Jin L. Single-cell RNA expression profiling of ACE2 and AXL in the human maternal–Fetal interface. Reprod Develop Med. 2020;4:7.

70. 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;32:956-962.

71. Allotey J, Stallings E, Bonet M, 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.

72. Hosier H, Farhadian SF, Morotti RA, et al. SARS–CoV-2 infection of the placenta. J Clin Invest. 2020;130:4947-4953.

73. Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA. 2020;323:2198.

74. Roberts J, Cheng JD, Moore E, Ransom C, Ma M, Rogers BB. Extensive perivillous fibrin and intervillous histiocytosis in a SARS-CoV-2 infected placenta from an uninfected newborn: a case report including immunohistochemical profiling. Pediatr Devel Pathol. 2021.

75. Rebutini PZ, Zanchetti AC, Stonoga ETS, et al. Association between COVID-19 pregnant women symptoms severity and placental morphologic features. Front Immunol. 2021;12:685919.

76. Colson A, Depoix CL, Dessilly G, et al. Clinical and in vitro evidence against placenta infection at term by severe acute respiratory syndrome coronavirus 2. Am J Pathol. 2021;191:1610-1623.

77. Marton T, Hargitai B, Hunter K, Pugh M, Murray P. Massive perivillous fibrin deposition and chronic histiocytic intervillitis in a complication of SARS-CoV-2 infection. Pediatr Devel Pathol. 2021;24:450-454.

78. Jang W, Lee S, Park S, et al. Pregnancy outcome, antibodies, and placental pathology in SARS-CoV-2 infection during early pregnancy. Int J Env Res Pub He. 2021;18:5709.

79. Vouga M, Favre G, Martinez-Perez O, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep-UK. 2021;11:13898.

80. Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. The Lancet Global Health. 2021;9:e759-e772.

81. Matute J, Finander B, Pepin D, et al. Single-cell immunophenotyping of the fetal immune response to maternal SARS-CoV-2 infection in late gestation. Res Sq. 2021.

How to cite this article: Zhu G-h, Liu L, Huang X-x, et al. The risk of intrauterine exposure to SARS-CoV-2 in female COVID-19 patients: A comprehensive review. Am J Reprod Immunol. 2023;89:e13528. https://doi.org/10.1111/aji.13528