Review Article

Update on the impacts of COVID-19 and vaccine on female reproductive system, pregnancies, and neonatal outcomes: a narrative review

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Background and Objective: Since its first reported, coronavirus disease 19 (COVID-19) has caused over 500 million illnesses and 5 million deaths. During a pandemic, women are always thought of as being mentally and physically vulnerable, especially pregnant and breastfeeding women. Therefore, throughout this protracted epidemic, females merit additional attention. Emerging evidence suggests that virus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) may infect female reproductive organs that express angiotensin-converting enzyme 2 (ACE2) and that this infection may have a variety of effects on female reproduction, fertility, pregnancies, and neonatal outcomes. Additionally, vaccination's effects on women are garnering a lot of attention since vaccination rates are gradually growing. The aim of this narrative review is to provide a comprehensive review of the effects of COVID-19 and its vaccine on the female reproductive system as well as pregnancies and neonatal outcomes.

Methods: The electronic databases PubMed, Medline, and Google Scholar were searched for pertinent English-language studies published from 2019, December, 1st to 2022, October, 30th.

Key Content and Findings: While there is disagreement on the expression level, ACE2 and transmembrane serine protease 2 are highly expressed in the reproductive organs. Women's reproductive systems, including menstrual cycles, sex hormones, and pregnancy outcomes, are impacted by COVID-19. The influence of COVID-19 on female fertility, the potential for sexual, vertical, and breastfeeding transmission of SARS-CoV-2, and newborn outcomes remain debatable. Furthermore, no proof receiving the COVID-19 vaccine has a deleterious impact on female fertility, pregnancy, or lactation.

Conclusions: The influence of COVID-19 and its vaccine on female reproduction remains controversial thus more long-term and large-scale research is needed. Only with the joint efforts of researchers, clinicians and policymakers can we understand it more comprehensively and profoundly.

Keywords: Coronavirus disease 19 (COVID-19); severe acute respiratory syndrome corona virus 2 (SARS-CoV-2); female reproduction; angiotensin-converting enzyme 2 (ACE2); vaccine

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Introduction

Background

Coronavirus disease 19 (COVID-19), which was caused by the virus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019 (1). On March 11, 2020, the World Health Organization (WHO) subsequently proclaimed it a worldwide pandemic (2). Three highly dangerous human corona viruses (CoVs) have been found, including the new SARS-CoV-2. The other two are the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), originally discovered in Saudi Arabia (3), and the SARS-CoV, which was first discovered in Guangdong, China (4). Researchers have discovered that SARS-CoV-2 is a capsulated single-stranded RNA virus that has 79.6% sequence similarity with SARS-CoV (5).

Rationale and knowledge gap

Similar to SARS-CoV, the transmission mode of SARS-CoV-2 is via respiratory droplets (5) and the infectious virus penetrates the lower respiratory tract (6), depending on angiotensin-converting enzyme 2 (ACE2) as the critical functional receptor, which is abundantly on respiratory epithelium such as type II alveolar epithelial cells (7). The infection might then trigger severe inflammatory reactions that harm the airways. The inflammation could also result in a cytokine storm, which would eventually induce multiple organ failure (8,9). Similarly, typical symptoms of COVID-19 are fever, cough, diarrhea, vomit, etc., but it also does damage to other systems expressing ACE2. Numerous research has concentrated on the degree of ACE2 expression in the female reproductive system, which suggested that SARS-CoV-2 may infect the female reproductive system and cause inflammatory reactions that ultimately impair female reproduction, fertility, pregnancy, and neonatal outcomes (10,11). Moreover, the influence of COVID-19 vaccine on the female reproductive system receives much attention and has never been truly determined. Further research on COVID-19 and its vaccine is still required since the pandemic scenario is still dire on a global scale.

Objective

In this review, we provided a comprehensive view of the role of ACE2 in the female reproductive system as well as the possible effects of COVID-19. We also discuss the COVID-19 vaccine's effects on the female reproductive system, which were not included in earlier reviews. We present this article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-39/rc).

Methods

An electronic database search (PubMed, MEDLINE, Google Scholar) was conducted using the keywords including COVID-19, SARS-CoV-2, female reproduction, angiotensin-converting enzyme 2, and vaccine. Two authors independently reviewed each study's whole text (YS, HC). If there were any disagreements over this selection, the other two writers would be consulted before a final choice was made (SY, JG). The reference lists of all pertinent English-language original articles, reviews, case reports and news reports published from 1st December, 2019 to 30th October, 2022 were examined to identify further studies that may be possibly included (*Table 1*).

The role of ACE2 in female reproductive system and the implication for COVID-19 related pathology

The molecular mechanism of ACE2 in SARS-CoV-2 infection

Previous studies have identified that ACE2 is a critical functional receptor for SARS-CoV (12) and it was proved that SARS-CoV-2 also uses ACE2 as an entry receptor without using other coronavirus receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4) (6,12-14). A coronavirus contains four functional proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (6,15). The S protein could bind to the ACE2 receptor to enter host cells (6,13), which indicated that the ACE2-expressing organs have the potential risk of being infected such as the lung, heart, small

Table 1 The search strategy summary

Items	Specification
Date of search	October 30, 2022
Databases and other sources searched	PubMed, Medline, and Google Scholar
Search terms used	COVID-19, SARS-CoV-2, female reproduction, angiotensin-converting enzyme 2, and vaccine
Timeframe	2019–2022
Inclusion criteria	Original article in English
Selection process	The entire texts of all studies were evaluated separately by two writers (YS, HC). In the event of conflicts about this pick, a final decision was reached after consultation with the other two writers (SY, JG)

intestine, and kidney (7,16-20). Studies have found that some specific cell types highly express ACE2, including type II alveolar cells (AT2), myocardial cells, proximal tubule cells of the kidney, ileum, and esophagus epithelial cells, and bladder urothelial cells (7,16,18,20). ACE2 is also high in the testes and prostate (21). In addition, the S protein could be activated by the transmembrane serine protease-2 (TMPRSS-2) (13,22,23) and the TMPRSS-2 expression pattern is similar to ACE2 expression (19). The expression level of ACE2 may explain why the respiratory system is the most vulnerable system when SARS-CoV-2 infects human bodies. In addition, ACE2 may serve as a suitable target for SARS-CoV-2 and affect the female reproductive system. Therefore, focusing on the ACE2 expression level in the female reproductive system may benefit the understanding of the mechanisms of SARS-CoV-2 infection and its potential effects on the female reproductive system.

ACE2 in the ovary, fallopian tube, uterus, and vagina

Many studies had explored the distribution of ACE2 mRNA and protein levels in female reproductive systems and some also investigated the heterogeneity between different tissues using single-cell RNA-sequencing (scRNA-seq) (24-29). One study extracted bulk RNA-seq profiles from the Tissue Atlas of Human Protein Atlas (HPA) (30), Genotype-Tissue Expression (GTEx) (31), and Functional Annotation of Mammalian Genomes 5 (FANTOM5) Cap Analysis of Gene Expression (CAGE) datasets (32) to investigated ACE2 expression in specific human tissues, their findings suggested that the ovary expresses a low level of ACE2 (25). Another study using published RNA-seq data found that ACE2 is mostly expressed in oocytes and granulosa cells of antral follicles and pre-ovulation follicles, while TMPRSS2 was almost absent in either oocytes or granulosa cells during folliculogenesis, suggesting a lack of co-expression of ACE2 and TMPRSS2 (29). Based on published scRNAseq data of ovarian tissues from young cynomolgus monkeys (33), Stanley *et al.* also found that co-expression of ACE2 and TMPRSS2 was only frequent in a subpopulation of oocytes, and was absent in ovarian somatic cells (26). Moreover, Goad *et al.* did not observe significant expression levels of either ACE2 or TMPRSS2 based on scRNA-seq datasets from the human uterus, myometrium, ovary, and fallopian tube (28). The low expression of ACE2 mRNA in the ovary, fallopian tube, uterus, and vagina was consistent with the aforementioned negative test of SARS-CoV-2 in COVID-19 patients' vaginal fluid, and the result of recent studies that the SARS-CoV-2 RNA was undetectable in oocytes from two women with COVID-19 infection (34). However, we can't ignore the fact that protein expression may be different from mRNA expression owing to the posttranscriptional regulation and other mechanisms that regulate mRNA and/or protein expression (35). Jing *et al.* analyzed data from the HPA and GeneCards datasets, their results showed that ACE2 is commonly presented in the female reproductive system, including the vagina, uterus, and ovary which was the tissue with the highest protein level of ACE2 (27). Wang *et al.* also evaluated the proteomic data in Human Integrated Protein Expression Database (HIPED) (36) and found that ACE2 was most abundant in ovary (25).

ACE2 in the embryo and neonate

Many pieces of research also aimed to detect the ACE2 and TMPRSS2 expression in embryos. In preimplantation embryos, one study determined that ACE2 was expressed

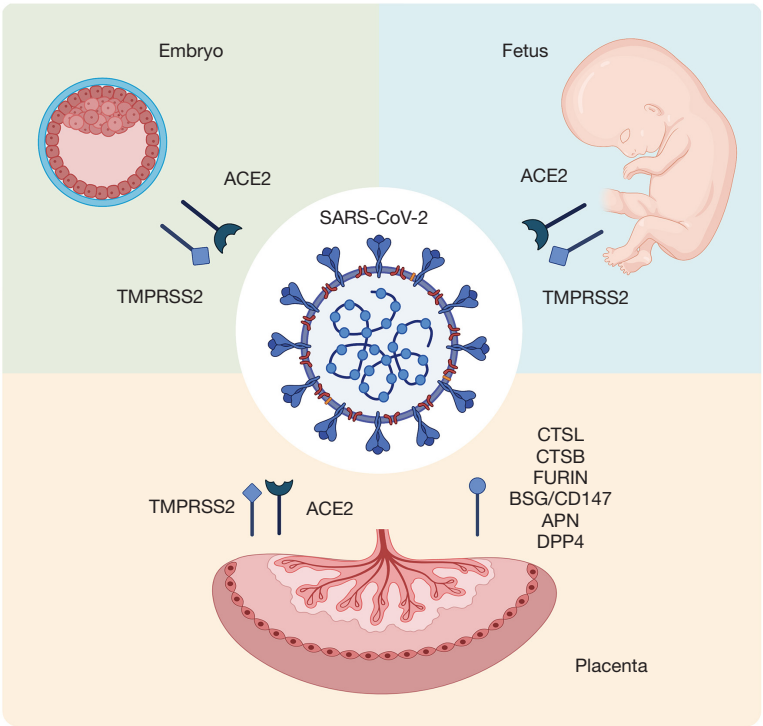

Figure 1 An illustration of how SARS-COV-2 enters the placenta, embryo, and fetus. ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane serine protease 2; CTSL, Cathepsin L; CTSB, Cathepsin B; FURIN, an endoprotease involved in processing of precursor proteins; BSG, Basigin; CD147, a glycoprotein that widely exists on the cell surface and participates in many physiological and pathological processes; APN, aminopeptidase N; DPP4, dipeptidyl peptidase 4. This figure was created with BioRender.com.

in early embryos before the eight-cell stage, and trophectoderm of late blastocysts, while TMPRSS2 was strongly expressed in the late blastocyst stage, and co-expression of ACE2 and TMPRSS2 was only observed in the trophectoderm of late blastocysts (29) (*Figure 1*). Interestingly, the authors also found that the co-expression pattern of ACE2 and TMPRSS2 in oocytes and preimplantation embryos in humans, mice, and rhesus monkeys were completely different, leading to the limitations of using animal models for evaluating the impact of SARS-CoV-2 on female reproduction. Another study detected ACE2 expression in fetal kidney, ileum, and rectum samples from 15 weeks onwards, but did not find evidence for ACE2 expression in fetal lung samples at 15^{+5} weeks onwards, also no ACE2 expression was detected in the brain or heart tissues (37). Another study using scRNA-seq also determined that the fetal adrenal gland, kidney, heart, and stomach expressed a high level of ACE2, and co-expression of ACE2 and TMPRSS2 were higher in the adrenal gland and kidney, but ACE2 expression was not detected in fetal lungs (38). Using published scRNA-seq data, one study found that the ACE2 expression pattern showed a significant gender difference in day 6 trophectoderm cells, day 6 primitive endoderm cells, and ACE2 positive-expressing syncytiotrophoblast, which was highly expressed in female. Their findings indicate that the day 6 embryos of female may be more or less susceptible to SARS-CoV-2 infection (39).

ACE2 in the placenta and breast

Previous studies indicated that ACE2 had over-expression and enhanced activity during pregnancy, especially in the placenta (40,41). Many studies had detected that ACE2 and TMPRSS2 genes were expressed in the placenta throughout the pregnancy, mainly in syncytiotrophoblast and cytotrophoblast of the placenta and stromal cells and perivascular cells in decidua (42-46). ACE2 expression was highest in the first trimester and declined with gestation development (47,48), and the distribution and level of ACE2

expression in the placenta of symptomatic COVID-19 patients did not show a significant difference compared with that in the control placentae (37,45). However, some studies reported the absence or very low level of co-expression of ACE2 and TMPRSS2 in the placenta (49,50). Pique-Regi *et al.* used a single-cell study (51) which has also been used in other studies along with another study (52), and their new single-cell/nuclei RNA-sequencing data, the results showed that very few cells co-expressed ACE2 and TMPRSS2 in the placenta throughout pregnancy as well as in chorioamniotic membranes of third-trimester (49). Another study found that infected placentae had significantly reduced ACE2 when SARS-CoV-2 was localized to cells expressing ACE2 (53). One study found that in the human placenta, while FURIN was broadly expressed by main placental villous cells, only trophoblasts co-expressed high levels of ACE2 and TMPRSS2, and the authors also found that primary trophoblasts were permissive to the entry of SARS-CoV-2 pseudovirus particles correspondingly (54). Other proteases [Cathepsin L (CTSL), Cathepsin B (CTSB), and FURIN], non-canonical receptor Basigin (BSG)/CD147, and other coronavirus family receptors (APN and DPP4) were also detected in most of the placental cells (43) (*Figure 1*). These results suggest other entry factors may be involved in the effects of SARS-CoV-2 on the placenta.

To understand the role of ACE2 in breastfeeding, much research had investigated the expression of ACE2 in the breast. Studies analyzing RNA-seq datasets also detected low expression of ACE2 in breast tissues and the absence of co-expression of ACE2/TMPRSS2 or ACE2/ CTSB/ CTSL (24,25,28). Previous studies using proteomic datasets to analyze the expression of ACE2 in breasts also suggested the existence of ACE2 in breasts but the expression level was low (25,27).

The impact of COVID-19 on the female reproductive system

The existence of SARS-CoV-2 in vaginal fluid and sexual transmission

The first study aiming to detect SARS-CoV-2 in the vaginal fluid of 27 women with COVID-19 infection reported that the SARS-CoV-2 was negative (55). Similarly, in other reports, vaginal fluid obtained from severe COVID-19 infected women (56,57), postmenopausal women with COVID-19 infection (57), pregnant women with COVID-19 (58) were also found to be negative (58,59). A case report from Japan has also demonstrated negative results for reverse transcriptase polymerase chain reaction (RT-PCR) tests of the placenta, umbilical cord, cord blood, amniotic fluid, vaginal fluid, breastmilk, newborn anal wipes, and nasopharyngeal samples, indicating the absence of SARS-CoV-2 (60). To date, only one study reported that among 35 women with acute SARS-CoV-2 infection, one premenopausal and one postmenopausal woman had a positive vaginal result for SARS-CoV-2 by RT-PCR test (61). And another recent study suggested that even though the RT-PCR test did not detect the SARS-CoV-2 virus in all fifteen participants, it was identified in the vaginal fluid of two premenopausal and one postmenopausal patient with the transcription-mediated amplification Panther System (62). A prospective study that recruited 50 SARS-CoV-2 infected pregnant women. All the samples from 50 neonates including vaginal secretion, breast milk, and nasopharyngeal swab were negative through the RT-PCR test, however, they detected the virus in one fetal membrane and amniotic fluid sample. Researchers also paid attention to asymptomatic patients who undergo assisted reproductive technology (ART) and did not detect SARS-CoV-2 mRNA in semen, follicular fluid, vaginal secretions, or residual medulla from ovarian tissue cryopreservation procedures (63). Another prospective study from India detected that 6 mothers had one or more positive results in amniotic fluid, placental membrane, and vaginal and cervical swabs. Researchers perceive that there is the possibility of antepartum or intrapartum transmission (64). Due to the sample size limitation, we could not draw any conclusion about the presence of SARS-CoV-2 in the vaginal fluid. Since the possibility of sexual transmission could not yet be ruled out, further studies aiming to investigate the evidence of sexual transmission of SARS-CoV-2 are still needed.

The effect of COVID-19 on menstruation

One study analyzed 177 patients with menstrual records and reported that 45 patients presented with changes in menstrual volume and menstrual cycle (28%), mainly a decreased menstrual volume and a prolonged menstrual cycle (65). But the authors did not observe changes in the average sex hormone and anti-Müllerian hormone (AMH) concentrations, the menstruation changes of these patients might be explained by the transient changes of sex hormones caused by suppression of ovarian function which quickly resume after recovery. Another study discovered that the menstrual status, menstrual volumes, phase of the menstrual

cycle, and dysmenorrhea history were similar between non-severe and severe COVID-19 women (66), suggesting the impact of COVID-19 on menstruation did not depend on the disease severity. An anonymous social media survey was conducted by Phelan *et al.* (67), and among the 1,031 women who responded, 46% reported that their menstrual cycle had changed since the pandemic began, while 53% reported worsening premenstrual symptoms, 18% reported new menorrhagia, and 30% new dysmenorrhea. The occurrence of missed periods was also found to be more frequent during the pandemic. Another study that enrolled 263 participants also found that the duration of period and menstrual volume changed compared to those before the outbreak of COVID-19, which were associated with an increased degree of anxiety and stress as a result of the COVID-19 pandemic (68). A prospective study in Arizona recruited 127 females, and 16% reported changes in the menstruation cycle with the median number of 57.5 (range, 28–222) days. In addition, reported changes include irregular menstruation, premenstrual symptoms, and infrequent menstruation (69). Taken together, COVID-19 could not only directly affect women's menstrual cycles, but also indirectly influence menstruation as an event of stress and psychological distress (70).

The effect of COVID-19 on sex hormones and ovarian reserve

Many studies have reported that premenopausal females with COVID-19 had milder symptoms and better outcomes compared with age-matched male patients, and had a shorter duration of hospitalization than menopausal patients (71-73). One study also found that estradiol (E2) was negatively correlated with disease severity (both $P<0.05$) (71). A retrospective study found that the fatality risk for post-menopausal female COVID-19 patients who received estradiol treatment was reduced by more than 50%, while for pre-menopausal women, COVID-19 fatality risk remained the same regardless of hormone therapy (74). It is known that estrogen plays an important role in providing immunity against SARS-CoV-2 infection. Studies found it could be involved in enhancing immunity by modulating cytokines storm and mediating adaptive immune alterations respectively (75). In COVID-19 patients, E2 was inversely correlated with interleukin (IL) 2R, IL-6, and tumor necrosis factor-alpha (TNF-α) in the luteal phase (all $P<0.05$) and C3 in the follicular phase ($P<0.05$) (71). Previous work has proved that different sex chromosomes and sex hormones could influence T cells, B cells, and neutrophils differently, causing sex-specific differences and disparity in immunity (76).

One study reported that compared with healthy age-matched participants, women with COVID-19 had significantly decreased serum AMH level (66). On the other hand, one study did not observe significant differences between the sex hormones and AMH levels of women of reproductive age with COVID-19 and those of age-matched healthy participants (65). Also, another study suggested that SARS-CoV-2 infection did not influence the patients' performance or ovarian reserve during their immediate subsequent in vitro fertilization (IVF) cycle, except for a reduced proportion of top-quality embryos (77).

The impact of COVID-19 on pregnancy (maternal and neonatal outcomes)

SARS-CoV-2 infection in pregnant women

Since the start of the COVID-19 epidemic, the effects of SARS-CoV-2 on expectant mothers have been a source of worry. To thoroughly understand the impact of SARS-CoV-2 on pregnancy and its underlying mechanisms, several research have been conducted (78-86). The clinical characteristics of pregnant women with COVID-19 mainly include fever and cough which were significantly less frequent than non-pregnant women with SARS-CoV-2 infection (87). Preterm labor serves as the main adverse obstetric outcome, and its rate is higher among pregnant with COVID-19 than among non-infected pregnant women (83,87). An overview of thirty-nine reviews found that in pregnant women with COVID-19, there are increased rates of cesarean sections (52.3–95.8%), preterm delivery (14.3–63.8%), and preterm labor (22.7–32.2%) rate. Maternal intensive care unit (ICU) admission (3–28.5%) and mechanical ventilation (1.4–12%) rates were high and the maternal mortality rate was less than 2% (88). Although the cesarean delivery rate was reported to be high, there was no evidence or recommendation supporting this delivery mode, especially when some studies found that the neonatal infection rate did not differ between babies born vaginally and babies born by Caesarean (89,90). Moreover, overcoming the limitation that previous studies mainly enrolled women in their second and third trimesters of pregnancy, a case-control study enrolled 225 pregnant women in their first trimester and found that the cumulative incidence of COVID-19 was similar between women with spontaneous abortion (11/100, 11%) and those

with ongoing pregnancy (12/125, 9.6%) (P=0.73). Logistic regression analysis also confirmed that COVID-19 was not an independent risk factor of early pregnancy loss [odds ratio (OR) =1.28, 95% confidential interval (CI): 0.53–3.08] (91).

Vertical transmission of SARS-CoV-2 and neonatal outcomes

Many efforts have been made to determine the possibility of vertical transmission of SARS-CoV-2. Some studies have reported that SARS-CoV-2 can be detected in the placenta of pregnant women with COVID-19 by real-time polymerase chain reaction (qPCR), histological examination, and electron microscopy (92-95). Notably, the placenta was vulnerable to COVID-19 infection, which can present histopathological abnormalities such as villous fibrin deposition, maternal vascular malperfusion, villitis/intervillositis, and fetal vascular malperfusion even when there were non-detectable or very low levels of SARS-CoV-2 mRNA or protein in the placenta from women with mild COVID-19 (96-99). A systematic review included a total of 1,287 pregnant women with confirmed SARS-CoV-2 infection from sixty studies and their findings suggested that 19 neonates were SARS-CoV-2 positive by RT-PCR of nasopharyngeal swabs (100). Another recent large systematic review consisting of thirty case reports and thirty-eight cohort or case series studies analyzed the records of 936 neonates from mothers with COVID-19 infection and found that 27 neonates had a positive result for SARS-CoV-2 RNA test using nasopharyngeal swabs, indicating a pooled overall proportion of 3.2% for vertical transmission. SARS-CoV-2 RNA testing was positive in 1 of 34 cord blood samples, 2 of 26 placenta samples, 3 of 31 fecal or rectal swabs, and none of the amniotic fluid or urine samples (101). Neonatal serology, based on the presence of IgM because it cannot cross the placenta due to its large molecular weight, was positive in 3 of 82 samples (101). Vertical transmission of SARS-CoV-2 seems to be possible. However, due to the scarcity of first-trimester data, we could not yet conclude the possibility and rates of vertical transmission during early pregnancy. Recently, a study enrolled 15 pregnant women found that exposure to SARS-CoV-2 during pregnancy will lead to a placental inflammatory response governed by T cells and macrophages, involving both maternal and fetal cells, but will not infect placental tissue. They found that although maternal antibodies against SARS-CoV-2 were transmitted to the fetus through the placenta, neither fetal antibodies nor SARS-CoV-2 was found in the placenta, which shows that the placenta can protect the fetus from infection and suggests that vertical transmission from mother to fetus may be extremely rare. However, due to the limited number of enrolled pregnant women, further researches are needed (102). An overview also determined the rate of stillbirth, neonatal ICU admission, mortality, and neonatal PCR positivity, which were <2.5%, 3.1–76.9%, <3%, and 1.6–10%, respectively (88). However, the actual rate of the aforementioned aspects differs from area to area, from time to time, and from person to person. During the SARS-CoV-2 pandemic, the stillbirth rate in 2 Philadelphia hospitals, USA during March to June 2020, had a decreasing trend from 5.4 per 1,000 births in the prepandemic epoch to 5.0 per 1,000 births (95% CI: –0.34–0.29) (103). This result might be related to a decrease in the hospitalization rate of pregnant women and more attention paid to protecting the fetus. However, in St George's University Hospital, London during the SARS-CoV-2 pandemic from October 2019 to January 2020, the stillbirth rate (9.31 per 1,000 births) was significantly higher compared to that (2.38 per 1,000 births) in the pre-pandemic period (95% CI: 1.83–12.0) (104). And this result might be associated with higher total births during the SARS-CoV-2 pandemic (n=1,718) compared with the pre-pandemic period (n=1,681) and the infection of SARS-CoV-2. Meanwhile, neonatal ICU admission strangely decreased during the SARS-CoV-2 pandemic from the first 9 weeks in 2020 to 10–17 weeks in 2020 with an adjusted incidence rate ratio (aIRR) of 0.76 (95% CI: 0.65–0.89) in Japan (105). This result might be associated with more home quarantine and more complete medical facilities and technology middle stage of the SARS-CoV-2 pandemic. Overall, the association between SARS-CoV-2 and neonatal outcomes is still elusive, and more multi-center and large-sample studies are needed.

COVID-19 and breastfeeding

Many case reports have also reported the presence of SARS-CoV-2 in breast milk (106-108). A systematic review identified 116 lactating women with confirmed COVID-19 who underwent RT-PCR tests in breastmilk from twenty-four case reports and ten cohort studies between December 2019 and 15 October 2020, 10 (6 from case reports) had positive results for SARS-CoV-2 RNA and the overall SARS-CoV-2 RNA detection rate in the breast milk of cohort studies was 2.16% (95% CI: 0–8.81%). The SARS-CoV-2 specific antibodies were also detected along with RT-PCR in the breast milk of six patients from four studies (109). In a case series including 20 COVID-19-

positive mothers who chose to breastfeed their offspring, none of the infants was infected by breastfeeding and no major complications were detected during the 1.8-month follow-up period (110). Another systematic review identified 655 pregnant women with confirmed COVID-19 and 666 neonates from 49 case-report studies between September 2019 and June 2020, 7 of 148 breastfed babies tested positive compared with 3 of 56 formula-fed babies (89). The rate of neonatal infection did not increase when the baby is breastfed, and it was unclear whether the babies were infected through breast milk or other routes of infection. Therefore, present studies could not provide sufficient evidence about the transmission of SARS-CoV-2 through breastfeeding.

The impact of the COVID-19 vaccine on female reproduction

Since the outbreak of COVID-19 the AstraZeneca/Oxford vaccine, Johnson and Johnson, Moderna, Pfizer/BioNTech, Sinopharm, Sinovac, COVAXIN, Covovax, Nuvaxovid, and CanSino vaccines against COVID-19 using either mRNA-based or adenovirus-based technology have been proved to be safe and efficient for most people 18 years and older by the WHO (111). As of 16 August 2022, a total of 12,409,086,286 vaccine doses have been administered (112).

The effect of COVID-19 vaccine on menstruation

Apart from some typical side effects like fever, fatigue, headache, and muscle pain (113), changes in menstruation after vaccination have been noticed. The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom has been collecting suspected side effects of the COVID-19 vaccine. The MHRA received 51,385 suspected responses to menstrual abnormalities including heavier-than-normal periods, delayed periods, and unexpected vaginal bleeding, up until July 27, 2022. However, the majority of people discover that the subsequent cycle sees their period return to normal. These data demonstrate that the observed menstrual alterations are mainly of a temporary character (114). Gibson *et al.* prospectively followed 14,915 participants in the Apple Women's Health Study (AWHS). According to their findings, the menstrual cycle briefly and slightly increased following the vaccination (115). Male *et al.* conducted a retrospective cohort that recruited 1,273 females over 18 years who received at least one dose of the COVID-19 vaccine. Respondents reported changes in the timing or flow of the period following their vaccination. They discovered a modest increase in the frequency of people with endometriosis who reported an earlier than usual period and in people with polycystic ovaries who reported a later than usual period. Menstrual changes following dose 2 are closely associated with those following dose 1 (116). Edelman *et al.* prospectively tracked 3,959 individuals' menstruation cycles. They found that cycle length increased by 0.71 day after the first dose and 0.91 day after the second dose. Although menses length changed, they thought it was not associated with vaccination (117). Rodríguez Quejada *et al.* observed changes of menstrual changes in frequency, regularity, duration, and volume after vaccination. Volume was the most significant alteration in their study, 41.84% of participants had heavier volume, 20.65% had lighter and 6.52% experienced amenorrhea or absence of menstruation (118). Baena-García *et al.* retrospectively collected data from 14,153 fully-accomplished vaccinated women and analyzed their menstrual bleeding, presence of clots, cycle length, and premenstrual symptoms. Higher menstrual bleeding (43%), more menstrual discomfort (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%), and shorter cycle length (32%) were reported to be the most significant alterations in menstruation. Additionally, the most common increases in premenstrual symptoms were headaches (28%), irritability (29%), melancholy (28%), abdominal bloating (37%), and greater tiredness (43%) (119). de leon *et al.* did an online survey of 4,171 females and collected their menstrual or menopausal symptoms. They discovered that 6.7% of women had worsening menopausal symptoms and 27.8% had irregular menstrual cycles. Moreover, participants with higher scores on measures measuring perceived stress, sadness, and anxiety were more likely to have reproductive cycle disruptions and participants perceived that these disturbances were related to the COVID-19 pandemic (120). These two studies suggest that variations in menstruation may be brought about by social-psychological variables.

The International Federation of Gynecology and Obstetrics (FIGO) considers a difference of less than eight days between a woman's shortest and longest cycles to be normal (121). Therefore, the small variations in menstrual cycles seen following vaccination in the majority of studies might be considered common. Changes in menstruation are likely the result of a cytokine storm produced by COVID-19, which may act as a stressor on

the hypothalamus-pituitary-ovarian axis (117,122). The recruitment of follicles therefore prolongs, the formation of the endometrial lining is inhibited, and the menstrual cycle lengthens as a result (123). In conclusion, there is no solid evidence to prove that COVID-19 vaccines will incur side effects of menstrual changes.

The effect of COVID-19 vaccine on fertility

Another concern is whether COVID-19 vaccination will lead to female infertility. As the spread of misinformation that the COVID-19 vaccine will lead to sterility, many reproductive-age women hesitate to get vaccinated. It is said that the SARS-CoV-2 spike protein is similar to syncytin-1, which is a key protein in developing embryos (124,125). The protective antibodies against the SARS-CoV-2 spike protein will cross-react with syncytin 1 leading to pregnancy loss (124). However, these reports are proven to be unfounded. First, although the SARS-CoV-2 spike protein's structure is similar to that of the placental syncytin-1, the longest similar amino acid sequence between them is only four amino acids long (126,127). Lu-Culligan *et al.* have also proved that convalescent serum from COVID-19 patients does not react with syncytin 1 (128).

On the contrary, a few studies indicated that the COVID-19 vaccine does not cause sterility. A non-clinical study demonstrates that a COVID-19 vaccine AZD1222 has no adverse effects on female fertility, embryo-fetal development, or postnatal development in mice and supports the inclusion of pregnant and breastfeeding people in clinical studies with AZD1222 (129). Bentov *et al.* observed the ovarian follicular function of vaccinated IVF patients. They measured steroidogenesis, follicular response to the LH/hCG trigger, and oocyte quality biomarkers and detected no measurable detrimental effect on ovarian follicular function but the SARS–CoV-2 IgG antibodies were detected in the follicular fluid and the concentration is in direct proportion to that in serum (130). Orvieto *et al.* also observed ovarian function including ovarian stimulation and embryological variables in IVF patients. They found that patients' performance and ovarian reverse did not be affected after vaccination (131). Morris *et al.* used frozen embryo transfer as a model to compare the implantation rates between vaccinated and SARS-CoV-2 seronegative women. They found no difference in serum hCG documented implantation rates or sustained implantation rates between the two groups. They also performed 67 transfers using euploid blastocysts; no statistically significant differences were found in the implantation, clinical, and sustained pregnancy rates (132). Hillson *et al.* analyzed pregnancies that occurred in four ongoing clinical trials of the COVID-19 vaccine and all participants were urine β-hCG negative before vaccination. They found no stillbirths or neonatal deaths were reported in four clinical trials, and the rate of miscarriage in the COVID-19 vaccine group was no higher than the control group, with a risk ratio of 0.67 (P=0.51) indicating that vaccination did not bring an extra risk of stillbirth (133). Safrai *et al.* conducted a retrospective cohort that recruited women who were currently being treated with an ICSI cycle exam documenting their IVF treatment parameters and pregnancies. The results show that all the parameters of ICSI cycles were similar before and after vaccination and the number and percentage of clinical pregnancies were of no significant difference (134). In conclusion, no evidence getting COVID-19 vaccines will incur sterility.

The effect of COVID-19 vaccine on pregnancy

Since pregnant women undergo physiological changes in the immune, respiratory, and cardiovascular systems, which may affect drug disposition (135) and make them become more vulnerable (136), it is of great importance to figure out the impact of the COVID-19 vaccine on them. WHO recommended that pregnant women get vaccinated because COVID-19 vaccines offer strong protection against severe illness from COVID-19 (137) and a growing body of research on the safety and efficacy of COVID-19 immunization during pregnancy shows that the benefits exceed the dangers wherever there is current or predicted community transmission of the virus. Shimabukuro *et al.* found that previous studies did not show that pregnant women who received mRNA COVID-19 vaccines are safe (138). Gray *et al.* enrolled 131 reproductive-age vaccine recipients and finds that participants who got vaccination produced more antibody titers than those pregnant women who are infected, and humoral immunity is boosted (139). In a case-control observational research, Bookstein Peretz *et al.* compared 390 pregnant women who had received the two-dose BNT162b2 vaccination to 260 age-matched non-pregnant women who had not received the vaccine. They discovered that there was a very low frequency of obstetric problems following vaccination. After the first dose, uterine contraction rates are 1.3%, and after the second, they are 6.4%. After the first dose, 0.3% of pregnant women suffered vaginal bleeding and 1.5% after the second. After the

second vaccine, the prelabor membrane rupture rate is 0.8%. Also, they came to the conclusion that there are no safety issues with vaccinations based on the negative consequences and short-term obstetric and neonatal outcomes. Although pregnant women who received the vaccine experienced a successful humoral immune response, their SARS-CoV-2 IgG levels were lower than those of non-pregnant vaccine recipients (140). 64 pregnant women who had received the COVID-19 vaccine and 11 pregnant women who had contracted the virus while pregnant were recruited by Nir *et al.* Their research showed a substantial positive association between mother serum levels of SARS-CoV-2 IgG and levels of SARS-CoV-2 IgG in cord blood, newborn blood spots, and breast milk. Also, pregnant women who received the vaccine had significantly greater SARS-CoV-2 IgG levels in their maternal serum and cord blood than recovered COVID-19 patients (141). Rottenstreich *et al.* found that antenatal SARS-CoV-2 vaccination induces an adequate maternal serologic response and has the potential to provide neonatal protection through transplacental transfer of vaccine-stimulated maternally derived antibodies (142). Furthermore, Zdanowski *et al.* held the view that it is of great importance to find out the time of transplacental transfer of antibodies after vaccination, which may determine the optimal timing of COVID-19 vaccination in pregnant women in the future (143). Recently, Stock *et al.* conducted a national prospective cohort study describing COVID-19 vaccine uptake and SARS-CoV-2 infection in pregnant women in Scotland. They found that the vaccine coverage rate of pregnant women is much lower than that of the general female population (77%) aged 18–44 years, and the monthly vaccination rate for pregnant women has been declining every month since August 2021. In their study, 77.4% of COVID-19 infections, 98% of severe hospitalizations, and all neonatal deaths occurred among pregnant women who had not been vaccinated with the COVID-19 vaccine at the time of diagnosis. They also stress that women should be vaccinated during pregnancy to avoid adverse maternal and neonatal consequences associated with COVID-19 (144).

Taken together, the effect of COVID-19 vaccine on pregnant women is unclear. Several researchers have suggested that the development of the COVID-19 vaccine should take gender into account particularly focusing on the safety of pregnant and lactating women (136,145-149). It is also suggested that more pre-clinical trials using non-human primate animal models should be done to evaluate the safety of the COVID-19 vaccine for pregnant women (149).

Pharmacometrics modeling such as population pharmacokinetics (popPKs) modeling and physiologically based pharmacokinetic (PBPK) modeling could be used in pharmacologic studies of pregnant and lactating women (135,150). Another promising method is organ-on-a-chip, a micro-engineered biomimetic model developed by combining microfluidics and microfabrication technologies. It could replicate the structures and functions of a particular organ and is regarded as an efficient surrogate for animal models (135,151-155). Furthermore, explant and organoid bioengineered models are likely to shed new light on the research frontier (154,156,157).

Conclusions

In summary, ACE2 and TMPRSS2 express extensively in the ovary, fallopian tubes, uterus, vagina, placenta, embryo, and breast albeit the expression level is debatable. Future research can focus on the relationship between the expression level and the severity of clinical symptoms. The female reproductive system, including menstrual cycles, sex hormones, and pregnancy outcomes, is influenced by COVID-19. The placenta is susceptible to COVID-19 infection, which can cause villitis/intervillositis, villous fibrin deposition, maternal vascular malperfusion, and fetal vascular malperfusion, among other histological abnormalities. However, the possibility of sexual, vertical, and breastfeeding transmission of SARS-CoV-2, the impact of COVID-19 on female fertility, and neonatal outcomes are still controversial. Moreover, the influence of COVID-19 on female fertility, the potential for sexual, vertical, and breastfeeding transmission of SARS-CoV-2, and the results for newborns are still up for debate. Furthermore, there is no proof that immunization harms female fertility or negatively affects pregnant or lactating women.

All things considered, there are still a lot of unanswered concerns regarding how COVID-19 affects female reproduction. More long-term and large-scale research using animal, pharmacometrics, organ-on-a-chip, explant, and organoid models are necessary to further understand this crucial topic. In clinical practice, clinicians are supposed to pay more attention to women who are suffering or suffered COVID-19 recently. We hope that clinicians could collected, summarized and reported their patients' data to help researchers understand the influence of COVID-19 more comprehensively. Since COVID-19 is still ongoing, policy makers should improve policies and regulations in particular considering what women are suffering to provide

convenience and guarantee for medical treatment as much as possible.

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Footnote

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