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COVID-19 clinical manifestations on different gender reproductive system

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a major threat to world health and safety, making it the primary concern of global community that requires immediate preventive measures. Several organs are affected by this disease simultaneously with possible long-lasting sequelae. Disease pathogenesis is influenced by, the type of virus and its mutation, the number of viruses, individual's immune system and their age, gender, nutritional status, homeostasis between the immune, nervous and endocrine systems, and also physical condition. All of these factors play a role in the onset, duration, severity, and recurrence of the disease. Since the exact mechanism of infection with this virus is not fully understood, in this study we aimed to investigate its effects on the reproductive system in male and female as well as pregnancy outcome.

Review

Implication for health policy/practice/research/medical education:
It is raising an urgent question of the presence of acute respiratory syndrome coronavirus 2 in the reproductive tract that may result in infertility and may have implications for sexual transmission, miscarriage, embryonic infection, mother-to-child transmission and congenital diseases.

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Introduction

Probably in 2017 when Graham and Sullivan were publishing a paper on emerging viral diseases, proposing the importance of preparation for the next pandemic, they had not the slightest idea that the world would be confronted with its biggest pandemic in a century in less than three years.

Infectious diseases are still at the top of the World Health Organization (WHO) list of 'years of life lost from premature death causes. Bacteria and viruses form two huge groups of these infectious agents and the latter comprises 23 families associated with human infection; one of which is the Coronaviridae family. The newest member of this family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19) has led to over 31 million confirmed cases and 967 000 deaths in 188 countries until September 22, 2020 (1). Infectious diseases target different organs and have various effects on the human body functions. The reproductive system is no exception and following an infection, its function may alter leading to reduced fertility or even infertility. Diseases such as gonorrhea and syphilis are among the best-known bacterial infections affecting the urogenital system. Up to now several viral infections with an impact on the reproductive system are recognized as well, while human papillomavirus (HPV)

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is one prominent example. It is presumed that HPV is associated with sperm cell quality (e.g. azoospermia) and quantity, embryonic cells apoptosis and miscarriages (2). Jin et al indicated mumps and HIV infection as known risk factors of primary ovarian insufficiency and Liu et al enumerated these two as viral infections inducing orchitis and subsequently resulting in male infertility. Roles of some other viruses targeting the reproductive tract are also discussed in the literature (3,4).

COVID-19, the primary concern of the global community in 2020, caused by RNA virus SARS-CoV-2, principally manifests with fever and respiratory symptoms. Nonetheless, other non-respiratory symptoms may also be present including myalgia and gastrointestinal tract symptoms such as diarrhea. COVID-19 has surprised the scientific community as everyday new findings are published indicating different organs involvement within the disease process. It is of extensive importance to study SARS-CoV-2 impact on the reproductive system, fertility, and pregnancy outcome for essential measures to be taken to minimize possible damages. Several endeavors have been made and there are papers published on this subject suggesting a role for SARS-CoV-2 infection on the reproductive system and pregnancy (5).

Objectives

In the following review study, we consider the currently available data on COVID-19 impact on the human reproductive system.

Role of ACE2 in SARS-CoV-2 infection

There is little knowledge of the mechanism of SARS-CoV-2 invasion to the reproductive system. One of the most famous candidates is angiotensin-converting enzyme 2 (ACE2) that is considered to act as a functional host receptor molecule of SARS-CoV-2 for binding and entry into host cells. Angiotensin-converting enzyme 2 is abundantly expressed in the reproductive system including ovary and oocyte as well as the testis and male reproductive tract dominantly localized to the Sertoli, Leydig cells, and seminiferous ducts cells (6).

Angiotensin-converting enzyme 2 interferes in the balance between the levels of angiotensin (Ang) II and Ang-(1-7), each of which possesses different functions in the ovary. Ang-(1-7) is a heptapeptide that can be produced from Ang I through endopeptidases or from Ang II by ACE2.

Angiotensin II facilitates follicle development, steroid secretion, oocyte maturation, and follicle atresia. Effects of Ang II in ovaries such as steroidogenesis and ovulation is variable among different animal species. Moreover, all findings demonstrated that Ang II plays an important role in reproductive processes. Ang-(1-7) induces the production of hormones such as estradiol and progesterone (P), ovulation, and the resumption of meiosis in the oocyte and finally promotes human oocyte maturation. It seems the expression of Ang-(1-7) can be regulated by gonadotropins and steroid hormones. It has been discovered in considerable amounts in the follicular fluid. SARS-CoV-2 might infect ovaries and oocytes. SARS-CoV-2 infection can elevate ACE2 in the ovary and it possesses a negative effect on follicles/ oocytes. Ovarian ACE2 malfunction can also be witnessed in the pathology of polycystic ovary syndrome and ovarian hyperstimulation syndrome (7).

Angiotensin-converting enzyme 2 mRNA transcripts have been observed in the human and rat uterus. ACE2 expression is higher in epithelial cells than stromal cells. Other studies showed that more ACE2 mRNA transcripts exist in the secretory phase than in the proliferative phase. Each of these angiotensins modulates the regeneration activity of endometrium and myometrium. While Ang II enhances the proliferation of epithelial and stromal cells in the uterus, Ang-(1-7) inhibits it. The natural function of Ang II in the ovary and uterus is necessary for regular menstrual cycles (8). SARS-CoV-2 may disturb the female reproductive functions through ACE2, leading to infertility and menstrual disorders due to increased oxidative stress and subsequent alterations in DNA methylation (9).

Levy et al have reported that during pregnancy, the amount of ACE2 mRNA doubles in the kidney, placenta and uterus. Therefore, this increase in ACE2 levels in pregnant women could pave the way for SARS-CoV-2. It should be noted that ACE2 not only acts as a receptor but also interferes with post-infection regulation of immune response, cytokine secretion, and viral genome replication (10). However, Zeng et al claim that ACE2 expression is very low in almost all human cell types of the early maternal-fetal interface, suggesting that the placenta has no susceptible cell to the SARS-CoV-2 (9).

SARS-CoV-2 infection impact on male reproductive system

Literature suggested that SARS-CoV-1 (2002-2004 SARS) had a significant adverse impact on the reproductive systems in both men and women including testicular architecture, orchitis, widespread germ cell destruction, no spermatozoa in seminiferous tubules, and leukocyte infiltration, increasing the possibility of the impact of SARS-CoV-2 as well. On the other hand, SAR-CoV-2 through various mechanisms such as fever and oxidative stress pathways, can disrupt in spermatogenesis and induce germ cell apoptosis leading to impairment in semen quality and fertility. Postmortem examination of the testes was performed in twelve SARS-CoV-2 patients

and five controls, reported pathological changes in favor of significant damage due to SARS-CoV-2. They observed edema and mild infiltration of inflammatory cells mostly T lymphocytes in the interstitium, significantly reduced number of Leydig cells (2.2 versus 7.8, $P < 0.001$), and mild, moderate, and severe seminiferous tubular injury in 18.2%, 45.5%, and 36.4% of cases, respectively. Besides, Sertoli cells showed swelling, vacuolation, and cytoplasmic rarefaction, detachment from tubular basement membranes, and loss and sloughing into lumens of the intratubular cell mass (11).

Scrotal discomfort had been reported by some patients which is suggestive of viral orchitis, but the genital examination was not performed and as the SARS-CoV-2 has been associated with coagulopathy, vasculitis could be the cause of the orchitis. Testicular pain and epididymitis were reported as well (11).

SARS-CoV-2 infection and semen parameters

Two studies provided semen parameters. The first study was conducted on 34 men, semen parameters (sperm concentration, the total number of sperm per ejaculate, total number of progressive motility, the total number of complete motility) seemed impaired in four patients with moderate infection defined as requiring hospitalization to achieve >92% peripheral oxygenation with up to 6 L oxygen supplied.

In the second study, 12 men provided semen samples at a median interval of 78.5 days from initial symptoms. Semen analysis showed normal sperm parameters and low DNA Fragmentation Index (DFI) (7.6 ± 2.2) in eight patients, low-sperm motility (defined as PR+NP <40%) with higher sperm DFI in four patients (20.05 ± 3.80 versus 7.6 ± 2.2 compared to other eight patients) and poor sperm morphology (defined as normal morphology <4%) in two participants. A slight reduction was observed in the total mobile sperm count in comparison to before SARS-CoV-2 records in 2 out of 3 patients that their semen analysis for before SARS-CoV-2 was available (12).

SARS-CoV-2 infection and female reproductive system

COVID-19 damages most organs in the body as well as the female reproductive system. The effects of COVID-19 on the female reproductive system needs more investigations (9). There is a hypothesis that if oocytes be vectors of SARS-CoV-2 transmission, can likely contribute to disease transmission from parents to children. The effect of SARS-CoV-2 on embryonal development from fertilization to blastocyst formation and implantation and further steps are not identified. Past investigations proposed that there are no data related to the transmission risk of SARS-CoV-2 to oocytes in infected women after controlled ovarian stimulation. On the other hand, the lack of enough information related to this topic cannot support nor refuse the safety of assisted reproductive techniques procedures in infected women (9). Few studies are assessing the SARS-CoV-2 in the female reproductive system. Henarejos-Castillo et al measured viral infection-related gene expression to investigate endometrial susceptibility to SARS-CoV-2 infection. There are different phases in a menstrual cycle and gene expression varies with each specific phase as well as age, but overall, endometrium seems to have a low-risk of infection by SARS-CoV-2 due to low-expression of ACE2. However, because of several limitations such as the small sample size, variability in the genetic profile of individuals, ethnicity, and medical comorbidities, susceptibility could differ based on viral cell entry mechanisms (13).

SARS-CoV-2 infection and sexual transmission

Although SARS-CoV-2 spreads mainly through respiratory droplets or close contact, few studies reported the presence of the SARS-CoV-2 virus in other body fluids and organs such as blood, urine, and facial/anal swabs, conjunctiva in addition to oropharyngeal swabs suggesting other potential means of transmission such as sexual transmission (14).

Sexual transmission in men

It is known that a broad range of viral families, including Zika, Ebola, human immunodeficiency virus (HIV), and hepatitis viruses B/C can be transferred into semen and result in sexual transmission (15). Eight studies explored SARS-CoV-2 in semen samples of patients and except a single study, other studies did not found SARS-CoV-2 in semen samples. These studies were conducted on both symptomatic and asymptomatic patients, hospitalized and non-hospitalized, at different stages of acute infection or recovery and with different serologic findings which lessens the possibility of sexual transmission through semen. In a study published in JAMA Network Open at the point of 6-16 days since onset of symptoms, 6 men out of 38 men that provided semen samples, had positive results for SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR), including 4 out of 15 patients at the acute stage of infection and 2 out of 23 patients at the recovery stage. Although most of the studies obtained semen samples in the recovery period, in a recent study by Kayaaslan et al the semen samples of 18-45 adult men were collected in the acute stage (median time of a day from positive nasopharyngeal swab test) of the disease. Consistent with other studies, they did not find SARS-CoV-2 in semen samples of patients (16).

Sexual transmission in women

Very few articles investigated sexual transmission of the

SARS-CoV-2 through female reproductive tracts. One study evaluated vaginal fluid of 10 postmenopausal women with severe SARS-CoV-2 at the point of 17-40 days after the onset of SARS-CoV-2 infection. It showed no detectable SARS-CoV-2 RNA in the vaginal fluid samples of any of these patients.

Another study evaluated vaginal fluid, exfoliated cells, and an anal swab of 35 Chinese women that were at reproductive age, postpartum, and postmenopausal. Among them, 27 cases had a positive RT-PCR for SARS-CoV-2 on throat swab and the remaining eight had a clinical diagnosis of the disease. SARS-CoV-2 was not detected in samples from the lower genital tract and one anal swab was positive (17). It might be explained by a low-concentration of SARS-CoV-2 receptors, in the vagina and cervix. Aslan et al tested the vaginal fluid of 12 pregnant women with moderate symptoms, and all samples were negative for the virus. Most of the studies reported no detection of the virus in vaginal fluid, so it reduces the possibility of the sexual transmission of SARS-CoV-2 in women (18).

SARS-CoV-2 infection and sex hormones

Studies that investigated the sex hormone in SARS-CoV-2 patients reported higher luteinizing hormone (LH) levels and lower testosterone levels. Although these findings together with increasing of follicle stimulating hormone (FSH) and cortisol in SARS-CoV-2 patients, high levels of ACE-2 receptor in Leydig cells, and no alteration of other pituitary hormones are in favor of testicular and Leydig cell damage, however it is not clear that whether these hormonal changesis the consequence of direct SARS-CoV-2 infection in testicular cells or indirect effects of an inflammatory condition caused by the virus such as suppression of hypothalamic–pituitary–testicular axis activity or combination of them (19).

Testosterone is also involved in the immune response through binding to the androgen receptor and activating antiviral pathway. Thus, a decrease in testosterone levels may play a role in the immune response against COVID-19. Moreover, it is also associated with higher levels of inflammatory cytokines and severity factors such as lactate dehydrogenase, neutrophil count, procalcitonin levels, C-reactive protein, and lymphocyte count. Additionally, higher prolactin level and lower testosterone: LH ratio, FSH: LH ratio, and dihydrotestosterone levels which is probably due to low testosterone levels were reported as well as elevated estradiol levels. The latter was associated with interleukin 6 (IL-6) level that is a poor prognostic marker in COVID-19 patients. In contrast, women had lower FSH levels which may indicate loss of ovarian function, higher levels of testosterone, and cortisol that correlated with elevated inflammatory cytokines, and normal dihydrotestosterone levels (16).

COVID-19 and pregnancy

Susceptibility to SARS-CoV-2 virus in pregnancy

Emerging viruses had always an important effect on pregnant women and their fetuses which among their latest examples are the increase in complications in pregnant women in the 2009 H1N1 influenza virus pandemic and the severe effects on the fetus in the Zika virus outbreak. In general, pregnant women are more susceptible to viruses and have a lower prognosis than non-pregnant women. However, previous studies on other viruses of the Coronaviridae family, such as SARS and the Middle East respiratory syndrome (MERS), have shown no evidence of higher susceptibility to infection during pregnancy (20).

Changes in the respiratory system

During the pregnancy, progesterone and relaxants in the first trimester can relax the ligaments in the ribs. Additionally, following the enlargement of the uterus and the compression of the abdominal cavity, the diaphragm goes up into the thoracic space. Besides, in the third trimester of pregnancy, the subcostal angle and transverse diameter of the thoracic cavity increase further. These anatomical factors, along with a reduction in chest wall compliance, reduce functional residual capacity by 20% to 30%. This result eventually increases the chance of hypoxia in the mother, which is compensated by increased tidal volume and hyperventilation (19). Moreover, elevated progesterone can stimulate the respiratory center by reaching the hypothalamus via estrogen-dependent progesterone receptors and increase the tidal volume by 50%. Hyperventilation also causes pregnant women to inhale more air at the same time, therefore pregnant women are exposed to more droplets and aerosols which may contain viruses. Furthermore, changes in the nasal mucosa due to progesterone during the pregnancy lead to the binding of viruses to the upper respiratory tract making it difficult to clear (21).

Cardiovascular changes, increased metabolism, increased oxygen consumption, decreased functional residual capacity and ventilation/perfusion mismatch, exacerbate hypoxia in mother. Hence, in case of infection with the virus, pulmonary vascular resistance increases which can lead to pulmonary hypertension and heart failure (21).

Alterations of the immune response

"A successful pregnancy is the result of the mother's tolerance to the allogeneic fetus" because about half of the fetal genome is from the father which is expressed as paternal antigens and may be recognized by the mother's immune system as a foreign pathogen (22). Therefore,

the mother's immune system needs to change to achieve a successful pregnancy, which can increase the chance of infectious diseases. The immune system during pregnancy is modulated but not suppressed (23).

Zhao et al have reported that the total number of $CD3^+$ T cells in pregnancy decreases (24). Increased estrogen and progesterone in the first trimester of pregnancy can lead to reversible degeneration in the thymus, which eventually reduces $CD4^+$ and $CD8^+$ T cells. In the study of Zhu et al, it has been reported that the number and activity of natural killer (NK) cells and T cells decrease in late pregnancy compared to the postpartum period, which can increase the susceptibility to viruses (22). During the pregnancy, weakening of cell-mediated immunity by T helper 1 (Th1) cells and dominance of Th2 [resulting in the production of IL-4, IL-10, IL-13, and transforming growth factor β (TGF-β)] make the mother susceptible to intracellular pathogens such as the viruses. In patients with SARS-CoV-2 infection, Th1 cells become more active, causing a dramatic increase in proinflammatory cytokines (IFN-γ, IL-1β, IL-6, and IL-12), resulting in severe lung damage. In COVID-19 patients, a range of immune responses has been proposed and early adaptive immune responses may indicate a milder severity of the disease. It is possible that hormonal changes affecting the immunological response to viruses as well as the physiological transition to Th2 and in result, increased expression of anti-inflammatory cytokines such as IL-4 and IL-10, are the dominant response to SARS-CoV-2 in pregnancy which causes milder disease in pregnant women compared to non-pregnant women (22).

Critical COVID-19 patients develop a condition in which pro-inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor-α (TNF-α) are elevated, resulting in the cytokine storm syndrome, which increases the mortality. Human chorionic gonadotropin and progesterone inhibit the Th1 pro-inflammatory pathway by reducing TNF-α. This modulated immune system can prevent the occurrence of cytokine storm syndrome in pregnant women and reduces morbidity and mortality in them (20).

Clinical manifestations of COVID-19 in pregnancy

Gestational rhinitis caused by estrogen-mediated hyperemia of nasopharyngeal mucosa occurs in about one-fifth of healthy mothers in late pregnancy and can cause nasal congestion and rhinorrhea, which can mask the coryzal symptoms of COVID-19.

Physiological dyspnea due to increased maternal oxygen demand can occur during pregnancy due to increased metabolism, gestational anemia, and fetal oxygen consumption. On the other hand, due to the physiological changes of the respiratory system in pregnancy, the normal function of the lungs in this period is disrupted. Dyspnea is also a very common symptom in COVID-19, and according to what has been mentioned, pregnant women are theoretically more prone to hypoxemic respiratory failure and we should distinguish between physiological and pathological dyspnea.

In studies about COVID-19 in pregnant women, the most common symptoms at the time of diagnosis were fever, cough, dyspnea, diarrhea, sore throat, fatigue, myalgia, and chills, respectively. Other symptoms, which accounted for less than 5% of cases, included nasal congestion, rash, sputum, headache, malaise, and loss of appetite (20). In a study conducted by Cheng et al on nine pregnant women diagnosed with COVID-19 in the third trimester of pregnancy, the clinical manifestations of these patients were not different from those of non-pregnant women (25). Accordingly, in the study of Zhu et al on nine pregnant patients with COVID-19, the clinical symptoms of patients with non-pregnant populations were not different (22).

In SARS and MERS epidemics, more than 35% and 41% of pregnant patients, required mechanical ventilation and their mortality was 18% and 25%, respectively. In contrast, most pregnant patients with COVID-19 were either asymptomatic or showed mild symptoms, with only a few cases requiring hospitalization in the intensive care units and only a few rare cases requiring mechanical ventilation. In the study of Cheng et al, none of the patients required mechanical ventilation, and no deaths were reported (25). Another study of COVID-19 in pregnant women included 55 patients which only one severe case and no death was reported (26). Takemoto et al identified 20 COVID-19-related maternal deaths, age range 20–43 years. Symptoms onset was reported as on pregnancy for 12 cases, postpartum for 3 cases, and during the cesarean section for 1 case. In 16 cases, death occurred in the postpartum period. At least one comorbidity or risk factor was present in 11 cases. Asthma was the most common risk factor . Ten cases occurred in the Northeast region, and nine cases occurred in the Southeast region (27). Therefore, according to these limited studies, the severity of COVID-19 in pregnant women is not different from non-pregnant women, however, it is not yet possible to comment on it with certainty.

Fetal and neonatal complications

Intrauterine transmission is one of the serious consequences of viral infections during pregnancy. Maternal-fetal transmission of most viruses (except herpes viruses) is hematogenous; since the virus from the mother's blood enters the placenta and reaches the chorionic villous tree and fetal blood vessels. According to the studies on the two previous pathogens of the Coronaviridae family, SARS-

CoV, and MERS-CoV, this mechanism of transmission has not been observed in these two viruses. In general, there is no evidence that SARS-CoV and MERS-CoV can be transmitted vertically to the fetus, but studies have shown that maternal infection is associated with intrauterine growth retardation, preterm labor, stillbirth, and perinatal death (27).

So far, there is no conclusive evidence of intrauterine transmission of SARS-CoV-2 virus and only rare cases of transmission from mother to fetus and positive RT-PCR test in an infant in the early hours after birth have been reported (22). In a systematic review of 66 studies in which a total of 1787 mothers-infants were studied, only in 2.8% of cases, the test result was positive (28).

Mullins et al conducted a meta-analysis on COVID-19 infected women during pregnancy and observed that from 32 affected women, none of the newborns died from COVID-19 related issues (29). Recently it was reported that two COVID-19-negative newborns were born from positive mothers in Lombardy. After that, 20 asymptomatic virus-positive newborns have been registered at the National Health Ministry. Various studies reported the birth of healthy newborns, without any problems from mothers with confirmed COVID-19 (17).

Dong et al (30) and Zeng et al (9), both reported the presence of virus-specific IgM antibodies in the neonatal blood of infants of mothers with COVID-19 immediately after birth, whereas reverse transcription polymerase chain reaction of the nasopharyngeal swab of these infants was negative. According to the fact that this IgM is not able to cross the placenta due to its macromolecular structure (22), it seems that this antibody was produced in the fetus in response to the vertical transmission of the virus. However, this claim has not been proven and may even have been due to placental changes that allowed IgM to pass or a false negative test result. It should be noted that there are several reports of SARS-CoV-2 in neonatal nasopharyngeal swabs, but only in very few cases, this finding has been observed. In a study by Penfield et al on 32 pregnant women with COVID-19 about vertical transmission, from each mother one placental swab (from the amniotic surface) and a membrane swab (from between the amnion and the chorion) were taken and evaluated by RT-PCR for SARS-CoV-2 RNA. In this study, SARS-CoV-2 RNA was observed in 11 samples, although the origin of this SARS-CoV-2 RNA was unknown. Then, nasopharyngeal swabs were taken from the infants on days one and five after birth. Only 3 out of 11 infants reported positive results and none were symptomatic (31). Although there were no clinical signs in the neonates in these studies, the results suggest the possibility of intrapartum viral exposure. Even if there is no evidence of vertical transmission of COVID-19 disease, there is still concern about fetal inflammatory response syndrome (FIRS). The mother's response to infection triggers an inflammatory response in the fetus, called the FIRS response, in which levels of inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α in the placenta increase however, there is a lack of culturable microorganisms. These cytokines affect the central nervous system and circulatory system and lead to fetal abnormal morphology (32). FIRS also increases the susceptibility to autism, schizophrenia, neurosensory deficits, and late-stage psychosis (21). Therefore, even if there is no vertical transmission in COVID-19 disease, the disease can cause adverse effects in the fetus.

Maternal respiratory disorder and subsequent hypoxia can lead to the release of vasoconstrictor factors such as endothelin-1 and hypoxia-inducible factor, which results in hypoperfusion of the placenta and reduced oxygen delivery to the fetus, which eventually limits fetal growth (20). Low- birth weight, preterm labor, and postpartum mortality have been reported in cases of SARS-CoV-2 (33). Fetal distress and preterm ruptures of membranes have also been observed in mothers infected with SARS-CoV-2 (33). In one case-control study, it was reported that the frequency of preterm labor in mothers infected with SARS-CoV-2 was higher than in healthy mothers (33). It should be noted that in existing studies on COVID-19 in pregnancy, the infection occurred in the third trimester of pregnancy, so the effect of infection in the first and second trimesters on pregnancy outcome is unclear (20).

Among the limited studies performed in the first trimester of pregnancy, we can mention the study of Cosma et al, which in this study, the cumulative incidence of COVID-19 was compared between 100 pregnant women with spontaneous abortion (case group) and 125 women with ongoing pregnancy (control group) which both groups of women were in the first trimester of pregnancy. The results of this study showed that the cumulative incidence of COVID-19 in the case group was 11% and in the control group was 9.6% and there was no significant difference between the two groups in this regard (P=0.73) (34). Besides in the study of Zhu et al, 12.5% of mothers with severe pneumonia had a spontaneous abortion in the second trimester of pregnancy (22). There is no evidence of the presence of SARS-CoV-2 in genital fluids; but, since the virus can be excreted in the feces, vaginal delivery is expected to be more likely to infect the neonate. Cesarean section is recommended for infected or suspicious mothers. Likewise, delay in umbilical cord clamping and skin to skin contact can increase the risk of transmission of the disease to the neonate, so they should be avoided. There is no conclusive evidence that breastfeeding is contraindicated in COVID-19. Limited studies have shown that the SARS-CoV-2 virus does not appear in breastmilk However, due to the close contact

between mother and baby during breastfeeding, the risk of transmission is high, thereby it is necessary to follow hygienic measures. Finally in terms of infants adverse outcome, including neonatal intensive care unit admission, respiratory disease and preterm birth, recent study by Flaherman et al suggested that there were no significant difference between neonates born from mothers tested positive and negative for SARS-CoV-2 (35).

Conclusion

Taking all this together it is raising an urgent question of the presence of SARS-CoV-2 in the reproductive tract that may result in infertility and may have implications for sexual transmission, miscarriage, embryonic infection, mother-to-child transmission, and congenital diseases. Few studies were investigating the SARS-CoV-2 in the reproductive system of SARS-CoV-2 patients, which have shown conflicting results. However, small sample size, lacking appropriate controls, not including the severe cases, long time intervals between the onset of symptoms and testing, using qualitative RT-PCR instead of quantitative PCR, and insufficient data of semen parameters, complicates the interpretation of the results. Further investigation with longer follow up periods and larger sample sizes will be needed to make a conclusive determination of COVID-19 symptoms on the reproductive tract.

Authors' contribution

Conceptualization: MB and YR.
Methodology: FA and LS.
Validation: FS.
Formal analysis: FRT and MMZ.
Investigation: MMZ.
Data curation: MB and YR.
Writing—original draft preparation: MB and YR.
Writing—review and editing: FRT and MMZ.
Visualization: FA and LS.
Supervision: FA and FS.
Project administration: MMZ.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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