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REVIEW

Potential risks of SARS-CoV-2 infection on reproductive health

BIOGRAPHY

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KEY MESSAGE

The potential pathogenicity of COVID-19 may influence testicular and ovarian function, and sperm and oocyte quality. Contraception is recommended not only during the antiviral treatment, but also after treatment (for not less than 8 months). However, there is no evidence to support the termination of pregnancy without medical indicators.

ABSTRACT

The outbreak of 2019 novel coronavirus disease (COVID-19) has become a major pandemic threat worldwide. Such a public health emergency can greatly impact various aspects of people's health and lives. This paper focuses on its potential risks for reproductive health, including the reproductive system and its functioning, as well as gamete and embryo development, which could be affected by the virus itself, drug treatments, chemical disinfectants and psychological effects related to panic during the COVID-19 outbreak.

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INTRODUCTION

Successful reproduction is fundamental to the continuation of all species. In humans, reproductive health encompasses a range of factors and processes, including physical, mental and social health, and is significant in maintaining the quality and quantity of successive generations. The current pandemic status of the 2019 novel coronavirus disease (COVID-19) and the treatment, prevention and control measures associated with it have caused people considerable worry in terms of the virus itself, the medicines used in treatment, environmental disinfectants, isolation conditions and psychological effects related to panic caused by the public health emergency. All these factors can affect reproductive health. In order to respond to people's concerns over the possible impact of these unprecedented events on reproductive health, this paper reviews the relevant literature regarding the protection of reproductive health overall.

CORONAVIRUS AND THE REPRODUCTIVE SYSTEM

COVID-19 is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), which shares 76% amino acid sequence homology with SARS-CoV and enters into target host cells via the same cellular receptor, angiotensin-converting enzyme 2 (ACE2), and cellular protease, transmembrane protease serine (TMPRSS) (*Lukassen et al., 2020*). In theory, organs with a high expression of ACE2 or TMPRSS2 are more vulnerable to infection. Currently, the respiratory, cardiovascular, digestive and urinary systems have been reported as potential target organs of COVID-19 infection (*Xin Zou, 2020*). Single-cell RNA sequencing raw sequencing data and results of immunohistochemistry have indicated that there is high expression of ACE2 in the testis (*Fan et al., 2020*, *Wang and Xu, 2020*), but there are no published data on expression of ACE2 in the female reproductive system. The potential risk of COVID-19 infection for fertility should thus be given more attention.

Male reproductive system

Wang and Xu (*Wang and Xu, 2020*) investigated the expression pattern of ACE2 and TMPRSS2 in adult male testis at the level of single-cell transcriptomes. The results indicated that ACE2 was predominantly enriched in spermatogonia, Leydig cells and Sertoli cells, while TMPRSS2 was expressed only in spermatogonia and spermatids. Gene ontology analysis showed that genes associated with viral reproduction and transmission were highly enriched in ACE2-positive spermatogonia, while the genes associated with male gamete generation were down-regulated. Intercellular junction and immune-related genes were increased in ACE2-positive Leydig and Sertoli cells, but genes related to mitochondria and reproduction were decreased. In addition, Fan and colleagues (*Fan et al., 2020*) found that ACE2 was highly expressed in renal tubular cells, Leydig cells and cells in the seminiferous ducts of the testis.

Xu and co-workers reported that orchitis was a complication of SARS and further indicated that the reproductive function should be followed and evaluated in recovered male SARS patients (*Xu et al., 2006*). Recently, Pan and colleagues reported that SARS-CoV-2 was not detected in the semen of males recovering from COVID-19, and ACE2-mediated viral entry of SARS-CoV-2 into target host cells was unlikely to occur within the human testicle based on the sparse expression of ACE2 and TMPRSS2; however, this study cannot definitively rule out the presence of SARS-CoV-2 in the seminal fluid during an acute infection with severe COVID-19 symptoms (*Pan et al., 2020*). We thus propose that clinicians should pay attention to assessment of and appropriate intervention in young patients' fertility, including sperm analysis and sperm cryopreservation in the early stage of disease, and follow-up of reproductive function in the following months.

Female reproductive system

To date, damage to the female reproductive system in COVID-19 patients has not been reported. There is evidence that the renin–angiotensin (Ang)–aldosterone system (RAS) is involved in female reproductive processes such as folliculogenesis, steroidogenesis, oocyte maturation and ovulation. Reis and colleagues (*Reis et al., 2011*) confirmed the existence of an Ang-(1–7)–Mas receptor–ACE2 axis and ACE2 markers in all stages of follicle maturation in the human ovary. ACE2 was also expressed in the endometrium, to a greater extent in epithelial cells than stromal cells, and moreover, the expression of ACE2 changed with the menstrual cycle, being more abundant in the secretory phase than the proliferative phase; this could interfere with the local Ang-II homeostasis and regulate endometrial regeneration (*Vaz-Silva et al., 2009*). In addition, previous studies have shown that ACE2 is expressed in bovine and rat ovarian granulosa cells, regulated by gonadotrophins, and is involved in follicular development (*Barreta et al., 2013*; *Pereira et al., 2009*).

Based on previous research, it is thus possible to suggest ways in which SARS-CoV-2 might affect female fertility: (i) SARS-CoV-2 might attack ovarian tissue and granulosa cells, and decrease ovarian function and oocyte quality, leading to female infertility or miscarriage; and (ii) SARS-CoV-2 might damage endometrial epithelial cells and affect early embryo implantation. However, there is still a lack of evidence on the effect of SARS-CoV-2 on the Fallopian tube, which should be paid greater attention in the future.

Early pregnancy

Recently, Chen and colleagues reported that there was currently no evidence for a vertical transmission of SARS-CoV-2 in the third trimester (*Chen et al., 2020*). However, the effect of SARS-CoV-2 on early pregnancy is still unknown. An individual participant data meta-analysis showed that pregnancy was a risk factor for severe influenza infection (*Mertz et al., 2019*), and influenza vaccination reduces the risk of mild to moderately severe lung clearance index disease during pregnancy (*Thompson et al., 2019*).

Furthermore, limited information associated with SARS might provide insights into the effects of COVID-19 during pregnancy. SARS during pregnancy could be associated with a high incidence of adverse maternal and neonatal complications, such as spontaneous miscarriage, preterm delivery, intrauterine growth restriction and disseminated intravascular coagulopathy. Wong and co-workers reported that, of seven women infected with SARS in the first trimester, four had a spontaneous abortion (*Wong et al., 2004*). During early pregnancy, human placental RAS was shown to be up-regulated and to play an important role in placental vascular development

(Pringle et al., 2011). Another study reported a high level of ACE2 mRNA in the placenta in early pregnancy, located in syncytiotrophoblasts and villous stroma; in addition, ACE2 regulated the release of Ang-1–7, which was beneficial for vasodilation in the maternal–fetal circulation and favourable for virus spread (la Pena et al., 2018). Zheng and colleagues analysed the mRNA expression profile and found that ACE2 had a very low expression in the different cell types (syncytiotrophoblast cells, decidual stromal cells and epithelial glandular cells) at the maternal–fetal interface, except for a slightly raised expression in the decidual perivascular cells cluster 1 (Zheng QL, 2020).

For the current study, the following potential effects of COVID-19 on early pregnancy were assumed. First, owing to the lack of 'susceptible cells' at the interface between mother and infant in early pregnancy, the rate of mother to infant transmission might be very low. Second, SARS-CoV-2 might change the expression of ACE2 at the interface between mother and infant in early pregnancy, leading to pregnancy loss.

DRUGS, DISINFECTANTS AND REPRODUCTIVE SYSTEMS

Drugs for the treatment of COVID-19 mainly include antiviral drugs (such as interferon, ribavirin and lopinavir/ritonavir), antibiotics (e.g. moxifloxacin and azithromycin) and steroidal drugs such as glucocorticoids. In addition, in order to stop the spread of the virus, large-scale disinfection has been carried out in medical institutions including hospitals, centralized isolation points, the homes of infected people's families, the homes of those in close contact with infected individuals or their families, communities, key units (including supermarkets and hotels), bazaars, public toilets, garbage transfer stations and many more. This section focuses on the effects of first-line drugs and disinfectants currently used to combat COVID-19 on reproductive health.

Antiviral drugs

According to the latest Coronavirus Pneumonia Diagnosis and Treatment Program (Sixth Edition) (thereafter referred to as the 'Sixth Edition') issued by the National Health Commission of China, interferon-alpha, and ribavirin (combined with interferon or lopinavir/ritonavir), Arbidol (umifenovir) and chloroquine phosphate have been recommended for use.

Ribavirin is a broad-spectrum antiviral drug. Animal experiments reported that ingestion of ribavirin decreased testosterone concentrations and impaired spermatogenesis (Almasry et al., 2017), and caused sperm abnormalities in rats (Narayana et al., 2002b). However, this toxic effect was reversible (Narayana et al., 2002a; Narayana et al., 2005). Clinical studies have shown that ribavirin combined with interferon treatment could affect male fertility, manifested through a decrease in sperm count (Bukhari et al., 2018; Drobnis and Nangia, 2017). Pharmacokinetic studies showed that the concentration of the drug in seminal plasma during serum antiviral therapy was twice that in serum, so contraception was strongly recommended during the medication period (Hofer et al., 2010). Moreover, ribavirin was able to cause sperm DNA fragmentation for up to 8 months (Pecou et al., 2009), so contraception was also recommended for a period after cessation of antiviral treatment.

There have been relatively few studies on the effects of ribavirin on the female reproductive system, but a clinical case was reported that involved a 36-year-old woman injected with ribavirin intramuscularly due to a suspected SARS infection during the first trimester of pregnancy, whose baby girl showed normal development at 8 months post-partum (Rezvani and Koren, 2006).

Lopinavir/ritonavir has been recommended for pregnant women with HIV infection to reduce HIV transmission, and no increase in the risk of birth defects has been observed (U.S. Department of Health and Human Services, 2019). In males, however, lopinavir/ritonavir has been reported to impair spermatogenesis in rats, possibly by oxidative damage (Adaramoye et al., 2015). Chloroquine phosphate has also been shown to impair spermatogenesis and epididymal function in male rats (Adeeko and Dada, 1998; Asuquo et al., 2007). To date, no studies have explored the impact of Arbidol on the reproductive system.

Glucocorticoids

Glucocorticoids can expand the interstitial space of the spermatogenic epithelium, destroy cell connections and affect the blood–testis barrier, thus allowing harmful substances to enter testicular tissue. Glucocorticoids can also cause germ cell apoptosis through receptors on germ cells. There is currently no literature demonstrating the effect of glucocorticoids on follicular development. It is recommended that glucocorticoids are only used for a short time in COVID-19 patients with progressive deterioration of oxygenation indicators, rapid progress on imaging manifestations and excessive activation of inflammatory reactions in the body. Small doses over a short period have minimal impact on the reproductive system.

Antibiotics

Inappropriate use of antimicrobial agents, especially the combination of broad-spectrum antimicrobials, should be avoided, although most antibiotics, especially the new generation of drugs, are highly specific and cause less damage to the human reproductive system.

Chemical disinfectants

At present, the commonly used chemical disinfectants can be divided into the following eight types: alcohol disinfectants, chlorine disinfectants, biguanide and quaternary ammonium disinfectants, iodine disinfectants, aldehyde disinfectants, phenol disinfectants, peroxide disinfectants and ethylene oxide. Alcohol 75% is the most used and safest disinfectant in medical institutions. However, compared with quaternary ammonium disinfectants, 75% alcohol would result in significantly higher levels of volatile organic compounds in IVF laboratories, which could increase the risk of egg fertilization failure, induce embryonic retardation and reduce developmental potential, leading to adverse outcomes of IVF (Brown, 1999). However, no alcohol is contained in the disinfectants currently used in IVF laboratories.

Chlorine disinfectants are widely used. This kind of disinfectant has been shown to increase abnormalities in sperm heads in mice (Meier et al., 1985). Peroxyacetic acid, also known as acetic acid, has a wide range of antibacterial activities in both its gaseous form and in solution. Studies have reported that zebrafish embryos exposed to 0.75 mg/l peracetic acid for 2–4 h after fertilization had an average mortality rate of 89.6 ± 3.4%, and there was a positive correlation between the peracetic acid concentration and embryo mortality (Marchand et al., 2013).

Phenolic disinfectants are mainly used for to disinfect livestock buildings, cages, sites and vehicles. A large number of animal experiments have demonstrated that phenolic disinfectants can lead to embryonic developmental deformities and even result in fetal arrest (El-Dakhly et al., 2018; Ton et al., 2012). Iodine-containing disinfectants include iodine tincture and povidone-iodine, the most important component of iodine-containing disinfectants being the iodine. Excessive intake of iodine may, however, lead to a decrease in sperm density (Sakamoto et al., 2004).

EMERGENT PANIC PSYCHOLOGY AND REPRODUCTIVE HEALTH

Previous studies have shown that the outbreak of emerging infectious diseases (such as SARS, Middle East respiratory syndrome [MERS] and H1N1 virus) was associated with psychological effects related to panic among patients, health workers and the public, including depression, anxiety, fear and post-traumatic stress disorder (PTSD) (Blendon et al., 2004; Hawryluck et al., 2004; Liao et al., 2014; Park et al., 2018; Wang et al., 2011; Wu et al., 2009). When confronted with the stressor of such an emergent crisis as the COVID-19 outbreak, people's risk perception and psychological distress can be aroused to high levels and lead to irrational nervousness or fear (Shi et al., 2003; Sim and Chua, 2004).

The consequence of this is an immediate disruption of the body's homeostasis and activation of the central stress response system (primarily regulated via the hypothalamic–pituitary–adrenal [HPA] axis). Although the acute HPA response to stressors is a self-protective mechanism, constant activation of the HPA axis by chronic or traumatic stressors may result in dysregulation of the HPA axis, which can inhibit the body's reproductive function, alter fetal development and hence lead to poor reproductive outcomes (Joseph and Whirledge, 2017). Furthermore, there are sex differences in the regulation of stress response, mainly due to the interaction between the HPA axis and the hypothalamic–pituitary–gonadal axis; such interactions could lead to abnormalities of stress responses, and the latter could in turn affect the former and thereby exacerbate psychological disorders (Oyola and Handa, 2017). Therefore, there are many complex mechanisms in the interactions between stressors and psychological disorders, and it is necessary to pay special attention to the impacts of panic psychology on human reproductive health during this current outbreak of COVID-19.

Male patients

There is growing evidence on the association between psychological disorders and poor male fertility. Female partners of men with psychological disorders (e.g. major depression) were less likely to achieve conception than those of men without psychological disorders (Evans-Hoeker et al., 2018). Poor fertility performance during a period of psychological crisis can be linked to decreased sperm quality and induced sexual dysfunction. Stress and negative moods (e.g. depression and anxiety) are able to influence detected seminal parameters at both macroscopic and cellular/subcellular levels, including a lower total sperm count, lower sperm concentration, lower semen volume and increased sperm DNA fragmentation (Gürhan et al., 2009; Vellani et al., 2013; Zou et al., 2018).

Activation of the HPA axis and subsequent alternations in hormone concentrations plays a critical moderating role between psychological disorders and poor sperm quality. For example, Eskiocak and colleagues indicated that psychological stress can lead to an increase in nitric oxide concentration and a decrease in arginase activity in the L-arginine–nitric oxide pathway (Eskiocak et al., 2006). In addition, Wdowiak and co-workers concluded that depression and anxiety among subfertile men are associated with a lower secretion of sex hormone-binding globulin and dehydroepiandrosterone sulphate, and a higher secretion of cortisol and prolactin (Wdowiak et al., 2017).

As well as poor sperm quality, the other important cause of the poor fertility performance among men with psychological disorders is sexual dysfunction, including, among others, less sexual activity, hypoactive sexual desire and erectile difficulties. For instance, Yehuda and co-workers established a model of sexual dysfunction in PTSD that was underpinned by an inability to regulate and redirect the physiological arousal needed for healthy sexual function (Yehuda et al., 2015). Likewise, other negative moods, such as depression, anxiety and fear, have been proved to be related to sexual dysfunction (Brotto et al., 2016).

Female patients

As for men, stress and psychological disorders also lead to both direct and indirect impacts on the female reproductive system. Through activation of the HPA axis, a close association between stress and women's reproductive function can be highlighted by a bodily stress response and hormone involvement. This association seems more likely to be reported in infertile rather than fertile women, although there are gaps in the evidence on a precise cause and effect relationship because of conflicting results and a lack of objective evaluation indicators (Palomba et al., 2018). Based on the theory and on previous studies, Prasad and colleagues also established a pathway of how stress affects the biology of female reproduction: stress leads to increased levels of reactive oxygen species (ROS) in the ovaries, and further accumulation of ROS beyond physiological level leads to oxidative stress, which reduces the growth and development of follicles and induces apoptosis of oocytes, finally leading to poor reproductive outcomes (Prasad et al., 2016).

If the psychological effects related to panic during the COVID-19 pandemic develop into chronic or traumatic dysfunction in a woman, this could have negative impacts on oocyte quality and reproductive outcomes. For example, an internet-based preconception cohort study conducted in the USA and Canada reported an association between severe depressive symptoms in women and a greater prevalence of irregular menstrual cycles, as well as decreased fecundability (compared with no or low depressive symptoms: prevalence ratio 1.80, 95% confidence interval [CI] 1.48–2.19; fecundability ratio 0.62, 95% CI 0.43–0.91, respectively) (Nillni et al., 2016, Nillni et al., 2018). Another example is that many markers for stress and anxiety (such as adrenaline, noradrenaline, adrenocorticotrophic hormone, natural killer cell levels and cardiovascular reaction to provoked stress) have been proved to be relevant in terms of lower pregnancy rates in IVF cycles (Campagne, 2006). Therefore, it can be concluded that stress and psychological disorders can impact oocyte quality and reproductive outcomes via complicated physiological mechanisms.

Furthermore, similar to their male partners, women with stress and psychological disorders are also troubled with sexual dysfunction. Increasing amounts of evidence show that women with negative moods and PTSD are more likely to experience sexual dysfunction (Brotto et al., 2016; McCabe et al., 2016; Yehuda et al., 2015). Therefore, sexual dysfunction may be a common symptom, although not specific, and more attention should be paid to it among both men and women showing psychological effects from the panic.

Early pregnancy

Panic psychology during early pregnancy may impact embryonic development and then lead to adverse maternal and fetal outcomes. Early pregnancy is a special period that is susceptible to neuroendocrine and immune dysregulation, which is common during the body's stress response and also primarily regulated by the HPA axis (Parker and Douglas, 2010). Neuroendocrine and immunological changes play a critical mediating role between stress exposures and risk in early pregnancy (e.g. pregnancy loss), by affecting arterial formation, placental development and uterine–fetal interactions (Frazier et al., 2018).

In addition to carrying an early risk for pregnancy in the short term, psychological stress also can lead to long-term impacts on pregnant women and their offspring. For instance, D'Souza and colleagues showed an association between increased oxidative stress during early pregnancy and the development of pre-eclampsia (D'Souza et al., 2016). From reviewing both human and animal studies, Hantsoo and co-workers proposed that inflammation is a mediator between maternal stress and neuropsychiatric risk in the offspring (Hantsoo et al., 2019).

As well as these pathological mechanisms and outcomes of panic psychology during early pregnancy, pregnancy termination without medical indicators is another tragic consequence of the panic, especially among pregnant women in the first trimester. During an outbreak of infectious diseases, some pregnant women may make a choice of pregnancy termination, especially in early pregnancy, because of excessive worries and fears of either known or unknown risks to themselves or their offspring (Meaney-Delman et al., 2017; Wong et al., 2004). Evidence has shown that pregnant women with severe depression have a higher risk perception of teratogenic risk and a higher rate of likelihood to terminate the pregnancy (Walfisch et al., 2011). Therefore, it is necessary to provide pregnant women with timely and reliable information and mental counselling, aiming to prevent unnecessary fears and avoid an overload of stress.

CONCLUSION

The pandemic of COVID-19 is rapidly spreading all over the world. As of 13 April 2020, there were over 1.7 million confirmed cases of COVID-19 globally, and the total number of deaths from this disease had surpassed 100,000 (World Health Organization, 2020). Many clinicians and members of the public are very concerned about its impact on reproductive health. Based on the limited evidence so far, it can be suggested that the potential pathogenicity and attack of COVID-19 on testicular tissues, ovarian tissue and granulosa cells might affect testicular and ovarian function, spermatozoa, oocyte quality and pregnancy outcomes. Attention should therefore be paid to assessment of and appropriate intervention in the fertility of young couples during and even after this pandemic, especially for those infected SARS-CoV-2.

The potential risk of SARS-CoV-2 infection on fertility should be paid more attention. Massive pneumonia and its treatment in the mother or father is likely to influence embryonic development and fetal health, and endangers the safety of the pregnancy. It is strongly suggested that contraception must be emphasized during the antiviral treatment of COVID-19, and continued for a period of time after treatment. There is no evidence to suggest that termination of pregnancy is required for patients in early pregnancy. At present, the main disinfectants used during prevention and control of the infection are 75% alcohol and chlorine disinfectants, which are both used at safe concentrations and will not cause damage to reproductive system, gametes and zygotes. During the COVID-19 outbreak, and especially for those with COVID-19, couples should be provided with reliable information and psychological consultation in time to avoid irrational fear and excessive stress.

The COVID-19 emergency also calls for an urgent demand for specific procedures and measures to be taken in assisted reproductive technology (ART) centres. In line with practical experience from ART centres in China, several recommendations should be paid more serious attention. First, adequate personal protective equipment should be provided for medical staff. Second, hygiene and disinfection should be strengthened in care settings, and procedures and physical spaces rearranged to avoid crowding and constraints on space, in order to reduce the risk of nosocomial infection. Third, all patients should be screened on arrival, including for epidemiological history, routine temperature measurement and enquiry into common COVID-19 symptoms. Fourth, counselling and follow-up should if possible be provided online to avoid unnecessary visits to care settings during the pandemic. Fifth, rapid training mechanisms should be initiated for key response capacities, including diagnosis, triage, clinical management and essential prevention and control of infection. Finally, health education for patients should promote basic infection prevention measures, such as hand hygiene, respiratory etiquette (e.g. wearing masks when talking face to face with others, and never sneezing at others) and physical distancing, as well as maintaining a healthy lifestyle during the pandemic.

Previous studies have indicated that the new coronavirus might have a potential impact on the reproductive system of both sexes, mainly due to changes in the use of drugs and in the environment. Medical professionals should make comprehensive assessments based on fertility needs and disease conditions, so as to give reasonable guidance and advice on fertility. At the same time, further study is needed to evaluate the long-term effects of SARS-CoV-2 infection (in men, women or both) on human fertility, pregnancy outcomes and the growth and development of the offspring, so as to accumulate more evidence on the reproductive effects of similar diseases.

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