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Impact of COVID-19 and other viruses on reproductive health

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Abstract

Male infertility is linked to some viral infections including human papillomavirus (HPV), herpes simplex viruses (HSV) and human immunodeficiency viruses (HIVs). Almost nothing is known about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) effect on fertility. The possible risk factors of coronavirus disease 2019 (COVID-19) infection on fertility comes from the abundance of angiotensin-Converting Enzyme-2 (ACE2), receptor entry of the virus, on testes, a reduction in important sex hormone ratios and COVID-19-associated fever. Recent studies have shown a gender difference for COVID-19 rates and comorbidity. In this review, we will discuss the potential effect of COVID-19 on male fertility and talk about what needs to be done by the scientific community to tackle our limited understanding of the disease. On the other side, we will focus on what is known so far about the risk of COVID-19 on pregnancy, neonatal health and the vertical transfer of the virus between mothers and their neonates. Finally, because reproduction is a human right and infertility is considered a health disease, we will discuss how assisted reproductive clinics can cope with the pandemic and what guidelines they should follow to minimise the risk of viral transmission.

KEYWORDS

assisted reproductive technologies, COVID-19, infertility, reproduction, SARS-CoV-2

1 | INTRODUCTION

In December 2019, a severe respiratory disease was first appeared in Wuhan, China and has now spread to many countries and affected many people around the world (WHO, 2020). This pandemic disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) and was found to be caused by a novel virus belongs to the family *Coronaviridea* (WHO, 2020; Zhou et al., 2020). Because of the high homology with the Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV), the novel virus was named as Severe Acute Respiratory Syndrome Corona Virus-2 SARS-CoV-2 (Zhu, Zhang, et al., 2020).

Coronaviruses have caused large health epidemics in the past, as SARS-CoV caused a health epidemic in 2003, and another large-pandemic outbreak caused by the Middle-East Respiratory Syndrome CoronaVirus (MERS-CoV) in 2012 (reviewed in Di Mascio et al., 2020). SARS-CoV and SARS-CoV-2 recognise the same human cell receptor; angiotensin-converting enzyme 2 (ACE2), while MERS-CoV binds to a different receptor called dipeptidyl peptidase 4 DPP4 (Petrosillo, Viceconte, Ergonul, Ippolito, & Petersen, 2020).

COVID-19 transmits from human to human through direct contact and through small droplets arrived from the infected people (Zhang et al., 2020). As of Sunday, 7 June 2020, around seven million people have had confirmed COVID-19 cases and around four hundred thousand people have died in more than 180 countries around the world, and the numbers keep rising dramatically everyday (https://coronavirus.jhu.edu/map.html; Romanov, 2020).

COVID-19 affects the respiratory system, and people with COVID-19 present some symptoms in the beginning of the illness including dry cough, fatigue, fever, breathing difficulties and

muscle pain, and these symptoms may develop to pneumonia, loss of taste and smell, diarrhoea and lymphopenia (Adhikari et al., 2020; Hoffmann et al., 2020; Rico-Mesa, White, & Anderson, 2020).

As the virus enters the host cell by binding to ACE2 receptor, it is predicted that cells expressing ACE2 receptor in different tissues and organs have the risk being affected (Zou et al., 2020). ACE2 receptor is expressed in many tissues and organs including lungs, intestine, kidney, testis and many others (Fan, Li, Ding, Lu, & Wang, 2020; Zou et al., 2020).

An important and interesting topic that emerges in COVID-19 time is the ability of the virus to affect males and females' reproductive abilities and whether pregnant women with COVID-19 are at increased risk of fatality or comorbidity. We will also review the effect of other known viruses such as human papillomavirus,

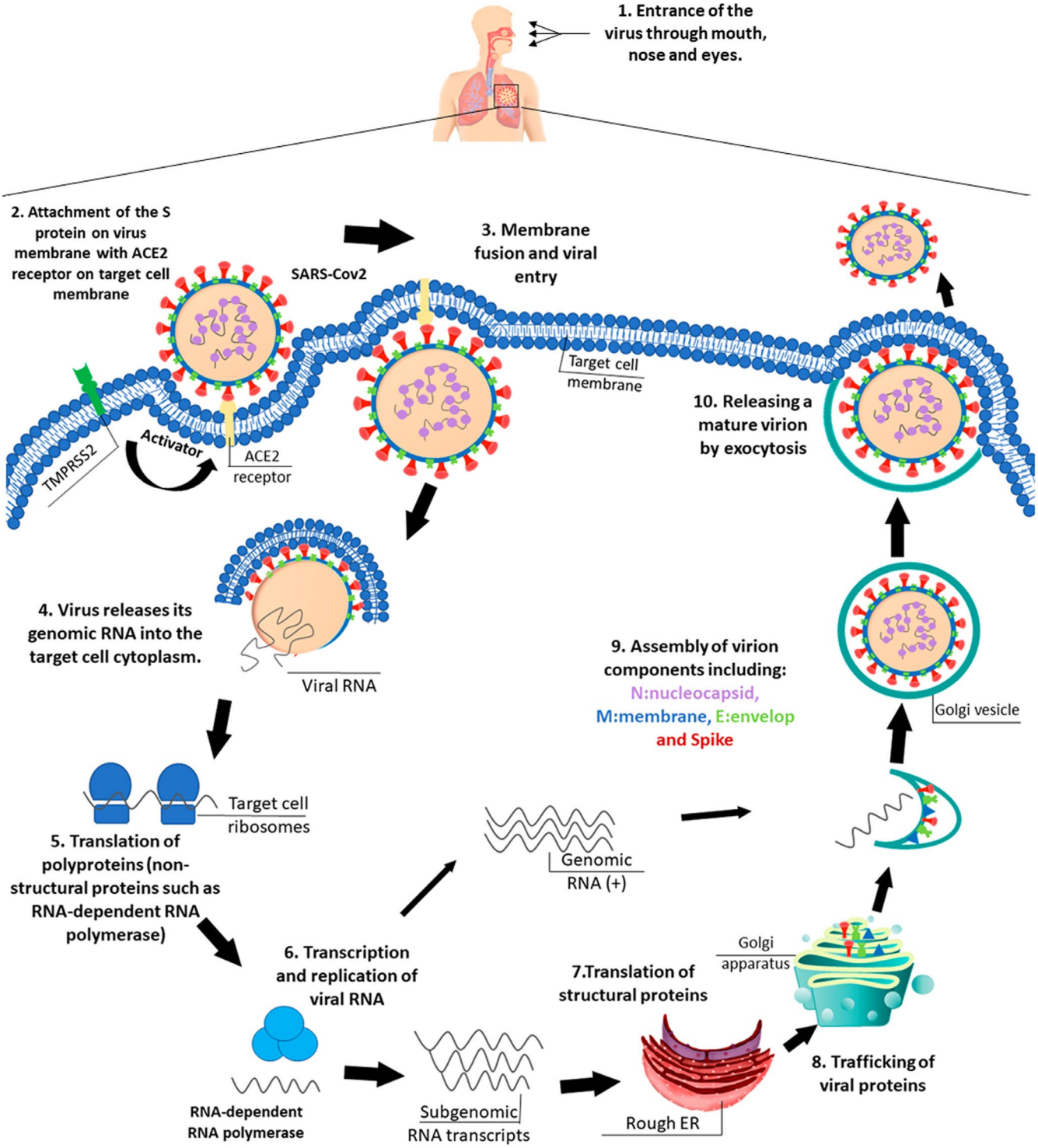

FIGURE 1 Infection cycle of SARS-CoV2. Please refer to the text for more description [Colour figure can be viewed at wileyonlinelibrary.com]

Herpes simplex viruses, hepatitis B and C viruses among others. Other interesting question is the virus ability to be transmitted vertically from the mothers to their neonates or vice versa. Finally, how Assisted Reproductive Technology (ART) clinics will manage their operations and what guidelines and recommendations to follow.

2 | MECHANISM OF INFECTION

Virus entry begins when the virus surface enzyme called Spike (S) glycoprotein binds to the angiotensin-converting enzyme 2 (ACE2) located on the host cell membrane (Hoffmann et al., 2020; Wang et al., 2020). S protein contains two different domain regions: S1 and S2, each one has its own role in virus entry. S1 domain is the part that binds directly to the host ACE2 receptor while the S2 domain helps the virus to fuse with the target cell membrane using its functional elements (Glowacka et al., 2011; Hoffmann et al., 2020). This process is also mediated by a Transmembrane Serine Protease 2 (TMPRSS2) located on the surface of the target cell membrane used for the priming of the S protein causing the virus entry (Hoffmann et al., 2020; Shen, Mao, Wu, Tanaka, & Zhang, 2017; Wang et al., 2020).

When the fusion of the virus with the target cell membrane occurs, the virus releases its genome and using the host cell organelles to replicates its RNA and releases new mature virion to target other cells (Boopathi, Poma, & Kolandaivel, 2020; Jiang, Hillyer, & Du, 2020) Figure 1.

3 | COMMON VIRUSES LINKED TO MALE INFERTILITY

Viral Infection is accepted as a possible cause of male infertility. The association between viral infection and infertility has been reported in many studies. In this section, we focus on common human viruses and their impact on male fertility.

3.1 | Human papillomavirus (HPV) and its impact on male fertility

Human papillomavirus (HPV) is a non-enveloped DNA virus and sexually transmitted worldwide. In some cases, it causes either warts or precancerous lesions (Ljubojevic & Skerlev, 2014). More than 170 HPV types have been identified and completely sequenced (Chouhy, Bolatti, Pérez, & Giri, 2013). Recent studies suggest that HPV infection affects male fertility. In cases of idiopathic asthenozoospermia, HPV DNA was observed in the sperm cells of infertile patients (Foresta et al., 2010; Lee, Huang, King, & Chan, 2002) confirming its role of infertility. Strong association between HPV infection and impairment of sperm parameters, especially a reduction in sperm motility and concentration, was observed in HPV-infected men (Garolla et al., 2012; Jeršovienė, Gudlevičienė, Rimienė, & Butkauskas, 2019). Garolla and coworkers (Garolla et al., 2012) reported that HPV can bind to the head of a spermatozoon and impair sperm motility in men. Certain sperm DNA exons undergo apoptotic fragmentation on HPV-infected men suggesting that HPV types degrade different exons of important genes (Lee et al., 2002). Collectively, these evidences suggest that HPV plays a role in male factor infertility.

3.2 | Herpes simplex viruses (HSVs) and their impact on male fertility

Herpes simplex viruses (HSVs) are enveloped DNA viruses of the family *Herpesviridae*. HSVs include two distinct viruses HSV-1 and HSV-2 (Whitley & Roizman, 2017). HSVs are sexually transmitted and targets reproductive system. HSV-1 causes oral and, occasionally, genital sores while HSV-2 is common cause of genital herpes which may lead to infertility problems in both males and females. HSV DNA was detected in semen from about 50% asymptomatic infertile males (Amirjannati et al., 2014; Bezold et al., 2007; Monavari et al., 2013; Neofytou, Sourvinos, Asmarianaki, Spandidos, & Makrigiannakis, 2009). A strong association of HSV infection and low sperm count, poor motility, and increased apoptotic cells were reported (Monavari et al., 2013). Haematospermia and a lower seminal volume and abnormal viscosity were found in HSV-2-infected males which indicate prostate dysfunction (Kurscheidt et al., 2018). Bezold et al. (2007) reported significantly reduced sperm concentration and motility as well as reduced citrate concentrations and neutral α-glucosidase in HSV-infected males, suggested impaired epididymal and prostate function.

3.3 | Human immunodeficiency viruses (HIV) and their impact on male fertility

Human immunodeficiency viruses (HIV) are two enveloped RNA viruses of the family *Retroviridae*. HIV infects cells in the human immune system mainly, T helper lymphocytes (specifically $CD4^+$ T cells) leading to their depletion and with time acquired immunodeficiency syndrome AIDS (Weiss, 1993). Several studies have assessed the association between HIV infection and characteristics of semen in HIV-positive males. HIV-RNA and HIV-DNA were detected in different semen components (Dulioust et al., 2002). Ejaculate volumes and sperm counts were significantly reduced in HIV-positive males (Dulioust et al., 2002; Muller, Coombs, & Krieger, 2009). More than 33% of HIV-infected men showed reduced rapid (a type) sperm motility and an increased slow (b type) motility (Dulioust et al., 2002). With the progression of disease, Dondero et al. (1996) found that normal sperm morphology and motility were reduced in HIV-positive men. Low sperm counts, abnormal morphologies and high percentage of spermatozoon with DNA damage, indicating impairment of spermatogenesis, were observed in HIV-positive men (Dulioust et al., 2002). The previous finding was supported by the results of Nicopoullos et al. (Nicopoullos, Almeida, Vourliotis, & Gilling-Smith, 2011) which

demonstrated a significant negative correlation between $CD4^+$ T cells and the sperm count, motility and morphology. All of these studies suggest that male fertility was reduced with the progression of disease and more research are needed to address the unanswered questions regarding the mechanisms that lie behind the reduction of fertility parameters in HIV-positive males.

3.4 | Hepatitis B virus (HBV) and its impact on male fertility

Hepatitis B virus (HBV) is a double-stranded DNA virus of the family *Hepadnaviridae*. It is one of the most common life-threatening viruses of human beings. HBV causes hepatic inflammation and severe liver diseases in patients. Impaired sperm motility (Oger et al., 2011), low sperm counts, poor morphology and instability of sperm chromosomes were reported in HBV-infected men (Huang et al., 2003; Lorusso et al., n.d.; Zhou et al., 2009). Su and coworkers (Su et al., 2014) found that the incidence of infertility in HBV-infected men was 1.59 times higher than those who were not infected. It was found that the viral genome integrates into the sperm chromosome as visualised by FISH (Huang et al., 2003). After HBV infection, this viral DNA integration leads to higher frequency of chromosomal aberrations (Huang et al., 2003). In dose-dependent manner, incubation of sperm cells with hepatitis B virus S protein (HBs) leads to a significant reduction of sperm motility (Zhou et al., 2009).

High level of reactive oxygen species was observed in sperm cells after exposure to HBs (Kang et al., 2012). It was suggested that HBs induces reactive oxygen species generation, lipid peroxidation, activation of caspases and DNA fragmentation in sperm cells resulting in apoptosis and sperm dysfunction (Kang et al., 2012).

3.5 | Hepatitis C virus (HCV) and its impact on male fertility

Hepatitis C virus (HCV) is an enveloped RNA virus of the family *Flaviviridae*. Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide (Choo et al., 1989). Several studies reported the effect of HCV on semen parameters. Lower sperm counts, abnormal morphology, reduced motility and decreased sperm lifetime were observed in HCV-seropositive men (Hofny et al., 2011; Karamolahi et al., 2019; Lorusso et al., n.d.). Poor sperm quality and decreased sperm liquefaction time were observed in HCV-infected men compared with non-infected group (Karamolahi et al., 2019).

3.6 | *Mumps orthorubulavirus* virus (MuV) and its impact on male fertility

Mumps orthorubulavirus virus (MuV) is an RNA virus of the family *Paramyxoviridae*. MuV is the causative agent of mumps which commonly leads to fever and parotitis (Kanda et al., 2014). Mumps is a risk factor for male infertility because in most cases, it is associated with orchitis (Bjorvatn, 1973). Within the first few days of infection, MuV attacks testes leading to testicular parenchymal inflammation and destruction (Bjorvatn, 1973), separation of seminiferous tubules (Masarani, Wazait, & Dinneen, 2006) and reduction of androgen production (Aiman, Brenner, & Macdonald, 1980). Up to 30% of male adolescent mumps cases develop orchitis which lead to a degree of testicular atrophy in more than third of the cases (Otto et al., 2010).

4 | POTENTIAL EFFECT OF SARS-CoV-2 ON MALE FERTILITY

The concern show that SARS-CoV-2 may affect male reproductive organ and thus results in male infertility stems from several observations. Early studies both in China and Italy showed that males are more susceptible to COVID-19 compared to females (Guan et al., 2020; Livingston & Bucher, 2020). A recent large cohort observational study from United Kingdom featuring around 20 thousands COVID-19 patients reported that males represented 60% of cases and considered the male sex as one of the risk factors for COVID-19 (Docherty et al., 2020). More alarming is the result of a new systematic review—included 48 recently published articles and 16 databases—where it found that men are more likely to suffer or to die from the complications of COVID-19 compared to women (Serge, Vandromme, & Charlotte, 2020). Large proportion of these vulnerable males is in their childbearing age, and thus their reproductive ability can be affected. Finally, like influenza, COVID-19 patients suffer from fever, which may affect sperm production. It was reported that febrile illnesses had an impact on semen parameters (Sergerie, Mieusset, Croute, Daudin, & Bujan, 2007). Total sperm count and motility percentage were reduced significantly at days 15, 37 after fever episode before going back to normal after several weeks (Sergerie et al., 2007). Increase of sperm DNA fragmentation index and alteration in the nuclear protein composition of ejaculated spermatozoon were reported after fever episode (Evenson, Jost, Corzett, & Balhorn, 2000).

Different viruses use different routes to enter into the host cells. SARS-CoV-2 uses the same ACE2 receptor used by its cousin, the SARS-CoV virus, with the help of TMPRSS2 (see **Figure 1**). Single cell expression analysis has detected the expression of ACE2 RNA not only in the lung epithelial cells, but also in several other organs, among them are the kidneys and the bladder (Fan et al., 2020; Lin et al., 2020; Tipnis et al., 2000). Protein expression analysis also confirmed the presence of ACE2 protein in multiple tissues (Hamming et al., 2004). Interestingly, the highest expression of ACE2 was found in the testes (Fan et al., 2020). The high expression of the ACE2 receptor in the testes raises a concern that the SARS-CoV-2 has the route to enter some if not all testicular cells and thus could cause damage.

To further analyse the types of testicular cells vulnerable for SARS-CoV viruses, Wang et al. studied single-celled ACE2

expression in the human testes (Wang & Xu, 2020). They found that ACE2 is mainly expressed in spermatogonia, leyding and Sertoli cell, while spermatocytes and spermatids had very low expression (Wang & Xu, 2020). Interestingly, TMPRSS2 expression is similar to ACE2, where TMPRSS2 was also enriched in spermatogonia and spermatids. It has been also shown that ACE2 positive spermatogonia cells express genes that are important for virus reproduction and transmission, while ACE2 positive leyding and Sertoli cells express genes that are required for cell–cell junctions and immunity. Collectively, these results highlight the risk of COVID-19 on testicular cells and on the spermatogenesis process.

The only direct evidence for the effect of COVID-19 on male reproductive function comes from a study where sex hormones namely testosterone (T), luteinising hormone (LH) and follicle-stimulating hormone (FSH) among others were compared between COVID-19 patients and healthy controls. While the T level was not different between the two groups, the ratio of T to LH and the ratio of FSH to LH were significantly decreased in COVID-19 patients (Ma et al., 2020). This might be the first direct evidence for the influence of COVID-19 on testicles' ability to produce sex hormones; however, the results of this study should be followed by a more direct analysis of the seminal fluid of COVID-19 patients to evaluate the effect—if any—on sperm count, volume, morphology or motility. It has been reported that SARS-CoV causes orchitis in addition to other complications (Xu et al., 2006), so it is also possible that SARS-CoV-2 may cause the same complication in males.

The transmission of COVID-19 has been suggested to occur through the respiratory route and close contact, while the faecal–oral route is also possible. While the presence of ACE2 receptor on the surface of some testicular cells may raise the concern of testicular damage or sexual transmission of the infection, a recent study has found no evidence of SARS-CoV-2 in semen or testicular specimens taken from COVID-19 patients which suggest that the disease has no sexual transmission route (Song et al., 2020).

5 | POTENTIAL EFFECT OF SARS-CoV-2 ON PREGNANCY LOSS/MISCARRIAGES

Pregnant women have been shown to be at high risk of comorbidity and mortality related to influenza infections (Rasmussen, Jamieson, & Bresee, 2008; Rasmussen, Jamieson, & Uyeki, 2012). The previous SARS infection showed that pregnant women had higher fatality rate (25%) compared to the general population (10%; Wong et al., 2004). With the rise of numbers of pregnant women and children affected by COVID-19, it is worth to know if pregnant women are a high-risk group for COVID-19 death or increased hospitalisation and also to evaluate the risk of vertical transfer either from the mother to the foetus or from the neonates to the mother.

Studies comparing the characteristics of COVID-19-infected pregnant women to non-pregnant women from Wuhan, China showed similar clinical characteristics and did not record maternal death due to the infection (Cao et al., 2020; H. Chen et al., 2020; Yu et al., 2020). The reports showed that infected pregnant women had mild COVID-19 symptoms; however, we should be cautious interpreting these results as the sample size was small and the female cases were infected at the end of their trimester. In the extreme contrary to these reports, a study from Iran reported a high maternal death (7 out of 9) among pregnant women affected with COVID-19 (Hantoushzadeh et al., 2020). The difference in mortality rate between these studies could be due to the severe comorbidity in the Iranian study, the stage of pregnancy at the time of infection as pregnant women where in the 2nd or 3rd trimester in the Iranian study, and could also be attributed to age as 5 of 9 of the females in the Iranian study were 35 years and above. It is worth mentioning that 4 out of the 7 Iranian dead pregnant cases—included in the study—had administered the anti-malaria drug hydroxychloroquine as part of their medication plan against COVID-19. The use of hydroxychloroquine could be directly or indirectly explain the maternal death as several side effects including blindness, heart failure and renal toxicity among others have been frequently reported (reviewed in Alanagreh, Alzoughool, & Atoum, 2020; Rosenberg et al., 2020).

Neonatal health is another important concern in the COVID-19-infected mothers. In a study from Wuhan, 33 neonates were born to mothers with COVID-19, and no health complications were reported except for shortness in breath in four cases (Zeng et al., 2020). Other studies, including less number of cases, did not report any neonatal health issues except for low birthweight (<2,500 g) and premature delivery (Cao et al., 2020; Chen & Lou, 2020). Two other studies from China and Iran reported two neonatal deaths out of 19 cases studied (Hantoushzadeh et al., 2020; Zhu, Wang, et al., 2020). No cases of miscarriages have been reported in the first trimester of COVID-19 pregnancies. Overall, it seems that neonates delivered by COVID-19 pregnant mothers have no increased risk of clinical complications compared to normal pregnancies and some of the reported neonatal complications could be related to mothers' overall health status rather than a consequence of COVID-19 infection.

The risk of vertical transfer of SARS-CoV-2 between the mother and the foetus is possible knowing that the ACE2 receptor is expressed in the placenta and uterus (Levy et al., 2008); however, most published data do not support this predication as most neonates born for mothers affected by COVID-19 tested negative (Chen et al., 2020; Liu et al., 2020; Yu et al., 2020). A few studies have reported a vertical transfer of SARS-CoV-2 from the mother to the neonates (Hantoushzadeh et al., 2020; Yu et al., 2020), but these studies should be carefully interpreted as they occur less frequently and possibly resulted because of the neonatal exposure to SARS-CoV-2 after delivery.

A recently published systematic review and meta-analysis reviewed the outcomes of three coronavirus infections (SARS, MERS and COVID-19) including around 80 hospitalised women, reported that maternal mortality rate is 0% for COVID-19 compared to 25%–30% for MERS and SARS infections (Di Mascio et al., 2020). Miscarriages were only reported in SARS infections. Pre-term birth, preeclampsia and caesarean delivery were more

common in COVID-19-infected mothers compared to SARS and MERS infections.

6 | MANAGEMENT OF ASSISTED REPRODUCTIVE TECHNOLOGY AT THE TIME OF COVID-19

Fertility services deal with patients for a longer time; in comparison with other healthcare services, it starts from preparation which includes the counselling, blood tests, clinical consultations, transvaginal ultrasounds and ART techniques to the procedures like genetic testing, hysteroscopy, laparoscopy and many others (Nikander, 2012).

Artificial reproductive techniques include intrauterine insemination (IUI), IVF injectable protocols, egg collection, embryo transfer and following the patient up until positive pregnancy test then for the whole duration of pregnancy (40 weeks); ultimately this will put infertile couples at more risk of infection and infection transmission (Liang & Acharya, 2020; Nikander, 2012).

Risk mitigation measures and guidance to deal with COVID-19 was published by most of reproductive medicine bodies all over the world which changed the practice dramatically (ASRM; ESHRE; JSF). The cornerstone of success, according to these guidelines, is to maximise telemedicine implementation and online education by uploading the website with the most updated available information and links. Electronic health solution should be used as an alternative for all treatment steps that do not require patient to be present physically. Strict adherence to the local lockdown instructions and compliance to the general health precautions of social and physical distancing at all times are very crucial. Before starting ART treatment, reproductive authorities advise to go for an online triage two weeks in advance and to repeat the triage at every clinic visit (ASRM; ESHRE; JSF). Patients with comorbidities like diabetes, hypertension, morbid obese, lung, liver or renal disease should not commence ART treatment until it is deemed safe by health authorities.

Risk of ovarian hyperstimulation syndrome should be taken very seriously during COVID-19 pandemic crisis and all guidelines clearly stated that reproductive endocrinologists should adopt gonadotropin-releasing hormone (GnRH) antagonist as a default protocol for ovarian stimulation with GnRH-agonist trigger to minimise the risk of ovarian hyperstimulation syndrome (OHSS), hospital admissions and intensive care unit (ICU) occupancy (ASRM; Carugno et al., 2020; ESHRE; JSF).

Guidelines advise to prescribe antibiotics after egg collection, which is not the routine practice before this pandemic, to minimise risk of infection (ESHRE; JSF). More measures should be taken to avoid the use of immune suppressant and immune modulators.

IVF units should encourage male patients to produce semen samples at home and then delivered to the laboratory. Semen sample must be considered as a potential source of infection, and sample preparation is recommended to be done using density gradient followed with swim-up technique. Repeated washing of oocytes and embryos should be done to dilute any possible chance of viral contamination, since zona pellucida acts as a physiological protective barrier to the oocyte from viral contamination, invasive procedures such as assisted hatching techniques should be abandoned (JSF).

Hysteroscopy procedures if needed should be done in an office, conscious sedation or regional anaesthesia thus avoiding the risk of viral dissemination by intubation and extubation with least use of fluids (Carugno et al., 2020).

Laparoscopy procedures hold more risk relatively as the artificial pneumoperitoneum comes with the risk of aerosol exposure and surgical smokes to the team upon insufflation and deflation, precaution of keeping the intraoperative pneumoperitoneum pressure as low as possible without compromising of laparoscopic view, to minimise thermal energy use and to reduce time of Trendelenburg position as much as possible (Zheng, Boni, & Fingerhut, 2020).

SARS-CoV-2 virus is potentially going to stay as a global health concern for quite some time and we have to learn how to live in harmony with this novel virus.

7 | CONCLUSIONS AND FUTURE DIRECTIONS

While writing these lines, COVID-19 has spread to a large proportion of the globe. Many countries like China and Jordan have managed to contain it with minimum percentage of fatalities, while many others are still struggling with high incidence and high death rates. With no available effective drug to treat or a vaccine discovered yet, the war is still on. The number of individuals who recovered from the disease is very high and there is no sign of recurrence and no side effect post-recovery was reported (Balachandar et al., 2020). However, without a thorough clinical follow-up assessment, a chance for some medical consequences might be still high.

Many health issues related to COVID-19 have been addressed in this review. Pregnancy and maternal health have been discussed. Many reports have evidences against a direct link between COVID-19 and maternal death. Neonates born to a COVID-19 mothers are not at increased risk of adverse health consequence compared to the ones born for COVID-19-unaffected mothers, and the possibility of viral vertical transfer has not been confirmed. Large cohort studies should be followed to confirm these results; additionally, first-trimester COVID-19 cases should be included and be evaluated for the risk of miscarriages.

The gender difference in COVID-19 incidence, comorbidity and death rates—males are at higher risk—requires prompt actions to understand the source of difference biologically and behaviourally. Viral infection by HPV, HSV, HIVs, HBV, HCV and MuV challenges reproductive health and can be considered as a risk factor for male infertility. These viruses have been detected in semen and can impair testicular function. Some viruses such as HIV, MuV and SARS-CoV are associated with orchitis resulting in male infertility, so it would be interesting to study if SARS-CoV-2 can cause the same problem. Because many males at childbearing

age are affected by COVID-19, the high expression of ACE2 receptor in the testes and the association of COVID-19 with fever; a multidimensional andrological translational research project was suggested (Salonia et al., 2020). This project aims to develop international collaboration for data registry, hormonal studies and genomic studies to better understand the sex difference for COVID-19 health-related consequences.

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