COVID-19: Pandemic Effect on Human Reproduction

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Introduction

Since its emergence as a cluster of severe viral pneumonia identified in Wuhan, China, at the end of 2019, the coronavirus disease-19 (COVID-19) had rapidly spread to become a global pandemic affecting, at the time of writing, close to half a billion people and resulting in 18.2 million fatalities worldwide [1]. This pandemic was the first in the era of modern medicine. It was also the first to be managed with a global coordinated response that included the development and introduction of multiple vaccines and specific treatments shortly after its eruption. Also, unlike the previous pandemic that occurred a century ago, the "Spanish Flu," this pandemic was faced with a popular movement of scientific denialism fueled by conspiracy theories and fractured sources of information [2]. COVID-19 is a multisystemic disease caused by a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has short-term effects caused by temporary loss of function as well as long-term effects caused by tissue damage. These may involve any organ system [3, 4]. Quite early during the pandemic, it was recognized that although most infected people will have either no or mild symptoms, there are several populations at risk for severe morbidity and mortality, among them pregnant women. Despite similar rates of contamination, pregnant women present with a higher rate of hospitalization (31.5% vs 5.8%), a higher adjusted risk for ICU admission [aRR 1.5, 95% confidence interval (CI): 1.2–1.8], a higher risk to receive mechanical ventilation [aRR 1.7, 95% confidence interval (CI): 1.2–2.4], and extracorporeal membrane oxygenation (ECMO) [aRR 2.4, 95% confidence interval (CI): 1.5–4.0]

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compared to their age-matched counterparts [5]. Together with apprehension of potential detrimental effects of COVID-19 and its vaccine on male and female reproductive function, this has led to an unprecedented public interest in this topic.

The SARS-CoV-2 is a coronavirus (CoV) that is found globally in many animal species. It is part of the "*Orthocoronaviridae*" subfamily that are divided into four groups α to δ, with only groups α and β affecting mammals. The highly pathogenic SARS-CoV, MERS-CoV, and SARS-CoV-2 are βCoV. CoV are RNA viruses, enveloped by a host-derived lipid membrane embedded with viral proteins. The proteins protruding from its membrane give these viruses their ultramicroscopic typical halo appearance that gave this group of pathogens their name corona (crown in Latin) [6]. The RNA of the virus is single stranded, and it has the same orientation as mRNA. CoV viruses have the largest genome of all RNA viruses. Due to the high rate of mutations related to its unique RNA-dependent RNA polymerase and homologous recombination, coronaviruses acquired a great diversity that enabled these viruses to infect many species and allow inter-species transmission [7]. Genomic sequencing of the virus showed it to be related to two other human CoVs: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) as well as to a bat CoV RaTG13.

The CoV RNA encodes four essential structural proteins including the nucleocapsid protein that surrounds the viral genome and three membrane proteins: the S-glycoprotein (spike protein), the matrix (M) protein, and the envelope (E) protein. The "spike protein" (S), a transmembrane glycoprotein of the CoV, has two subunits: S1 responsible for the attachment to the host cell receptor and S2 that allows virus-host membrane fusion. The virus attaches to the angiotensin-converting enzyme 2 (ACE2), a receptor found mostly on surfaces of human respiratory cells and uses it as a point of entry [8, 9]. The ACE2 receptor serves as a critical port of entry to SARS-CoV and SARS-CoV-2 but not MERS-CoV [10]. The S1 protein has a high affinity to the ACE2 receptor; however, for fusion to occur, the virus needs to shed the S1 protein and activate S2. The cleavage of the covalent bond between S1 and S2 occurs after the assembly of the virus inside the host cell via the action of a Furin protease (Fig. 1.1). The cleavage of this covalent bond allows for an easier shading of S1 subunit and is a prerequisite for the activation of the S2 subunit. The next stage involves the activation of S2 subunit by cleavage of the S2′ site by the action of the co-expressed transmembrane serine protease-2 (TMPRSS2) present at the cell surface. The activation of the S2 component initiates membrane fusion by creating fusion pores that enable the insertion of the viral genome into the cell. Membrane fusion leads to endocytosis of the virus into the cell and into its nucleus to start replication. The newly formed viral DNA is used to form the viral proteins which are then packaged, transferred to the cell membrane, and released to infect other cells (Fig. 1.1) [11]. It is therefore imperative for tissues to co-express the ACE2 receptor and TMPRSS2 genes to become targets for the SARS-CoV-2. Co-expression of ACE2 and TMPRSS2 is only present on the lung, large and small intestine, esophagus, brain, heart, kidney, testis, and fallopian tubes [12]. Although there is a clear preference of the ACE2-TMPRSS2 mode of host cell entry, an alternative route of host cell entry in cells devoid of TMPRSS2 has been described. This

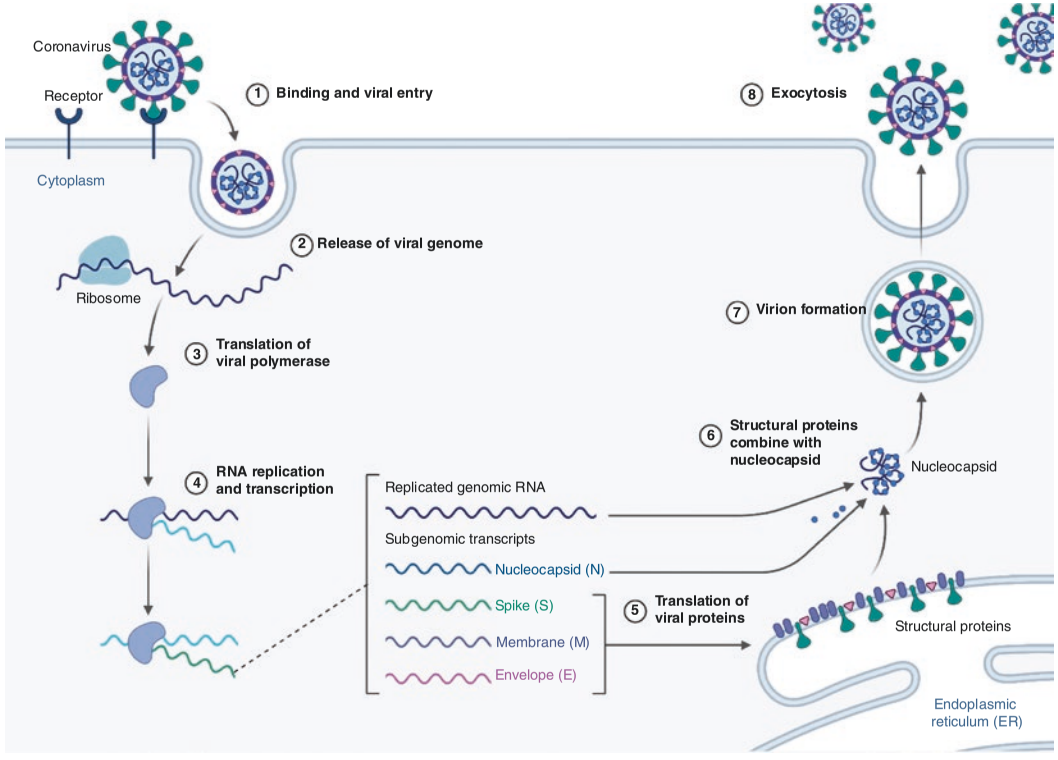

Fig. 1.1 The cycle of the SARS-CoV-2 virus starts with binding to the ACE2 receptor, followed by membrane fusion and internalization of the virus into the cell and release of the viral RNA. The viral RNA then using the cell's machinery replicates its RNA and translates it into the four viral proteins: the nucleocapsid, spike, membrane, and envelope proteins. These components are than assembled to create the virion which is then released from the cell in a process of exocytosis to infect other cells

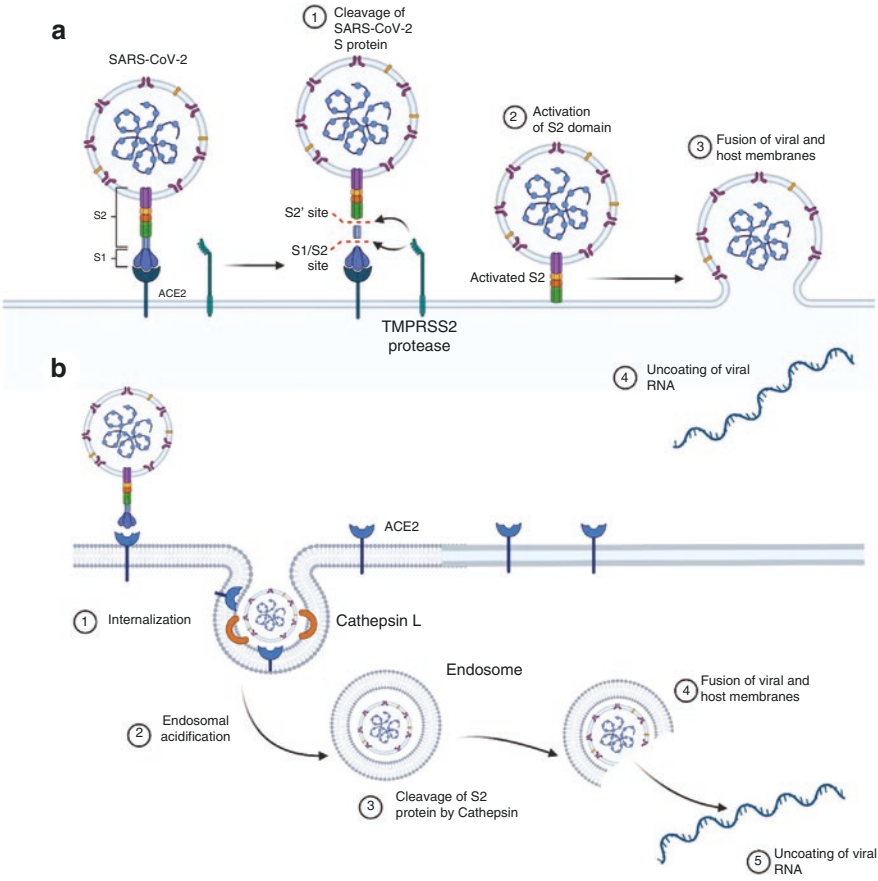

Fig. 1.2 An infection by the SARS-CoV-2 virus follows its entry into a cell via one of two mechanisms. (**a**) This is by far the preferred mode of entry for SARS-CoV-2. It necessitates the co-expression of the ACE2 and the TMPRSS2 protease on the cell's membrane. Following binding of the S1 subunit to the ACE2 receptor, the TMPRSS2 protease activates the S2 subunit that acts as a membrane fusion facilitator. Thus, leading to internalization of the virus into to the cell. (**b**) In the absence of TMPRSS2 expression on the cell's membrane, the bound virus is internalized into an endosome for the purpose of its degradation. However, the combined result if the acidification of the endosome and action of the cathepsin L protease may lead to the activation of the S2 protein and membrane fusion

path involves internalization of the ACE2-bound virus via endocytosis. There, in the endolysosome, the S2′ is cleaved by the action of cathepsins, and the S2 subunit is activated (Fig. 1.2). However, the limited effect of hydroxychloroquine, a known inhibitor of endosomal acidification, suggests that this is not the main mode of entry used by the SARS-CoV-2 virus [13]. The ACE2 is a key element in counterbalancing the action of the renin–angiotensin–aldosterone system (RAAS). The RAAS system is activated to compensate for low blood pressure by activation of the angiotensin receptor 1 (ATR1) that leads to vasoconstriction and increased absorption of

sodium and water but also to cell proliferation, inflammation, and fibrosis. ACE2 acts through activation of its mediators, angiotensin 1–7 [ANG-(1–7)] and the major receptor mitochondrial assembly 1 (MAS1). Their activation leads to vasodilatation and has prevention of inflammation, fibrosis, and cell proliferation thus balancing overactivation of RAAS. SARS-CoV-2 may inhibit the protective action of ACE2 thereby leading to dysregulation and overactivation of RAAS leading to an increased expression of membranous ACE2 that serves as a port of entry to other SARS-CoV-2 viruses (Fig. 1.3) [10]. Studies had also reported on a wide expression of ACE2 in human placenta and its vasculature that peak in early gestation [14, 15]. Thus, potentially both male and female reproductive systems seem to be susceptible to SARS-CoV-2 infection and a short-term or long-term dysfunction. Also, common symptoms associated with the acute infection, such as fever and

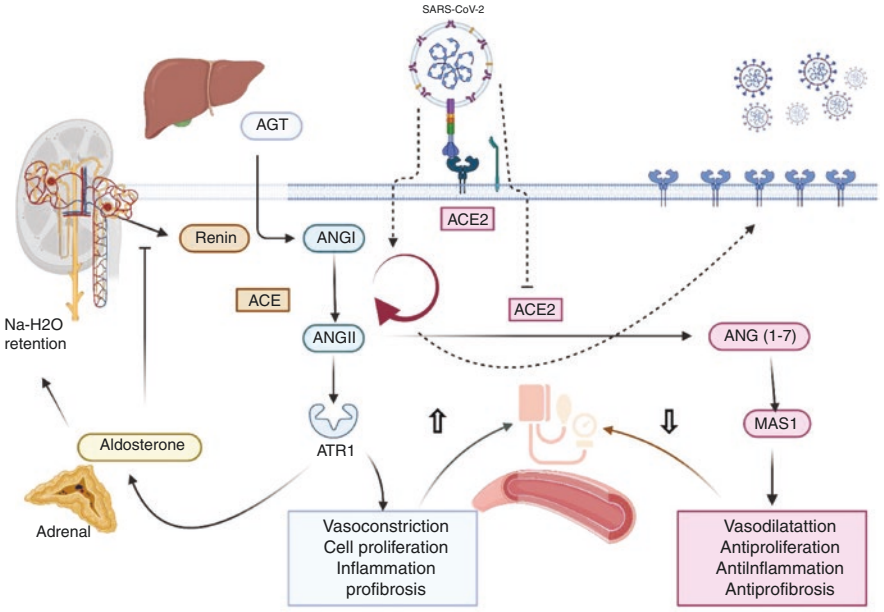

Fig. 1.3 The renin–angiotensin–aldosterone system (RAAS) is a short circuit regulatory system that responds to changes in blood pressure and solute composition at the juxtaglomerular apparatus in the cortex of the kidney. Activation of the system leads to secretion of renal renin, an enzyme that cleaves the constantly produced hepatic angiotensinogen (AGT) to angiotensin I (AGT I). The second phase of the activation of this hormone is facilitated by the action of the angiotensin-converting enzyme (ACE) that creates its active form, angiotensin II (AGT II). AGT II following binding to its receptor (ATRI) leads to vasoconstriction as well as to the adrenal secretion of the mineralocorticoid, Aldosterone that in turn promotes renal absorption of sodium and water. These actions that lead to an increase in blood pressure, simultaneously activate a counter-regulatory mechanism to prevent an over response. This involves the activation of the ACE2 receptor that via its mediators, the angiotensin 1–7 and the mitochondrial assembly system 1 promote vasodilatation as well as anti-inflammatory and anti-proliferative actions. The SARS-CoV-2 virus by binding and inactivating the ACE2 leads to over net effect of RAAS and in response an increased expression of membranous ACE2 that promotes further viral cell entry

hypercoagulability, may affect both male and female reproduction. In addition, viral proteins show similarity to placental proteins and could, in theory, interfere with placenta formation [16, 17]. Patients undergoing fertility treatment are in even more complicated circumstances; as they cannot conceive naturally, their future pregnancy may be postponed until the risk of infection declines, while attempts to conceive during the pandemic put them in a potentially higher risk of infection due to frequent visits to fertility clinics or hospitals in which the likelihood of exposure to the virus is higher. Furthermore, some of the reported risk factors among pregnant women for severe COVID-19-related complications were age over 25 years, pre-pregnancy obesity, chronic hypertension, and pre-pregnancy diabetes [18]. All these risk factors are significantly more common among patients conceiving following in vitro fertilization (IVF) treatment as opposed to spontaneous conceptions, suggesting that pregnant women following IVF may be at a particularly elevated risk for COVID-19-related complications [19]. Worldwide, there were different policies with regard to the activity of IVF clinics during the pandemic. Although in some countries, clinics needed to scale down or stop their activity during waves of high infectivity, for the most part, IVF treatment cycles were conducted during the pandemic excluding patients with a current infection [20]. Under these circumstances, couples undergoing IVF treatments need to cope with the added uncertainty of the potential risk posed by COVID-19 to the safety and success of treatment and the possible implications in case of a pregnancy [21].

Effects of COVID-19 on Female Fertility

Several studies examined the short-term effects of COVID-19 on different aspects of female reproduction. Although ACE2 is expressed in the human ovary, whether this virus binds to ACE-2 receptors in the ovary and which effects, if any, this infection would have on ovarian function, and oocyte quality remains unclear. To date, no studies have presented evidence of SARS-CoV-2 infecting the female reproductive system. However, several studies demonstrated the presence of anti-SARS-CoV-2 IgG in the FF. The reported linear ratio of serum to FF antibody concentration supported an unregulated serum filtration model. Herrero et al. reported on a negative correlation between FF anti-SARS-CoV-2 IgG titer and oocyte and mature oocyte yield and a positive correlation with time interval from infection [22, 23].

Follicular Fluid (FF)

The follicular fluid (FF) is a complex mixture of hormones, cytokines, metabolites, and other proteins that originate from serum filtration as well as granulosa cell secretions. It represents the microenvironment of the oocyte, and its composition has been associated with its quality. Several studies compared FF composition in SARS-CoV-2 recoverees to non-exposed IVF patients. Heparan-sulfate-proteoglycan-2 (HSPG2) is the main estrogen-binding protein in FF and was found to be the FF protein with the highest predictive value for oocyte fertilization and the resulting

embryo implantation. Comparison of HSPG2 FF concentration between recent SARS-CoV-2 recoverees [98.14 days from recovery to sampling (range 48–169 days)] to non-exposed showed no difference [23]. Another study showed a lower concentration of IL-1β and VEGF in FF from COVID-19 recoverees. In vitro exposure of granulosa cells to this FF was associated with markers of DNA damage [22].

Oocyte Yield

Several studies compared oocyte yield in COVID-19 recoverees. All the reports show the total number of retrieved oocytes as well as the number of mature oocytes to be unaffected by recent exposure to SARS-CoV-2. The study by Youngster et al. found oocyte yield to be lower in the group of COVID-19 recoverees with exposure to IVF treatment interval of 6 months or longer [22–25].

Steroidogenesis

Other than oocyte maturation, the ovaries are the source of the female sex steroids. The production of estradiol during the follicular phase of the cycle serves several essential physiological roles as well as a marker of the adequacy of ovarian response. Several recent publication studies compared peak serum estradiol as well as FF estradiol of COVID-19 recoverees and non-exposed controls during IVF treatment, all reporting no difference [22–24].

Fertilization Rate and Embryo Quality

The rate of oocyte fertilization is determined by oocyte and sperm function and the quality of their genetic material. Unlike fertilization by intracytoplasmic sperm injection (ICSI), oocyte fertilization by standard IVF is also affected by sperm parameters such as motility, Zona receptor binding, capacitation, and acrosomal reaction. A study that compared oocyte fertilization by either standard IVF or ICSI reported on similar rates in COVID-19 recoverees and non-exposed controls [24]. A comparison of embryo quality as determined by morphological grading was reported by two publications. No measurable difference could be demonstrated between recent COVID-19 recoverees and non-exposed controls [23, 24].

Ovarian Reserve

Serum anti-Mullerian hormone is regarded as the most reliable measure of the residual ovarian reserve, as it is a product of ovarian follicles, not operator dependent, and shows little intra- or inter-cycle variability. Several studies compared serum AMH between COVID-19 recoverees and non-exposed controls. These cohort studies compared women recovering from COVID-19 in different levels of severity.

Three of the four studies showed no detectable difference in AMH, and one study reported a lower AMH among the COVID-19 recoverees. Of note, a much larger cohort study that examined early follicular FSH as a marker of ovarian reserve showed a higher FSH among recoverees, suggesting a lower functional ovarian reserve [26].

Menstrual Cycle Disturbances

Carp-Veliscu et al. recently reviewed publications reporting on menstrual disturbances post COVID-19. The review included 11 recently published studies. Most of these studies were questionnaire-based retrospective cohort studies, and results were inconsistent. Reports ranged from no effect to over 80% reporting on menstrual cycle either shorter or longer as well as changes in flow and dysmenorrhea. Some of the studies associated menstrual cycle changes with the severity of COVID-19 symptoms or levels of stress [26].

Effects on Male Reproduction

Concerns over the impact of COVID-19 on male fertility span over three main questions: (1) Does SARS-CoV-2 infest the testis? (2) Are there short-/long-term detrimental effects of COVID-19 on sperm quality? (3) Can COVID-19 be sexually transmitted via infected sperm?

Despite intense research since the outbreak of the pandemic, there is still no clear answer to these questions [27]. To date, 27 viruses have been detected in human semen in association with viremia. It has been speculated that the presence of viruses in semen may be more common than appreciated and that traditional non-sexually transmitted viruses may be present in the genital secretions. As mentioned earlier, both the ACE2 receptor and TMPRSS2 are expressed in the male reproductive system. There are also multiple reports of detection of the SARS-CoV-2 virus or the spike protein in post-mortem testicular biopsies and semen from COVID-19 patients. There had also been reports of orchitis detected in an autopsy of a COVID-19 patient as well as observations of significant infiltration of immune cells in tests of COVID-19 patients. Yet in most of these reports, contamination of the sample could not be ruled out. Pathological examination of testicleless of man infected with SARS-CoV-2 had also demonstrated changes in the seminiferous tubules, damaged Sertoli cells, and reduction in the number of Leydig cells together with peritubular membrane thickening, fibrosis, and immune cell infiltration. These changes were often associated with low serum testosterone despite relatively elevated LH and FSH. Although these reports may suggest a direct detrimental effect of the virus on testicular function, these changes may also be attributed to the effect of fever commonly experienced by COVID-19 patients. In fact, comparison of sperm parameters between fever-positive and fever-negative male COVID-19 patients showed a significantly lower volume, concentration, and total motility in the febrile group [27]. With regard to the question on SARS-CoV-2 transmission via sperm, there have two recently published reports,

the first analyzing semen samples within 24 h of the positive nasopharyngeal swab. This study showed 1/32 samples to be positive for SARS-CoV-2 RNA, however commenting that oral contamination during sample production could not be ruled out [28]. A second report analyzed semen samples from recovered men that were obtained 11–64 days after testing positive for SAR-CoV-2 infection. In this study no viral RNA was detected in any of the samples [29].

IVF Outcome

Several studies compared the outcome of IVF treatment between COVID-19 recoverees and non-exposed patients (reviewed by [24, 26]). These studies were either case-control or cross-sectional cohort studies. Although none of the studies demonstrated a decline in oocyte or mature oocyte yield, some of these studies reported on a decline in embryo quality as defined by either embryo morphological assessment or rate of euploid embryos. However, the reported rates of fertilization, number of cryopreserved embryos, and clinical pregnancy rate were similar [24]. A recent study reported on the outcome of IVF treatments in the county of Lombardy, Italy [30]. Lombardy was one of the areas hardest hit in the early stages of the pandemic. The authors compared several outcome parameters of the pre-exposure cohort, comprised of all the patients undergoing both fresh and frozen IVF treatment cycles before the pandemic (November 2018–March 2019) to the potentially exposed cohort, composed of all IVF cycles conducted during the peak of the COVID-19 outbreak (November 2019–March 2020). Although asymptomatic patients were not tested for SARS-CoV-2, 28% of blood donor samples from that period tested positive for anti-SARS-CoV-2 IgG, suggesting that a similar number of patients undergoing IVF were exposed to the virus. The authors found similar rates of clinical pregnancy, early pregnancy loss, and extrauterine pregnancies [30].

Pregnancy Outcome

A study by Viotti et al. found trophectoderm cells of a day 6 embryo to have the highest co-expression of the ACE-2 and TMPRSS2 and that they are susceptible to the infection through the ACE2 receptor [26]. Therefore, concern over the potential risk to developing pregnancies was expressed. A meta-analysis that studied the incidence of potential vertical transmission reported on 800 newborns testing positive for SARS-CoV-2 out of 308,540 newborns, representing an incidence of 2.6%. However, intrapartum exposure could not be ruled out [31]. A study by Calvo et al. [32] reported on the perinatal outcome of 1347 pregnant women, among them 74 who conceived following IVF, who were infected with SARS-CoV-2 during pregnancy. This multicenter study compared the rate of early pregnancy loss, pregnancy complications, and mode of delivery according to exposure status. They were only able to show a significant increase in the rate of cesarean sections among exposed patients [32]. A meta-analysis of 17 observational studies had also found the rate of early pregnancy loss among COVID-19 patients to be within the expected range

[33]. A recent meta-analysis compared the outcome of over two million births taking place during the pandemic with over 28 million births from the pre-pandemic period. The study showed that pregnancies during the pandemic were associated with a lower rate of spontaneous preterm births (PTB) (nine studies, uaOR 0.91, 95% CI 0.88–0.94) but not in induced PTB (eight studies, uaOR 0.90, 95% CI 0.79–1.01), similar odds for stillbirths (32 studies, uaOR 1.07, 95% CI 0.97–1.18, and 3 studies, aOR 1.18, 95% CI 0.86–1.63), and an increase in average birth weight (nine studies, mean difference 21 g, 95% CI 13–30 g) [34]. A review of several small studies reported on a similar rate of congenital malformations among exposed and exposed pregnancies [35].

The Anti-SARS-CoV-2 Vaccine

Conventional vaccines such as inactivated, live attenuated viruses or their subunits had been at the forefront of humankind's combat against infectious disease. These traditional-type vaccines had proven to be both safe and efficacious, yet their development and production may take many years. With the advent of the COVID-19 global pandemic, there was an urgent need for large-scale development and deployment of a vaccine to halt its rapid expansion. Messenger RNA-based vaccines had been studied since the 1970s. Their non-dependence on animal products or cell culture as well as the rapidness and low cost of their production placed them in the forefront of vaccine research. Yet, implementation of this technology in vaccine development had to await the maturation of a technology that will allow the mRNA segments access into the cell to be translated to the target protein. The development of liposomal nanoparticle carriers in the beginning of the 1990s provided the needed mechanism for cell entry, and by 2017, the stage was ready for the first mRNA anti-rabies vaccine to begin phase I trials. The rapidness of development of the ant-SARS-CoV-2 mRNA vaccines was unprecedented. Only 7 months after the first case of COVID-19 outside of China was diagnosed and 4 months after the WHO declared COVID-19 as a global pandemic, two pharma companies, Moderna and Pfizer, began phase III trials of mRNA COVID-19 vaccines. The FDA approval for use of the first mRNA vaccine (Pfizer's BNT162b2) only 5 months after phase II trials results showed high efficacy, and safety was met with both great enthusiasm and apprehension [36]. In light of reports of severe COVID-19 among parturients, the CDC added pregnancy to the list of high-risk conditions to prioritize vaccination, and the American College of Obstetricians and Gynecologists (ACOG) recommends not withholding vaccination from pregnant women at any stage of the pregnancy [37]. The enthusiasm surrounding the vaccine rollout was accompanied by unsubstantiated rumors, spread via social media, suggesting that the vaccine may lead to female sterility [38]. Several studies looked at the effects of the anti-SARS-CoV-2 mRNA vaccines on male and female fertility, IVF, and pregnancy outcome. A study by Gonzalez et al. compared sperm quality before and 70 days post anti-SARS-CoV-2 mRNA vaccine [BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)] among healthy volunteers. Results showed similar semen volume and sperm concentration and improved motility post vaccination [39]. Assessment of

the effect of the BNT162b2 on ovarian reserve as assessed by serum AMH 3 months post vaccination showed no difference [40]. There were two studies that compared IVF treatment outcome in vaccinated and unexposed fertility patients [23, 41]. The comparison included oocyte yield, mature oocyte yield, estrogen and progesterone production, fertilization rate, blastocyst formation rate, embryo quality based on morphology staging, or euploid embryo rate which showed no difference between the two groups. One of the studies had also compared clinical and ongoing pregnancy rate as well as early pregnancy loss, again showing no measurable differences [41]. Another study examined the risk for early pregnancy loss among women vaccinated shortly before or during pregnancy and found the rate to be within the expected age-specific range [42]. The "V-safe study" had also reported that the rate of fetal congenital malformations among patients vaccinated with either the BNT162b2 or mRNA-1273 vaccines was within the expected range (2.2%) [43]. Interestingly, similarly to reports from COVID-19 recoverees, patients vaccinated with mRNA anti-SARS-CoV-2 vaccines had also reported on menstrual cycle changes. However, the mean change in menstrual cycle length was only for 1 day, and no changes were recorded in the length of menses [44].

Conclusion

COVID-19 is the first global epidemic to be managed with a coordinated worldwide effort to limit its spread and life toll. This action included the development and deployment of several effective vaccines in an unprecedented short time frame. The fast-tracking of the deployment of the vaccines led to an unparalleled social movement of anti-vaccine activism. Early reports on severe morbidity and mortality among pregnant women as well as of a potential vertical transmission led regulatory bodies to approve vaccination of women immediately prior and during pregnancy with the mRNA vaccines. Since, despite the emergence of new variants, the clinical safety and efficiency of these vaccines remains. Also, despite initial concerns, other than a transient decline in sperm quality in COVID-19 affected males, the reproductive system, IVF treatment outcomes, and early pregnancy do not seem susceptible to direct detrimental effects of the SARS-CoV-2 virus.

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