Prior and novel coronaviruses, Coronavirus Disease 2019 (COVID-19), and human reproduction: what is known?

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Objective: To summarize current understanding of the effects of novel and prior coronaviruses on human reproduction, specifically male and female gametes, and in pregnancy.
Design: Review of English publications in PubMed and Embase to April 6, 2020.
Method(s): Articles were screened for reports including coronavirus, reproduction, pathophysiology, and pregnancy.
Intervention(s): None.
Main Outcome Measure(s): Reproductive outcomes, effects on gametes, pregnancy outcomes, and neonatal complications.
Result(s): Seventy-nine reports formed the basis of the review. Coronavirus binding to cells involves the S1 domain of the spike protein to receptors present in reproductive tissues, including angiotensin-converting enzyme-2 (ACE2), CD26, Ezrin, and cyclophilins. Severe Acute Respiratory Syndrome Coronavirus 1 (SARS–CoV-1) may cause severe orchitis leading to germ cell destruction in males. Reports indicate decreased sperm concentration and motility for 72–90 days following Coronavirus Disease 2019 (COVID-19) infection. Gonadotropin-dependent expression of ACE2 was found in human ovaries, but it is unclear whether SARS–Coronavirus 2 (CoV-2) adversely affects female gametogenesis. Evidence suggests that COVID-19 infection has a lower maternal case fatality rate than SARS or Middle East respiratory syndrome (MERS), but anecdotal reports suggest that infected, asymptomatic women may develop respiratory symptoms postpartum. Coronavirus Disease 2019 infections in pregnancy are associated with preterm delivery. Postpartum neonatal transmission from mother to child has been reported.
Conclusion(s): Coronavirus Disease 2019 infection may affect adversely some pregnant women and their offspring. Additional studies are needed to assess effects of SARS–CoV-2 infection on male and female fertility. (Fertil Steril® 2020;113:1140–9. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Novel coronavirus, COVID-19, reproduction, pregnancy, review

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The rapid spread of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS–CoV-2) has led to a pandemic of Coronavirus Disease 2019 (COVID-19) across the globe. As of April 8, 2020, there are more than 1.4 million cases and 86,000 deaths attributed to the virus worldwide. As a result, nations have implemented suppression and mitigation strategies to control community spread, including

mandated social distancing, restrictions to nonurgent medical care, and closure of nonessential businesses. Despite these efforts, the spread of SARS–CoV-2 is ongoing, creating a public health crisis and impacting the population world-wide.

Coronaviruses are a group of viruses that can cross species barriers and become human pathogens. All seven identified human coronaviruses originated from animal reservoirs including domestic animals, bats, or mice. Although most human coronaviruses cause mild illness, severe acute respiratory syndrome coronavirus (SARS–CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and the novel SARS–CoV-2 have been associated with severe lower respiratory tract infections, acute respiratory distress syndrome, and death (1).

The novel SARS–CoV-2 virus spreads rapidly, with 2–3 people infected from every index case, a reproduction number (R_0) or transmission rate of 2.24–3.58 (2). In contrast, the 2009 H1N1 seasonal influenza had an R_0 of 1.46–1.48. The incubation period for SARS–CoV-2 ranges from 2–14 days, and asymptomatic spread occurs prior to onset of symptoms (3, 4). Transmission is thought to be mainly through respiratory droplets and fomites (5). In one experiment, viable virus was detected in aerosols for up to 3 hours, with an estimated half-life of 1.1 hours. In addition, virus was detected on surfaces for days after application, with viable SARS–CoV-2 identified on plastic and stainless steel up to 72 hours (6). SARS–CoV-2 RNA also has been detected in blood and stool and it is not yet known whether the infection can be acquired through exposure to nonrespiratory bodily fluids (7).

Symptoms of SARS–CoV-2 infection include fever, cough, fatigue, shortness of breath, sputum production, headache, and myalgias. In addition, patients may report gastrointestinal symptoms (8) or anosmia. The severity of infection ranges from asymptomatic carriers, to mild flu-like disease, to critical illness and death. Critically ill patients may experience respiratory failure, shock, or multiorgan dysfunction. Approximately 80% of infections are mild with flu-like symptoms, 15%–20% are severe, requiring hospitalization and supplemental oxygen, and 5% are critical and require mechanical ventilation (9). Risk factors for severe illness include age and underlying medical comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer (10). Death may occur in up to 3% of infections. Death from SARS–CoV-2 is more common in individuals older than 60 years of age or with underlying medical issues but can occur in younger persons, perhaps related to the inoculum. Associated cardiac arrhythmias may be fatal.

While persons of advanced age are most likely to experience severe symptoms, women of reproductive age are also at risk for development of severe disease and death. Furthermore, reproductive age women can act as asymptomatic carriers and increase viral transmission.

OBJECTIVE

The aim of this review is to summarize what is currently known about the impact of prior coronaviruses and the novel SARS–CoV-2 infection on reproduction and pregnancy.

METHODS

A systematic search in the literature published in the PubMed and Embase databases was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Literature review was done of available literature in English, both published and peer-reviewed on-line publications from 1996 to April 6, 2020. Additional sources were identified from citations of retrieved literature. The search strategy for the PubMed and Embase searches is shown later in this article. There was no limitation on sample size. Published reports of experiences with the SARS–CoV-2 virus have increased greatly in the past months, but no randomized trials to date regarding possible treatments were identified. Most reports pertaining to reproduction or pregnancy involved small cohorts, case reports, guidelines, and editorials. Similarly, prior publications of other coronaviruses were limited in number.

We reviewed all titles for eligibility. All reports including pregnancy or reproductive tissues were included. We excluded editorials and publications of guidelines. We excluded articles that were duplicates or did not contain information related to pregnancy or reproduction, the presence of virus in reproductive tissues, effects on gametes, pregnancy outcomes, or neonatal complications. Case reports were included. Because of the limited nature of the reports and the absence of randomized trials we did not use the Cochrane RoB 2.0 tool. Similarly, because of the limited scope of the cohort studies, we did not use the Newcastle-Ottawa Scale to rate the studies.

Full-text articles were then reviewed and evaluated for inclusion by authorship teams. There were two independent reviewers (J.S. and Z.K.). Any disagreements were resolved through discussion with a third reviewer (J.K.). The authors acknowledge the number of publications about the novel SARS–CoV-2 virus is increasing at an exponential rate and there may be bias toward reporting of positive findings.

Search Strategy

We used a broad inclusive search strategy so as not to miss a seminal contribution. The comprehensive search was conducted by an experienced information specialist. Search phrases for PubMed included the following: (("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 ncov"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR (corona[All Fields] AND ("viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields])) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) OR ("COVID-

19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields])) AND (("gravidity"[MeSH Terms] OR "gravidity"[All Fields] OR "pregnant"[All Fields]) OR ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) OR ("live birth"[MeSH Terms] OR ("live"[All Fields] AND "birth"[All Fields]) OR "live birth"[All Fields]) OR ("abortion, spontaneous"[MeSH Terms] OR ("abortion"[All Fields] AND "spontaneous"[All Fields]) OR "spontaneous abortion"[All Fields] OR "miscarriage"[All Fields]) OR ("abortion, induced"[MeSH Terms] OR ("abortion"[All Fields] AND "induced"[All Fields]) OR "induced abortion"[All Fields] OR "abortion"[All Fields]) OR ("parturition"[MeSH Terms] OR "parturition"[All Fields] OR "birth"[All Fields]) OR ("J In Vitro Fert Embryo Transf"[Journal] OR "ivf"[All Fields]) OR ("IUI"[Journal] OR "iui"[All Fields]) OR ("sex"[MeSH Terms] OR "sex"[All Fields]) OR ("fertility"[MeSH Terms] OR "fertility"[All Fields]) OR ("infertility"[MeSH Terms] OR "infertility"[All Fields]) OR ("germ cells"[MeSH Terms] OR ("germ"[All Fields] AND "cells"[All Fields]) OR "germ cells"[All Fields] OR "gamete"[All Fields]) OR ("oocytes"[MeSH Terms] OR "oocytes"[All Fields] OR "oocyte"[All Fields]) OR ("embryonic structures"[MeSH Terms] OR ("embryonic"[All Fields] AND "structures"[All Fields]) OR "embryonic structures"[All Fields] OR "embryo"[All Fields])).

The Embase strategy of phrases included the following: ('2019 ncov' OR 'sars cov 2' OR 'corona virus'/exp OR 'corona virus' OR (corona AND ('virus'/exp OR virus)) OR 'coronavirus'/exp OR coronavirus OR 'covid 19' OR covid19) AND (pregnant OR 'pregnancy'/exp OR pregnancy OR 'live birth'/exp OR 'live birth' OR (live AND ('birth'/exp OR birth)) OR 'miscarriage'/exp OR miscarriage OR 'abortion'/exp OR abortion OR 'birth'/exp OR birth OR 'ivf'/exp OR ivf OR iui OR 'sex'/exp OR sex OR 'fertility'/exp OR fertility OR 'infertility'/exp OR infertility OR 'gamete'/exp OR gamete OR 'oocyte'/exp OR oocyte OR 'embryo'/exp OR embryo).

RESULTS

The search revealed 663 articles after removal of duplicates. Ninety-seven articles related to pregnancy and coronavirus and only seven were related to embryos or early reproduction. Small cohorts, case reports, comments on guidelines, guidelines, and editorials were retrieved. After exclusion, 79 articles were included in the review based on relevance and new data.

PATHOPHYSIOLOGY OF CORONA VIRUSES

Molecular features of the viral coronavirus family, which includes SARS–CoV, MERS-CoV, and the recently identified novel Coronavirus (SARS–CoV-2), have been well-elucidated. A review of the coronavirus structure and function help to inform us on the pathophysiology of coronavirus infectivity. Coronaviruses are large, single-stranded, enveloped RNA viruses approximately 32 kilobase (11). The viral RNA genome is housed inside a nucleocapsid, which itself is contained within a viral envelope (12). This envelope comprises three distinct proteins: a "membrane protein" and "envelope protein," which are both directly responsible for viral assembly, as well as a "spike protein," which mediates viral

entry into host cells (12). When viewed with electron microscopy, these spike proteins are surface-exposed markers that produce a recognizable "crown-like" appearance to the virus. The spike proteins serve a critical step in initiating human infection, as well as determining host tissue specificity and inducing host immune response (13–15). The coronavirus spike protein is composed of two unique subunits that facilitate viral-host binding (16–19). The S1 domain of the spike protein functions in viral binding and attachment to the host cell membrane. Numerous receptors on the human cell membrane that are involved in S1 subunit binding have been identified to date, including angiotensin-converting enzyme-2 (ACE2), CD26, Ezrin, and cyclophilins (20, 21). The S2 domain of the spike protein is responsible for fusion of the viral and host cell membranes, allowing the SARS–CoV-2 viral genome to enter the host cell. This process involves a complex interaction between viral and host machinery, which culminates in rapid viral replication within target cells. International research efforts are currently underway aimed at using the S1 domain of the spike protein as a target for therapeutic anti-viral therapy, as well as vaccine development.

The involvement of SARS–CoV-2 infection within human male and female reproductive systems has yet to be elucidated fully. However, results from other coronavirus subtypes, specifically SARS–CoV, help inform knowledge of tissue-specific viral pathophysiology. Current data suggest that the female reproductive system may be spared from viral infection. Immunohistochemical and in situ hybridization studies on tissues from a small cohort of deceased patients that were infected with SARS–CoV failed to identify SARS–CoV viral RNA within the female reproductive tract, including both ovarian and uterine tissue (22), although ACE2 receptors can be found there. Importantly, there is evidence to suggest that coronavirus infection may impact the male reproductive tract. The ACE2 protein, a main receptor for coronavirus viral entry, is expressed selectively by Leydig cells of the adult testes (23). There are numerous reports of male reproductive injury after SARS–CoV infection. Leading theories postulate that this is an immune-mediated response to infection because direct inoculation of the coronavirus RNA within testicular tissue has not been described. In a 2005 study of eight postmortem SARS–CoV patients, testicular tissue contained focal atrophy despite lacking identifiable SARS viral RNA (24). Accordingly, there have been reported cases of SARS–CoV causing severe orchitis, as evidenced by extensive immunoglobulin (Ig) G precipitation in testicular interstitial tissue causing germ cell destruction and widespread testicular leukocyte infiltration (25). Further studies on the reproductive involvement of coronavirus infections are warranted, particularly within recovered patients.

CORONAVIRUS EFFECTS ON MALE AND FEMALE GAMETES

There are limited data regarding the impact of SARS–CoV-2 on human reproduction because the virus is novel and has only recently infected humans. To date, there have been no reports of the virus in the female reproductive tract, in vaginal

secretions, in amniotic fluid, or in peritoneal fluid. Although there is nothing to suggest that female or male gametes would be impacted directly by infection with SARS–CoV-2 or other coronaviruses, there is evidence that fever can impact spermatogenesis. Therefore, male fertility may be diminished for 72–90 days following COVID-19 due to decreased sperm concentration and motility (26, 27).

The SARS–CoV-2 virus uses ACE2 receptors to gain entry into human cells. The male reproductive system expresses ACE2 within adult Leydig cells in the testis and there are data to suggest that ACE2 plays a role in spermatogenesis. The presence of ACE2 receptors is much more prominent in the male reproductive system than the female reproductive system, but gonadotropin-dependent expression of ACE2 has been reported in human ovaries (28, 29). At this time, it is unknown if the SARS–CoV-2 virus uses ACE2 receptors in the reproductive system and what, if any, impact this would have on oocyte quality, embryo development, or ensuing pregnancy.

Gametes obtained from patients with other viral illnesses, such as human immunodeficiency virus and hepatitis, must be treated with special precautions aimed at reducing exposure of the noninfected partner and cross-contamination of reproductive tissue within the laboratory (30). These precautions are not recommended currently for SARS–CoV-2, given the lack of evidence for transmission through blood or sexual contact (31). Similarly, there is no current recommendation for screening oocyte or sperm donors for SARS–CoV-2. These are areas in which further investigation is necessary to assure the safety of stored gametes and the safety of patients undergoing assisted reproduction.

CORONAVIRUS EFFECTS ON PREGNANCY OUTCOMES

Coronavirus epidemics have occurred three times in the past 20 years: in 2003, SARS; in 2012, MERS-CoV; and now in 2020, COVID-19. Although perhaps more lethal than COVID-19, both SARS and MERS had more limited spread. And although they all cause respiratory disease, their effects on pregnancy differ.

SARS

The case fatality rate (CFR) for all reported cases of SARS in pregnancy (n = 17) was 15% (32–37), and was higher among pregnant women. Mechanical ventilation was required three times more often in pregnant versus nonpregnant women. A case control study comparing ten pregnant to 40 nonpregnant women affected by SARS reported a 60% intensive care unit admission rate and a 40% case fatality rate in the pregnant group compared with only an 18% and 0% rate in the nonpregnant group (32).

Four of seven pregnant patients with SARS miscarried in the first trimester (37). Four of five women infected after 24 weeks of gestation were delivered prematurely, largely due to their deteriorating maternal condition from SARS, at 26, 28, and 32 weeks of gestation (38). The infants born at 26 and 28 weeks developed respiratory distress syndrome requiring surfactant, but were normal weight for gestational age. However, among infants born weeks (5 to 7) after initial infection, fetal growth restriction and fibrin deposition on placental interface were seen in two of three pregnancies, suggesting compromise. There was no evidence of vertical transmission. Overall, SARS was a very serious disease for pregnant women and their fetuses.

MERS

Among pregnant patients with MERS (n = 12), 63% were admitted to the intensive care unit (7/11) and three died (CFR of 23%) (39–43). The only woman known to contract MERS in the first trimester went on to deliver a healthy infant at term (44). Of those contracting the disease after the first trimester (n = 9), one had a spontaneous loss at 20 weeks of gestation (45), one presented at 34 weeks of gestation with pre-eclampsia and had an intrauterine fetal demise (40), and a third with pre-existing respiratory issues developed MERS at 24 weeks gestation and then acute respiratory distress syndrome. Despite ventilation and cesarean delivery, both the neonate and mother subsequently died (40). Three of nine other patients were delivered preterm due to maternal hypoxia. MERS also had a high fatality rate and premature delivery rate.

COVID-19

Through April 5, 2020, there have been 19 case reports or series and two case-control reports of pregnant COVID-19 patients and/or their neonates (43, 46–62). All but four are based on the Chinese experience. The US, Israel, Korea, and Honduras have published one experience each (43, 46, 54, 63). These reports taken together report the experience of 162 COVID-19–positive pregnant patients and their 184 infants (Fig. 1). The majority of these patients presented in labor or near term; only 12 cases before 36 weeks of gestation are reported. There is only one reported case of miscarriage. No studies have yet directly examined pregnant COVID-19 patients at earlier stages of pregnancy.

The evidence from the two case-control studies (involving 46 patients and 287 controls) so far shows that COVID-19 during early pregnancy is not more severe than among nonpregnant women (53, 63); similar patterns of symptomatology, disease severity, and outcome were seen. Nonetheless, some infected pregnant patients do develop very serious disease requiring mechanical ventilation, and most very ill COVID-19 patients are delivered soon after the disease becomes severe, whether premature or full term. At least five pregnant patients have required mechanical ventilation, and two patients have died.

Full-term infants born when their mothers have active COVID-19 infections have done well overall. Most are normal weight and have normal Apgar scores. Although most have been delivered electively using cesarean section to reduce the risk of maternal transmission and reduce disease acuity, 18 cases of fetal distress have been reported. Among the 184 fetuses reported, one had intrauterine growth restriction, 13 were delivered prematurely, 12 were small for gestational

FIGURE 1

COVID-19 pregnant patients: summary of publications through April 5, 2020. abnl = abnormal; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CT = computerized tomography; CXR = chest x-ray; ECMO = extracorporeal membrane oxygenation; GA = gestational age; Ig = immunoglobulin; IUGR = intrauterine growth restriction; LBW = low birth weight; LGA = large for gestational age; neg = negative; NND = neonatal death; NP = nasopharyngeal (swab); PCR = polymerase chain reaction; PTL = preterm labor; pos = positive; RDS = respiratory distress syndrome; SGA = small for gestational age; SOB = shortness of breath.

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age, and one was large for gestational age. One stillbirth and one neonatal death were reported.

Table 1 summarizes the pregnancy-related experience of the three coronavirus epidemics. Peer-reviewed case reports to date suggest the following:

- COVID-19 has a lower maternal case fatality rate than either SARS or MERS.
- Pregnant patients display similar signs and symptoms of COVID-19 as nonpregnant patients.
- Pregnant patients are not more susceptible to coronavirus infection, nor at higher risk for severe illness.
- Severe illness may precipitate premature labor or lead to early delivery.
- Adverse infant outcomes have been reported, but it is unclear whether these outcomes are related directly to COVID-19 infection.

Coronaviruses and Vertical Transmission

Given the teratogenicity concerns associated with viruses such as Zika, there remains the question of whether vertical transmission is possible with SARS–CoV-2. Although no known cases of vertical transmission have been noted with similar respiratory viruses such as SARS and MERS, this cannot be assumed for SARS–CoV-2 (64, 65). Numerous cases reports have described pregnant women who were infected by SARS–CoV-2. In one study of 38 women from China, COVID-19 infection did not lead to maternal deaths and there were no confirmed cases of vertical transmission (66). A case series of nine COVID-19–positive women who delivered via cesarean section showed no viral RNA in the amniotic fluid, cord blood, or breastmilk (47). However, a recent case report in *JAMA* (50) suggests that vertical transmission may be possible. In this

case report, an otherwise healthy infant was born by cesarean section to a 29-year-old with reverse transcriptase polymerase chain reaction (RT-PCR)–confirmed SARS–CoV-2 infection. This infant was placed immediately into isolation and a blood sample at 2 hours of age was noted to show an elevated SARS–CoV-2 IgG level. Although the IgG can be secondary to transplacental transfer, the infant was also positive for SARS–CoV-2 IgM, which cannot be explained by maternal-fetal transfer (50). Furthermore, IgM antibodies only appear 3–7 days after infection. All five RT-PCR tests on the infant were negative for SARS–CoV-2 (50). The antibody profile of this infant is suggestive of exposure to SARS–CoV-2 in utero. A follow-up study done on six infants born to COVID-19–positive mothers showed positive IgM antibodies in two of them. Yet, all throat swabs and blood samples from the neonates tested negative for the virus. Overall, evidence of vertical transmission in the setting of COVID-19 infection is currently inconclusive. Continued observation is necessary as more data is gathered during the course of this pandemic.

Prohibitions on the Use of Potential Therapies in Pregnancy

As of March 31, 2020, there were no identified vaccines or targeted therapies for the treatment of COVID-19. Currently, treatment is aimed at supportive methods such as oxygenation/mechanical ventilation and treating complications. Because no effective treatment has been identified, a barrage of potential therapies are being trialed both within and outside of research protocols. Although this list is ever-changing, the majority of these medications target the ability of the virus to replicate or are designed to suppress or modulate the immune system, thereby limiting inflammatory

TABLE 1

Pregnancy and coronaviruses: a summary of published, peer-reviewed reports.

Characteristic	COVID-19	SARS	MERS
Cases, n	162	17	12
Age, y	23–40	27–44	31–39
GA at infection	150 at 36+ wk; 12 earlier	4–32	4–38
Symptoms at presentation, %			
Fever	50	100	58
Cough	34	76	67
Dyspnea	16	35	58
Investigations, %			
CXR/CT evidence of pneumonia	85	100	100
Maternal complications, %			
Mortality	2	18	25
Mechanical ventilation	4	35	41
Fetal complications, %			
Miscarriage	2	25	18
IUGR	9	13	9
Preterm birth	38	25	27
Neonatal complications, %			
Neonatal deaths	2	0	9
Vertical transmission	Low vs. none	0	0

Note: COVID-19 = coronavirus disease 2019; CT = computerized tomography; CXR = chest x-ray; GA = gestational age; IUGR = intrauterine growth restriction; MERS = Middle East respiratory syndrome; SARS = Severe Acute Respiratory Syndrome; GA = gestational age; IUGR = intrauterine growth restriction.
(Updated with more recent reports of COVID-19 cases, but otherwise from Dashraath P, Jing Lin Jeslyn W, Mei Xian Karen L, Li Min L, Sarah L, Biswas A, et al: Coronavirus Disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020 doi: https://doi.org/10.1016/j.ajog.2020.03.021.)

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damage (67, 68). During pregnancy these potential remedies fall into three different departments: those established to be safe in pregnancy, those with unknown status, and those that have clear or relative contraindications during pregnancy. It is imperative to consider that, although some of these interventions are safe in pregnancy, none so far have been identified as definitive treatment and all have potential risks. These concerns need to be considered as an additional risk assumed by pregnant women; some potential therapies may carry risk to the fetus or be unavailable to pregnant women.

Several investigated medical treatments for COVID-19 are known either to be safe or nonteratogenic in pregnancy. These include various immune modulators such as hydroxychloroquine/chloroquine, methylprednisolone/glucocorticoids, and the anti-viral medications lopinavir-ritonavir (69–73). It is important to note that, although nonteratogenic, the use of glucocorticoids in pregnancy has been associated with diabetes, weight gain, preterm premature rupture of membranes, hypertension, and intrauterine growth restriction. Interferon therapy, often used in hepatitis C treatment, has been well established to be safe in pregnancy (74). The use of convalescent plasma, or plasma derived from individuals who previously contracted COVID-19, has been shown to reduce disease sequela in those with severe disease (75). Given that its risk profile should be similar to a blood transfusion, there are no overt contraindications in pregnancy.

Remdesivir is an anti-viral that was seen to both prevent and treat infection caused by MERS-COV in monkeys (76). Although current clinical studies exclude pregnant women, Remdesivir may be administered in critically ill pregnant patients (NCT0428070500) (77). To date, no information is available concerning the effects of Remdesivir in pregnancy. Due to the increased release of cytokines and subsequent inflammatory damage during COVID-19, Tocilizumab, a monoclonal antibody that binds the receptor interleukin-6, has been used in China, with at least one clinical trial that is ongoing (NCT04310228) (78, 79). A major concern for pregnant patients is that IgG isotype antibodies cross the placenta at an increasing rate in accordance with gestational age (79). However, the effect of each medication on fetal development is unknown. Furthermore, in the rheumatology literature it is recommended that Tocilizumab be avoided during pregnancy given the lack of data on adverse fetal effects (80). Other antiviral medications that have been used that have clear evidence of teratogenicity, either in humans or animal models, include Favipiravir and Ribavirin (68, 81, 82). Notably, the aforementioned medications are experimental, thus it is imperative to have a risk-benefit discussion with patients given the medication side-effect profiles, potential effects in pregnancy, and unknown benefits. Until randomized trials with adequate controls are completed, it is difficult to draw definitive conclusions concerning the efficacy of any of these treatments (71).

Neonatal Morbidity and Mortality

Thus far, there has been no indication that infants born to COVID-19–positive mothers experience any significant morbidity or mortality. In the aforementioned case series of nine COVID-19–positive patients who underwent cesarean section, all of their infants had negative COVID-19 testing and had 1-minute Apgar scores of 8–9 and 5-minute Apgar scores of 9–10. In addition, none of the infants in this series experienced asphyxia or neonatal death (47). Three newborns have been confirmed with COVID-19 and their infection was likely secondary to exposure to infected caregivers. All three neonates experienced either fever, cough, or vomiting, then subsequently recovered with no severe sequelae (67). Given the disease course seen in older children, the disease severity can be expected to be worse for neonates with pre-existing cardiac or pulmonary conditions such as congenital heart disease (67).

Coronaviruses and Maternal Infectivity

There are a significant number of unknowns concerning COVID-19 and pregnancy, especially regarding the infectivity of a pregnant woman. Therefore, the majority of data are extrapolated from previous experience with other coronaviruses, SARS–CoV and MERS-CoV, as well as influenza pandemics such as the 1918 flu and the Asian flu in the late 1950s (35, 83). However, pregnant women are not more likely than nonpregnant woman to become infected with SARS–CoV-2, based on data from regions with the first COVID-19 exposures and from previous pandemics (84). Nor do

pregnant women appear to suffer a more severe disease course or higher mortality rate compared with nonpregnant women of a similar age.

It has been established that SARS–CoV-2 is spread by respiratory droplets, yet the potential for other routes of transmission, particularly during labor, is unknown (84). Limited data are available for COVID-19, but it is possible to extrapolate from limited information available on SARS–CoV-2 and other coronaviruses. In the SARS–CoV outbreak, small case reports showed no viral RNA in placental, umbilical cord blood, amniotic fluid, or breastmilk (35, 37, 84). It is important to note that fecal matter that was aerosolized via the flushing of toilets was noted to spread disease (35). One could hypothesize that amniotic fluid could become aerosolized and infect others if viral RNA was present through mixing with fecal matter. MERS-CoV had an extremely high death toll, however, only 12 cases were documented in pregnancy, and no information is available on viral RNA in pregnancy-specific tissue (35).

To date, there is limited information concerning which fluids in labor potentially could transmit SARS–CoV-2 directly or by aerosolization. Although a single maternal vaginal swab in the only suspected case of vertical transmission was negative, it is too early to conclude whether transmission can occur via vaginal secretions (50). Rectal swabs have not been obtained in pregnant patients; however, a series of ten pediatric patients did confirm SARS–CoV-2 RNA in rectal specimens (85). Thus, information regarding vaginal deliveries, although limited, remains concerning. As previously noted, case reports have shown no viral RNA in amniotic fluid, cord blood, or breast milk (47). Until more information is gathered, it is prudent for personnel present during delivery to treat all fluids as potentially contagious and wear appropriate personal protective equipment.

DISCUSSION AND CONCLUSIONS

On January 7, 2020 thanks to the initial efforts of the late Dr. Jixian Zhang, the SARS–CoV-2 virus was identified as a cause of severe cases of pneumonia that began on December 8, 2019, in Wuhan, China. In the first 3 months of 2020, the novel virus has infected more than 1.4 million people and caused more than 87,000 deaths. Declared a pandemic by the World Health Organization on March 11, 2020, the sickness has overwhelmed healthcare resources as it spread. Containment of SARS–CoV-2 has proven to be exceptionally difficult due to asymptomatic and presymptomatic spread of disease, as well as the relatively high person-to-person transmission. As the virus moved from host to host, as is typical of the single-stranded RNA viruses, SARS–CoV-2 has mutated. Notably, there is an enormous phenotypic difference in disease severity from asymptomatic infection to death, but the reasons for this striking variability remain obscure. Despite the overwhelming magnitude of the disease and its worldwide prevalence, information regarding the effects of the novel coronavirus on human reproduction are currently limited. This lack of evidence should not be considered reassuring because only 3 months have elapsed since the novel coronavirus jumped species and infected humans.

There is reason to be concerned based on data from other coronaviruses. As is typical of this family of viruses, the SARS–CoV-2 spike protein binds the ACE2 receptor, a protein found in many reproductive tissues, including the testis. Of concern, evidence exists that related coronaviruses have caused severe orchitis. Although sperm counts can be reduced by high fever alone, the question of other possible long-term effects on male and female gametes is pressing, specifically, whether there might be shedding of virus in some individuals that might affect the safety and storage of gametes. As noted, evidence continues to emerge regarding effects of the novel coronavirus in pregnancy and some initial reports suggest that complications, particularly after delivery, may be increased. Additional studies are urgently needed.

Because of the risk of viral transmission between patients, staff, physicians, and providers, and to comply with local restrictions for nonemergency surgeries, many programs of assisted reproduction have suspended procedures throughout the globe during the height of the pandemic. As the assisted reproductive technology programs resume operations it will be important to gather information regarding the status of individuals infected with the novel coronavirus, and to assess gametes and reproductive outcomes for those who had COVID-19. These studies will be enabled by the availability of serologic testing and more widespread RNA testing for the novel coronavirus. Likewise, researchers should collect data regarding outcomes of pregnancies in women who became infected during pregnancy. Although a vaccine may prevent disease, until one is available, information is needed on the safety of medical treatments and outcomes in pregnancy.

One limitation of this review is that because of the rapidly increasing number of publications, it is possible that new information may be published contradicting the findings. Because of concern about possible adverse effects, there may be a risk of bias toward reporting positive outcomes. Additionally, because reports have focused on the acuity of treatment, the reproductive effects may be present, but not yet reported. The strength of this report is that our search was comprehensive and conducted, as much as possible, in accordance with PRISMA guidelines.

The immense impact of the COVID-19 pandemic in lives lost, healthcare expenses, and economic consequences for countries and individuals is inestimable because the epidemic is still rampant throughout the globe. Although data are limited, and incomplete at this time, there is justifiable concern that reproductive consequences of the novel coronavirus may have lasting effects for male reproduction and for some pregnant women and children.

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Coronavirus previos y nuevo, Enfermedad del coronavirus 2019 (COVID-19), y reproducción humana: ¿qué sabemos?

Objetivo: Resumir el conocimiento actual sobre los efectos del nuevo coronavirus y los previos en reproducción humana, específicamente sobre gametos masculinos y femeninos y en gestación.

Diseño: Revisión de publicaciones en inglés en Pubmed y Embase hasta 6 abril 2020.

Métodos: Se seleccionaron artículos que incluyeran informes acerca de coronavirus, reproducción, patofisiología, y gestación.

Intervención (es): Ninguna

Variable principal (es): Resultados reproductivo, efectos sobre los gametos, resultados gestacionales y complicaciones neonatales.

Resultados: Setenta y nueve artículos constituyen la base de esta revisión. La unión del coronavirus a las células se produce mediante el dominio S1 de la proteína espicular y los receptores presentes en los tejidos reproductivos, incluyendo el enzima conversor de angiotensina-2 (ACE2), CD26, Ezrin y ciclofilinas. El coronavirus 1 causante del síndrome respiratorio agudo severo (SARS-CoV-1) puede causar orquitis severa dando lugar a la destrucción de las células germinales en varones. Los artículos indican una disminución en la concentración y la movilidad espermática durante 72-90 días tras la infección por Coronavirus 2019 (COVID-19). En humanos está descrita la expresión de ACE2 dependiente de gonadotropinas, aunque no está claro si el SARS-Coronavirus 2 (CoV-2) afecta negativamente a la gametogénesis femenina. Las evidencias sugieren que la infección por COVID-19 tiene una tasa de mortalidad materna menor que SARS o Síndrome respiratorio de Oriente Medio (MERS), aunque informes anecdóticos sugieren que mujeres infectadas asintomáticas pueden desarrollar síntomas respiratorios tras el parto. Las infecciones por Coronavirus 2019 durante la gestación se asocian con el parto prematuro y está descrita la transmisión neonatal postparto de la madre al recién nacido.

Conclusiones: La infección por Coronavirus 2019 puede afectar de forma negativa a algunas mujeres embarazadas y su descendencia. Se necesitan estudios adicionales para evaluar los efectos de la infección por SARS-CoV-2 en la fertilidad masculina y femenina.