Reproductive challenges during the COVID-19 pandemic

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Abstract

SARS-CoV-2, the coronavirus responsible for the ongoing pandemic, seems to have a vast spectrum of consequences, affecting almost all systems and organs. The clinical presentation may vary from asymptomatic to severe disease, both in non-pregnant and pregnant positive patients. Respiratory and cardiovascular effects are vehiculated and studied for a while now and the scientific community also started to wonder how procreation is affected by SARS-CoV-2 infection and the pandemic context. Although more research is needed, it has become apparent that the effects on reproduction are not to be neglected, whether we talk about fertility, pregnancy outcome or demographic trends.

Keywords: *COVID-19, SARS-CoV-2, pregnancy, fertility*

Rezumat

SARS-CoV-2, coronavirusul responsabil pentru pandemia în curs, pare să aibă un spectru vast de consecințe, afectând aproape toate sistemele și organele. Tabloul clinic poate varia de la lipsa oricărui simptom până la boală severă, atât în cazul pacientelor negravide, cât și al celor gravide. Efectele respiratorii și cardiovasculare sunt vehiculate și studiate de ceva vreme, iar cercetătorii au început să își pună întrebări și referitor la impactul asupra procreației pe care îl au infecția cu SARS-CoV-2 și contextul pandemic. Deși este necesar să se continue cercetările, datele disponibile fiind insuficiente, devine evident că efectele asupra reproducerii nu trebuie neglijate, indiferent că vorbim despre fertilitate, prognostic materno-fetal sau trend demografic.

Cuvinte-cheie: *COVID-19, SARS-CoV-2, sarcină, fertilitate*

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Introduction

In December 2019, a new infectious respiratory disease appeared in Wuhan, Hubei province, China[1-3]. The initial outbreak was linked to a seafood market, possibly due to contact with infected animals, but soon after, human-to-human transmission occurred and the disease, named coronavirus disease 19 (COVID-19), rapidly spread[4-6].

The etiologic agent of this new disease proved to be a novel type of coronavirus, SARS-coronavirus 2 (SARS-CoV-2), closely related to SARS-CoV, which was responsible for the SARS pandemic in 2002[3,5].

By the time we started to write this article, worldwide there were confirmed almost 230 million persons infected with SARS-CoV-2 and 4.7 million had lost the fight with this virus[7]. The long awaited first dose of vaccine was administrated on December 8, 2020[8], and today, more than nine months later, the end point of this pandemic seems much further than perceived at that time.

SARS-CoV-2 infection in the general population

SARS-CoV-2 is a positive-sense single-stranded RNA virus that presents, like any other human coronavirus, a nucleocapsid and an envelope layer which are formed of four structural proteins: E (envelope), S (spike), M (membrane), and N (nucleocapsid)[8]. SARS-CoV-2 attaches to the membranal functional receptors ACE2 (angiotensin converting enzyme 2) expressed on alveolar epithelial type 2 cells[2]. After attachment, the S protein is primed by another membranal receptor – TMPRSS2 (transmembrane serine protease-2), this process being necessary for the entrance of the virus in the host cell (through endocytosis or fusion with the cell membrane), after which the viral genome and nucleocapsid are released in the cytoplasm[5,8-10]. The viral RNA enters the host cell's nucleus, replicates and, with the help of mRNA, the viral proteins biosynthesis occurs. This is followed by maturation of the new viral particles, followed by their packing in vesicles, transfer to the cellular membrane and release. Thus, for the infection to occur, the coexpression of both ACE2 and TMPRSS2 genes is necessary[2,6,11].

Giving that ACE2 expression is not limited to the lung, SARS-CoV-2 extrapulmonary spread was observed[5]. ACE2 expression seems to be present in 7.5% of the myocardial cells, 30% of the ileal cells, 4% of the kidney cells, while in the respiratory tract it is present in approximately 2% of cells[12,13]. Current data suggest that all tissues expressing ACE2 receptors in more than 1% of cells could be a target for SARS-CoV-2[13]. The reproductive tract seems not to be spared either, giving that ACE2 is highly expressed in the vagina, uterus, ovaries, secretory endometrium, placenta, testes, Leydig cells, Sertoli cells and spermatogonia[14-16].

In COVID-19 patients, we deal with a broad spectrum of symptoms that include fever (85.6%), cough (65.7%), tiredness (42.4%), shortness of breath (21.4%), dyspnea

(18.6%), headache (13.6%), joints/muscle pain (14.8%), anosmia/hyposmia (52.73%), gustatory dysfunction (43.93%), nausea and vomiting (5%), diarrhea (3.7%) and conjunctival congestion (0.8%)[12,17].

SARS-CoV-2 infection may cause several sequalae such as severe acute respiratory distress syndrome, severe lower respiratory tract infections, coagulopathy, stroke (even in young adults), vascular disease, neurological defects (anosmia, ageusia), kidney disease, Kawasaki syndrome (in young children) and even death. The symptoms may vary a lot, the patients being asymptomatic/with mild symptoms in 81% of cases, and presenting severe symptoms and requiring hospitalization and oxygen support in 14% of cases. In 5% of cases, the patients are critical and require mechanical ventilation[17,18].

The severity of the disease proved to be related to age and comorbidities. Patients over 60 years of age with diabetes and/or hypertension seem to have the worst prognosis, approximately 44.5% of them suffering a severe form of the disease[17]. The mortality rate of COVID-19 in the general population is about 3% and is 10- to 15-fold higher compared to other coronaviruses[1,4,17-19].

COVID-19 affects the reproductive functions and fertility in female patients, being known that a severe acute illness may alter the function of the hypothalamic-pituitary gonadal axis, with the decreasing of endogenous production of estrogens and progesterone[20].

SARS-CoV-2 can affect the follicular membrane and the granular cells in ovaries, this leading to poor quality oocytes and even to infertility[21].

Transmission of SARS-CoV-2 through the reproductive tract

Both vertical and sexual transmission of SARS-CoV-2 are theoretically possible and, practically, many studies sustained this hypothesis, with laboratory findings showing the presence of antibodies, inflammation and liver injury in infants[22].

In regard to sexual transmission of SARS-CoV-2, some may claim there is no need to investigate genital secretions, giving that air droplets constitute the main spreading route for this virus, and this happens during sexual activity anyhow[23]. Current data show, however, that the sexual transmission is possible to cause delayed outbreaks after the first wave of infections, and the absence of the virus in genital secretions should not be assumed[6].

On the other hand, there are data suggesting that it is unlikely that the female genital tract is a route of SARS-CoV-2 transmission, since several studies ruled out the presence of the virus in the female genital tract secretions, and these studies included women from all age ranges and with varying degrees of disease severity[24-26].

Transmission *via* semen is especially relevant in case of patients undergoing ART, giving the theoretic possibility of the direct transmission through intracytoplasmic sperm injection and the possibility that the virus could affect the early embryogenesis[27].

By definition, the vertical transmission can occur *in utero* through the placenta, during delivery or after birth through breastfeeding. The vertical transmission of SARS-CoV-2 was suggested because the virus can be detected in the blood of newborns from mothers with COVID-19[28].

Kotlyar et al., in their meta-analysis of 38 case series, that included a total of 936 COVID-19 positive pregnant women, reported a pooled proportion of 3.2% neonatal infection (in the first 48 hours postpartum), supporting the vertical transmission hypothesis[29]. Similarly, the Zeng et al. research included 33 COVID-19 positive pregnant women of whom resulted three neonates who proved to have suffered an intrauterine transmission of SARS-CoV-2[30]. On the other hand, in the Huntley et al. research, including 284 patients who gave birth to 310 newborns, there was no vertical transmission detected[31].

Therefore, it appears to be necessary to separate newborns from their COVID-19 positive mothers and to avoid breastfeeding in order to reduce the risk of neonatal infections. To be more accurate, it is required to avoid the close contact of the mother and newborn, not the feeding with maternal milk since, similarly to SARS infection, SARS-CoV-2 has not been detected in breast milk either[32].

The best candidate to assess *in utero* the vertical transmission is IgM, giving that this antibody cannot cross the placental barrier[32]. Many studies reported the presence of IgM antibodies in the serum of newborns from women with COVID-19[22,33,34]. Yu el al., in their case report, showed that neither SARS-CoV-2, nor IgG anti-SARS-Cov-2 were present in positive pregnant women's amniotic fluid[35].

SARS-CoV-2 and pregnancy

A study assessing pregnant women hospitalized for delivery in a New York City healthcare facility showed that 15.7% were positive at the moment of their admission and only 20% of the confirmed positive women presented symptoms during their hospital stay[36].

SARS-CoV-2 infection has raised concerns in the case of pregnant woman due to the physiological changes they undergo, and which translate into immunological response alteration, increased maternal susceptibility to respiratory infections, increased oxygen requirements, not to mention the risks associated with the disease specific treatment during pregnancy[6].

In order to tolerate the semi-allogeneic fetus, pregnant women acquire a specific immune status – to be more precise, they have transient immunosuppression (due to the effect of suppressive T cells), and this makes them more susceptible to viral infections[37,38].

In SARS-CoV-2 positive patients, the T helper 17 immunity is significantly increased, and this results in the release of numerous inflammatory cytokines. The cytokines and complement system dysfunction caused by viruses, according to current available data, have adverse effects on the growth of the fetal brain, and newborns of SARS-CoV-2 positive women can be in an inflammatory state, promoted by their mothers' systemic immune response. The immune balance being very important for a normal pregnancy, when Treg cells decrease and Th17 cells increase, as happens in

COVID-19, the odds for adverse events like recurrent pregnancy loss, preeclampsia and preterm birth to happen also increase. The above imply that the inflammatory reaction associated to COVID-19 infection could in fact promote many obstetrical complications, with short- and long-term adverse maternal and fetal outcomes[18,39].

The respiratory tract during pregnancy, especially in the third trimester, is characterized by a decreased lung volume due to the elevated diaphragm and by an increased oxygen consumption subsequent to both the reduction of respiratory gases exchange surface and the expanded circulatory territory through the presence of the fetoplacental unit. These changes in lung volume and vasodilation determine airway edema with increased respiratory secretions, making pregnant women to poorly tolerate hypoxia[18].

The spectrum of symptoms is similar in SARS-CoV-2 positive pregnant women and in non-pregnant women suffering the infection. COVID-19 symptoms present in pregnant patients, in order of their frequency, are the following: fever (40%), headache (40%), cough (39%), chills (28%), loss of smell and taste (16%), shortness of breath (13.2%), malaise (13%), muscle pain (10%), diarrhea (3.7-7%), sore throat (3.4%)[6,40].

Most of the symptoms seem to be less frequent during pregnancy[40,41], SARS-CoV-2 positive pregnant women, comparing to non-pregnant women of reproductive age, being less likely to report fever (OR 0.43; five studies; 80,521 women) and myalgia (OR 0.48; three studies; 80,409 women), but they need more often admission to an intensive care unit (ICU) (OR 1.62) and invasive ventilation (OR 1.88; four studies, 91,606 women)[6,40].

Allotey et al., analyzing the data from 26 studies (11,580 women), found 73 deaths among SARS-CoV-2 positive pregnant women (0.63%)[40], while the fatality rates for pregnant women during previous pandemics were 27-50%, 25-30% and approximately 40% for the 1918 Spanish influenza, SARS-CoV, respectively MERS[42].

The same authors found that 13% of SARS-CoV-2 positive pregnant women (21 studies, 2271 women) developed a severe form and 4% required admission to an intensive care unit (ICU) (17 studies, 10,901 women), 3% (13 studies, 10,713 women) needed invasive ventilation, and in 0.4% of cases (nine studies, 1935 women) extracorporeal membrane oxygenation was necessary[40].

Hsu at al. also studied symptom progression in SARS-CoV-2 positive pregnant patients compared to non-pregnant women and showed that an even higher percentage, respectively 8.3% (36/431), had severe disease, and of these patients, 86% (31/36) had to be admitted to the ICU[43].

Huntley et al., after analyzing 13 studies including 462 SARS-CoV-2 positive pregnant patients, presented the following findings: 3% (8/263) were admitted to the ICU and, although no maternal deaths were reported (0/313), 1.4% (3/209) of patients had critical disease[31].

Blitz et al., in their study including 332 non-pregnant and 82 pregnant symptomatic SARS-CoV-2 positive females, found the rate of admission to the ICU to be 9.8% (8/82) for pregnant women and 15.1% (50/332) for non-pregnant ones. However, their finding was not statistically significant (p=0.22), and they did not take into consideration any comorbidities or causes for admission to the hospital/ICU and more than half (28/50) of non-pregnant SARS-CoV-2 positive females were in the age group 40-49 years old[44].

Ellington et al. also concluded that SARS-CoV-2 positive pregnant women have higher chances to be hospitalized compared to non-pregnant positive women, respectively 31.5% versus 5.8%, and they found that the fatality rate was similar in both groups: 0.2% (16/8207 for pregnant women) and 0.25% (208/83,205 for non-pregnant women)[41]. These authors also did not present the causes of hospitalization, respectively pregnancy-related procedures or COVID-19 related complications.

Collin et al., in another report (from Sweden), showed that the incidence of admission to ICU for SARS-CoV-2 positive pregnant/post-partum patients was 14.4/100,000 versus 2.5/100,000 for non-pregnant SARS-CoV-2 positive women and the risk of requiring mechanical ventilation for admitted pregnant/post-partum SARS-CoV-2 positive women to be four times higher than in the case of non-pregnant group[45].

The preexisting maternal comorbidities that seem to correlate with increased severity are preexisting diabetes (OR 2.51; two studies; 858 women), high Body Mass Index (OR 2.38; three studies; 877 women), chronic hypertension (OR 2; two studies; 858 women) and higher maternal age (OR 1.78; four studies; 1058 women)[6].

Fetal outcomes in relation to COVID-19 during pregnancy

The spontaneous preterm birth rate was 6% in Allotey et al. meta-analysis (10 studies; 870 women) in patients with COVID-19, with an OR of 3.01 of preterm birth among SARS-CoV-2 positive pregnant women compared to negative pregnant women (two studies; 339 women)[40]. Huntley et al. reported an even higher preterm birth rate (20.1%; 51/284) and in their case there was one neonatal death (0.3%; 1/313)[31].

Current data suggest that almost 25% of all newborns coming from mothers with COVID-19 need admission to neonatal ICU, the risk of admission being in their case higher compared to the risk of those born to mothers without SARS-CoV-2 infection (OR=3.13; one study, 1.121 neonates)[40].

The desire to procreate during the COVID-19 pandemic

The COVID-19 pandemic also had an impact on the desire for parenthood, as shown in an Italian research that included 944 women and 538 men, aged 18-46 years old, in heterosexual stable relationships. 37.3% of the subjects who had the intention to procreate before the pandemic debut abandoned their plan during the quarantine, due to concerns regarding the potential risks for the pregnancy (58%) or eventual financial difficulties (58%). 11.5% of subjects developed a new desire for parenthood during quarantine, many in the need for

positivity (40%), although only a small percentage (4.3%) actually tried to conceive[46].

Another study assessed the willingness to go ahead with procreational plans among infertile women and 44.6% of them declared they would seriously consider postponing their pregnancy plan in the context of the COVID-19 pandemic[47].

Conclusions

To sum up, when comparing to non-pregnant SARS-CoV-2 positive women, the positive pregnant ones seem to be less likely to manifest COVID-19 related symptoms and the maternal outcomes are usually favorable, but they do have higher odds of needing ICU admission when developing a severe form of the disease. Preterm birth rates are higher in pregnant women with COVID-19 and vertical transmission may be possible. Although it is difficult to quantify the impact that the anxiety and stress associated to the pandemic context have on fertility, there is evidence that SARS-CoV-2 has direct negative effects on spermatogenesis, ovarian function and pregnancy health, but further research is needed in order to elucidate the full ramifications of COVID-19 pandemic impact on reproductive health. ■

Conflicts of interests: The authors declare no conflict of interests.

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