ORIGINAL ARTICLES

Impact of SARS-CoV-2 infection on fertility: concerns in Reproductive Medicine

Infeção por SARS-CoV-2 e fertilidade: o seu impacto na Medicina da Reprodução

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ABSTRACT

The coronavirus disease 2019 pandemic brought repercussions on health services providing fertility treatments. Approximately 0.3% of the overall livebirth rate corresponds to infants conceived using assisted reproductive technology treatments every year. Besides its negative impact relative to cycle cancelations, it is thought that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may affect the human reproductive system through angiotensin-converting enzyme 2 (ACE2) receptor, and consequently lead to infertility. The SARS-CoV-2 infection may disrupt the hypothalamus-pituitary-ovary (HPO) axis, and hence oocyte quality. Moreover, the endometrial ACE2 expression raises concerns about endometrial and placental dysfunctions related to obstetrical complications when pregnancy is achieved. Furthermore, an association between COVID-19 and changes in menstrual patterns was observed. However, in men, ACE2 expression levels on testicular cells is low and presence of SARS-CoV-2 mRNA in semen is controversial. Still, imaging signs of orchitis and epididymitis in COVID-19 recovered patients and clinical hypogonadism may be responsible for impairing male fertility during the pandemic. The international recommendations firstly encouraged the gradual re-establishment of fertility treatments by identifying those patients who should be prioritized. Therefore, we assessed the importance of fertility preservation during coronavirus disease 2019 pandemic to urgent subgroups of patients (mainly oncological patients and autoimmune diseases) that are usually submitted to gonadotoxic and teratogenic treatments that cannot be deferred indefinitely awaiting for the pandemic to end. The implications of SARS-CoV-2 effects on assisted reproductive technology (ART) outcomes are also explored in this review.

Keywords: COVID-19; fertility; reproductive medicine

RESUMO

Aproximadamente 0,3% da taxa anual de nados-vivos corresponde a recém-nascidos concebidos por técnicas de procriação medicamente assistida, pelo que o novo coronavírus trouxe repercussões negativas aos serviços de saúde que garantem tratamentos de fertilidade. Além do seu impacto em relação ao cancelamento de novos ciclos, pensa-se que o coronavírus 2 associado a síndrome respiratória aguda (SARS-CoV-2) pode também afetar os sistemas reprodutivo humano através do recetor da enzima conversora de angiotensina 2 (ACE2) e, consequentemente, conduzir a infertilidade. A infeção por SARS-CoV-2 pode afetar o eixo hipotálamo-hipófise-ovário (HHO) e, portanto, a qualidade dos ovócitos. Além disso, a expressão endometrial de ACE2 pode estar associada a quadros de disfunção endometrial e placentária que podem conduzir a complicações obstétricas quando a gravidez é alcançada. Também foi observada uma associação entre a COVID-19 e alterações nos padrões

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menstruais das mulheres. Contudo, nos homens, os níveis de expressão da ACE2 nas células testiculares são baixos e a presença do mRNA da SARS-CoV-2 no sémen é controversa. Ainda assim, sinais imagiológicos de orquite e epididimite em doentes recuperados da COVID-19, ou casos de hipogonadismo clínico podem ser responsáveis por prejudicar a fertilidade masculina durante a pandemia.

As recomendações internacionais começaram por encorajar o restabelecimento gradual dos tratamentos de fertilidade, identificando os doentes que deveriam ser priorizados. Por conseguinte, avaliámos a importância da preservação da fertilidade durante a pandemia em subgrupos urgentes de doentes (principalmente doentes oncológicos e em doentes autoimunes) que são geralmente submetidos a tratamentos gonado-tóxicos e teratogénicos, que não podem ser adiados indefinidamente enquanto se aguarda o fim da pandemia. As implicações dos efeitos da SARS-CoV-2 nos resultados das técnicas de procriação medicamente assistida são também exploradas nesta revisão.

Palavras-chave: COVID-19; fertilidade; medicina da reprodução

INTRODUCTION

The first case reports of the acute respiratory syndrome caused by SARS-CoV-2 were described in the city of Wuhan, Hubei province, on 31st December 2019.[1] Since then, the ongoing pandemic of coronavirus disease 2019 (COVID-19) has affected more than 194 million people in Europe, bringing physical and mental consequences as well as a significant socioeconomical burden worldwide.[2] At first, the information about the impact of SARS-CoV-2 infection in human fertility was scarce, leading to a discontinuation of assisted reproduction techniques, involving new cycles or non-urgent gamete cryopreservation.[3] However, time runs for infertile couples, accounting for 8 to 12% of couples of reproductive age, whose chances to procreate decrease as the treatment becomes postponed. [4] Furthermore, cessation of treatments impacts the psychosocial health of these couples, who feel obligated to delay their family plans.

This review aims to summarize the available information about the impact of SARS-CoV-2 infection on human fertility as well as on assisted reproductive technology (ART).

Influence of SARS-CoV-2 on the reproductive system

Several mechanisms have been thought to be involved in the impairment of human fertility during or even following SARS-CoV-2 infection.

The ACE2 protein is part of the renin-angiotensin-aldosterone system (RAAS) and is expressed in about 72 different human tissues. [5] Unlike ACE, which catalyzes the formation of vasoconstrictors (angiotensin I and II), ACE2 generates vasodilatory, anti-inflammatory and antifibrotic Ang 1-7 from angiotensin II (Ang II), providing a negative feedback regulation of the RAAS through Mas-receptor signaling.[5,6] The co-expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) is a key point for coronavirus human hosting.[7] Besides the pulmonary tract, these proteins have also been identified in the reproductive system.[1,8] The potential deleterious effect of COVID-19 is based on the downregulation of ACE2, as it becomes saturated by the viral envelope binding in patients with SARS-CoV-2 infection, consequently increasing free Ang II levels, which has pro-apoptotic and pro-inflammatory properties.[8,9] Hence, as ACE2 is present in the testes and the female reproductive system, we aimed to evaluate how COVID-19 may impact on human steroidogenesis, germ line cells and reproductive human health.

1. Male reproductive system

The RAAS components were detected in the male reproductive system, mostly in the testes and epididymis.[6] Specifically, the ACE2 in the human testes was recently identified at the level of the spermatogonia, Leydig and Sertoli cells, but also in a small percentage of prostatic cells.[1,5,6] On the other hand, the Ang-(1-7) and its Mas-receptor were detected in the testes (mainly the Leydig cells) and on seminiferous tubules. Their expression levels increase with age, starting at puberty, reaching their highest percentage during the reproductive life.[6,10] As Leydig cells are responsible for steroidogenesis, it is suggested that ACE2, Ang-(1-7) and Mas cellular expression could be involved in testosterone synthesis, production of vascular factors to modulate the interstitial volume and modulation of spermatogenesis.[11] Nonetheless, neither Ang-(1-7) nor Mas-receptor have been identified in the seminiferous tubules of men with non-obstructive azoospermia.[5,6,10] All of these findings suggest that RAAS components play an important role in male fertility, notably in regulation of steroidogenesis and spermatogenesis.[11] We could then postulate that a downregulation of ACE2 brings deleterious effects on the male reproductive system following a SARS-CoV-2 infection.[11] As explained before, cellular hosting of SARS-CoV-2 requires the simultaneous expression of both ACE and TMPRSS2 proteins in testicular cells. However, recent research has demonstrated that SARS-CoV-2 entry at the testicular level through ACE2 receptors may be questionable, as only 4 of 6490 testicular cells

contained mRNA of both proteins expressed, making its impact on reproduction unlikely.[12] In addition, studies in ACE2 knockout mice have shown that their fertility is preserved, suggesting the existence of alternative pathways.[10]

SARS-CoV-2 RNA detection in semen samples is controversial, raising concerns about assisted reproduction and vertical transmission. [13] Two different studies analyzed SARS-CoV-2 presence in semen samples. A cross-sectional observational study by Pan *et al*. did not detect SARS-CoV-2 mRNA in any of semen samples among thirty-four COVID-19 reported cases. In contrast, Li *et al*. identified six cases of positive SARS-CoV-2 semen samples out of thirty-eight examined patients, two of them corresponding to recovered cases and four during the acute phase of infection.[14,15] The prostate gland also secretes prostate fluid, one of the main components of the seminal fluid.[5] As mentioned above, the prostate epithelium also co-expresses ACE2 and TMPRSS2 and is thus more likely to host SARS-CoV-2 and to affect its secretions. This mechanism could be an explanation for the positive SARS-CoV-2 semen samples of the study referred above.[5] Moreover, Li *et al*. also reported that 39% of COVID-19 patients had oligozoospermia (i.e. <15 x 10^6 spermatozoa/mL) when compared with age-matched male controls. As the impact of COVID-19 on semen is still debatable, international guidelines state that semen freezing of COVID-19 positive cases should only be recommended in specific situations and it should be submitted to a two-step preparation technique (similar to situations of human immunodeficiency virus/Hepatitis B infection) for intra-uterine insemination or *in vitro* fertilization (IVF).[16]

Despite of the immunological protection provided by the blood–testis barrier, SARS-CoV-2 can reach the testes causing scrotal discomfort as well as imaging findings of epididymitis or orchitis, which have been reported in up to 22,5% of acute SARS-CoV-2 infection cases.[1] A histopathological study compared the testes and epididymis from deceased male patients with COVID-19 and control cases, revealing signs of interstitial edema, red blood cell exudation, seminiferous tubules injury (with higher levels of epithelial shedding and apoptosis) and T-lymphocytes (CD3+) and CD68+ macrophages infiltration.[12] These events are responsible for inflammatory responses in the testes and epididymis that may coexist in a viral infection. This inflammation might lead to deleterious effects such as focal testicular atrophy and germ cell destruction, resulting in a reduced number of spermatozoa.[1,12] Additionally, the inflammatory cell infiltration affects the function of Leydig cells impairing steroidogenesis, notably testosterone production, and contributes to the disruption of the blood–testis barrier.[1,12] The release of inflammatory cytokines (IL6, TNF-α and MCP-1) induces oxidative stress and activates a secondary autoimmune response. It consequently leads to the production of anti-sperm antibodies, and deposition of immunoglobulin G complexes within the seminiferous tubules in COVID-19 patient, which may also impair male fertility.[1,5,12]

Regarding the hormonal changes in COVID-19 patients, many studies have shown significant increases in serum luteinizing hormone (LH) and prolactin levels in males. In contrast, decreases in testosterone to LH ratio (T:LH) and follicle-stimulating hormone (FSH) to LH ratio (FSH:LH) were observed when compared to healthy men.[5,11] A possible explanation for the LH increase is the stimulation of the reduced pool of Leydig cells through mechanisms of negative feedback, which temporarily increase the testosterone production. [17] However, if the inflammatory process continues, there is a risk of clinical hypogonadism, which consequently worsens the sperm quality parameters.[5,11] Currently, a follow-up in recovered patients for three to six months, with a serum LH and T:LH to exclude primary hypogonadism is recommended.[1]

2. <u>Female reproductive system</u>

Although expression of ACE2 receptors is more pronounced on the male reproductive system than on the female, its presence has also been reported in human ovaries.[1,5] Co-expression of ACE2 and TMPRSS2 was noted in both granulosa cells and oocytes, raising the possibility of SARS-CoV-2 impact on female fertility.[1] Ang II is important to regulate the follicular development, oocyte maturation and ovulation and it is predominant in granulosa cells.[18] On the other hand, Ang-(1-7) is present in theca-interstitial cells; it participates in steroidogenesis, oocyte meiosis resumption, but it is also involved in follicular development and atresia.[18] The follicular fluid levels of Ang-(1-7) correlate positively with the proportion of mature oocytes. [18] The RAAS components are present in all stages of follicular development, and their expression levels depend on gonadotrophin synthesis.[1] A downregulation of ACE2 induced by SARS-CoV-2 could disrupt the normal ovarian cycle, impair the oocyte quality and it also seems to be associated with significantly lower serum anti-mullerian hormone (AMH) levels in contrast to higher testosterone (T), LH and prolactin (PRL) levels.[13,19] These findings suggest a deleterious effect on endocrine function and a poor ovarian reserve in COVID-19 recovered patients when compared with unaffected women.[19] The decreased AMH and elevated T could be explained by an ovarian dysfunction, mainly caused by injury to theca and granulosa cells. [19,20] On the other hand, the increase in LH and hyperprolactinemia in COVID-19 patients could result from a dysfunction of the HPO axis. Some of the possible causes of HPO are central nervous system injuries affecting the pituitary gland or even anxiety disorders, as the incidence was increasing during pandemic. [20] Some authors advocate that ovarian damage can also be an indirect result of an immune/inflammatory response from viral infection, induced by Ang II, which increase the synthesis of reactive oxygen species (ROS). [1]

ACE2 mRNA has also been identified in the human uterus, reaching a greater expression in the secretory phase in both epithelial cells and stromal cells of the endometrium.[18,21] In contrast, Ang II and the AT1R expression are higher in the proliferative phase, demonstrating the variations of RAAS system during the cycle.[21] Ang II participates in spiral artery vasoconstriction, contributing to regular menstrual

cycles and enhances the proliferation of epithelial and stromal cells, causing endometrial fibrosis.[18] The balance between Ang-(1-7) and Ang II is important to maintain the integrity of the endometrium through its regeneration and contributes to myometrial activity. In situations of imbalance of their expression or changes in distribution of their receptors, cases of dysfunctional uterine bleeding and endometrial hyperplasia may develop.[1,18] Infection by SARS-CoV-2 may be one of the causes of such imbalance, as it can theoretically host endometrial cells, and in this manner, affect the early embryo implantation.[22] Furthermore, it was also demonstrated that the viral gene expression seems to increase with age, suggesting that the endometrium of older women undergoing ART is at higher risk of viral infection.[13,23]

It was previously known that some viral infections could be correlated with changes in the female reproductive system, such as the menstrual pattern.[24] In human immunodeficiency virus (HIV)-positive women, amenorrhea and prolonged cycles have been already described.[25] In the context of the COVID-19 pandemic, an anonymous survey was answered by 1031 women, 46% of whom reported changes in their menstrual cycles.[25] Observational studies were then carried out and the main changes in the menstrual cycle were dysmenorrhea and irregular menses, including prolonged and decreased menstrual flow, with an incidence up to 32% and 15%, respectively.[13,24,25] After evaluating the menstrual pattern of 177 women, Li *et al* (2021) demonstrated that 84% returned to a normal menstrual volume and 99% presented a normal menstrual cycle within one to two months after COVID-19 recovery, suggesting that all of these changes were transient.[24] Khan *et al* (2022) also demonstrated that menstrual changes are more likely to be reported in women who presented more COVID-19 symptoms (e.g headache, myalgia, dyspnea, fatigue), however no correlation between menstrual irregularities and severity of disease has been found in the literature.[24-26]

The ACE2 is widely expressed in the placental cells, even more than in the pulmonary tract, posing the possibility of vertical transmission of SARS-CoV-2 through the placenta.[22,24,27] In the placental villi, the ACE2 is mainly found in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi, reaching the highest expression level in early gestation.[22,27] ACE2 is also present in decidual cells of the maternal stroma and, in the umbilical cord, it is expressed in smooth muscles and the vascular endothelium.[27] Other components of the RAAS system seem to be present in placental cells since six weeks of gestation and they interact mainly to regulate fetal haemodynamics and development.[22] Ang-(1-7) and ACE2 are involved in vascular events as angiogenesis/vasculogenesis and development of uteroplacental circulation, in contrast to Ang II, which stimulates trophoblast invasion.[22] Hence, an abnormal expression of Ang II is associated with hypertensive disorders of pregnancy, and low placental levels of ACE2 and Ang-(1-7) have been reported in pregnancies complicated with fetal growth restriction (FGR), which had also been reported in

pregnant patients with COVID-19 infection.[22,27] All of these RAAS components could be SARS-CoV-2 target points to enter the human placenta. Still, the co-expression of ACE2 with TMPRSS2 within the placenta has not been yet identified, suggesting it may act as a barrier to vertical transmission of SARS-CoV-2. Nevertheless, more evidence is still needed to confirm the possibility of transplacental COVID-19 infection and its potential impact on fertility outcomes.[22,24] Notwithstanding the immunosuppressive status of pregnancy, the risk of SARS-CoV-2 infection in pregnant women seems to be similar to those non-pregnant. However, COVID-19 might be associated with higher complication rates, such as preterm birth, fetal distress, higher rates of cesarean section and even FGR, as described above.[1]

Impact of COVID-19 for couples in need of fertility preservation

Since May 2020, the gradual re-establishment of Reproductive Medicine encouraged to prioritize access to fertility treatments.[5] The international recommendations included the cancelation of elective diagnostic procedures, suspension of fresh and frozen embryo transfers and the deferral of new cycle treatments, the only exceptions being those patients who were currently "in-cycle" or who require fertility preservation for medical indications.[5,28]

Under normal conditions, oocyte and embryo cryopreservation as well as sperm freezing are validated procedures in female and male fertility preservation (FP) in oncological patients. However, during the COVID-19 pandemic it was necessary to implement safety protocols to proceed with FP programs, particularly with the cryopreservation process.[29] It is important to note that these patients, submitted to gonadotoxic radiotherapy and/or chemotherapy protocols, are usually in childbearing age, requiring urgent FP that cannot be delayed in relation to the increased risk of SARS-CoV-2 infection.[31] Briefly, the best strategy of FP for a specific oncological patient is established according to the final diagnosis and prognosis of the patient's disease.[28,29] The European Society for Medical Oncology (ESMO) recommends the controlled ovarian stimulation in women with an adequate ovarian reserve followed with the cryopreservation of mature oocytes in women.[30] In situations in which the ovarian stimulation did not achieve multiple growth follicles, the ovarian cortex cryopreservation (OCC) for future reimplantation may be an alternative procedure.[28,29] Juvenile patients and adult patients affected by hormone-sensitive cancers, requiring urgent gonadotoxic treatments, could be considered for OCC, yet it is not a widespread practice.[28,29] It is currently recommended that the FP program might be canceled if the patient becomes infected during the ovarian stimulation process. However, if the follicular puncture has already been performed, the oocytes cryopreservation can be carried out if it is proven that they are COVID-19 free.[29] Some challenges have also emerged regarding the embryo transfer in some subgroups of oncological patients.[28] Women with endocrine responsive breast cancers are usually submitted to endocrine therapy that might last

for five to ten years, and that could decrease fecundity at the end of the treatment. An international panel of oncologists has proposed a temporary interruption of endocrinological therapy, that should be no longer than twenty-four months, allowing patients to conceive and to deliver naturally or with ART. [32] For men of reproductive age with oncological diseases, semen cryopreservation or even oocyte fertilization for subsequent embryo cryopreservation are largely adopted FP procedures that do not imply delaying antitumoral therapies. [28,29]

Another group of patients currently considered in preservation of fertility includes those women with systemic autoimmune diseases (SADs), which affects 5% to 10% of the population, but attains mainly (around 80%) female individuals of childbearing age. [5,33] The fertility potential of these patients may be reduced by different mechanisms. Firstly, these SADs patients are usually exposed to gonadotoxic drugs and teratogenic agents, such as mycophenolate mofetil, cyclophosphamide or alkylating agents, to control the disease.[28] Moreover, these women also present with a chronic inflammatory status that might disrupt the ovarian tissue and the hypothalamic-pituitary-ovarian axis, impairing the ovarian reserve.[6] Time compels for SADs patients (e.g. systemic lupus erythematosus, antiphospholipid antibody syndrome, Sjögren's syndrome, rheumatoid arthritis, idiopathic inflammatory myopathies and vasculitis, among others), as they need to discontinue their treatments and achieve the "remission window" at least six months before ovarian stimulation and pregnancy can be considered.[1,6] The "remission window" corresponds to the period in which the inflammatory process is controlled and for some couples this period was coincident with the beginning of the pandemic, raising a dichotomy: either they stopped their therapeutics for extended periods, with the risk of a a flair up, or they restarted medication aware of the poorer outcomes of postponing ART.[1,28]

Lastly, the stratification of women with low-prognosis of conceiving (POSEIDON - Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) established groups of patients whose fertility preservation or ART should not be delayed.[28] The POSEIDON group 3 represents also a "time-sensitive" category of patients, as they are younger than thirty-five years-old, but present a dramatically reduced ovarian reserve. In fact, the remaining window to respond to ovarian stimulation is narrow, which is similar to oncological patients awaiting chemotherapy.[28] To improve fertility outcomes in low-prognosis patients at the beginning of the pandemic, POSEIDON group 4 (≥ 35 years with low ovarian reserve) was considered for either embryo freezing or fresh embryo transfer, while both POSEIDON group 2 (≥ 35 year with normal ovarian reserve but suboptimal oocyte retrieval in a previous ART cycle) and group 3 were only proposed for ovarian stimulation and oocyte/embryo freezing.[1,28]

Currently, Reproductive Medicine centers have almost resumed their activity for all infertile couples, according to local protocols and international guidelines elaborated to face the emerging problems of the pandemic era.[3]

Impact of COVID-19 for patients undergoing ART and practical considerations

Worldwide, over 1.5 million *in vitro* fertilization (IVF) cycles are performed every year, resulting in approximately 400.000 newborns, and ART babies represent 0.3% of the overall live birth rate. These numbers highlight the negative repercussions for infertile couples and for society if fertility treatments get suspended for prolonged periods during the lockdown.[28,34] Additionally, telemedicine is not even a possibility unlike some other medical fields, as long as fertility treatments require multiple in-person appointments, including frequent monitorization during ovarian stimulation, and involve multidisciplinary teams of healthcare professionals that does not allow a physical distancing.[35]

As stated earlier, time is critical for a subgroup of infertile patients, notably for older women and for those who tend to lose their fertility potential rapidly, belonging to the established POSEIDON groups. [1,28] The POSEIDON group introduced new criteria based on female's ovarian reserve, age and previous results of ovarian stimulation, if any previous cycle has been already performed, to help identifying the low-prognosis patients undergoing ART.[28] POSEIDON groups 2 and 4 represent women aging thirty-five years or more, which correspond to vulnerable groups during COVID-19 pandemics. It is important to note that by postponing ART, the probability of obtaining an euploid embryo declines after the age of thirty-four. Moreover, the risk of embryo euploid relative loss increases with woman age, from 6.7% to 15.7% at 35 and 40 years-old, respectively.[28] Evidence has also shown that to obtain at least one euploid embryo for transfer, more oocytes are needed from older patients, which means that female's age also affects the success rates of ART. For example, a predictive model developed to estimate the number of mature oocytes needed in couples undergoing ART has shown that in women aged 34 years, only six oocytes were required to obtain at least one euploid embryo, in contrast to 39 years-old women, who needed no fewer than 16 oocytes in the same conditions.[36] In fact, the estimated livebirth rate after ART cycles in women younger than 35 years-old is about 41%, which dramatically decreases to less than 5% in patients above 40 years-old.[37]

Psychological distress in infertile couples is estimated in about 36%, and besides being age-related, it also depends on the duration of infertility and on previous history of fertility treatments.[34,35] During the pandemic, the lockdown brought deprivation of freedom and the cancelation of fertility treatments, which negatively affected the emotional status of those who were planning to conceive with ART. [38] A survey including 558 women undergoing fertility treatments concluded that 85% of participants were moderately to extremely distressed by their cycle cancelation due to the COVID-19 pandemic. Of them, nearly half of participants had continued their fertility treatments despite the risks of SARS-CoV-2 and a quarter considered cycle cancelation as distressing as a loss of a child.[35] The anxiety levels were also significantly higher in women older than 35 years-

old, as well as in women with high duration of infertility and a lower ovarian reserve.[39] As we know, the periconceptional period is an opportunity for both partners to modify some behaviors that could have a negative impact in ART and pregnancy outcomes. Among infertile couples, Cirillo *et al* (2021) have identified an increase in smoking habits, from 16% to 27%, an increase of 60% in sleeping disorders needing medical therapy, and a change to unhealthy nutritional habits, due to changes in job activity, household income and even an increase in emotional eating disturbances, particularly among anxious women.[38] Therefore it is necessary to look for negative psychological effects and behavioral changes following the pandemic as they may be associated with the development and progression of cardiovascular diseases, commonly associated with poorer outcomes of ART.[38]

Based on international guidelines and local policies, the gradual resumption of ART and fertility care started at the end of May 2020, according to epidemiological criteria.[34] However, several questions have arisen in regard the COVID-19 short-term repercussions in fertility outcomes that must be pointed out. As an example, fever is a common sign of SARS-CoV-2 infection, being thought to impact male and female fertility.[1] In male patients, fever can transiently impair spermatogenesis and the sperm quality (in terms of count, DNA integrity and motility) for a period of 50 to 90 days, according to various studies.[19,40] Furthermore, it can also lead to a cytokine storm syndrome (hemophagocytic lymphohistiocytosis), which will negatively impact testicular function, as the cytokine microenvironment may be tumorigenic.[19,40] On the other hand, COVID-19 negatively affects follicular development and estradiol production in female patients undergoing ovarian stimulation for IVF, which suggests that these patients should discontinue all treatments in the acute phase of infection.[19] Despite the inherent complications of SARS-CoV-2 infection the risk of developing pulmonary and renal injuries, as well as the thromboembolic risk, increases if a COVID-19 patient presents an ovarian hyperstimulation syndrome (OHS).[1,19] To avoid OHS, AMH measurements and antral follicle counting should be performed before starting ovarian stimulation, in order to guide the dosage of gonadotrophins. In these situations, the most effective protocol to minimize the risk of OHS is the gonadotrophin-releasing hormone (GnRH) antagonist protocol, with GnRH agonist triggering oocyte maturation and elective cryopreservation of embryos.[1] Additionally, in order to reduce the risk of coagulopathy, the administration of prophylactic low-molecular weight heparin and segmentation of IVF technique may also be considered.[1,28] Similarly to ART patients, pregnant women are also at higher risk of adverse obstetrical outcomes as stated earlier, which explains why ESHRE advises deferred embryo transfer during or immediately after a COVID-19 infection.[1,38]

CONCLUSION

Besides the great impact that COVID-19 might have had on infertile couples, by deferring their chances of conceiving and delivering a healthy human being, it also brought dramatic consequences to society as a whole, as the overall rate of ART livebirths is increasing every year. There is a suggestion that SARS-CoV-2 infection influences both female and male fertility, and the adoption of general principles to avoid its transmission and the establishment of individualized ART treatments seem to be an essential key to improve chances of success after resumption of fertility care. Significantly, the psychological support of infertile couples is also of great importance to reduce the negative impact of the period of uncertainty in which we live. Nevertheless, further research on COVID-19 repercussions on the reproductive system as well as on fetal and maternal outcomes is still needed in order to establish better healthcare policies in Reproductive Medicine.

AUTHORSHIP

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