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COVID-19 and female fertility: the flaws of Italian Law 40/2004 on assisted procreation in pandemic times

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Abstract. *Background and aim:* SARS-CoV-2 has infected over 614 million people worldwide, killing more than 6.5 million. COVID-19 impact on fertility may have far-reaching ramifications, considering that only in Italy, over 20 million people have been infected, many more considering unconfirmed cases. *Methods:* The authors aimed to outline the repercussions of COVID-19 on female reproductive capabilities, through an analysis of underlying mechanisms and dynamics liable to cause long-term COVID-19 complications and sequelae, including direct virus-induced tissue damage. *Results:* The entry receptor for SARS-CoV-2, Angiotensin-converting enzyme 2 (ACE2) can be found in several tissues and organs within the human body, including ovaries, oocytes and placenta. In order to assess the fertility-damaging potential of the disease, it is necessary to clarify highly complex mechanisms such as the ovarian renin–angiotensin system (OVRAS) affecting ovarian physiology and dysfunction. COVID-19 and its potential to undermine the fertility prospects of millions cannot be underestimated. It is therefore essential for lawmakers to solve inconsistencies such as those in Italy's Law 40/2004, which has been all but dismantled by Constitutional Court and European Court of Human Rights rulings, and cannot therefore offer a sufficient degree of certainty and reliability. *Conclusions:* When crafting novel, updated standards, norms and regulations to govern access to medically-assisted procreation, national leaders need to take into account the grave threat to fertility in a country such as Italy, which already has one of the world's lowest birth rates, posed by COVID-19 in light of currently available research findings outlining its impact on reproductive capacity. (www.actabiomedica.it)

Key words: COVID-19 pandemic, fertility, Angiotensin-converting enzyme 2 (ACE2), Medically-assisted procreation

Introduction

The COVID-19 pandemic upset our lives and daily activities for over two years, and only recently has it shown signs of subsiding and possibly becoming endemic, allowing for a newfound normalcy, albeit still marked by uncertainty as the cold season approaches. As of this writing, 30th September 2022, 614.385.693 confirmed cases of COVID-19 have been reported by the World Health Organization (WHO), along with 6.522.600 fatalities. Vaccines, of which over 12.6 billion doses have been administered worldwide, have been an invaluable achievement by virtue of their major contribution to slowly taming the pandemic (1).

COVID-19, the disease caused by SARS-CoV-2 infection, has the capability to upset and compromise immune system responses. Such disruptions may cause local and systematic tissue damage mostly impacting the lower respiratory tract. Nonetheless, extrapulmonary COVID-19 repercussions have also been reported (2, 3), e.g. kidney damage, gastrointestinal issues, hepatic damage, myocardial disorders and arrhythmia, among others. Research data on COVID-19 as it pertains to reproductive functions and fertility are still

inconclusive, yet currently available findings are indeed worrisome in light of the fact that over 22 million cases have been reported just in Italy, a nation of 59 million.

Male infertility linked to SARS-CoV-2 has been researched, on account of the susceptibility of sperm to viral infection; viral mRNA has in fact been detected in the semen of COVID-19 patients, due to the fact that male gonads, with their high expression of ACE2 receptors, are likely to be particularly vulnerable.

COVID-19 long-term complications: not fully clarified but still alarming

This writing will briefly focus on female fertility and possible adverse consequences arising from COVID-19 and compromising reproductive functions. Such possible linkages are indeed relevant, in light of the scale of the COVID-19 pandemic, unprecedented in our lifetime, and the potential long-term damage to fertility prospects (4).

The underlying mechanisms and dynamics which can give rise to long-term COVID-19 complications have not yet been fully clarified. However, research findings delineate a significant array of viral pathophysiological mechanisms determining longer-term sequelae, including direct virus-induced tissue damage. Angiotensin-converting enzyme 2 (ACE2) has been acknowledged as the entry receptor for SARS-CoV-2 and can be found in several tissues and organs within the human body. Hence, the virus is capable of penetrating target cells, which it does by activating the spike protein (SP) on its surface. The SP is in fact a major antigen capable of engaging with ACE2 receptor, thus it is instrumental in enabling the virus to enter host cells by means of transmembrane serine protease 2 (specifically, transmembrane protease/serine subfamily member 2, encoded by the TMPRSS2 gene), a known human airway and alveolar protease) (5). Transmembrane serine protease 2 is in fact highly relevant, in that it plays a major role in various physiological and pathological mechanisms and dynamics, and its up- and down-regulation is determined by multiple hormonal processes. In addition, many viruses use transmembrane serine protease 2 in order to enter host cells. Among such viruses, influenza viruses and the human coronaviruses HCoV-229E, MERS-CoV (Middle East respiratory syndrome–related coronavirus, which appeared in 2012 and by July 2015, had been reported in over 21 countries) (6), SARS-CoV (7-9), responsible for the 2002–2004 SARS outbreak, and most notably, SARS-CoV-2 (10). ACE2 receptors are found in epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, among others (11). That seems to point to direct tissue damage as a distinctive trait of SARS-CoV-2 infection, which is reasonable to assume can at least partly explain the longer-term complications reported thus far (12). Endothelial cells have been reported to exhibit high ACE2 expression, along with the compromised integrity of the vessel barrier resulting in a state of procoagulation, all arising from COVID-19 infection (13). As many as 71% of patients who had survived COVID-19 have been found to have radiologically detected pulmonary abnormalities, and 25% reported functional disruptions three months after infection (14).

COVID-19 and fertility damage: a gathering storm?

The exact ways in which COVID-19 can affect female reproductive capabilities have not yet fully understood. Nonetheless, currently available findings are still highly meaningful. Abnormally high levels of interleukin (IL)-6, IL-8,IL-10, and the cytokine tumour necrosis factor-α, all reported in COVID-19 patients with varying degrees according to severity (15), can bring about a procoagulant state which is not conducive to the development of blastocyst or fetus in uterus (16). Fetal and neonatal complications such as preterm delivery, intrauterine growth restriction, miscarriage and even death have been reported in a 2020 epidemiological study, which seems to corroborate the gravity of the COVID-19 threat for pregnancy and childbearing (17). In order to fully appreciate and assess such associations, it is worth remarking that animal studies conducted in 2009 on rats, long before the pandemic, have found ACE2 in stroma and granulosa cells and in immature ovaries (18). Then in 2011, ovaries from reproductive-age and postmenopausal women were found to have ACE2 mRNA transcripts (19, 20). Just as significantly, ACE2

has been found to be highly expressed in oocytes as well. Such findings point to both ovaries and oocytes as potential SARS-CoV-2 targets. Moreover, pregnancy complications related to COVID-19 have also been hypothesized, by virtue of the fact that ACE2 is widely expressed in human placenta (21), particularly in placental villi (syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi). ACE2 presence has also been reported in the invading and intravascular trophoblast and in decidual cells in the stroma, in the arterial and venous endothelium and in the umbilical cord (smooth muscle) (21). ACE2 levels are reportedly at their highest in early gestation (22). ACE2 presence appears to vary according to pregnancy stages. ACE2 has in fact been found in the primary and secondary decidual regions, duct area and glandular epithelium at early pregnancy stages, whereas its presence has been detected in the labyrinthine placenta and epithelium of the yolk sac and amniotic sac in late pregnancy (23). Moreover, Ace2 in rat placenta begins to increase from mid-gestation (24). ACE2 expression has in fact been found to be even greater in the placenta than in the lungs, which seems to point to a possibility of placental viral infection of the placenta (17). The complex interactions between ACE2 and angiopoietins, which are mainly produced by the placenta and critically affect endothelial cell survival, are also worthy of mention. Throughout childbearing, Ang II, ACE2 and Ang-(1-7) prominently determine the regulation of blood pressure and fetal development, while their complex interactions contribute to normal uterine physiology. An abnormal or altered expression of Ang II, ACE2 and Ang-(1-7) have been associated with gestational hypertension, in turn linked to pre-eclampsia, also known as toxemia, and eclampsia (25). The likely connection of low placental ACE2 and Ang-(1–7) with intrauterine growth restriction has in fact been detected in pregnant COVID-19 patients. Such association may point to COVID-19 placental infection triggering major pregnancy complications (26). In that regard, a large multinational cohort study has reported adverse maternal outcome in 47 pregnant women with COVID-19 out of 388 (12.1%), with an 11.1% rate of admission to intensive care unit (ICU), despite a relatively low maternal mortality rate (0.8%) (27, 28). Adverse perinatal outcomes in fetuses from women with COVID-19 were found to be determined primarily by early gestational age at infection, maternal ventilatory supports and low birthweight, while a low rate of vertical transmission was reported (29). However, an accurate risk stratification of women with COVID-19 is needed to ascertain the association between different maternal characteristics or clinical findings and adverse perinatal outcomes, in order to more appropriately tailor their management. Moreover, the highly relevant role of the ovarian renin–angiotensin system (OVRAS, regulated by gonadotropins) in ovarian physiology and anomalies has been well established. Oocyte maturation, folliculogenesis, angiogenesis, ovulation, and steroidogenesis are some of the key processes deeply affected by OVRAS, in addition to the underlying dynamics at the root of apoptosis and ovarian atresia. Higher plasma levels of renin have been found in patients with polycystic ovarian syndrome (PCOS, i.e. the most common endocrinopathy that has been linked to impaired fertility and which involves 5 to 20% of reproductive-age women globally) who are undergoing ovarian stimulation than in tubal infertility patients. Such finding seems to substantiate an abnormal OVRAS expression in this disease. An involvement of OVRAS in the pathophysiology of ovarian hyperstimulation syndrome (OHSS) has also been hypothesized (30), in light of the fact that locally activated OVRAS can cause neovascularization and capillary permeability, both frequently associated with OHSS, by enhancing the activity of ACE2 (31).

The linkage between PCOS has therefore already been investigated, albeit not yet fully figured out, and could adversely impact fertility prospects as well (32). Recent findings highlighted multiple inositols roles form breast density (33) to PCOS and menopausal symptoms treatments. A cohort study on female COVID-19 patients who required intensive care show that as many as 60% of them had high testosterone levels. That is important in light of the fact that hyperandrogenemia (higher than normal circulating androgens) has been found in roughly 80% of all PCOS patients (34). Furthermore, COVID-19 positive outpatient women with PCOS reportedly have a higher incidence of COVID-19-associated symptoms (e.g. dry cough, low-grade fever, anosmia, ageusia) in

comparison to female COVID-19 patients who did not have hyperandrogenemia (35).

Such a particular category of patients often resort to freeze-all techniques, through vitrification, for future use during ovarian stimulation in order to preserve their fertility (36). It therefore appears quite safe to assume that COVID-19 is a major threat to fertility, pregnancy and to fetal well-being, particularly in presence of other risk factors (37), with research showing higher rates of premature birth, fetal distress, premature rupture of fetal membranes and cesarean section. In order to meet such majorly consequential challenges, healthcare systems need to prepare and adapt in order to face the emergencies that might be looming on the horizon. Many of our vulnerabilities have to do with the fact that restrictions, social distancing and the reallocation of resources have caused the discontinuation of "nonessential" healthcare services. Yet, postponing some interventions could potentially worsen outcomes, including pregnancy-related services (38) and even cancer treatment and screening (39, 40). At the same time, the proper training of healthcare professionals should never be compromised. Limitations on training during the Covid-19 pandemic may have severely impacted the opportunity to learn key clinical and surgical skills. A potential innovative approach for overcoming or mitigating such limitations was offered by simulation activities (41) that can enable trainees to keep developing their skills and knowledge under emergency circumstances, receive essential training and prevent what has been described as a "lockdown" of their learning and development of skills (42).

COVID-19 impact on fertility: legislative responses and the Italian case

As it is quite apparent from currently available research data, however partial and inconclusive at this stage, the procreative rights and prospects of millions of couples are jeopardized by the COVID-19 pandemic, and potentially by so-called "long COVID" syndrome, which has been reported to affect menstrual cycles, which has also been observed in the form of a decrease in menstrual volume and greater length of the menstrual cycle itself (43). That could be somehow even related to the mental and psychological impact of COVID-19 (44), although currently available data are still indecisive to draw conclusions, and equally inconclusive are the findings drawing an association between COVID-19 vaccinations and menstrual disorders (45, 46). Nonetheless, in light of the possibility that more and more couples in the future may need medically-assisted procreation (MAP), now more than ever is time to adapt the legislative frameworks governing access to such techniques. If on the one hand, MAP is controversial from a legal, moral and ethical perspective, it is essential for everyone trying to achieve parenthood to be able to rely on a set of norms and regulations aimed at equality and justice. In Italy, access to MAP is governed by Law n. 40, which was passed on 19th February 2004. Such a piece of legislation has been devised to introduce measures aimed at safeguarding embryos. Lawmakers did so by putting in place bans and restrictions broader than in most other European countries. In its original version, Law 40 in fact banned the use of human embryos for experimentation and the ban on surrogacy (both are still in place), in addition to the still banned cryopreservation of embryos and the limit to no more than three embryos which could be produced (all three had to be implanted in the same procedure); also, preimplantation diagnosis on embryos prior to implantation was illegal as well, even if the biological parents were carriers of genetically transmissible diseases; it was eventually legalized through Constitutional Court ruling n. 96/2015, which declared articles 1, subsections 1, 2 and 4 unconstitutional (47); heterologous fertilization was also prohibited and MAP techniques were only for couples with a history of sterility or infertility, where the cause is more than 50% linked to male factors (48), before the Constitutional Court overturned such provisions as well on grounds of unconstitutionality (49). Such consequential interventions by the Court have arguably made Law 40 more adherent to the principles codified by the Italian constitutional and the precepts and priorities enshrined in the he Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (also known as the Oviedo Convention) (50, 51) and in the European Convention on Human Rights (52, 53). Significantly, in fact, it was the the

European Court of Human Rights itself which eliminated the 3-embryo limitation, charging doctors with deciding on a case-by-case individual basis how many embryos should be implanted, in order to best uphold the patient's reproductive rights (54, 55). Moreover, the supernumerary embryos (i.e. those left over after the cycles and not implanted) can, as a result of that ruling, be cryopreserved. Such adjustments have gone a long way towards making Law 40 more coherent and better suited to the needs of infertile couples, but now, with the pandemic still not over and the possibility of adverse effects on the fertility of millions, it is all the more urgent to overhaul the legislation further (56). If uncertainties and lack of clarity linger in terms of gaining access to MAP procedures, an element of inequality and discrimination may be affirmed: citizens with financial means in fact travel abroad, to countries with less restrictive sets of norms and then bring the children back to Italy, engaging in "fertility tourism". That too however has risks: Law n.40/2004 offers no indication as to the legal status of children born through MAP procedures abroad, in case of surrogacy, for instance, and brought back to Italy by the commissioning parents . It is worth remarking, in that regard, that The European Court of Human Rights has urged member states to recognize and codify the legal registration of donor-conceived children born abroad (57, 58). Such children should therefore have the right to citizenship, in addition to all other rights such as inheritance, freedom of movement and so on (59, 60), while the right to know one's genetic origins is more controversial, since it would conflict with donor anonymity (61-65). According to the European judges, recognition ought to be granted even though the intended parents' country of origin does not allow it (66).

Conclusions

The angiotensin-converting enzyme (ACE) receptor is known to play a prominent role in COVID-19 pathogenesis: viral genetic material enters the cells via ACE2 receptors and is replicated by intracellular proteins. ACE2 receptors are highly expressed in cell membranes of various tissues in the body, including, ovaries, uterus, vagina, placenta, and testes. Hence, research aimed at figuring out the risks and repercussions for fertility arising from COVID-19 is of utmost importance. Against the backdrop of a still ongoing pandemic, and the impact of the disease on fertility still not fully clarified, MAP treatments ought to be accessible and implemented in accordance with broadly shared, harmonized standards and evidence-based guidelines at least among countries such as European Union members, which share a common set of core values. A higher degree of harmonization would go a long way towards reducing the trend towards fertility travels. the timing of egg collection and drop-out rates are critical for scheduling future treatments now that the curve of infection has peaked, plateaued and finally declined in every country, especially as it relates to severe cases. Urgent oocyte collections for cancer patients need to be guaranteed at all times, and oocyte retrieval procedures for women of advanced maternal age or reduced ovarian reserve should no longer be deferred, despite the backlog caused by the suspension of MAP procedures during the pandemic. Just as importantly, new technologies needs to be harnessed in order to ensure that the training of professionals be prioritized and never penalized in the event of a new pandemic emergency. It is an ethical imperative to enable infertile couples to achieve parenthood with reasonable expenses in order to avoid any form of discrimination compared to fertile couples, who can autonomously exercise their reproductive rights during the global emergency sparked by COVID-19.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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