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COVID-19 and ART: the view of the Italian Society of Fertility and Sterility and Reproductive Medicine

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Abstract

The COVID-19 pandemic is an unprecedented global situation. As ART specialists we should be cautious, carefully monitoring the situation whilst contributing by sharing novel evidence to counsel our patients, both pregnant women and would-be mothers. Time to egg collection and drop-out rates are parameters critical to scheduling treatments once the curve of infections has peaked and plateaued in each country. In order to reduce both parameters, infertile patients now require even more support from their IVF team: urgent oocyte collection for oncologic patients must be guaranteed, and oocyte retrievals for women of advanced maternal age and/or reduced ovarian reserve cannot be postponed indefinitely. This document represents the position of the Italian Society of Fertility and Sterility and Reproductive Medicine (SIFES-MR) in outlining ART priorities during and after this emergency.

Keywords: COVID-19; SARS-CoV-2; oncologic patients; advanced maternal age; reduced ovarian reserve; poor prognosis patients

COVID-19 infection: from China and Italy to a pandemic

Thirteen years ago, Cheng et al reported on *Clinical Microbiology Review* that “Coronavirus are well-known to undergo genetic recombination, which may lead to new genotypes and outbreaks: the presence of a large reservoir of SARS-CoV-like viruses in the horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb” (Cheng et al., 2007). At the beginning of January 2020, China announced a new major epidemic foci of coronavirus disease 2019 (COVID-19), now rapidly expanding worldwide. Despite contrasting theories regarding the origin of this virus, its natural development was recently demonstrated (Andersen et al., 2020). On March 11 2020, the General Director of the World Health Organization (WHO) declared the disease COVID-19 a pandemic (https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2). In this regard, many countries are using a combination of containment and mitigation activities with the intention of delaying major peaks of patients to manage the limited number of hospital beds/facilities demands (Bedford et al., 2020). Following China, Italy was the country which had the highest number of cases (on March 30, 2020: 101739 cases, 3981 currently in ICUs and 11591 deaths). During the first 10 days of March 2020, data from Italy has shown that 9–11% of actively infected patients with COVID-19 required intensive care (Remuzzi and Remuzzi, 2020). Lisa Rosenbaum recently stated in the *New England Journal of Medicine*: “Though the Italian health system is highly regarded [...], it has been impossible to meet the needs of so many critically-ill patients simultaneously. Elective surgeries have been cancelled, semi-elective procedures postponed, and operating rooms turned into makeshift ICUs. With all beds occupied, corridors and administrative areas are lined with patients, some of them receiving noninvasive ventilation” (Rosenbaum, 2020). The author further elegantly stated “the tragedy in Italy reinforces the wisdom of many public health experts: the best outcome of this pandemic would be being accused of having over

prepared” and we, as the Italian Society of Fertility and Sterility and Reproductive Medicine (SIFES-MR), undoubtedly share her stance and drafted this report for ART specialists worldwide.

The aim of this manuscript is to propose a strategy to re-calibrate the approach of ART specialists who must deal with this potentially long-lasting COVID-19 emergency.

COVID-19 emergency and pregnancy

Although the impact of this infection on babies is low (Dong et al., 2020), newborns or children might be asymptomatic carriers of the infection, which might go undetected whilst being spread to the population. Moreover, confirmation of infection at present consists mainly of PCR for acute illness and, although many serological tests to identify antibodies are being developed, they require validation with well-characterized sera before being considered reliable.

The current scenario is fluid especially dealing with the impact of COVID-19 on gestations. To date, Fan et al hypothesized no vertical transmission of SARS-CoV-2, which was not reported in all screened products of conception and newborns (two whose mothers were infected) (Fan et al., 2020). Evidence confirmed this also in 9 late pregnancies described in the Lancet by Chen et al (Chen et al., 2020). Clearly, infected (or suspected to be infected) mothers must avoid close contact with the newborns, especially avoiding breastfeeding, as highlighted by Qiao in its comment to Chen’s report (Qiao, 2020). In general, all these evidences must be confirmed in larger studies, especially since equally-underpowered and possibly-biased reports of adverse gestational/neonatal outcomes have been also reported (Liu et al., 2020b, Liu et al., 2020a).

When it comes to the first or second trimester of gestation, the latest updates from the Centers for Disease Control and Prevention (CDC) did not report any issue to date (https://www.cdc.gov/coronavirus/2019-ncov/prepare/pregnancy-breastfeeding.html?CDC_AA_refVal=https://www.cdc.gov/coronavirus/2019-

ncov/specific-groups/pregnancy-faq.html), but conclusive information on its risks are clearly missing (Liang and Acharya, 2020). Of note, the drugs and the aid actions required in case of gestational issues are strongly contra-indicated in the first and second trimester. Yet, to our knowledge no scientific society has issued recommendations to discourage fertile couples from conceiving spontaneously during the COVID-19 emergency.

COVID-19 emergency: the position of Italian and international scientific societies in the field of ART

The authority for ART in Italy, Superior Institute of Health (ISS) and the National Center of Transplants (CNT), delivered their “Prevention measures of transmission of new Coronavirus infection (SARS-CoV-2) in Italy for reproductive cells and treatments of ART” on March 17, 2020 (Prot.605/CNT2020: http://www.trapianti.salute.gov.it/imgs/C_17_cntAvvisi_233_0_file.pdf). They recommended to: (i) avoid gamete donation programs which are not urgent; (ii) suspend IVF programs and office activity for couples that did not start ovarian stimulation yet, unless the treatment was urgent because of cancer or advanced maternal age (AMA); (iii) start new treatments only if no symptoms of infection are reported. La Marca et al summarized these recommendations in a comprehensive comment published in *Fertility and Sterility* (La Marca et al., 2020), and SIFES-MR together with PMA Italia issued their own preliminary recommendations for Italian IVF centers (<http://www.pma-italia.it/IT/news.xhtml/news/258-comunicazione-congiunta-fondazione-pma-italia-e-sifes>), as other Italian scientific societies in the field of ART did. In the international scenario, ESHRE suggested on March 19 to prevent the establishment of novel pregnancies through deferred embryo transfer, to prevent the patients from travelling for fertility treatment, and to avoid additional stress to healthcare systems. On March 23, the annual meeting has been canceled and 2 days later a “COVID-19 working group to monitor scientific reports relevant to reproductive medicine” has been formed (<https://www.eshre.eu/Press->

Room/ESHRE-News#COVID19WG). The ASRM Task Force instead released an official document on March 17 (<https://www.asrm.org/news-and-publications/covid-19/>) then updated on March 30 (<https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate1.pdf>) suggesting to suspend all new treatments, to cancel embryo transfers, to continue the cure for patients already in cycle or requiring urgent stimulation and cryopreservation, to suspend elective surgery and non-urgent diagnostic procedures, to minimize inter-person interaction, and to increase the adoption of tele-medicine. The aim of all these national and international documents is to safeguard the health of ART operators, of the couples undergoing ART and of the newborns, who must all deal with this COVID-19 emergency. These precautionary measures are based on the principles of responsibility and solidarity and are aimed at preventing the contagion, the overload of the healthcare system, as well as the establishment of a pregnancy in this situation.

Infertility in Italy: a constant decreasing trend in the number of live births and the key role of ART

The Italian population (60.7 millions) decreases 0.2% every year with a life expectancy of 82.5 years. It is amongst the oldest population in the world and is facing difficulties in financing pensions due to a lack of younger tax-payers. We have 1.35 births per woman versus 1.96 in France and 1.8 in the USA. In Italy, as well as in the majority of other countries, infertility occurs in approximately 20% of the population with many women undergoing ART at >37 years old and 35.2% of total candidates being older than 40. There are more than 300 IVF centers which overall performed 71686 cycles in 2017 and resulted in 2.5% of the live births of the whole Country (2.9% of which through gamete donation programs) (<https://www.epicentro.iss.it/focus/pma/aggiornamenti>). Clearly, ART covers a key role in our Country, a detail which cannot be overlooked.

COVID-19 emergency: putative strategy to schedule the ART treatments after the peak of infections

A precautionary approach is strongly recommended until reliable data will be produced (Schwartz and Graham, 2020). SIFES-MR suggests to all patients who already started controlled ovarian stimulation to consider deferring embryo transfer via oocyte/embryo cryopreservation. It is preferable to postpone pregnancy until reliable evidence would be produced on the relationship between COVID-19 and a gestation.

Dealing with oocyte retrievals, it is our opinion that the recommendation of scientific societies like the ASRM to continue “urgent [infertility] treatments which are time-sensitive” should not be limited to patients scheduled for “gonadotoxic therapy or extirpative reproductive surgery”, but it should include other categories of time-sensitive patients. In this regard, infertility is “a disease” according to the ICMART-WHO glossary of infertility (Zegers-Hochschild et al., 2009b, Zegers-Hochschild et al., 2009a) upon which the impact of the “time” variable is critical, especially in populations of AMA and reduced ovarian reserve women, whose chances sharply decrease over time. Further postponing ovarian stimulation and the time to oocyte retrieval to an indefinite period of time in these women will certainly affect their chance to achieve a live birth. Therefore, SIFES-MR suggests scheduling oocyte/embryo cryopreservation in these patients first, soon after the peak of COVID-19 infections will be finally overcome in each Country, while always guaranteeing oocyte retrievals for oncologic patients.

During this pandemic, some important aspects become essential: (i) the careful identification of the infertile women falling in these time-sensitive categories; (ii) the efficient personalization of the stimulation based on maternal age and ovarian reserve; (iii) and the prevention of the ART-related risks (ovarian hyperstimulation syndrome, OHSS; complications associated with the oocyte retrieval; multiple gestations).

It is implicit that only ART clinics with high expertise in the management of potentially-infectious specimens, equipped to cope with putative complications, competent in the vitrification and warming procedures, and following the recommendations of scientific societies of embryologists like the Italian Society of Embryology, Reproduction and Research (SIERR; <https://www.sierr.it/comunicazioni-news-embriologia-ricerca/emergenza-covid-19-raccomandazioni-sierr-per-il-laboratorio-di-pma.html>; translated in English and currently in press in Human Reproduction) should be allowed to perform oocyte retrievals in this emergency. Given these prerequisites, all ART clinics are also tissue centers inherently characterized by a protected setting and environment which constantly safeguards both patients and operators.

Of note, infected (or suspected to be infected) patients/operators or patients/operators that got in touch with infected (or suspected to be infected) people should undergo quarantine as a duty towards the community, and must be restricted from entering the clinic.

Prevention of OHSS

Tailoring the gonadotrophin dose with fixed GnRH antagonist protocol, GnRH agonist triggering and freeze-all of oocytes or embryos, is the first choice in this emergency period for women undergoing ART. This protocol almost eradicates the risk for OHSS (Devroey et al., 2011). Moreover, in Italy embryo cryopreservation is allowed only to protect women and newborns' safety, therefore a freeze-all approach in this COVID-19 emergency respects the current regulation, standing the absence of evidence of SARS-CoV2 effect on gestation (Legge 40/2004, Sentenza 151, May 2009).

ART-related complications

The risk for multiple gestations and putative gestational issues does not exist if transfer procedures are not performed. Dealing with oocyte retrieval instead, its putative surgical complications can be managed in the clinic; if not, this procedure must not be allowed during this emergency period. Nevertheless, the true prevalence

of oocyte retrieval-related complications is negligible and does not justify a suspension of ovarian stimulations to not overload hospitals: hemoperitoneum prevalence is 0.2%; infections or abscesses prevalence is 0.04% (only 60% of which require hospitalization); anesthesia-dependent issues (e.g. hypotension, pneumothorax, pulmonary edema, malignant hyperthermia) prevalence is also 0.04% (Levi-Setti et al., 2018).

Summary of SIFES-MR recommendations

To guarantee the prosecution of ART treatments and reduce the time to oocyte retrieval and drop-out in time-sensitive patients, we suggest:

- To use telehealth (consultations via phone or videoconferencing) where appropriate for new and returning patients. Where face-to-face consultations are required, it is advisable to minimize the number of people attending, limiting the number of people in the waiting room, ensuring one meter distance between them, scheduling the appointments and texting patients when they are ready to be seen, wear face masks, gloves and overshoes. Generally, consider reducing the number of non-essential monitoring visits.
- To prioritize the access to new ART treatments as follows: oncologic patients to be always guaranteed, then AMA and reduced ovarian reserve women soon after the peak of infections in each Country.
- To screen the patients for putative symptoms of infection both via telephone interview before they attend any clinical space and in-person on their arrival (chaperones should also be screened).
- To avoid treating patients at higher risk for COVID-19 infection due to pre-existing clinical conditions, e.g. renal disease, diabetes, hypertension, liver disease, heart problems and all diseases causing immunocompromise, such as AIDS, cancer, malnutrition.
- Intensify the cleaning and disinfection of common spaces in fertility clinics according to relevant recommendations of authorities.

- Avoid procedures like ovulation induction for timed sexual intercourse and intrauterine inseminations as these procedures are more frequent to younger women for whom the “time” variable is less important.
- Adopt personalized ovarian stimulation protocols based on AMH and antral follicle count with fixed dose of gonadotrophins and fixed antagonist protocol, agonist trigger for oocyte maturation, and freeze-all approach. These actions aim to minimize the need for ultrasound monitoring, the risk for OHSS and to avoid embryo transfer procedures.
- Emergency plans should be in place for the management of potential staffing shortages, supply shortages and unintended exposure of staff members to the risk of COVID-19 infection. In particular, the whole IVF team (clinicians, embryologists, nurses, technicians, secretariats) should be organized in groups of persons always working together in order to guarantee the quality and safety levels of the procedures and the continuity of care in case of quarantine.
- Support the couples via honest counseling regarding the still unknown COVID-19 effects on a putative gestation.
- Advise clinical and psychological support to infertile patients seeking a pregnancy, to avoid that a feeling of uncertainty (depending on or additional to this pandemic scenario) might negatively affect their future reproductive choices, thereby resulting in an increased prevalence of treatment drop-out (Gameiro et al., 2012).

Conclusions

COVID-19 disease is an unprecedented global situation which is drastically changing our daily life and perspective. As ART specialists we should be precautionous, carefully following the situation whilst contributing by sharing novel evidence to counsel our patients, both pregnant women and would-be mothers. All recommendations issued during this emergency are clearly subject to future updates. In this scenario, time to egg collection and drop-out rates are critical to schedule future treatments once the curve of infections will have peaked and finally plateaued

in each Country. In order to reduce them both, infertile patients now require even more the support of their clinicians and of the whole IVF team: urgent oocyte collections for oncologic patients must be always guaranteed, and oocyte retrievals for AMA and reduced ovarian reserve women cannot be postponed indefinitely. It is our duty towards our patients, since infertility is increasing over time, and simultaneously towards Countries like Italy which are suffering a constant decline in the live birth rates. Lastly, we consider it ethically correct to allow infertile couples to maintain a viable chance of a future pregnancy throughout this pandemic. These patients would be otherwise discriminated from fertile couples that can still autonomously choose to conceive during this possibly long-lasting global emergency.

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