Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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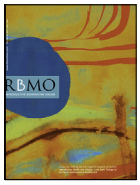

COMMENTARY

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 assisted reproductive technology (ART) specialists, we should be cautious, carefully monitoring the situation while 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 critical parameters for scheduling treatments once the curve of infections has peaked and plateaued in each country. In order to reduce the values for these two parameters, infertile patients now require even more support from their IVF team: urgent oocyte collection for oncology 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.

COVID-19 INFECTION: FROM CHINA AND ITALY TO A PANDEMIC

Thirteen years ago, Cheng and colleagues reported in *Clinical Microbiology Reviews* that:

> Coronaviruses 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 start of January 2020, China announced a new major epidemic focus of coronavirus disease 2019 (COVID-19), now rapidly expanding worldwide. Despite contrasting theories regarding the origin of this virus, its natural development has recently been demonstrated (*Andersen et al., 2020*). On 11 March 2020, the General Director of the World Health Organization (WHO) declared the disease COVID-19 to be 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 and facilities demanded (*Bedford et al., 2020*).

Following China, Italy was the country that had the highest number of cases (on 30 March 2020, 101,739 cases, with 3981 patients currently in intensive care units [ICU] and 11,591 deaths). During the first 10 days of March 2020, data from Italy showed that 9–11% of patients actively infected with COVID-19 were requiring intensive care (*Remuzzi*

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and Remuzzi, 2020). Lisa Rosenbaum recently stated in the *New England Journal of Medicine*:

Though Italy's 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, semielective 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 overprepared' and we, as the Italian Society of Fertility and Sterility and Reproductive Medicine (SIFES-MR), undoubtedly share her stance and have thus drafted this report for assisted reproductive technology (ART) specialists worldwide.

The aim of this manuscript is to propose a strategy to recalibrate 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 while being spread to the wider 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 when dealing with the impact of COVID-19 on gestation. To date, Fan and colleagues have postulated a lack of vertical transmission of SARS-CoV-2, virus not being reported in any screened products of conception or in newborns (two of whom had an infected mother) (*Fan et al., 2020*). Evidence published in *The Lancet* by Chen and co-workers confirmed these results in nine late pregnancies (*Chen et al., 2020*). Clearly, infected mothers (and those suspected to have the infection) must avoid close contact with their newborn, especially avoiding breastfeeding, as highlighted by Qiao in their comment on Chen's report (*Qiao, 2020*). In general, all this evidence must be confirmed in larger studies, especially because equally underpowered and possibly biased reports of adverse gestational/neonatal outcomes have been also reported (*Liu et al., 2020a*; *Liu et al., 2020b*).

In relation to the first or second trimester of gestation, the latest updates from the Centers for Disease Control and Prevention (CDC) have not reported 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 the risks from the virus are clearly absent (*Liang and Acharya, 2020*). Of note, the drugs and treatments required in case of gestational issues are strongly contraindicated in the first and second trimesters. However, no scientific society has yet, to our knowledge, 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, the 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 17 March 2020 (Prot.605/CNT2020; 2020 http://www.trapianti.salute.gov.it/imgs/C_17_cntAvvisi_233_0_file.pdf). They recommended the following: (i) avoidance of non-urgent gamete donation programmes; (ii) suspension of IVF programmes and office activity for couples who have not yet started ovarian stimulation, unless the treatment is urgent because of cancer or advanced maternal age; and (iii) starting new treatments only if no symptoms of infection are reported. La Marca and colleagues 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 centres (http://www.pma-italia.it/IT/news.xhtml/news/258-comunicazione-congiunta-fondazione-pma-italia-e-sifes), as did other Italian scientific societies in the ART field.

Internationally, on 19 March 2020 the European Society for Human Reproduction and Embryology (ESHRE) suggested preventing the establishment of new pregnancies through deferred embryo transfer, preventing patients from travelling for fertility treatment and avoiding additional stress on healthcare systems. On 23 March, ESHRE's annual meeting was cancelled, and 2 days later a 'COVID-19 working group to monitor scientific reports relevant to reproductive medicine' was formed

(https://www.eshre.eu/Home/COVID19WG). The American Society for Reproductive Medicine (ASRM) Task Force released an official document on 17 March 2020 (https://www.asrm.org/news-and-publications/covid-19/), then updated on 30 March (https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate1.pdf), suggesting that all new treatments should be suspended, embryo transfers suspended, treatment for patients already in the cycle or requiring urgent stimulation and cryopreservation continued, and elective surgery and non-urgent diagnostic procedures suspended, thus minimizing interperson interaction, with an increase in adoption of telemedicine.

The aim of these national and international documents is to safeguard the health of ART operators, of couples undergoing ART and of 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, avoiding overload of the healthcare system, as well as establishing 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 million) decreases by 0.2% every year and has a life expectancy of 82.5 years. It is among the oldest-aged populations in the world

and is facing difficulties in financing pensions due to a lack of younger taxpayers. There are 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 when they are over 37 years old, and 35.2% of the total number of candidates being older than 40. There are more than 300 IVF centres in Italy, which overall performed 71,686 cycles in 2017 and resulted in 2.5% of the live births of country's live births (2.9% of IVF-derived live births being through gamete donation programme) (https://www.epicentro.iss.it/focus/pma/aggiornamenti). Clearly, ART has a key role in Italy, a fact that cannot be overlooked in the current emergency.

COVID-19 EMERGENCY: PUTATIVE STRATEGY TO SCHEDULE ART TREATMENTS AFTER THE PEAK OF INFECTIONS

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

In terms of oocyte retrieval, 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 should include other categories of time-sensitive patients. In this regard, infertility is 'a disease', according to the International Committee for Monitoring Assisted Reproductive Technologies (ICMART)–WHO glossary of infertility (*Zegers-Hochschild et al., 2009a*; *Zegers-Hochschild et al., 2009b*), for which the impact of the 'time' variable is critical, especially in populations of women who are of advanced maternal age or have a reduced ovarian reserve, whose chances sharply decrease over time. In these women further postponement of ovarian stimulation and increasing the time to oocyte retrieval for an indefinite period will certainly affect their chance of achieving a live birth. Therefore, SIFES-MR suggests scheduling oocyte/embryo cryopreservation in these patients first, soon after the peak of COVID-19 infection has been passed in each country, while always guaranteeing oocyte retrieval for oncology patients.

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

It is implicit that the only ART clinics that should be allowed to perform oocyte retrieval in this emergency are those which have high expertise in the management of potentially infectious specimens, are equipped to cope with putative complications, are competent in vitrification and warming procedures, and are following the recommendations of scientific societies of embryologists such as 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; *De Santis et al., 2020*). Given these prerequisites, all ART clinics are also tissue centres that are inherently characterized by a protected setting and environment that constantly safeguards both patients and operators.

Of note, infected patients/operators, those suspected to be infected and those who have been in contacted with infected individuals (or those suspected to have the infection) should undergo quarantine as a duty towards the community, and must be restricted from entering clinics.

Prevention of OHSS

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

ART-related complications

The risk of multiple gestations and putative gestational issues does not exist if transfer procedures are not performed. As oocyte retrieval would be done instead, the putative surgical complications could 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 so as to not overload hospitals: the prevalence of haemoperitoneum is reported to be 0.2%, that of infection or abscess 0.04% (only 60% of patients requiring hospitalization), and that of anaesthesia-dependent issues (e.g. hypotension, pneumothorax, pulmonary oedema and malignant hyperthermia) also 0.04% (*Levi-Setti et al., 2018*).

SUMMARY OF SIFES-MR RECOMMENDATIONS

To guarantee the execution of ART treatments and reduce both the time to oocyte retrieval and risk of drop outs in time-sensitive patients, we suggest the following:

- Using telehealth (consultations via telephone 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 at least 1 m distance between them, scheduling the appointments and texting patients when they are ready to be seen, and wearing face masks, gloves and overshoes. Generally, consider reducing the number of non-essential monitoring visits.
- Prioritizing access to new ART treatments as follows: oncology patients always to be guaranteed treatment, with treatment then for women with advanced maternal age or reduced ovarian reserve women soon after the peak of infection in each country.

- Screening patients for putative symptoms of infection both via a telephone interview before they attend any clinical space and in person on their arrival (chaperones should also be screened).
- Avoiding treatment of patients at higher risk of COVID-19 infection due to pre-existing clinical conditions, for example renal disease, diabetes mellitus, hypertension, liver disease, heart problems and all diseases leading to immunocompromise, such as AIDS, cancer or malnutrition.
- Intensifying the cleaning and disinfection of common spaces in fertility clinics according to the authorities' relevant recommendations.
- Avoiding procedures such as ovulation induction for timed sexual intercourse and intrauterine insemination as these procedures are more frequent with younger women, for whom the 'time' variable is less important.
- Adopting personalized ovarian stimulation protocols based on anti-Müllerian hormone concentration and antral follicle count with a fixed dose of gonadotrophin and a fixed antagonist protocol, agonist trigger for oocyte maturation, and freeze-all approach. These actions aim to minimize the need for ultrasound monitoring and the risk of OHSS, and will 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 and secretariats) should be organized into 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.
- Supporting couples via honest counselling regarding the still unknown effects of COVID-19 on a putative gestation.
- Advising clinical and psychological support for infertile patients seeking a pregnancy, to avoid them having a feeling of uncertainty (depending on or additional to this pandemic scenario) that 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 that is drastically changing our daily life and perspective. ART specialists should be precautious, carefully following the situation while 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 for scheduling future treatments once the curve of infection has peaked and finally plateaued in each country. In order to reduce both time to egg collection and drop-out rate, infertile patients now more than ever require the support of their clinicians and of the whole IVF team; urgent oocyte collections for oncology patients must be always guaranteed, and oocyte retrievals for women who have advanced maternal age or reduced ovarian reserve cannot be postponed indefinitely. This is our duty towards our patients, as infertility is increasing over time, simultaneously in countries such as Italy with a constant decline in the live birth rate. Finally, we consider it ethically correct to allow infertile couples to maintain a viable chance of a future pregnancy throughout this pandemic. These patients would otherwise be discriminated against in relation to fertile couples who can still autonomously choose to conceive during this possibly long-lasting global emergency.

REFERENCES

Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F. **The proximal origin of SARS-CoV-2.** Nature Medicine 2020; 26: 450–452 doi: 10.1038/s41591-020-0820-9

Bedford, J., Enria, D., Giesecke, J., Heymann, D.L., Ihekweazu, C., Kobinger, G., Lane, H.C., Memish, Z., Oh, M.D., Sall, A.A., Schuchat, A., Ungchusak, K., Wieler, L.H., Strategic, W.H.O. **TECHNICAL ADVISORY GROUP FOR INFECTIOUS, H.. COVID-19: towards controlling of a pandemic.** Lancet 2020; 395: 1015–1018 doi: 10.1016/S0140-6736(20)30673-5

Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., Li, J., Zhao, D., Xu, D., gong, Q., Liao, J., Yang, H., Hou, W., Zhang, Y. **Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records.** Lancet 2020; 395: 809–815

Cheng, V.C., Lau, S.K., Woo, P.C., Yuen, K.Y. **Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection.** Clin. Microbiol. Rev. 2007; 20: 660–694

De Santis, L., Anastasi, A., Cimadomo, D., Klinger, F.G., Licata, E., Pisaturo, V., Sosa Fernandez, L., Scarica, C. **COVID-19: the perspective of Italian embryologists managing the IVF laboratory in pandemic emergency.** Hum. Reprod. 2020 pii:deaa074. doi: 10.1093/humrep/deaa074

Devroey, P., Polyzos, N.P., Blockeel, C. **An OHSS-Free Clinic by segmentation of IVF treatment.** Hum. Reprod. 2011; 26: 2593–2597

Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., Jiang, Z., Tong, S. **Epidemiology of COVID-19 Among Children in China.** Pediatrics 2020 pii: e20200702. doi: 10.1542/peds.2020-0702

Fan, C., Lei, D., Fang, C., LI, C., Wang, M., Liu, Y., Bao, Y., Sun, Y., Huang, J., Guo, Y., Yu, Y., Wang, S. **Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should We Worry?** Clin. Infect. Dis. 2020 pii: ciaa226. doi: 10.1093/cid/ciaa226

Gameiro, S., Boivin, J., Peronace, L., Verhaak, C.M. **Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment.** Hum. Reprod. Update 2012; 18: 652–669

La Marca, A., Niederberger, C., Pellicer, A., Nelson, S.M. **COVID-19: Lessons From the Italian Reproductive Medical Experience.** Fertil. Steril. 2020 pii: S0015-0282(20)30297-1. doi: 10.1016/j.fertnstert.2020.03.021

Levi-Setti, P.E., Cirillo, F., Scolaro, V., Morenghi, E., Heilbron, F., Girardello, D., Zannoni, E., Patrizio, P. **Appraisal of clinical complications after 23,827 oocyte retrievals in a large assisted reproductive technology program.** Fertil. Steril. 2018: 109

Liang, H., Acharya, G. **Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?** Acta Obstet. Gynecol. Scand. 2020; 99: 439–442

Liu, D., Li, L., Wu, X., Zheng, D., Wang, J., Yang, L., Zheng, C. **Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis.** AJR Am. J. Roentgenol. 2020: 1–6

Liu, Y., Chen, H., Tang, K., Guo, Y. **Clinical manifestations and outcome of SARS-CoV-2**

infection during pregnancy. J. Infect. 2020 pii: S0163-4453(20)30109-2. doi: 10.1016/j.jinf.2020.02.028

Qiao, J. **What are the risks of COVID-19 infection in pregnant women?** Lancet 2020; 395: 760–762

Remuzzi, A., Remuzzi, G. **COVID-19 and Italy: what next?** Lancet 2020; 395: 1225–1228 doi: 10.1016/S0140-6736(20)30627-9

Rosenbaum, L. **Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line.** N. Engl. J. Med. 2020 doi: 10.1056/NEJMp2005492

Schwartz, D.A., Graham, A.L. **Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections.** Viruses 2020; 12. pii: E194. doi: 10.3390/v12020194

Zegers-Hochschild, F., Adamson, G.D., De Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., Sullivan, E., Van Der Poel, S. **INTERNATIONAL COMMITTEE FOR MONITORING ASSISTED REPRODUCTIVE, T. & WORLD HEALTH, O. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009.** Hum. Reprod. 2009; 24: 2683–2687

Zegers-Hochschild, F., Adamson, G.D., DE Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., Sullivan, E., Vanderpoel, S. **INTERNATIONAL COMMITTEE FOR MONITORING ASSISTED REPRODUCTIVE, T. & WORLD HEALTH, O.. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009.** Fertil. Steril. 2009; 92: 1520–1524

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