

Medically assisted procreation in times of COVID-19: what impact on health care system organization and the reproductive rights of couples?

Giuseppe Rallo¹, Francesca Negro¹, Valeria Piersanti¹, Francesca Consalvo¹, Susanna Marinelli²

¹ Department of Anatomical, Histological, Medicolegal and Orthopedic Sciences, Sapienza University of Rome, Italy;

² School of Law, Marche Polytechnic University, Ancona, Italy

Abstract. *Introduction:* The emergency caused by the spread of COVID-19 has overwhelmed health care facilities and required the reorganization of health systems in many nations worldwide. *Objective:* The article aims to illustrate the measures aimed at containing the spread of SARS-CoV-2 and their impact on those seeking medically-assisted procreation procedures. *Materials and Methods:* By drawing upon international sources and documents from ethics committees and scientific societies about the COVID-19 pandemic and MAP, the article aims to expound upon and assess the measures issued by the Italian government in order to counter the spread of COVID-19. *Results:* The coronavirus disease 2019 (COVID-19) has had a major impact on infertile couples. Since the pandemic broke out, Italy, like most European countries, has interrupted most ordinary activities of the centers operating in the field of assisted fertilization. *Discussion:* Such measures are based on the principles of responsibility and solidarity, essential to stave off the saturation of health systems, curb contagion, but also to lay out a set of rules to starting a pregnancy while preserving the health of couples, operators and newborns. The authors also expound upon the rights claimed by couples seeking access to MAP (i.e. the right to become a parent, the couple's right to health). *Conclusions:* We believe that access to assisted fertilization techniques by sterile and infertile couples should be part of the right to health rather than of the supposed right to become parents or the increase in the birth rate, also evoked as the COVID-19 pandemic unfolded. (www.actabiomedica.it)

Key words: COVID-19, pandemic emergency, medically assisted procreation, constitutional rights

Introduction

The SARS-CoV-2 outbreak, which causes the COVID19 disease, has become one of the most significant threats to public health in recent times, so much so that the WHO on 11th March 2020 declared a pandemic status (1) due to the global spread of the virus which has caused unprecedented strain on health care systems worldwide, due to the massive number of hospitalizations (2, 3). One and a half year later,

this disease still constitutes a major threat, mostly because of the speed and ease with which it spreads. For this reason, national and supranational institutions have put in place restrictive measures affecting daily activities (4) and basic freedoms (closing of gathering places such as bars, restaurants, cinemas, theaters, gyms), thus inevitably impacting the normal functioning of almost all aspects of daily and social life, while undermining and hobbling the entire world economy. Psychological wide-ranging ramifications

have also been observed (5) and in individuals with addiction issues (6, 7) suffering considerably. The measures gradually adopted in recent months, together with the increase in tests and contact tracing (8), have had a positive effect in terms of limiting the spread of COVID-19 and flattening the curve of the infection. This has allowed the piecemeal gradual reopening of activities in the new phase of coexistence with the virus which continues to affect the lives of citizens, also in light of the recently identified variants of the virus posing a higher risk of diffusion and severity than the original virus (9). The most widespread variant in Europe is the so-called he Delta variant, also known as lineage B.1.617.2, which, based on new data, has now become the most dominant strain across much of the region (10). MAP is an ethically controversial healthcare service, as it involves the idea of family and parenthood, which may not necessarily coincide in a diverse and transforming society such as ours.

COVID-19 vaccination and MAP techniques: the current state of affairs according to scientific societies

Since early 2021, large-scale COVID-19 vaccination campaigns have been launched in Italy. All scientific societies have agreed on the need to inform and provide counseling for women and couples as to the risks versus benefits of currently available COVID-19 vaccines, both before and during MAP procedures and pregnancy (11). Although pregnant women have so far been excluded from trials, vaccination of such patients has been encouraged in Italy by the Italian Ministry of Health and scientific societies, which stressed how maternal mortality in women with COVID-19 is 22 times higher (12). Vaccination is even more important if the patient has underlying clinical conditions that could expose her to a high risk of severe complications from COVID-19, for example, in case of organ transplant, diabetes, obesity, major respiratory problems such as cystic fibrosis and severe asthma, need for immunosuppressive therapies, dialysis or chronic kidney disease and congenital or acquired heart disease (13). On November 13, 2020, the European Parliament approved a resolution (14) by which it urged member

states to uphold fundamental rights, including the right to health and services related to the sexual and reproductive needs, such as contraception, abortion and MAP procedures. Secondly, and regardless of the uncertainties related to the perinatal transmission of the virus - which indeed also affect pregnancies started without MAP - the necessary mobility of patients (sometimes even between different regions), in addition to the involvement of multiple facilities necessary for the completion of MAP procedures, have highlighted the need for particular precautions, which have resulted in the temporary suspension of almost all such treatments. Thirdly, even during this suspension phase, it has become necessary to specify which services related to sexual and reproductive health should be deemed urgent and therefore not deferrable. On the heels of the pandemic outbreak, the WHO has prompted fertility clinics to stop ordinary activities or to ensure only emergency care and the best protection of patients and health personnel through appropriately devised protocols. Such provisions were intended to limit the movement of people and access to clinical facilities in order to contain possible infections and to minimize the need for hospitalization after cycles of MAP, in the event of any complications. Most Human Reproductive Societies, such as the American Society of Reproductive Medicine (ASRM) (15), European Society of Human Reproduction and Embryology (ESHRE) (16) and the International Federation for Fertility Societies (IFFS) (17) have issued guidelines advising patients, especially those suffering from systemic diseases, such as diabetes, hypertension, heart, lung and liver or kidney diseases, and those using immunosuppressive therapy (i.e. post-transplant patients) to consult a specialist to evaluate their clinical conditions and the opportunity to start treatments at a safer time after the pandemic (18). In particular, the ASRM has advised patients who tested positive for Sars Cov-2 to freeze the oocytes or embryos and avoid their transfer until full recovery (19). In a second document, ASRM (20) and ESHRE (21) have laid out a set of recommendations for patients planning ART treatments, regardless of confirmation or suspicion of COVID-19 infections, specifically: defer new treatment cycles such as ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF)

including egg retrievals and frozen embryo transfers, in addition to non-urgent gamete cryopreservation; consider cancellation of all fresh or frozen embryo transfers; continue to care for patients who are currently undergoing treatment (“in-cycle”) or need urgent stimulation and cryopreservation; put off elective surgeries and non-urgent diagnostic procedures; keep in-person interactions to a minimum and take full advantage of telehealth-based care. In addition, priority ought to be given to all patients suffering from anxiety linked to the planning of their treatment program. Following the indications of the scientific societies, the fertility centers cancelled the treatments (22), despite the lack of scientific evidence regarding the transmission of the virus through the application of MAP techniques in the very early stages of embryonic development. Indeed, the statements on the ESHRE website warn that that “there is low probability of contamination of gametes or embryos by SARS-CoV-2, as washing steps, culture and freezing protocols appear to reduce the potentially transmitted viral load, although they may not eliminate it. The possible absence of SARS-CoV-2 receptors on gametes (spermatozoa, oocytes) and embryos would strongly support this assumption, while the presence of zona pellucida in the oocytes and embryos up to the sixth day of development cannot argue in favour of the notion that the virus may have a negative impact during IVF treatments” (16). Studies published thus far also seem to confirm that vertical transmission of SARS-CoV-2 from mother to fetus, which would likely entail medicolegal repercussions for professionals and facilities (23), is still not provable (24, 25), although not to be ruled out.

The Italian regulatory framework to combat the spread of the virus and the restrictions on MAP codified in Law 40/2004

In order to tackle the rapid expansion of the epidemic, the Italian Ministry of Health issued a release no. 7422 of March 16, 2020 (26), which draws a distinction between activities (whether outpatient or inpatient) that can be postponed in relation to the spread of the virus, and activities that cannot, based on a risk-benefit analysis. Among non-programmable activities,

urgent hospitalizations and hospitalizations of cancer patients have been included. With a subsequent release no. 8076 of 30 March 2020 (27), the Ministry of Health has recommended to include among the activities that cannot be postponed, both in- and outpatient, some services “aimed at the protection of maternal and child health”, including MAP procedures, “solely for patients already under ongoing treatment who have to carry out egg retrieval and embryo transfer”. In Italy, the National Transplant Center and the National Institute of Health on March 17, 2020 issued guidelines in which they recommended the suspension of the practice of gamete donation not only for subjects positive to COVID-19, but also for those deemed “even potentially contagious” (28). MAP centers that use gametes from foreign banks have also been urged to ascertain that the donor was COVID-19 negative, and advised to suspend “out of caution” outpatient activities and any treatments (with or without donation of gametes) for couples who have not yet started hormonal stimulation and who do not have “indications of urgency for treatment due to age or health situation”. Since these activities are not urgent in nature, it was recommended to temporarily suspend donations of reproductive cells destined for heterologous MAP procedures. Instead, the two health care bodies have recommended to keep the cryopreservation procedures of gametes for cancer patients available, and in any case, for patients candidates for or already undergoing gonadotoxic therapies, ruling out only those who presented symptoms pointing to an ongoing infection. Along the same lines, the Italian Society of Fertility, Sterility and Reproductive Medicine (SIFE-MR) has recommended only urgent treatments linked to cancer or advanced maternal age, and to start new treatments only if no symptoms of infection are reported (29). Following the gradual discontinuation of the restrictive and precautionary measures implemented during the first phase of the epidemic, on 5th May 2020 the Istituto Superiore di Sanità and the National Transplant Center issued new guidelines (30), in which they laid out how to gradually and safely resume MAP procedures. In particular, the document recommended completing the interventions suspended during the first phase of the pandemic and starting the path of MAP for couples who, for age reasons or due to clinical conditions, (e.g.

couples whose female partner had a reduced ovarian reserve) could not wait. All regulatory initiatives aimed at stemming the spread of the virus, even by limiting access to MAP procedures need to abide by the existing legislation on the matter, Law 40/2004, which has been framed for the fundamental purpose of ensuring a set of safeguards for embryos (31, 32), in the form of various stricter restrictions than in most other European countries. Nonetheless, subsequent Italian Constitutional Court rulings have done away with several such restrictions, among which: the ban on the production of more than three embryos and the obligation to implant them all in the same procedure (ruling n.151/2009), the ban on fertile couples carriers of genetic conditions from accessing heterologous fertilization (ruling n. 162/2014), the ban on preimplantation genetic diagnosis for infertile couples only (ruling n. 96/2015) (33). The prohibition of using embryos for research purposes has been left in place, and so has the ban on same-sex couples or singles from accessing MAP procedures (34). Likewise, surrogacy is banned in all its forms, with all the repercussions such a ban entails for children born abroad in countries where the practice is legal, and whose intended parents seek to bring back to Italy and have legally registered (35–44). The ethical, moral and legal complexities are likely to increase even further, with medical advancements and the development and future possible widespread use of procedures such as uterus transplant (45, 46).

Infertility in Italy: how the pandemic weighed on MAP

COVID-19 has affected medically assisted procreation procedures in a major way. In November 2020, the Italian High Institute of Health (ISS) reported 9289 fewer cycles in the first four months of 2020 compared to 2019, 1500 fewer children born and a 34.1% reduction in ART activities, peaking to 40% in northern regions, the ones most severely affected by the pandemic. An online survey by the ISS-run Italian National Registry of Medically-Assisted Procreation has found that as many as 60% of MAP centers had suspended all activities by 17th March 2020. Out of 176 centers, just three had not completely discontinued

their activities during the nationwide lockdown. Moreover, just half of centers reportedly carried out MAP procedures involving gamete donation, i.e. heterologous fertilization. Over half (56.2%) of such 89 centers had decided to suspend such procedures (47).

The age factor in MAP access in Europe

Thirty-four of the 43 countries have legal age limits for treatment. In 21 (including Czech Republic, Denmark, Greece, Portugal, Spain, Sweden, UK) males and females must be above 18 years. Maximum female age is also a legal limit in 18 countries, ranging from 45 years in Denmark and Belgium (in the latter this limit applies to egg retrievals while embryo replacement and insemination are allowed up to 47 years) to 51 in Bulgaria. There are no legal age limits in Finland, Germany, Norway, while current legislation in Spain sets a female upper limit at the “age of the menopause”, and the Netherlands at age 49. Some countries, including Austria, Hungary and Poland, have not set an age limit for granting access to MAP (48). In 2017, the biomedicine agency in France set an age limit of 43 for women. While that age limit is still in place, in June 2021 French lawmakers amended the legislation to lift the ban on single women and lesbian couples from accessing MAP procedures (49). The Italian law n. 40/2004 indicates “the age of child-bearing potential” among the subjective requirements for access to MAP treatments (Article 5); it therefore does not rigidly set the maximum age of access, but rather establishes that one must take into account the average age at which women and men can reproduce “naturally” and with their own gametes, an age that gynecological and andrological science have identified for women around the age of 51, while it has no limit for men. Also the Italian Constitutional Court, in its rulings that modified the law n. 40 of 2004, clearly stated that the legislator cannot impose decisions on technical-scientific issues, but must let experts or doctors reasonably adapt the rules to different situations. Therefore, it is the doctor who is charged with establishing, also in terms of age, what risks the woman would face following the application of a technique (e.g. ovarian stimulation), the achievement of

pregnancy (probability of miscarriage, for instance) or childbirth, following a clinical evaluation to be carried out on a case-by-case basis and in light of the woman's conditions. For this reason, the law has avoided setting strict age limits and has instead entrusted the autonomy and responsibility of the doctor with gauging the clinical risks, according to the peculiarities and distinctive traits of each individual case. In Italy, the Ministry of Health in 2017 included the services of homologous and heterologous MAP in the list of Essential Assistance Levels (LEA) (50) which establish the age limit ("up to the age of 46") and the maximum number of cycles ("up to 6 cycles") that can be provided by the Italian national health care system. It should be noted that art. 64, co. 2, of the Decree of the President of the Council of Ministers (D.P.C.M.), enacted on 12th January 2017, states that such provisions will enter into force only after the approval of a decree that have not yet been issued. Therefore, to date, the provisions approved by individual regional legislatures remain in force. In the so-called phase two of the COVID-19 health emergency, scientific societies (51) and advocacy groups (52) asked the Ministry of Health to raise the age limit for women, in order to prevent those who had reached such a limit during the suspension of the activity or were about to reach it, from being unfairly denied access through the NHS.

Conclusions

According to a recent set of directives issued by the National Center for Transplants and the Italian MAP Register, MAP procedures suspended due to the COVID-19 pandemic must resume. The two healthcare bodies have in fact argued that "the basic conditions for the resumption of MAP procedures and the initiation of new cycles have been met. Couples under emergency circumstances arising from age or underlying clinical conditions should be prioritized, as should the treatments already started and discontinued due to the pandemic scenario". The procedures should be "gradually" resumed, "including triage evaluations for couples who need to start or complete treatment and for all health care personnel operating in MAP centers. Such triage protocols are aimed at the

early identification of risk scenarios, so that all necessary infection containment measures can be put in place in a timely fashion". The resumption of MAP treatment includes both heterologous and homologous procedures, and fertility clinics have been urged to reconfigure and update their facilities in order to guarantee safety conditions. The rapid resumption of MAP activity could also be related to the fact that the WHO has recognized infertility as a disease (53) which, if not treated, could have a profoundly negative impact on the psycho-social health of infertile couples, as highlighted by the American Society for Reproductive Medicine, ESHRE and the International Federation of Fertility Societies in the guidelines earlier cited (15-17, 20, 21). In fact, most patients are anxious and fearful of the possibility to further compromise pregnancy expectations, and there is no denying that delays in treatment can significantly decrease the chances of success for such couples. The choice of the couple suffering from reproductive diseases to rely on assisted reproduction techniques to become a parent must be part of the right to health established by Article 32 of the Italian Constitution, which codifies the right to obtain the service if there are the legal conditions to access it, in addition to the obligation for health administrations to make access to the aforementioned techniques possible through proper organizational frameworks.

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Correspondence:

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Francesca Negro, MD Department of Anatomical, Histological, Medicolegal and Orthopedic Sciences, University of Rome "Sapienza",
Viale Regina Elena 336 – 00161 Roma
Tel 00390649912622 - 0039068411967
E-mail: francesca.negro@uniroma1.it