REVIEW ARTICLE

Fertility treatment during the COVID-19 pandemic: A systematic review

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Abstract

The COVID-19 pandemic has led to challenges in fertility preservation practices and has led to ethical issues, especially in developing countries. This paper provides a systematic review on this topic. At the beginning of the pandemic, several countries issued directions to suspend fertility treatments except among cancer patients. However, fertility preservation practices resumed gradually. The pandemic has evoked three major issues. First, many voices call for treating infertility as an essential medical condition in individual cases. There is no or negligible risk of transmission of COVID-19 through fertility treatment procedures or pregnancy. Second, there are weaknesses in health systems, especially in African countries. Third, there is enhanced discrimination and, in particular, a need to seriously consider inequality and social stratification in Africa. Oncofertility practices may be unevenly provided**.** The use of telemedicine to reduce nonessential contacts and the role of the Oncofertility Consortium in developing countries are highlighted. *(Afr J Reprod Health 2021; 25[5]: 161-178).*

Keywords: Oncofertility; cryopreservation / cryostorage / cryobanking; discrimination; infertility; developing countries

Résumé

La pandémie de COVID-19 a entraîné des défis dans les pratiques de préservation de la fertilité ainsi que des questions éthiques, en particulier dans les pays en développement. Cet article propose un examen systématique de ce sujet. Au début de la pandémie, plusieurs pays ont émis des instructions imposant la suspension des traitements de fertilité, à l'exception des patients atteints de cancer. Cependant, les pratiques de préservation de la fertilité ont repris progressivement. La pandémie a entraîné trois enjeux majeurs. Premièrement, de nombreuses voix appellent à traiter l'infertilité comme une condition médicale essentielle dans des cas individuels. Le risque de transmission du COVID-19 dans le cadre de procédures de traitement de l'infertilité ou de suivi de grossesse est nul ou négligeable. Deuxièmement, les systèmes de santé présentent des faiblesses, en particulier dans les pays africains. Troisièmement, la discrimination est accrue et il est nécessaire de prendre sérieusement en compte les inégalités et les stratifications sociales en Afrique. Les traitements d'oncofertilité peuvent être proposées de façons inégales**.** L'utilisation de la télémédecine pour réduire les contacts non essentiels et le rôle que peut jouer l'Oncofertilty Consortium dans les pays en développement sont mis en évidence. *(Afr J Reprod Health 2021; 25[5]: 161-178).*

Mots-clés: Oncofertilité ; Cryoconservation / Cryostockage / Cryobanque ; Discrimination ; Infertilité ; Pays en voie de développement

Introduction

Biotechnology in the field of fertility treatments has made considerable progress and includes techniques that are indicated for infertile individuals and couples, oncologic patients and those who decide to postpone motherhood. Common malignancies that occur at young age are childhood cancers, breast cancer, and blood cancers. Breast cancer is the most common cancer in women of reproductive age. These cancers often necessitate aggressive anticancer therapies, including alkylating chemotherapy and ionizing radiation, that may lead to gonadotoxicity. However, fertility preservation can be performed before commencing gonadotoxic therapies (chemotherapy and/or radiotherapy), urgently even in limited resource settings. Oncofertility is a word that has been coined to describe an interdisciplinary field (at the intersection of two disciplines – oncology and fertility) that aims to help young women with cancer protect their future reproductive health[1]. Advances in oncofertility have given young cancer patients much hope to

preserve future fertility[2]. To prevent the infertility risk induced by anticancer gonadotoxic treatments, the most established methods for female patients are oocyte cryopreservation after hormone stimulation or ovarian cortex cryostopreservation, while sperm freezing is a widely used method available to men[3-5].

Importantly, while semen cryopreservation is a procedure that does not imply any delay in starting anticancer treatments, most fertility preservation (FP) procedures regarding females imply a delay in starting anticancer treatments[6,7]. Freezing of embryos can be attempted or freezing of eggs after controlled ovarian stimulation. Controlled ovarian stimulation (COS) to induce multiple follicular growth (MFG) usually requires approximately 9–15 days and may not be achievable (as in prepubescent patients) or allowable for aggressive cancers urgently requiring gonadotoxic protocols. If this is the case, ovarian tissue cryopreservation can be performed[8], which requires laparoscopic surgery. In vitro maturation and vitrification of oocytes could be attempted (especially in prepuberal patients or adult patients affected by aggressive cancers); however, artificial ovary technology "is still challenging and cannot be relied upon as an effective oncofertility option in limited resource settings". Gonadal shielding might be needed in the case of combined irradiation of ovaries. Ovarian temporary suppression of gonadotropin-releasing hormone (GnRH) agonists[8] and fractionation of chemo- and radiotherapy may be performed where considered suitable. Autotransplantation of ovarian tissue can be offered to restore fertility when it is not contraindicated. Neoadjuvant cytoprotective pharmacotherapy and stem cell reproductive technology are still very experimental and "not yet reliable as an effective oncofertility option"[6,7].

As the COVID-19 outbreak challenges all medical specialties, including reproductive medicine, many countries suspend fertility services as part of measures to limit the impact of the disease. The pandemic has brought new challenges in providing oncofertility treatments. During the COVID-19 pandemic, the potential utilization and safety of FP procedures (such as embryo/oocyte cryopreservation or ovarian cortex cryostorage) for cancer patients in their oncologic treatments should be defined [7]. Note, however, that delaying fertility treatment (for an unforeseeable period of time) could be very harmful to fertility patients who are not cancer patients. There may be urgent fertility treatment procedures in fertility patients who are not cancer patients.

During the COVID-19 pandemic, some issues have been raised related to the topic "FP in the time of the COVID-19 pandemic", such as:

1. FP procedures and further transmission of the coronavirus
2. Are fertility treatments essential? To that effect, to what extent might the interruption of these treatments in the time of the COVID-19 pandemic be acceptable?
3. Regarding COVID-19 and gametes/embryo/pregnancy, what is the impact of COVID-19 on gametes and reproductive tissues? Is the coronavirus transmissible to gametes? Are they additional risks for embryos? Is there risk of cross-contamination through cryobanking services? Is there risk of vertical transmission from mother to child? Does the coronavirus affect the pregnancy?

Might FP treatments be distributed unevenly in limited resource settings due to increased discrimination against certain minorities in the time of the COVID-19 pandemic?.

Methods

Design

A literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify a wide range of studies related to the aims of the study, assess comprehensive knowledge in a systematic manner and assure a replicable search strategy.

Information sources

Relevant articles were retrieved through a systematic search in electronic databases to identify peer reviewed articles. The process involved searching the PubMed and SCOPUS electronic databases. The final set of search terms used was "Fertility preservation" OR "Oncofertility" OR "In vitro fertilization" OR "In vitro fertilization" OR "In vitro fertilization" OR "In vitro fertilization" OR "IVF" OR "fertility treatment" OR "infertility preservation" OR "assisted reproductive

technology" OR "assisted reproductive technologies" combined [AND] with the term "COVID-19". These search terms were combined in keyword searches in all three databases. Additional articles were identified through other sources.

Eligibility criteria

Papers were included if they 1) were published in peer reviewed journals; 2) were written in the English language; and 3) obtained data involving essential or important knowledge related to the aims of the study.

Papers were excluded if data were published in a way that data relevant to the aims of the study could not be deciphered from overall reported data. Furthermore, papers were excluded if they: 1) reported data on the topic of interest which did not make a substantial contribution to the review; 2) were focused on data relating to particular countries which are not Western or African; or 3) were focused purely on presenting, analysing and interpreting scientific data that were not directly or indirectly related to our research questions.

Study selection and data extraction

The documents identified through database searching were screened to identify relevant studies. The relevant studies were read through carefully to determine if they were eligible for analysis. Titles, abstracts and full texts of the records were screened by the reviewer in accordance with the inclusion criteria. Titles, abstracts and full texts that were assessed as ineligible for further analysis according to the inclusion/exclusion criteria or inappropriate for full-text analysis were excluded. Reference lists and citations of eligible articles were also screened and reviewed to identify additional studies.

The literature search resulted in a total of 606 documents (PubMed= 354, SCOPUS= 252). While searching two important databases for a newly appeared topic (as is the topic of interest), a considerable amount of overlapping content (duplicate documents) was retrieved. After removal of duplicates and initial screening of titles, 218 titles, abstract and full-text records were identified for screening. Ultimately, 96 articles that were assessed as eligible for review according to the inclusion/exclusion criteria were retained for further analysis (see flow chart of the systematic review process, Figure 1).

Results

Minimizing the spread of the virus

Sirohi and Lambertini describe the common hurdles fertility patients face when "dealing with the fear of both the known and unknown risks of complications from COVID-19 during cancer treatment and the additional fertility preservation treatments....", in a ***way*** that best ***reflects the reality*** of situation[2]. For instance, the authors put it best in saying that "the anxieties from the fear of contracting the virus during hospital visits leading to isolation and quarantine are real enough for some to even consider opting out of fertility preserving treatments whilst fighting their most basic desire to procreate. For health care providers, the novel challenges of providing safe and optimal care while dealing with undefined risks remain"[2].

Patients and health providers should strictly respect protective measures when accessing fertility centres. Among the mandatory measures are cleanliness, sanitization protocols, training of staff, minimum number of people present at the fertility centre at the same time, minimization of contacts between staff and patients, work behind screens when serving the public, priority given to couples with a diminished ovarian reserve, conforming to the guidelines in force, nobody apart from the couple must be allowed into the centre, the use of face masks, the use of alcohol hand sanitizers and/or gloves and shoe covers, a limited number of people allowed in the waiting room, and social distancing[9,10].

Dealing with undefined risks

Dellino et al. stated that "very few data or scientific information are today available on cautionary and protective measures to be adopted for the ART procedures in cancer patients"[7]. Therefore, complete oncofertility counselling with both oncologists and oncofertility specialists on an individual level balancing the benefits and realistic risks (of COVID-19 infection) of a fertility preservation procedure before initiating gonadotoxic anticancer therapy should be provided during the COVID-19 pandemic[2,7].

Moreover, COVID-19 testing appears to be necessary for patients before undergoing an FP procedure. For instance, it has been argued that COVID-19 testing appears to be necessary for patients before undergoing pelvic surgery to obtain ovarian tissue for cryopreservation, an ovarian transposition suggested before the start of pelvic radiation therapy or even the temporary ovarian suppression of GnRH agonists during anticancer treatment[2]. At the beginning of the pandemic, on 18th March, the Sterility Special Interest Group (GISS) and the entire Italian Society of Gynaecology and Obstetrics (SIGO) stressed the "need to refrain from initiating assisted reproduction treatments during the rise to the peak of infection to avoid spreading contagion" because the movement of people and their access to the clinical facilities may increase the risk of contamination of infertile patients and the personnel of the assisted reproduction centres[9]. This recommendation was absolutely justified provided that in the time of the COVID-19 pandemic, cancer patients are considered at high risk. *Liang et al.* argued that the risk of COVID-19 infection is definitely higher in cancer patients[11].

At the beginning of the pandemic, all societies agreed that fertility treatments should be "postponed to the fall from the peak, forecast over a period of time of no more than two or three months"[9,12].

In Italy, the Superior Institute of Health has endorsed some recommendations implying "the prosecution of the FP programs, particularly for the cryopreservation procedures, with a careful concomitant evaluation of the existing COVID-19 symptoms"[7]. In this regard, a preventive triage of patients with fever and/or respiratory symptoms in accordance with local guidelines is considered absolutely necessary during FP counselling for cancer patients and essential to prevent exposure to other patients as well as to health care providers[13]. The implementation of screening by serum detection of antibodies and COVID-19 proteins and the use of a nasopharyngeal buffer for the screening of the infection seems mandatory in cancer patients seeking to undergo FP treatments[7]. In this regard, *Alviggi et al*. describe a three-scenario approach to exclude patients at a high risk of COVID-19 infection/complications from fertility treatment[9]. An initial questionnaire-based telephone triage form should be completed 7–10 days before the start of the fertility preservation procedure. The contents of the triage form will be updated periodically.

Scenario 1 Patient and partner with no symptoms and a negative triage result. Fertility treatment cycles can be continued unless significant symptoms appear after the questionnaire has been completed.

Scenario 2 In the case of a positive triage result, a rapid test should be carried out to determine whether the procedure will be carried out.

Scenario 3 In the case of a positive triage result, the procedure will have to be deferred, with the exception of oocyte retrieval in patients with a high risk of severe ovarian hyperstimulation[9].

Similarly, Silvestris and Depalo hold the opinion that routinely screening all cancer patients undergoing FP with a prophylactic nasopharyngeal swab for COVID-19 RNA detection seems mandatory[5]. FP can be pursued when molecular testing is negative[5]. Importantly, no structured recommendations have been issued in Italy for isolating asymptomatic patients considered virus-free through negative serological tests, who may still have access to FP programs and hence unwittingly may transmit the virus to others. Day stated that as most people infected with COVID-19 show no symptoms but are still able to infect others, it should be mandatory to perform large-scale blanket testing to find and isolate asymptomatic individuals[14]. The aforementioned position of the Italian Superior Institute of Health, which might be described as "cautiously permissive", along with other organizations' positions (as presented below) indicates a trend towards loosening the restrictions on access to FP treatments, thus lending support to the assumption that fertility treatments are essential.

Furthermore, it is to be noted that according to the Italian Ministry of Health report to the Parliament (2019), the surgical complications related to FP procedures that may occur and might increase the eventual burden on hospitals are extremely rare: 0.13% of haemoperitoneum after the oocyte retrieval, 0.04% of pelvic abscesses or infections and 0.35% of hyperstimulation syndromes[9].

Communication by increasing telemedicine and telephone contact has been proposed to minimize in-person interaction. The available literature highlights the role of

telemedicine in FP and ART (artificial reproductive technologies) practices during the time of the COVID-19 pandemic (Rodriguez-Wallberg; deSouza)[15,16]. Remote consultation, remote diagnostics, and remote monitoring might be available through telemedicine and telephone contact[9]. Moreover, to make a preliminary clinical assessment prior to undergoing FP procedures, an initial telephone triage form should be completed[9].

Possible impact of COVID-19 on gametes and reproductive tissues, risk of cross-contamination through cryobanking services

Currently, there is no adequate evidence in the available literature on whether SARS-CoV-2 is present "in the human reproductive system, the follicular fluid or the seminal plasma or whether it adheres to oocytes, spermatozoa and embryos"[9]. Therefore, in clinical practice, gametes can be cryopreserved. However, SARS-CoV-2 testing should be mandatory for all infertility patients undergoing fertility preservation[7,10,17]. Below, we provide some further details on the topic.

Regarding semen, to date, the few studies carried out on the topic have reported conflicting evidence. Yakass and Woodward state: "At the time of writing, there are contradictory reports as to whether SARS-CoV-2 can be shed into semen of infected men"[18]. There is controversial evidence on the presence of SARS-CoV-2 in seminal plasma[19]. Vishvkarma and Rajender reported controversial findings. One out of two studies reported the presence of virus in the semen sample, whereas the other study did not find any virus in the semen sample[20]. Li *et al*. found SARS-CoV-2 in the semen in 26.7% of patients in the acute phase of infection and in 8.7% of recovering patients[21]. Conversely, Pan and colleagues failed to detect the virus in the semen of 34 patients diagnosed with COVID-19[22]. Similarly, Paoli and colleagues failed to detect the presence of the virus in the semen of one patient 8 days after SARS-CoV-2 PCR detection[23].

In conclusion, the presence of SARS-CoV-2 in the semen of infected patients cannot be completely ruled out, especially in asymptomatic cases[19,24]. Note, however, that it is strongly supported that the virus in the seminal fluid of COVID-19^{+} cancer males has not been confirmed[25]. In line with this assumption, it is suggested that sperm cryopreservation could be adopted for FP programs[7]. However, as "SARS-CoV-2 could be present in semen samples and in liquid nitrogen in cryostores across the world", the "use of highly secure devices" is recommended" [26].

Even in the absence of the virus in the semen, SARS-CoV-2 may cause damage to the testicular tissue among the adult male population, which may significantly impair spermatogenesis [20]. In addition, it is of great importance that fever induced by COVID-19 can impair sperm parameters even in the absence of the virus in the semen[27-29]. Holtmann *et al*. reported impairment of semen parameters in patients with moderate infection and in the absence of the virus in the semen[30]. An immune response in the testis or autoimmune orchitis may occur in some COVID-19 patients, resulting in impairment of spermatogenesis[31]. Importantly, it may take a long time before sperm parameters return to previous levels, especially in infertile men[27,28]. As a consequence, it seems quite reasonable to delay fertility treatments for three months while monitoring sperm parameters in men who have been diagnosed with COVID-19-induced fever[32].

In short, the COVID-19 pandemic may affect male fertility in various ways. The virus may be shed into the semen of infected men, impair spermatogenesis and affect sperm function. Anifandis *et al*. put it best in saying that "the possibility of the virus affecting sperm function and egg performance cannot be excluded. In addition, an indirect effect of the virus on gametes and embryos during their manipulation cannot be ruled out"[33].

Regarding the female reproductive system, it is argued that the female reproductive tract is less impacted by SARS-CoV-2 than males[34]. To date, there are no reports supporting the presence of SARS-CoV-2 in female gametes and reproductive tissues[19,35,36]. This may (at least partly) be because the zona pellucida acts as a physical barrier against viral infection[37]. Nevertheless, there is no evidence that transmission of COVID-19 to oocytes in infected women after their COS and oocyte recruitment following the MFG are possible. Therefore, the suitability and safety of fertility treatment procedures in infected females with cancer remain to be proven[7].

Regarding cryopreservation, to date, there is no sufficient evidence to suggest a risk of cross-contamination between SARS-COV-2-infected

samples and uninfected samples stored in the same container[9]. However, given that viruses such as HIV, hepatitis, influenza virus and papillomavirus retain their infectivity after cryopreservation[19], concerns about the risks of cross-contamination between SARS-COV-2-infected samples and uninfected samples seem reasonable. According to ASRM [38], transmission of viral hepatitis and HIV in assisted reproduction is possible, but the magnitude of the risk is unknown[38]. At least, the samples from patients potentially at risk should be cryopreserved in "high-safety" devices[9]. Porcu *et al*. argue very recently that "high-security closed devices are efficient and safe to protect human oocytes from potential risk of viral contamination during vitrification and storage"[39].

Cross-contamination during cryostorage is possibly related to the type of cryopreservation device used. Specific devices have been devised aiming at reducing the risk of cross-contamination[40-45]. However, the risk cannot be negated[46]. As cryobanking using LN2 (liquid nitrogen) implies the risk that cross-contamination by viral pathogens may occur, it is important to take precautionary measures. "Some of the measures include testing both partners for SARS-CoV-2 before initiating treatment, use of closed-carrier cryodevices, sanitary cryostorage protocols and efficient washing of gametes or embryos during cryopreservation…."[19].

Finally, it should be noted that many literature sources highlight the need for recommendations and guidelines on the management of infertility patients, as well as in safe handling and cryopreservation of biomaterials during fertility preservation at the time of the SARS-CoV-2 pandemic[7,17,47-49].

Possible impact of COVID-19 on pregnancy and vertical transmission from mother to child)

ASRM recommended that only infertility patients already undergoing emergency fertility preservation should complete their treatments while at the same time advising these patients to cryopreserve their embryos (ASRM, 17/3 + 30/3)[10]. On 19 March, in a similar vein, the ESHRE advised all infertility patients considering or planning treatment to avoid becoming pregnant at this time[17]. ESHRE advised these infertility patients to defer pregnancy with oocyte or embryo cryopreservation despite the current lack of strong evidence of a negative impact of COVID-19 on pregnancy, especially at the early stages. Note, however, that recommendations to avoid pregnancy have become more stringent over time due to "uncertainties about adverse outcomes, including the risk of teratogenicity and miscarriage, and worries about the capacity of providing health care in a pandemic situation"[15].

On 8 April 2020, Rodriguez-Wallberg and Wikander, 2020 stated, "According to WHO, research is currently underway to establish the impact of COVID-19 on pregnant women. Current data do not suggest that pregnant women would be at higher risk of severe illness compared with the general population"[15].

To our knowledge, there is only one study (meta-analysis) carried out by Mullins *et al*.[50] concerning COVID-19-infected women during their pregnancy. The authors reported that of 32 affected women, serious morbidity occurred in only two women. Requena *et al*. argue that pregnant women are not at high risk for developing severe infection [51]. Seven of these women gave birth to asymptomatic newborns, while two babies required intensive care units (ICUs). None of the newborns died from causes related to COVID-19. Allotey *et al*. argue that preterm birth rates may be due to COVID-19 [52]. Note, however, that Mayeur *et al*. "did not recover an increased rate of miscarriage after ART" [53].

Furthermore, the authors found that preterm delivery affected 47% of women hospitalized with COVID-19[7,50], and based on news from mass media, they concluded that "at present, there is no evidence for putative transplacental transmission of the infection"[7]. Nonetheless, the authors state that more studies are necessary to confirm that the coronavirus cannot be transmitted to foetuses[7]. Alviggi *et al*. put it best in saying that "there seems to be no or negligible vertical transmission of COVID-19 from mother to child"[9]. Moreover, de Souza *et al*. found no clear evidence of vertical transmission of the virus to the foetus in COVID-19-positive patients[16]. Note, however, that ASRM in UPDATE #6 (July 10, 2020 through August 10, 2020) states, "No data yet exist regarding the impact of SARS-CoV-2 infection on the foetus during the first or second trimesters of pregnancy…Evidence of vertical transmission of

COVID-19/SARS-CoV-2 is still unclear but possible…"[10]. More recently, the WHO (Sept 2, 2020) stated, "We still do not know if a pregnant woman with COVID-19 can pass the virus to her foetus or baby during pregnancy or delivery"[54]. Very recently, in the same line, the Royal College of Ostetricians & Gynaecologists (RCOG) stated: "Current evidence from the UK suggests that pregnant women are at no greater risk of becoming seriously unwell than other healthy adults if they develop coronavirus. The majority of pregnant women experience only mild or moderate symptoms"[55]. The RCOG also stated, "Current evidence suggests that if you have the virus, it is unlikely to cause problems with your baby's development, and there have been no reports of this thus far"[55].

Interestingly, the ESHRE COVID-19 Working Group states that according to their research, "it can be assumed that the unknown risk of vertical transmission was not a major factor in decision-making" about whether the suspended fertility preservation services would resume[56].

Are fertility treatments essential?

The uncertainties related to the COVID-19 pandemic led to the suspension of fertility treatments. Furthermore, the COVID-19 pandemic has a disproportionate impact on and gave rise to structural discrimination against minority groups and people with low socioeconomic status[57,58]. Moreover, the costs associated with fertility treatment become "higher" in the context of unprecedented economic crises that our societies are facing. In this landscape, the following questions are pushed into the foreground: Are fertility treatments essential? Does genetic relatedness have intrinsic or social value? Should we re-consider the social value of genetic relatedness?

These questions are not new. There has long been debate over whether fertility treatments should be considered essential[59,60]. Note, however, that in the clinical definition of infertility used by the World Health Organization (WHO), infertility is defined as a disease of the reproductive system[61]. Infertility affects more than 50 million couples around the world[62]. Second, the debate over whether biological ties between parents and children are intrinsically valuable is also not new. The absence of intrinsic value of the biological ties has been strongly suggested in the literature[63]. Irrespective of whether biological relatedness has intrinsic value or social norms motivate people's (especially women's) willingness to have biological offspring and hence undergo fertility treatment, it is true that sub-fertility has profoundly negative psychological implications, especially for women[64].

It is true that framing fertility treatments as "essential" places considerable emphasis on the intrinsic value of biological relatedness. Conversely, framing fertility treatments as "nonessential" not only de-emphasizes the value of biological relatedness but also lessens the pressure to conform to social norms.

At any rate, Cavaliere put it best in saying that even if social norms motivate people's (especially women's) willingness to have biological offspring, this does not mean that people lack the capacity to critically engage with these norms and formulate their preferred procreative projects[65]. The author states: "need to protect and promote prospective parents' reproductive freedom and enable them to satisfy their preferred parenthood project"[65]. Furthermore, Brock states, "Individuals' interest in autonomy is their interest in making significant decisions about their lives for themselves and according to their own values or conception of a good life…Because the choice of whether to reproduce has such far-reaching impact on people's lives, their autonomy interest in making it is typically great"[66]. Indeed, the autonomy to consider people's family planning should remain "intact" even in times of health care crisis[16]. This autonomy truly is essential[65]. de Souza *et al*. take into consideration the following two "WHO key concepts: first infertility is a disease, and should be viewed as such. Second, all women should have autonomy to consider their family planning even in times of health-care crisis"[67]. de Suza *et al*. put it best in saying: "…new data on COVID-19 continue to emerge and as research increases, new realities present themselves in different countries, regions, states or cities…Therefore, individualized recommendations, taking under consideration such geopolitical scenarios are urgently required"[16]. Alviggi *et al*. in defence of a strong right to reproduce, refers to the Italian legal framework. The authors state: "Sterility treatment is considered a right of couples with reproduction problems; this

is underlined several times in law no. 40, confirmed by the Constitutional Court in its changes to the law and, finally, implemented by the Ministry of Health as ART treatments were added to the List of Minimum Healthcare Provisions" [9]. In connection with this statement, it is noteworthy that Pennings is right when he states: "Given the generally accepted right to reproduce, the burden of proof is on those who want to restrict this right"[68].

Moreover, there have been some points of consideration in the literature in support of the assumption that fertility treatments should be considered "essential". First, many Western countries have old infertile populations with reduced possibilities of fertility treatment success. Alviggi *et al*. found that every month of inactivity in Italy means a potential monthly loss of approximately 1500 births[9]. Second, as anticipated above according to the current evidence, in all likelihood there is no transmission of COVID-19 to gametes and reproductive tissues, there is no risk of cross-contamination through cryobanking services, and there is no vertical transmission from mother to child**.** In addition, there is no sufficient evidence to support the negative impact of COVID-19 on pregnancy. Third, as anticipated above, surgical complications related to FP procedures that may occur and might increase the eventual burden on hospitals are extremely rare.

Due to the uncertainties related to the outbreak of SARS-CoV-2 in the first few months of 2020, 'nonessential' fertility treatment services were suspended in the USA, Latin America, the UK and other European countries (REDLAR\A, Ferguson, Miller)[69-71]. Following the guidance of the UK Human Fertilisation and Embryology Authority (HFEA) (issued on 17 March 2020)[72], The American Society for Reproductive Medicine (ASRM)[10] and the European Society of Human Reproduction (ESHREa)[17] several countries issued directions to suspend fertility treatments (with the exception of fertility preservation for cancer patients), a) to reduce nonessential contacts and minimize the spread of the virus, b) to support the necessary reallocation of health care resources and reduce the impact on health care services due to eventual complications of fertility treatments, such as ovarian hyperstimulation syndrome (Human Fertilisation and Embryology Authority-HFEA)[72], and c) to prevent possible maternal and foetal complications and COVID-19-related complications of pregnancy[73]. Alviggi *et al*. state, "The GISS (Sterility Special Interest Group of the Italian Society of Gynaecology and Obstetrics (SIGO) feels that the only exceptions to the suspension of activities are represented by stimulation cycles already started and fertility cryopreservation procedures in cancer patients, which will be guaranteed by the designated facilities, considering their urgency and undeferrability"[9]. In a similar vein, the British Fertility Society stated: "It is expected that UK licenced fertility centres will now be working to suspend treatments"[74].

The organizations directed the interruption of any fertility treatment (including gamete cryopreservation) while maintaining these services for cancer patients receiving gonadotoxic therapies[7]. This exception for young cancer patients is completely reasonable. Sirohi and Lambertini "urge oncologists and fertility specialists… to support young cancer patients optimizing their future fertility and reproductive health even during this pandemic"[2] . The authors state: "Let us not allow the COVID-19 outbreak to sidetrack us on this important issue"[2]. The fertility preservation (FP) procedures available for cancer patients must be considered "a topic of relevant interest during the COVID-19 crisis"[7].

In most European countries, fertility treatment practices suspended in March, that is, "when the epidemiologic curve hit the exponential phase", during the "second half of April, treatments resumed gradually in different countries", namely, when the daily new cases of COVID-19 declined (ESHRE)[56]. Fertility treatment suspension and restart were significantly determined by the recommendations of international scientific societies. In that connection, it should be noted that the suspension of fertility treatment services for noncancer subjects has had a severe impact on fertility patients[65], thereby calling into question their description as 'nonessential' treatments. This suspension (namely, postponing ART cycles) might represent disastrous consequences for patients of advanced reproductive age and reduce pregnancy rates in regard to patients with reduced ovarian reserve or those with financial problems[73]. This may be more apparent in countries with weak health care systems[75]. Note, however, that while some literature sources share the assumption that infertility is a nonemergency health problem[17,19,76],

it is also argued that fertility preservation (such as cancer treatment) is an emergency requirement even in limited resource settings and should not ideally be delayed[6]. It should be noted that a (more elaborated than previous statements) statement published by ESHRE in early April 2020 advised the suspension of all fertility treatments[17]. However, it is of great importance that the statement included an exception for urgent fertility preservation treatments…for patients who otherwise could potentially become sterile[17]. More recently, new directions have been issued to guide fertility treatments where COVID-19 infection is decreasing, in line with local regulations[10,17]. Relatedly, it has been suggested that fertility treatments should be suspended with exemptions not only for cancer patients with urgent need for fertility preservation but also for individual situations (i.e., low ovarian reserve patients), where delaying fertility treatment (for an unforeseeable period of time) could be more harmful to fertility patients than proceeding with it[16]. With regard to the male population, Esteves *et al*. proposed that the same permissive approach for sperm banking granted for men with cancer should be expanded to other subgroups of vulnerable male infertility patients to mitigate the consequences of a prolonged suspension of fertility services due to the SARS-CoV-2 pandemic[77]. Moreover, the authors aimed to help authorities and health care providers identify which patients should be prioritized for fertility preservation after testing for SARS-CoV-2[77].

de Souza *et al*. highlighting the individualization of infertility cases, states that "there is a huge pression from infertility patients" … "most patients are anxious and scared with the real possibility of compromising even further their chances of pregnancy" [16]. Interestingly, the authors state: "Brazilian law authorities, bioethics specialists and ART professionals made it clear that medical judgement should prevail in the individualization of infertility cases, as well as patient autonomy" and "Good judgement is essential to allow ART clinics to keep caring for both their staff, and their patients"[16].

According to Alviggi *et al*., although (in Italy) fertility treatments have "been reserved only to urgent cases as oncologic patients asking for fertility preservation", "the relevance of such policy on natality rate and on ovarian ageing has soon induced the main scientific societies to ask for a fast return to action, considering that infertility should be treated as an urgent condition"[9]. Vaiarelli *et al*. state that oocyte retrievals for women of advanced maternal age and/or reduced ovarian reserve cannot be postponed indefinitely[49]. Indeed, due to advanced female age, "probably thousands of potentially fertile couples were lost while waiting…"[78]. Smith *et al*. reported that "the discontinuation of fertility treatment for even 1 month in the USA could result in 369 fewer women having a live birth, due to the increase in patients' age during the shutdown"[79].

Furthermore, fertility treatment suspensions may entail negative effects on people's mental health. In our review, we found that many studies reported the negative psychological status of infertile patients who had fertility treatment interrupted or postponed due to the COVID-19 pandemic. According to recently published empirical studies, fertility clinic closure during the COVID-19 pandemic has been associated with a sharp increase in depression, anxiety and stress among infertile patients[80]. Another study demonstrated negative emotions, stress, worry, frustration and perhaps anger, "hopelessness and deteriorating well-being and mental health"[81]. Advancing age remains a major stressor for infertile women seeking treatment[82]. Lawson *et al* argue that supplemental education cannot decrease the distress that most people experience by delaying fertility treatments[83]. As a consequence, fertility treatment suspensions may have a considerable negative impact on people's (especially women's) mental health and quality of life[84,85], necessitating the need to triage these patients.

In line with the aforementioned information, the ESHRE COVID-19 Working Group highlights that infertility has been recognized by the WHO [61] as a disease, and the significant impact that a suspension of fertility treatment services might have on the mental health of infertile individuals and couples, which is highlighted in joint Statement[86] from the ARSM[10], ESHRE[17] and IFFS[87], may be the main reasons for resuming fertility treatment practices in Europe[56]. It is noteworthy that very recently (5–1-2021), HFEA declares: "As the UK wide regulator of fertility clinics, we consider fertility clinics can continue to safely offer treatment during the latest lockdown"[72].

Barriers to oncofertility practices during the COVID-19 pandemic

The ESHRE COVID-19 Working Group published evidence that "fertility preservation treatments and patient supportive care for patients remained available" in Europe during the COVID-19 pandemic[56]. However, the ESHRE COVID-19 Working Group provided evidence that showed "a large variation in the time and the phase in the epidemic in the curve" when fertility treatments were suspended and resumed[56]. This was reasonable "as the impact of the COVID-19 pandemic differed between regions of the same country"[56].

At any rate, however, during the COVID-19 pandemic, oncofertility practice in limited resource settings has become a critical topic. On April 9, 2020, a joint statement was issued from the Alliance for Fertility Preservation and the Oncofertility Consortium on Fertility Preservation for Patients Receiving Gonadotoxic Therapies During the COVID-19 epidemic [88]. While the pause in fertility treatment services (advised by ERSHE, ASRM, etc.) does not apply to urgent fertility preservation for cancer patients receiving gonadotoxic therapies**,** the statement recognizes that "it may impact practices' standard operations which could, inadvertently affect these patients' access to some services" and that "evolving geographic, legal, and practical constraints may cause interruptions or delays" although "clinicians and leaders in the fertility preservation community remain committed to handling these urgent cases"[88].

Salama *et al*. state, "Installation of specific oncofertility programs for common cancers such as childhood cancer, breast cancer, and blood cancer in developing countries according to their contemporary challenges and opportunities is highly recommended"[6]. Therefore, it is very important to learn more about oncofertility practice and better understand the barriers to oncofertility practice as well as the resources necessary to provide oncofertility treatments in limited resource settings in developing countries[6]. Regarding the barriers to oncofertility practice, according to the results of a study carried out by the Oncofertility Consortium, 14 developing countries (including Nigeria) "continue to experience common challenges such as shortage of health care services provided to young patients with cancer, lack of awareness among providers and patients, cultural and religious constraints, lack of insurance coverage, high out-of-pocket costs for patients, and lack of funding to support oncofertility programs"[6]. Note, however, that "despite these barriers, many opportunities exist and create a great potential for the future"[6]. An important barrier to providing oncofertility treatments in developing African countries is the weaknesses of the health care systems of these countries. In that regard, it is noteworthy that Affun-Adegbulu *et al*. state that in "India, Nigeria[89] and other low- and middle-income countries, fertility care is often not on the health financing agenda at all, and even international organizations providing sexual and reproductive health services tend to overlook it"[90].

Tedros Adhanom Ghebreyesus, the WHO's director-general, said, "…Our greatest concern is the potential for this virus to spread to countries with weaker health systems, which are ill-prepared to deal with it"[91]. The Ojong (2020) stated that "the state of the health systems on the continent was captured by the WHO's Regional Office for Africa: "There is a critical shortage of treatment facilities for critical cases of COVID-19 in Africa […] The total number of beds in intensive care units (ICU) available for use during COVID-19 in 43 countries in Africa is fewer than 5000. This is about five beds per million people in the reported countries compared to 4000 beds per million people in Europe […]. In 41 countries, … functional ventilators in public health services are fewer than 2000"[92]. At any rate, it is crucial to bear in mind that the pandemic has brought to the fore the weaknesses of health systems not only in African countries due to the economic and political forces that have contributed to the severe weakness of health systems of West African countries[75] but also in Western countries due to years of budget cuts[92]. However, while in most cases Western countries have the "capacity to mobilize resources needed by health care systems at short notice", African countries "often do not have that capacity"[92].

Salama *et al*. found that developing countries (including Nigeria) adopt different domestic standards for oncofertility practice in limited resource settings[6]. The Oncofertility Consortium will continue to engage more stakeholders in developing countries to help "establish a strong global network in which members share resources,

methodologies and experiences"[93] and build a "sustainable oncofertility core competency worldwide"[6]. For instance, adopting oncofertility cryobanking strategies with a low risk of cross-contamination in developing countries with limited resources requires a strong global network[19].

Another important barrier to oncofertility practices during the COVID-19 pandemic is the fact that the pandemic gives rise to discrimination concerns. Not surprisingly, fertility treatments in a given society may be distributed unevenly. Sabatello *et al*. arguably state that in the US, 'The COVID-19 pandemic 'gives a face to decades of segregation, racism and structural discrimination' and has 'disproportionate impact on historically marginalized communities'[58]. In that connection, it should be noted that Bambra *et al*. put it best in saying that the COVID-19 pandemic, like previous pandemics, is "experienced unequally with higher rates of infection and mortality among the most disadvantaged communities—particularly in more socially unequal countries"[57]. The authors write that the COVID-19 pandemic "exacerbates existing social inequalities in chronic disease and the social determinants of health"[57]. Moreover, the authors made a valid point when they stated that "It seems likely that there will be a post-COVID-19 global economic slump—which could make the health equity situation even worse, particularly if health-damaging policies of austerity are implemented again"[57]. Thus, it is noteworthy that Obeng-Odoom put it best in saying that "COVID-19 highlights the need to take inequality and social stratification in Africa seriously"[94].

Discussion

Barriers to fertility treatments during the COVID-19 pandemic may violate all the fundamental principles of biomedical ethics (namely, the principles of autonomy, beneficence, nonmaleficence and justice). Reproductive autonomy has the power to decide and control contraceptive use, pregnancy, and childbearing[95]. When the COVID-19 pandemic is what truly drives political decision-making, policies can (stealthily or openly) limit reproductive autonomy, which, however, is intrinsically valuable[96]. This is something that should be particularly reflected. As presented above, where analysed further, all women should have autonomy to consider their family planning even in times of health-care crisis"[67].

Furthermore, respect for persons and, more precisely, protection of vulnerable populations includes beneficence and justice (especially social justice). Beneficence is understood as a principle seeking positive benefits (i.e., good health) and requiring that people (and particularly physicians) prevent and remove harm. Fertility is instrumentally valuable for the wellbeing not only of an individual (especially a woman) but also of humankind. Barriers to fertility treatments during the COVID-19 pandemic may prevent physicians from promoting and protecting the wellbeing and health-related interests of an individual (especially if health is holistically positively understood and fertility treatments are considered essential according to the reviewed literature). That is, barriers to fertility treatments during the COVID-19 pandemic may prevent physicians from providing benefit to an individual in need. Infertility falls on a continuum of severity. The more a patient (or a group of patients) is considered a disadvantaged and vulnerable individual (or group), the more extensive the physicians' moral obligation to act for his or her benefit. Vulnerability should not be regarded as a yes/no consequence related to a situation or some characteristic of a group. Vulnerability should be regarded as falling along a continuum that represents the different degrees of the extent to which a situation or characteristic places an individual or the community at risk[97]. According to our review of the literature, noncancer low ovarian reserve patients might be regarded as severely vulnerable. Barriers to fertility treatments for these people might be regarded as a severe violation of the principle of beneficence.

The principle of nonmaleficence requires that people (and particularly physicians) have a duty to do no harm or prevent harm from being caused to individuals or the community at large. Barriers to treatments for people with fertility problems during the COVID-19 pandemic may allow significant harm to be caused to noncancer low ovarian reserve patients (especially if health is holistically positively understood, according to the reviewed literature). It should be noted that reproduction has to do with the community at large. Moreover, it should be noted that according to the reviewed literature (current evidence), in all

likelihood there is no transmission of COVID-19 to gametes and reproductive tissues, there is no risk of cross-contamination through cryobanking services, and there is no vertical transmission from mother to child**.** Therefore, the violation of the principle of nonmaleficence is not waived.

Social justice is "broadly defined in the literature as equitable access to resources, the promotion of human rights, and the dismantling of oppressive social conditions"[98]. The law should be committed to equality to be in line with the principle of social justice. "Equity" is one of the principles of social justice that aims for an equal outcome and takes into account the effects of discrimination such as racial inequality. Social justice is at the core of the principle of justice and enables people to receive basic benefits. Health equity is social justice with respect to health, namely, striving to equalize opportunities to be healthy. According to the reviewed literature, the pandemic has brought to the fore the weaknesses of health systems not only in African countries but also in Western countries. Furthermore, the pandemic has brought to the fore and escalated structural discrimination, especially against certain minorities. For instance, the American Psychological Association states, "Asian and Black Americans are more likely than other groups to report negative experiences related to their race or ethnicity during the pandemic, finds the Pew Research Center"[99]. Moreover, it is important to note that in the absence of workplace support, "many women who undergo fertility treatment still hide it from employers because they fear dismissal"[100].

Conclusion

From the beginning of the COVID-19 pandemic, several countries issued directions to suspend fertility treatments with the exception of fertility preservation for cancer patients. Common malignancies that occur at young age are childhood cancers, breast cancer, and blood cancers. The main reasons for that suspension were a) to reduce nonessential contacts and minimize the spread of the virus, b) to support the necessary reallocation of health care resources and reduce the impact on health care services due to eventual complications of fertility treatments, and c) to prevent possible maternal and foetal complications and COVID-19-related complications of pregnancy. Note, however, that in European countries, fertility preservation treatments remained available during the pandemic. While the pause in fertility treatment services (advised by ERSHE, ASRM, etc.) does not apply to urgent fertility preservation for cancer patients receiving gonadotoxic therapies**,** the statement recognizes that "it may impact practices' standard operations which could, inadvertently affect these patients' access to some services"[88] and that "evolving geographic, legal, and practical constraints may cause interruptions or delays"[88]. Note, however, that when the number of people testing positive, decreased fertility treatments resumed gradually.

First, the pandemic has brought to the fore the longstanding question of whether fertility treatments are essential. Irrespective of whether biological relatedness has intrinsic value or the willingness to have offspring is socially determined, it should be recognized that a strong person's right to freely and autonomously decide whether to have biological children. This right must be respected even in limited resource settings, to the extent possible. In that regard, there have been some points of consideration in the literature in support of the assumption that fertility treatments should be considered "essential". The first point to note is that many Western countries have old infertile populations with reduced possibilities of fertility treatment success. The second point to note is that, as anticipated above according to the current evidence, in all likelihood there is no transmission of COVID-19 to gametes and reproductive tissues, there is no risk of cross-contamination through cryobanking services, and there is no vertical transmission from mother to child**.** Note, however, that there is controversial evidence on the presence of SARS-CoV-2 in human reproductive cells and tissues, especially in males. In addition, there is no sufficient evidence to support the negative impact of COVID-19 on pregnancy. The third point to note is that, as anticipated above, surgical complications related to FP procedures that may occur and might increase the eventual burden on hospitals are extremely rare. As a consequence, the same permissive approach for patients with cancer should be expanded to other individual situations (i.e., low ovarian reserve patients) where delaying fertility treatment (for an unforeseeable period of time) could be more harmful to fertility patients

than proceeding with it. Such a provision should be included in forthcoming guidelines. At any rate, however, note that the risks related to COVID-19 are still undefined.

Second, the pandemic has brought to the fore the weaknesses of health systems not only in African countries due to the economic and political forces that have contributed to the severe weakness of health systems of West African countries but also in Western countries due to years of budget cuts. The role of the Oncofertility Consortium in building a "sustainable oncofertility core competency worldwide"[6] and especially in developing countries is highlighted.

Third, the pandemic has brought to the fore structural discrimination, especially against certain minorities. It should be noted that the COVID-19 pandemic "exacerbates existing social inequalities in chronic disease and the social determinants of health"[57]. Importantly, "COVID-19 highlights the need to take inequality and social stratification in Africa seriously"[94]. Finally, note that the role of telemedicine in providing oncofertility practices has been highlighted during the COVID-19 pandemic to reduce nonessential contacts. In conclusion, oncofertility practices may be unevenly provided and may raise issues related to social justice. States, individually and collectively, should make provisions and take appropriate measures to avert this phenomenon. In this regard, the role of the Oncofertility Consortium in developing countries should be highlighted.

Preparing for the post-pandemic era, efforts should be made to ensure that fertility services will be part of the post-COVID-19 health care recovery[90]. At present, in the context of controversies and a lack of evidence, it is important to implement proactive risk assessment (thus maximizing the safety of patients and staff) prior to resuming fertility treatment activities[101]. Maggiulli *et al*. put it best in saying "Except for cell-cell contamination, which was considered highly unlikely, failure modes during patient-staff, staff-staff and staff-cell interactions were estimated as carrying a moderate to high risk of infection"[102]. Moreover, to promote patient autonomy, considerable emphasis should be placed on ensuring that comprehensive information has been provided, and then valid consent was given prior to initiating any fertility treatment[103]. Further efforts should be made to develop better guidelines aiming to help reproductive health professionals provide safe and ethically sound fertility treatment at the time of the COVID-19 pandemic.

Conflicts of interest

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Contribution of authors

Voultsos P. conceived, designed and supervised the study, co-reviewed the literature, co-analysed the data, and wrote the manuscript. Taniskidou A-M collected, co-reviewed the literature and co-analysed the data. Both authors have prepared, read, revised and agreed to the submitted version of the manuscript.

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