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IVF during Coronavirus pandemic: who comes first? The POSEIDON viewpoint

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ABSTRACT

COVID-19 is the world's most massive epidemic known to date. In order to prevent hospital burdens, governments around the world have adopted restrictive containment measures. Such measures have led to a temporary suspension of all non-urgent clinical procedures. With the reduction of contagions, in some country there is a slow and gradual restoration of clinical treatments including reproductive medicine. Even with all safety precautions, the risk of infection is real for infertility patients, medical staff, and the community, making it crucial to establish which infertile patients should be prioritized for treatment provision. Indeed, postponing treatments in infertile patients who show a strictly time-dependent reproductive prognosis, could definitely affect reproductive chances. In this sense, POSEIDON group propose the use of a specific algorithm that could help clinicians to most optimally manage who need immediate IVF treatment during COVID-19 pandemic.

SOMMARIO

COVID-19 rappresenta tra le più grandi e devastanti pandemie conosciute. Al fine di prevenire il sovraccarico ospedaliero, i governi di tutto il mondo hanno adottato misure di contenimento restrittive. Tali misure hanno portato a una sospensione temporanea di tutte le procedure cliniche non urgenti. Con la riduzione dei contagi, in alcuni paesi si è assistito a un graduale ripristino delle cure cliniche compreso quelle concernenti la medicina della riproduzione. Ciononostante, il rischio di infezione è reale per i pazienti infertili, il personale medico e la comunità, rendendo fondamentale stabilire a quali pazienti infertili dovrebbe essere data la priorità per la fornitura di cure. Infatti, posticipare i trattamenti in pazienti infertili che mostrano una prognosi riproduttiva strettamente dipendente dal tempo, potrebbe sicuramente influenzare le possibilità riproduttive. In questo senso, il gruppo POSEIDON propone l'uso di un algoritmo specifico che potrebbe aiutare i medici a gestire in modo ottimale chi necessita di un trattamento IVF immediato durante la pandemia COVID-19.

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BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (COVID-19) is the world's most massive epidemic known to date. As of November 26th, the World Health Organization (WHO) reports over 60,000,000 confirmed cases of COVID-19 disease, including over 1,400,000 deaths globally (<https://www.worldometers.info/coronavirus/>). COVID-19's clinical, social, and economic impact is so devastating that it took on the appearance of a real tragedy. Because of this colossal and unpredictable phenomenon, world governments have taken extreme measures to reduce contagion, including curfews, shutting of borders, and mandatory quarantining of individuals suspected to be infected. In the health community, the choice to postpone all non-urgent procedures, in the same way, reflected the need to contain the spread of the disease and to reduce the number of hospitalizations. While crucial for the containment of the infection, procrastinating most medical treatments has important consequences in global health management.

Reproductive implications for the patients with low reproductive prognosis in the COVID-19 era

About 400,000 babies are born globally every year as a result of in vitro fertilization (IVF) cycles (1); these figures represent about 0.3% of the total number of live births every year. In the first phase of COVID-19 spread, the most recognized fertility societies recommended suspension of IVF procedures and non-urgent gamete cryopreservation (2). Although such a restrictive approach was necessary at the beginning of the pandemic, it might lead to population growth's detrimental consequences. Indeed, it is widely acknowledged that the delay in the initiation of IVF treatment has a negative impact on both the reproductive prognosis and psychological burden of infertile couples (3, 4). The scenario is more dramatic in Italy in which a dramatic reduction of births in the last year (www.istat.it).

However, in the latest pandemic period, the reduction of contagions in many countries worldwide has gradually allowed restarting IVF treatments. To keep a safe clinical practice, European Society of Human Reproduction and Embryology (ESHRE) guidance recommends vigilance and preventive measures for patients, clinicians and anyone attending the IVF center. The use of personal

protective equipment (PPE) and social distancing are mandatory. All patients planning to start IVF treatments must answer a triage questionnaire to ensure that they present no suggestive symptoms of COVID-19 infection (fever, cough, *etc.*), that they have not had contact with infected people or travelled to high-risk areas. IgM/IgG testing or equivalent tests should be administered to patients suspected of infection after triage. The access to IVF treatments is reserved only for couples with negative triage for COVID-19 (5). Conversely, couples deemed positive for triage are excluded from treatment and tested for COVID-19. Even with all safety precautions, the risk of infection is real for infertility patients, medical staff, and the community, making it crucial to establish which infertile patients should be prioritized for treatment provision. Indeed, postponing fertility treatments should be avoided in specific subgroups of low prognosis infertile patients, whose reproductive prognosis is strictly dependent on the "time- variable" (6);

The low prognosis women undergoing assisted reproductive technology (ART) can be identified using female age, ovarian reserve markers, and previous response to controlled ovarian stimulation (6, 7, 8).

Female age represents a critical factor in IVF prognosis, with a dramatic decrease in success rates among patients above 35 years old. The percentage of women achieving a live birth decreases dramatically from 41.5% in patients younger than 35 years to less than 5% in those above 42 years old (3). The age factor explains why the American Society for Reproductive Medicine (ASRM) recommends an expedited fertility evaluation in women above 35 years old (3).

Women with a diminished ovarian reserve have a low ovarian response to controlled ovarian stimulation and reduced fecundity compared with age-matched women of normal ovarian reserve (9). Antral follicle count and Anti-Müllerian hormone are the most reliable biomarkers commonly used in clinical practice to estimate the ovarian reserve (10, 11). Lastly, IVF prognosis is also strictly related to the number of oocytes retrieved in a previous stimulation and ovarian sensitivity (6, 7, 12, 13). Patients with a poor (≤ 3 oocytes) or a suboptimal response (4-9 oocytes) show lower cumulative live birth rates than those with normal ovarian response (*e.g.*, > 9 oocytes retrieved). Along these lines, the ovarian sensitivity reflects the ovarian responsiveness to stimulation with exogenous gonadotropins. In particular, a specific subgroup of women, defined as hy-

po-responders, displays a reduced ovarian response despite normal ovarian reserve values (14-18).

On this basis, an international panel of experts (Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group) has introduced a new classification of women with low prognosis in ART combining age, ovarian responsiveness to exogenous gonadotropin, and results of ovarian reserve markers (AFC and/or AMH) (6, 7, 18) (**figure 1**). Such classification may help clinicians to most optimally manage a waiting list of women who need immediate IVF treatment (**figure 2**).

Women belonging to POSEIDON 4 present the worst prognosis among all POSEIDON patients (19). In these patients, the accumulation of oocytes and embryos could optimize the number of eggs thus counteracting the effect of oocyte/embryo aneuploidy in a shorter time. Accordingly, multiple ovarian stimulations (*e.g.*, consecutive stimulation or DuoStim) with or without preimplantation genetic testing for aneuploidies (PGT-A) have been suggested (20). Another vulnerable group is that fitting into POSEIDON group 2, represented by patients above 34 years and normal ovarian reserve. These patients have an unexpected low or suboptimal number of oocytes retrieved after conventional ovarian stimulation using exogenous gonadotropins in a previous IVF cycle. For these patients, LH supplementation, especially in those aged between 35-40, seems

useful to optimize the effects of ovarian stimulation on oocyte yield and pregnancy outcomes (16, 23).

A crucial category at risk of early menopause is POSEIDON group 3. Despite being younger than 35 years, these patients already have a reduced ovarian reserve. The “window time” to preserve or achieve fertility might not be very long in these patients (24). Therefore, IVF treatment should be prioritized as a way to secure an optimal chance of IVF success. Interestingly, the ART calculator –a predictive model to estimate the number of oocytes need to achieve at least one euploid blastocyst for transfer in women undergoing ART– indicates that POSEIDON groups 1 and 3 patients (*i.e.*, younger than 35 years) need less oocytes than POSEIDON groups 2 and 4 (35 and older) (25, 26).

In addition to the patient categories mentioned above, fertility preservation strategies devoted to oncologic patients should always be allowed (27). In these cases, IVF for fertility preservation could represent the only opportunity to obtain a pregnancy after the end of gonadotoxic treatment. Besides oncologic patients, women affected by systemic autoimmune disorders (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, systemic sclerosis, Sjögren’s syndrome among others) should also be considered for immediate IVF treatment. In these patients, fertility preservation is strictly conditioned

Figure 1 Classification of low prognosis patients according to POSEIDON group.

Figure 2 The individualized clinical management of low prognosis women during COVID-19.

to the “remission window” (28), and those under clinical remission, postponing IVF could severely compromise their reproductive chances.

CONCLUSIONS

The COVID-19 pandemic has been one of the most unpredictable events of the last millennium, with unprecedented repercussions to patients, medical community and society as a whole. Likewise, reproduction is crucial for the well-being of the individual and the community. Recently, the reduction of contagions has allowed the gradual reintroduc-

tion of IVF treatment in some countries. Nonetheless, until a valid vaccination program against COVID-19 is available, IVF activity should be reestablished gradually using a clinical priority scale. In this sense, POSEIDON classification might help identify the more “time-sensitive” patients for whom a delay in IVF treatment could be potentially irremediable.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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