Deep inside the pandemic, from inactivity to action: let's be ready

The novel coronavirus (SARS-CoV-2) that arose in China in December 2019 resulted in an epidemic that quickly expanded with particular intensity in the United States and European countries, particularly Italy and Spain, devastating the foundations of our nations in one of the most significant public health threats of our time. Sadly, this disease has spread globally, and from March 12 on, the American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology made similarly cautious recommendations on managing patients who were undergoing infertility therapy or desiring pregnancy, but without clear evidence of any negative effect of SARS-CoV-2 infection on pregnancy according to the latest updates from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html/). Even in mid-March, when a state of emergency was initiated in most countries, we never expected that the cumulative cases would reach the levels that we observed and, even more surprisingly, the proportion of deaths per infected that were reported in some countries, such as Spain (https://covid19.isciii.es/). Understandably, most of the centers of assisted reproduction had to make decisions with a lack of scientific evidence. Initially, these included taking extreme precautions with infectious patients, avoiding alarm and transmitting calm, maintaining caution with working groups, and finally, interrupting the start of any ovarian stimulation protocol (1). We closed the IVF laboratory, became inactive, and began planning how to open again once the state of emergency was over.

During this period, the laboratory was maintained with a minimum of functioning equipment. In principle, only what was necessary for any oncologic patients with urgent needs for fertility preservation was left operating. For the main room and airlock, the environment was maintained with a minimum of activity. Because there was no thermal load from the equipment, such as incubators and laminar flow hoods, or from workers, the temperature was kept constant. The room with nitrogen banks was maintained with minimum operations to prevent the accumulation of nitrogen vapors. The few staff remaining cared for the maintenance and quality control of banks, refrigerators, freezers, and their mechanics. Material that could degrade was carefully inventoried to best estimate when to place new orders.

Treatment of infertile patients is a fundamental need for humanity. Our obligation as care providers is to resume activity as soon as the state of emergency ends. During the initial shock of realizing that we were in a pandemic, we placed our resources and personal protective equipment (PPE) at the disposal of local and national health systems, expecting that once our services were no longer needed, there would be an urgent need to treat infertile patients, not only oncologic ones, but also those with advanced maternal age, for whom any delay would diminish the chance for a healthy baby.

Planning reopening is mandatory. That means that we must go through an initial phase in which we make the transition from inactivity to allowing some activities, including IVF procedures. One of the main reasons for the initial closure was to protect staff from infections inside the clinic. The first action after the pandemic ebbs will be to reinstate staff, including clinicians, embryologists, and nurses. We should test all for immunity, because those who are immune would be safest to restart the clinic and obviate the necessity for the use of PPE. Those who are not immune, assuming that we do not yet have a vaccine, are a dilemma. One approach would be regular evaluation of symptoms, tracking contacts with known cases, temperature checks, and, if possible, regular viral tests (2).

We face two types of patients. The first are those already immunized. A few months after the pandemic struck, several million citizens will have become immune to the virus. Most will never be diagnosed, because the symptoms are absent or moderate in perhaps 80% of cases. If these patients are tested and verified to be immune, a method such as a "biological passport" could allow access to medically assisted reproduction treatments. The test would ideally be performed on asymptomatic patients with a combination of polymerase chain reaction (PCR), to detect the presence of active viral particles, and quantification of IgG antibodies to confirm immunity. The current IgG test is only qualitative, and we must await quantitative analysis to determine the levels at which patients are fully immunized and free of reinfection (3). All IVF units should have these tests available to assess immunity in all individuals entering the centers. Meanwhile, until this biological passport is available, we must wear masks, keep safe distances, and do viral testing by means of PCR for those with any symptoms.

The second type of patients are those not yet infected. For those patients, we may implement an epidemiologic survey that would include a symptomatic evaluation, such as fever, fatigue, cough, etc. (2). A contact history for those in an endemic area may already have been gathered, and we can add our own investigation of potential infectious encounters during the preceding 14 days. We can add a temperature check, although an elevated temperature may not be present in some carriers (3). We may also consider implementing the gathering of patient information through a mobile app.

We can learn from this pandemic to guide our future cautionary behavior, because this is likely not the last that we will face. We would best be served by a prevention policy in which strict control of access to the clinic is implemented. It would also logically include wearing surgical masks, washing hands before and after patient contact, using gloves during follicle monitoring, and wearing N95 masks during egg retrieval and embryo transfer.

In the IVF laboratory, we will need to carefully schedule the ordering of culture media and laboratory material. We must add to that a detailed agenda of disinfection, commissioning, and control of all equipment. A period of preparation may require at least eight working days for the IVF

laboratory: three for cleaning and disinfecting the equipment, and five for incubator activation and control. For working conditions, we can adjust the number of embryologists and technicians to the number of procedures on a daily basis. We may also prepare specific liquid nitrogen tanks and incubators for the post-pandemic period and use the highest level of protection possible in the laboratory. We need to consider the air disinfection of patient rooms, such as those used for drawing blood, ultrasound monitoring, etc. Although laborious, sterilization of each room used for egg or sperm collection for every single patient is safest. Also in the IVF laboratory, we must begin to consider the use of reagents such as disinfectants, which have traditionally been avoided in large volume owing to the release of volatile organic compounds. The filters that we use in our laboratories and procedure rooms are high efficiency particle air (HEPA) filters that are able to filter 97% of 0.3-μm particulate matter, but respiratory droplets carrying virus may vary from 0.01 to 10 μm. HEPA filters may consequently not be sufficient to prevent contamination (2, 4).

Finally, we must consider those patients who cryopreserved gametes or embryos before this forced hiatus of the IVF program. Some may have already been infected by SARS-CoV-2. However, we do not know whether the virus is present in the freezing media or liquid nitrogen used for these patients. Studies performed with entirely different types of viruses, such as human immunodeficiency virus, hepatitis C virus, or hepatitis B virus, failed to detect viral sequences after culture and vitrification of oocytes and embryos from seropositive patients (4). We must also consider that the surface-spike glycoproteins of the virus would be able to recognize its functional receptor, the metallopeptidase angiotensin-converting enzyme 2, in the sperm, the oocyte, or the blastomeres. This protein is abundant in the epithelia of the lung and small intestine (5). It is also observed in arterial and venous endothelial cells and arterial smooth muscle cells in all organs, which of course include the endometrium, ovaries, and testes (5). Whether the virus exists in these organs and how it might be cleared by future antiviral therapy remains an open question.

There are still so many questions that urgently need to be addressed. Of those patients in whom COVID-19 is diagnosed during ovarian stimulation, which future palliative treatments (e.g., hydroxychloroquine) could safely be applied rather than cancelling the cycle? What steps should we add to processing and manipulating gametes and embryos to make these procedures safer? Should we use specific nitrogen containers for post-pandemic infected patients? Is cross-contamination possible?

The COVID-19 pandemic appeared suddenly, a plague that has devastated the lives of hundreds of thousands, perhaps millions. It forced the immediate cessation of medically assisted reproduction across the world. It is time to plan our new beginnings. These are our considerations. Let's be ready.

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