

COVID-19: lessons from the Italian reproductive medical experience

By the time you're reading this, much will have transpired. That's the story with the exponential spread of an infection across the globe: it all happens so fast.

On December 31, 2019, the Health Commission of Hubei Province, People's Republic of China, announced a cluster of unexplained cases of pneumonia. The virus was isolated, its genome was sequenced, and it was identified as the 2019 novel coronavirus (2019-nCoV). On February 11, 2020, the International Committee on Taxonomy of Viruses defined the virus as "acute severe respiratory syndrome coronavirus 2" (SARS-CoV-2) with the associated respiratory disease COVID-19 (CO-rona VI-rus D-isease 2019). The COVID-19 pandemic brought unique challenges to the global healthcare community, with rapid escalation of the number of affected individuals and associated mortality over a handful of weeks. Clinical and public health guidance has tried to minimize the potential health impact using the best available scientific advice and evidence to inform decision making to help contain the virus, delay its spread, and mitigate its effect on those infected with it. Countries have adopted their own timing of risk-reduction strategies reflecting their differential risk assessments, with Italy having the largest number of affected cases outside of China. The impact and reorganization of clinical services that have been required by Italy will likely be faced by those around the globe in the weeks ahead given the anticipated trajectory of COVID-19.

The COVID-19 epidemic in Italy started on January 30, when two tourists tested positive. An outbreak was subsequently detected in a few patients in Lombardy on February 21, which quickly became 60 patients the next day. As of March 17, 2020, there were 31,506 positive cases from the 148,657 swabs tested, with 2,941 people who have fully recovered since testing positive and 2,503 who died. Among the measures to contain the infection, as early as February, 11 municipalities had been quarantined. Nobody could enter and leave those territories. Following the expansion of the areas with confirmed infection, the area of limitation of human activities was extended to various northern regions including Lombardy, Emilia, and Veneto, and from March 9, the entire country with 60 million citizens was placed in lockdown.

The societal and economic impact of these changes at this time is too large to assess. All schools are closed requiring childcare to be provided at home, social and professional meetings are cancelled, public spaces closed, the mobility of people is restricted to only attend work or for health reasons, and many businesses are closed, including all restaurants and entertainment venues. These measures are combined with existing recommendations from the World Health Organisation for people to wash their hands frequently; avoid touching their eyes, nose, and mouth; by covering the mouth and nose with a tissue when sneezing or coughing and disposing of the tissue immediately and washing hands; keeping an

interpersonal distance of at least one meter; avoiding gatherings; and using a surgical mask in the presence of people suspected of being sick. The primary aim of these measures is to flatten the growth curve of new cases, thereby reducing the number of people who will simultaneously require intensive care as well as the overall mortality. As of March 11, 2020, 1,028 of the approximately 5,200 intensive care beds within Italy were already occupied with COVID-19 patients (1). Parallel to these governmental directives, the Ministry of Health implemented extensive reorganization of national healthcare services to facilitate the treatment of the large numbers of patients who will need intensive support therapy.

Professional bodies including the American College of Obstetrics and Gynecology (ACOG) (2) and the British Royal College of Obstetricians & Gynaecologists (RCOG) (3) have provided specific guidance for pregnant women based on very limited data and experience with prior coronaviruses including SARS-CoV and MERS-CoV: compared with the general population, pregnant women may be at higher risk of severe illness, morbidity, or mortality, and adverse perinatal outcomes including preterm birth (4, 5). There is little historical information available for women considering pregnancy or embarking on assisted conception. Given the modelling of the pandemic, including the time to peak and subsequent tail, considerable delays in conception to substantially mitigate risk may be required, which will inevitably impact overall success rates.

Reproductive medicine units in Italy that continue to offer clinical treatments necessitate specific changes to their organization. These include strict adherence to the generic health precautions with clearly visible signs within the clinics at the entrance and throughout the clinics, including private spaces, to remind patients of these general measures. Exposure by scheduled in-person meetings may be reduced by cancelling attendance, and all staff are to consider personal risk when commuting. All non-essential visits by external businesses or academic collaborators are to be avoided and replaced by telecommunications and online platforms. Patient informational events may be held via webinars. Outpatient consultations can be moved to a telemedicine model where feasible, with strict adherence to scheduled appointments for ultrasounds and lab tests to reduce waiting room exposure, coupled with a request to patients to attend alone and to wait outside in their own vehicle until the scheduled appointment to reduce overall risk of transmission. Working agendas are altered to reduce the sharing of common spaces by staff, including the creation of shift teams to reduce the risk that the whole clinic staff is affected and required to self-isolate. Managerial, administrative, and IT staff are similarly to be moved to a rotational schedule to reduce the risk of all being infected simultaneously. Access to common areas of the clinic is strictly limited, with deliveries made outside at specific entrances. All staff must be trained in the processes and protocols for dealing with COVID-19 cases and the use of general precautions and certified particulate filtering face masks to reduce transmission. Should the team members

themselves present with respiratory symptoms, the Italian authorities have mandated that, if accompanied by a fever, they are required to abstain from work.

For patients, it is very useful to develop a written multi-lingual summary of the scientific evidence of pregnancy with the coronavirus, including frequently asked questions which align with international guidance and are under daily review that is available both online and within the clinics. Patients are screened by telephone prior to attendance and instructed not to come to the clinic and to postpone their treatment if they are suspected to have an acute respiratory infection with at least one of the following symptoms: fever, cough, dyspnea; or they were, in the previous 14 days, in a country with community transmission of the virus according to the CDC; or in close contact with a confirmed case of COVID-19; or have been in a hospital where COVID-19 patients were hospitalized. Websites must be updated with the most recent available information and links. When entering the clinic, patients are again interviewed regarding the presence of respiratory symptoms or at-risk behavior.

Should medical staff suspect that a patient has COVID-19, a strict protocol is invoked. The healthcare staff isolate the patient in a designated insulated room and wear the following protective health equipment: a waterproof gown, viral particulate-filtering face mask, eye protection, and double gloves; the patient is also provided with a face mask. Decisions are made based on the stage of medically assisted reproduction therapy. If the patient is positive during ovarian stimulation, the optimal solution is to cancel the cycle. If the patient has already had oocyte retrieval, then cryostorage of oocytes or embryos will be undertaken with avoidance of embryo transfer until the patient is proven disease-free due to the risks of further disease deterioration, particularly during pregnancy. On completion of the consultation and the explanation that treatment will be deferred, the patient is transported outside the clinic using a predetermined route to minimize the possible exposure of health personnel, other patients, and visitors. All rooms and areas are then carefully sanitized using an alcohol-based disinfectant containing $\geq 75\%$ alcohol or 5% chlorine. After use, the disposable protective devices are carefully removed, folded in on themselves with hand sanitization with alcohol gel at each stage of removal before final disposal in an appropriate container for infected waste. The patient is then directed to the appropriate regional or national center.

For patients receiving ovarian stimulation, mitigation of the risk of ovarian hyperstimulation syndrome is grave, as COVID-19 infection in a woman experiencing the hypovolemic and electrolyte imbalance typically associated with the syndrome may lead to an amplified risk of lung and kidney complications. Consequently the use of mild stimulation, GnRH antagonist control of the luteinizing hormone (LH) surge, GnRH agonist triggering, and single embryo transfer or freeze-all, are the first choice in this period for women entering in vitro fertilization.

The Italian authorities have mandated that even in the absence of evidence of transmission of the virus within reproductive cells, all donors should be interviewed regarding

the presence of respiratory symptoms and for recent travel to high-risk areas. For donors who have returned from an area at risk, a 2-week suspension is required, and in the case of respiratory symptoms, a 2-week suspension from the end of symptoms is necessitated, as compared to the 28-day period recommended by the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC). For homologous fertility treatments, there are no specific regulatory restrictions except for patients with symptoms in progress suggestive for COVID-19 with separate closed cryostorage systems. When importing gametes from abroad, an additional declaration is required from the sending center indicating that the risks of SARS-CoV-2 infection for the specific donor have been assessed. The declaration is necessary only for new donations and not for material cryopreserved prior to the SARS-CoV-2 outbreak. Patients are advised not to pursue fertility tourism due to the strict travel bans in place.

We have described how Italy was consumed by the COVID-19 pandemic and how we adapted our reproductive medical system to its challenges. It's a moving target, and our processes will continue to adjust. Other countries will face this threat, and we hope that others can learn from our experience. On March 15, 2020, the European Society of Human Reproduction and Embryology (ESHRE) published a statement recommending a precautionary approach that all fertility patients considering or planning treatment, even if they do not meet the diagnostic criteria for COVID-19 infection, should avoid becoming pregnant at this time. For those patients already having treatment, it is suggested to consider deferring pregnancy with oocyte or embryo freezing for later embryo transfer.

On March 17, 2020, the American Society for Reproductive Medicine (ASRM) issued guidance for patient and clinical management during the coronavirus (COVID-19) pandemic. Key recommendations were to: 1) suspend initiation of new treatment cycles, including ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation; 2) strongly consider cancellation of all embryo transfers whether fresh or frozen; 3) continue to care for patients who are currently "in-cycle" or who require urgent stimulation and cryopreservation; 4) suspend elective surgeries and non-urgent diagnostic procedures; and 5) minimize in-person interactions and increase utilization of telehealth. Recognizing that the situation is highly fluid, this guidance would be revisited periodically as the pandemic evolves.

COVID-19 is an unprecedented challenge to our healthcare systems. Italy was the first in line after China to experience the explosion in infections from this pandemic. As we write this, the United States is close behind with an infection incidence mirroring that of Italy and with a time shift of approximately a week and a half. The federal government has declared a national emergency and many states and cities are implementing measures like cancellations of entertainment and sporting events, and closures of schools, bars, and restaurants, but there is as yet no fully coordinated

response. We fear the worst is yet to come. And in parts of the world, for example, Mexico with its population approximately twice that of the United Kingdom, at the time of this writing no substantial measures are underway. It is likely that we are only at the beginning of this pandemic.

We must learn from our experiences. What Italy is doing in reproductive medicine may not be enough, but taking action is the first step and communicating it to the world community is the second. Educating ourselves with the experiences of our colleagues around the world is critical. At *Fertility and Sterility*, we've created a virtual real-time conversation in our Dialog where doctors and scientists can share what they're learning about COVID-19 and reproductive medicine. Please contribute your thoughts and observations at <https://www.fertstertdialog.com/rooms/871-covid-19>

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