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COVID-19: The Reality for Italian Reproductive Medicine

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On 31 December 2019 the Health Commission of Hubei Province, China announced a cluster of unexplained cases of pneumonia. Isolation and genome sequencing of the virus identified it as the 2019 novel coronavirus (2019-nCoV). On the 11 February 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-ronavirus D-isease 2019). The COVID-19 pandemic has brought unique challenges to the global healthcare community, with rapid escalation of the number of affected individuals and associated mortality over recent weeks. Clinical and public health guidance has primarily focused on minimising 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 infected individuals. Countries have adopted individualised 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 reorganisation of clinical services that have been required by Italy may be faced by many of us in the weeks ahead given the anticipated trajectory of COVID-19 globally.

The COVID-19 epidemic in Italy started on January 30, when two Chinese tourists tested positive. An outbreak was subsequently detected from few patients in Lombardy on 21 February, which had already become 60 patients the next day. As of March 13, 2020, there were 14 955 positive cases of coronavirus, including 1 439 people healed and 1266 people dead, and 73 154 swabs were made for the virus. 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 (Lombardy,

Emilia, Veneto) and from the 9th of March to the entire country with 60 million citizens being placed in lockdown.

The societal and economic impact of these changes cannot be underestimated, all schools are closed requiring childcare to be provided at home, social and professional meetings cancelled, closure of public spaces, the mobility of people restricted to only attend work or for health reasons, and closure of many businesses including all restaurants and entertainment venues. These measures are combined with existing recommendations from the World Health Organisation to wash your hands frequently, avoid touching your eyes, nose and mouth, cover your mouth and nose if you sneeze or cough with a tissue, dispose of it immediately and wash your hands, keep the interpersonal distance of at least one meter and avoid gatherings and use 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 and overall mortality. As of 11 March 2020, 1028 of the approximately 5200 intensive care beds within Italy were already occupied with COVID-19 patients (1). Parallel to these governmental directives, the Ministry of Health has undertaken extensive reorganisation of national healthcare provision to facilitate the treatment of the totality 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 and Gynaecologists (RCOG) (3) have provided specific guidance for pregnant women as based on very limited data and previous coronaviruses (SARS-CoV and MERS-CoV): pregnant women may be at higher risk of severe illness, morbidity, or mortality compared with the general population and adverse perinatal outcomes including preterm birth (4,5). For women considering pregnancy or

embarking on assisted conception there is substantially more limited evidence. Given the modelling of the pandemic including the time to peak and subsequent tail, considerable delays in conception to substantially mitigate risk would be required, which will inevitably impact on the overall success rates.

Reproductive Medicine Units that continue to offer clinical treatments necessitate specific changes to the 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. You may reduce exposure to external meetings by cancelling attendance and all staff have considered personal risk when commuting. All non-essential visits by external businesses or academic collaborators should be avoided and can be replaced by web platforms. Patient information events may be taken with webinars. Out-patient consultations can be moved to a telemedicine model where feasible, with strict adherence to timetabled appointments for ultrasounds and bloods to reduce waiting room exposure coupled with asking patients to attend alone and to wait outside in car until scheduled appointment to reduce overall footfall and risk of transmission. Working agendas are to be 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 may be required to self-isolate. Managerial, administrative and IT staff are similarly to be moved to a rotating rota of shared work / remote working to reduce the risk of all being infected simultaneously. Access to common areas of the clinic must be strictly limited, with deliveries dropped outside at specific entrances. All staff must be trained in the processes and protocols for dealing with COVID-19 cases and use of general precautions and FFP2 face masks to reduce transmission. Should the team members

themselves present with respiratory symptoms, the Italian Authorities have suggested 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 relationship and evidence base of coronavirus with pregnancy, including frequently asked questions which align with international guidance and are under daily review that is available both online and within the clinics. Patients should be screened for risk by telephone prior to attendance and if they are suspected to have an acute respiratory infection (with at least one of the following symptoms: fever, cough, dyspnoea); 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 COVID19 patients are hospitalized, they can be considered at risk of being positive to the virus and must be asked not to present to the clinic and to postpone the treatment. The websites must be updated, with reminders on the footers of all correspondence regarding COVID-19, including those sent by SMS. Upon entering the clinic, patients are interviewed again regarding the presence of respiratory symptoms or at-risk behaviour.

Despite all these screening measures, should medical staff suspect that the patient has COVID-19, a strict protocol is invoked. The healthcare staff allocate the patient to a specific insulated room and wear the following protective health equipment; waterproof gown, FFP2 face mask, eye protection and double gloves, the patient is also provided with a face mask. During the consultation the decisions will depend on the stage at which the treatment is. If the patient is positive during ovarian stimulation the optimal solution is to cancel the cycle with the financial implications of this differing between clinics with some choosing to bear the cost and others recouping costs to date from the patient. If the patient already had oocyte

retrieval, then cryostorage of oocytes or embryos will be undertaken with avoidance of embryo transfer until disease free, due to the risks of further disease deterioration particularly during pregnancy. On completion of the consultation and explanation of deferment of treatment 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 based. After use, the disposable protective devices are carefully removed, with folding in on themselves, with hand sanitisation at the different stages of removal with alcohol gel before being finally disposed of in the appropriate containers for infected waste. The patient is then notified to the appropriate regional or national centre.

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

The Italian authorities have established 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 at risk area, a two-week suspension is required, and in case they have respiratory symptoms a two-week suspension from the end of symptoms is required, as compared to the 28-day period recommended by the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC). For homologous fertility

treatments there are no specific restrictions at regulatory level except for patients with symptoms in progress suggestive for COVID-19, as noted above with separate closed cryostorage systems in place. In the case of importation of gametes from abroad there is a need to have an additional declaration from the sending centre where 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 cryopreserved material prior to the SARS-CoV-2 outbreak. Patients have been advised not to pursue fertility tourism due to the strict travel bans in place.

As the Italian experience is highly likely to replicate in other countries, the epidemic will proceed at a pace that may lead governments to severely limit human activities including all travel outside the home and non-essential healthcare. For this scenario we anticipate further reduction in clinical activity, with continuation of only non-deferrable healthcare activities. Although stimulation cycles could be cancelled, we anticipate that completion of ongoing ovarian stimulation with segmentation of the cycle will be feasible.

COVID-19 is an unprecedented challenge to our healthcare systems. The impact that we have observed in Italy and the strategies that we have developed will continue to be refined as multidisciplinary teams across the world continue to examine all aspects of this disease including pregnancy and neonatal outcomes, enabling accurate guidance for the professional reproductive care community, their patients, and policymakers.

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