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COMMENTARY



A picture of the covid-19 impact on IVIRMA fertility treatment clinics in Spain and Italy

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ABSTRACT

The emergence of the novel coronavirus infection that arose in Wuhan, China in December 2019 has resulted in an epidemic that has quickly expanded to become one of the most significant public health threats in recent times. Unfortunately, the disease has spread globally. On March 11th (2020) World Health Organization (WHO) declared Covid-19 a pandemic and has called governments to take urgent and aggressive action to change the course of the outbreak. Within the context of Assisted Reproduction, both reproductive medicine professionals and patients are also fighting against this unprecedented viral pandemic. In view of events, most of us had to make serious decisions, some of them with a lack of scientific evidence due to the circumstances and with the only objective of ensuring the safe care of our patients, reduce non-essential contacts and prevent possible maternal and fetal complications in future pregnancies. Pregnant women should not be considered at high risk for developing severe infection. Up to date, there are no reported deaths in pregnant women with Covid-19, while in the cases that have presented pneumonia because of Covid-19, the symptoms have been moderate and with a good prognosis in recovery

INTRODUCTION

The emergence of the novel coronavirus infection that arose in Wuhan, China in December 2019 has resulted in an epidemic that has quickly expanded to become one of the most significant public health threats in recent times. This newly emergent coronavirus was isolated in China in early January 2020 and initially referred to as 2019-nCov and subsequently termed SARS-CoV-2. The disease it causes has been termed Covid-19 (Zhan *et al.*, 2020 March 19).

Unfortunately, the disease has spread globally. On March 11th (2020) World Health Organization (WHO) declared Covid-19 a pandemic and has called

governments to take urgent and aggressive action to change the course of the outbreak. Robust plans and policies to avoid the disease development seen in the worst-hit countries are urgently needed. Governments must now take decisive action to control more aggressively the outbreak. Covid-19 represents a substantial risk to large sectors of the population. As the outbreak progresses balanced, coherent and consistent communication, based on science, will be essential (Lancet Respir Med 2020).

The global expansion of this pandemic makes it very difficult to assess the impact that Covid-19 may have on Assisted Reproduction, hence the objective of our work is to evaluate

how this pandemic affects the activity of a Reproductive Medicine center, by establishing a series of measures taken in parallel with government decisions and scientific societies as well as assess how the infection can affect pregnant women.

IMPACT OF COVID-19 ON ASSISTED REPRODUCTION

Within the context of Assisted Reproduction, both reproductive medicine professionals and patients are also fighting against this unprecedented viral pandemic. Our priority is to maximize the wellbeing of patients, staff, and society at large. However, we are aware that there is a confusing picture of the effect of Covid-19 on fertility treatments with the advice and

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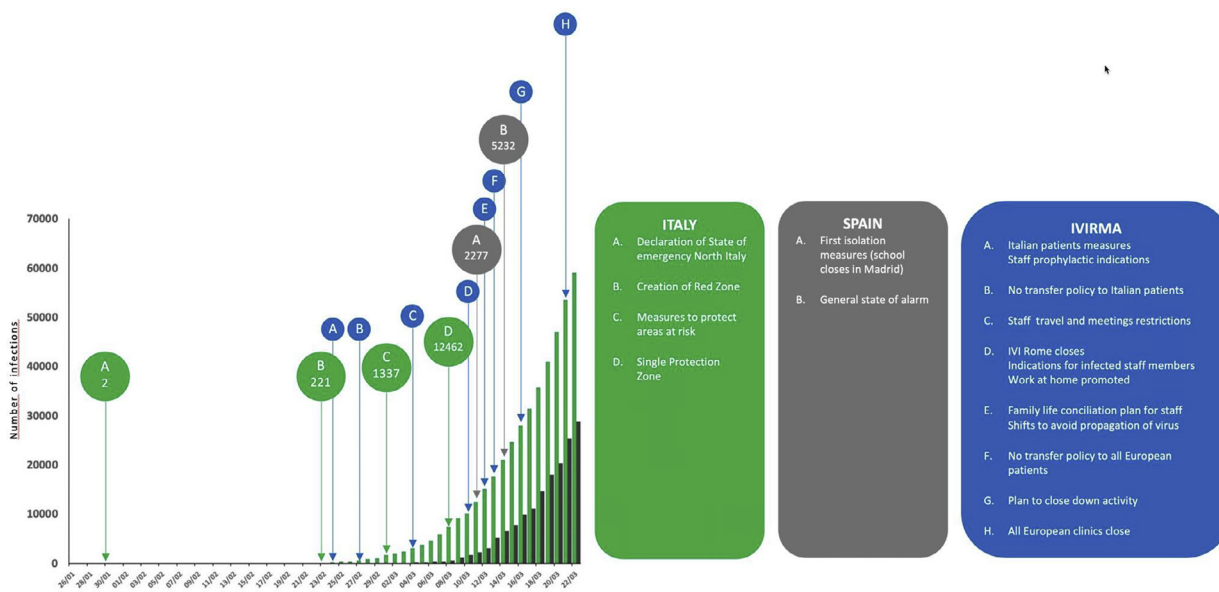


FIGURE 1 Measures implemented by IVI Group with the progressive increase of cases in Spain and Italy

guidance coming from several different resources (ASRM, 2020; ESHRE, 2020). In view of events, most of us had to make serious decisions, some of them with a lack of scientific evidence due to the circumstances and with the only objective of ensuring the safe care of our patients, reduce non-essential contacts and prevent possible maternal and fetal complications in future pregnancies. As we can see in **FIGURE 1**, as the number of cases increased in both Spain and Italy, we arranged a series of measures focused on progressively reducing healthcare activity in all its centers in Italy and Spain.

Since the state of emergency was declared in Northern Italy on January 31st and a red zone of isolation was subsequently enclosed on February 23rd as the number of population affected by the epidemic increased (La Marca et al., 2020), our first decision was to establish online visits to patients from Northern Italy, while asymptomatic patients from the rest of the country were able to continue with their initial treatment plan. At the same time, specific prevention and prophylaxis information started to be given to IVIRMA staff both in Italy and Spain for patients coming from these Italian areas. Since the situation in Italy did not improve, and in anticipation of a possible lock-down of the country (which occurred on March 9th), restrictive measures were expanded to any cycle of a patient coming from Italy to be performed in Spain. These restraints included the halt of most oocyte

donation treatments and all embryo transferences from Italian patients, recommending a “freeze-all” strategy and a later embryo transfer when the situation has normalized. Moreover, egg donation treatments were canceled, as oocytes or frozen embryos for later use.

Continuing with the measures taken initially, and considering that in Spain the situation of the public health began to be critical with an almost total suspension of all non-urgent procedures and following the Spanish Fertility Society recommendations, we decided to interrupt the start of any ovarian stimulation protocol, both in self-cycles and oocyte donors and most embryo transfers. As our patient profile is healthy and asymptomatic and that CDC has not considered them as a potential focus of infection, we decided to continue with the ongoing cycles of patients with their own gametes until oocyte retrieval in order not to harm those couples who had already started an Assisted Reproduction treatment.

The application of these actions resulted in a complete reorganization of the clinic staff. In order to protect our workers and keep the decreasing activity of our labs, we developed an infectious disease awareness and response plan, whose main objective was to establish two work shifts completely separated one from each other so in case of infection, avoid quarantining of the whole group. This decision especially affected the IVF

laboratory staff, since we considered that they belong to one of the most sensitive activities of the clinic.

At this point, we would like to highlight how the decision to reduce healthcare activity for our patients has affected our caseload. **FIGURE 2** shows a comparison of the number of embryo transferences performed in the same period in 2019 and 2020. As we can see, since the implementation of the first measures because of the pandemic, the decline has been progressive during the month of February followed by a pronounced drop in activity since March 10th, a date almost coinciding with the declaration of the state of alarm in Spain; on the other hand, and as we expected, the number of fertility preservation procedures increased gradually as the rest of treatments decreased, according to the recommendations established by the different scientific societies. These data could be considered a reflection of the acceptance that our recommendations have had among our patients.

Another point to consider is how these containment measures can affect infertile patients and the impact in the short-medium term on their opportunities to become mothers. Due to the pandemic and the lack of awareness of its immediate consequences on reproduction, some scientific societies such as American Society of Reproductive Medicine (ASRM, 2020) have classified certain Reproductive

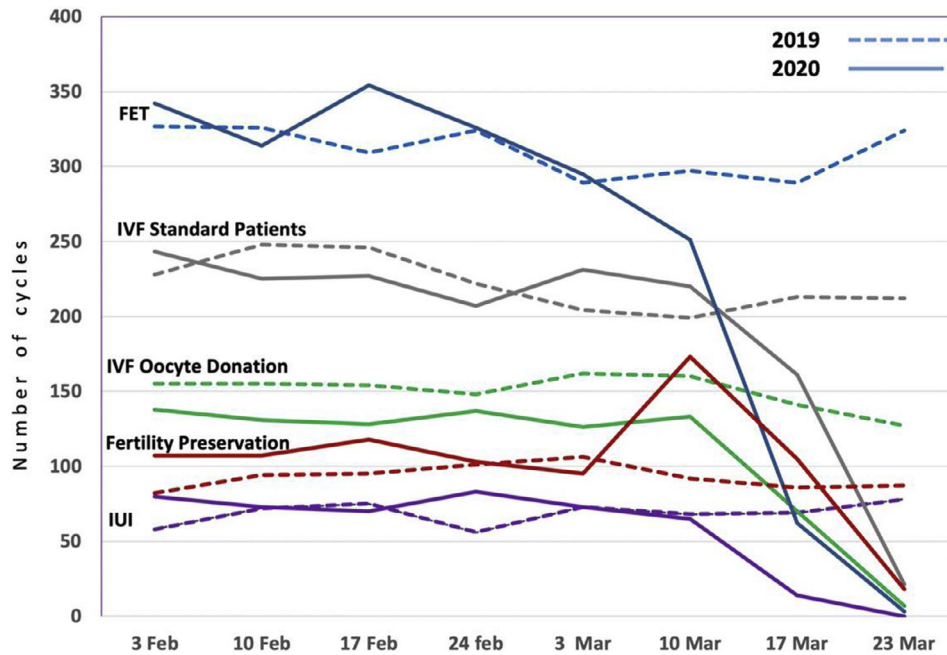


FIGURE 2 Decrease in the number of embryo transferes compared to the same period during last year

Medicine procedures as elective or non-urgent; this definition has generated a great controversy since it underestimates the importance of the time for some specific sectors of the population such as women with advanced maternal age and/or diminished ovaria reserve. In line with the position adopted by the Italian Society of Fertility and Sterility and Reproductive Medicine-(SIFES-MR) (Vaiarelli *et al.*, 2020) we think that limiting indefinitely the access to Assisted Reproduction treatments to these patients will certainly affect their chance to conceive once this outbreak ends.

We consider that both advanced maternal age and diminished ovarian reserve are conditions as urgent as the fertility preservation for an oncological patient, so our proposal would be to consider performing a treatment via oocyte or embryo cryopreservation. In this way, a precious time would not be lost to enhance the pregnancy opportunities of these women. In order to successfully develop this proposal, it is necessary to optimize the recovery of oocytes in a single retrieval and having facilities and qualified staff that guarantee the achievement of excellent results in vitrification and later thawing. Moreover, as established by FDA Statement on Feb 14th, while respiratory viruses are not known to be transmitted by implantation, transplantation, infusion, or transfer of human cells, tissues, or cellular or

tissue-based products (HCT/Ps), the potential for transmission of COVID-19 by these means is unknown at this time. There have been no reported cases of transmission of COVID-19 via these products. Our rationale is that Assisted Reproduction treatments are not via contagion for respiratory viruses.

Chronic viral diseases have been a matter of concern for practitioners of Assisted Reproduction treatments. There may not be a lot of information about the Covid-19 and fertility. According to this issue, the latest update from ESHRE stated that any risk of viral contamination to gamete and embryos in the IVF laboratory is likely to be minimal because the repeated washing steps required for the culture and freezing protocols. Even with no specific data available, it is assumed that sperm, oocytes and embryos do not have receptor for Covid-19 and are unlikely to be infected (ESHRE, 2020). These statements agree with previous publications (Cobo *et al.*, 2012) in which it was concluded that there are not viral sequences after culture and vitrification of oocyte/embryos derived from seropositive patients.

Following with this argument, and as long as the health alert has been controlled, there is no saturation in intensive care units and the risk of infection has decreased with the application of

preventive measures and appropriate medication, our future approach is to consider age as an emergency time-sensitive factor and infertility as a disease to resume treatments for obtaining oocytes and euploid embryos, although embryo transfer could be postponed for later. At this point, and when the occasion arises, we would like to highlight the importance of transferring the embryos one by one during this period of pandemic, with the aim of not aggravating with a twin pregnancy the condition of a pregnant woman who could be affected by the virus.

IMPACT OF COVID-19 ON PREGNANCY

Interim guidance has been issued by the WHO and CDC on managing Covid-19, which include some recommendations specific to pregnant women mostly drawn on experience from previous coronavirus outbreaks. These recommendations have been dynamic, evolving as more knowledge about epidemiology, pathogenesis, disease progression and clinical course among infected pregnant patients has been gathered (Liang and Acharya, 2020).

There is a limited knowledge regarding coronavirus infection that occur during pregnancy, although as the Covid-19 outbreak unfolds, prevention and control of the infection among pregnant

women and the potential risk of vertical transmission have become a major concern (Quiao, 2020). What is known has, for the most part, been the results of epidemics resulting from two different diseases, SARS and MERS. The latest researches provide some insight into the clinical characteristics, pregnancy outcomes and vertical transmission potential of Covid-19 infection in pregnant women (Chen et al., 2020a, 2020b; Rasmussen et al., 2020; Zhu et al., 2020); despite the fact these publications include a small sample size, these findings are valuable for preventive and clinical practice. It remains to be seen during the current epidemic which factors modulate obstetrical disease and outcomes including the timing of maternal exposure by gestational age, the effects of medications or other treatment regimens, differences in host immune responses, occurrence of coexisting medical and obstetrical conditions, and other covariables (Schwartz and Graham, 2020).

Pregnant women should not be considered at high risk for developing severe infection. We have been extrapolating clinical outcomes of SARS and MERS in pregnant women with Covid-19. Although is widely described that in pregnant women, pneumonia, regardless of its etiology, has a higher complication rate that in the general population, the next question we must ask ourselves is what is the proportion of pregnant women infected with Covid-19 who have developed pneumonia (confirmed and unconfirmed cases), considering the large number of probable cases that have not been diagnosed. According to WHO reports, the overall mortality rate for COVID-19 was 2.9% (2247 in 76769); however, the mortality rate varied among studies. The differences in the results among different studies could be due to the study population, as well as the differences among the studies in terms of disease severity. Up to date, there are no reported deaths in pregnant women with Covid-19, while in the cases that have presented pneumonia because of Covid-19, the symptoms have been moderate and with a good prognosis in recovery (Liu et al., 2020 March 18).

Regarding neonatal outcomes, coronaviruses can also result in adverse outcomes for the fetus and although further studies are needed to completely rule it out (Zheng et al., 2020; Dong

et al., 2020; Kimberlin and Stagno, 2020 March 26), perinatal Covid-19 could have adverse effects on the newborn related with the loss of fetal wellbeing. During this current outbreak, there are very few reported cases of neonatal infection with Covid-19. In considering whether these and future cases of neonatal infection are acquired prior to delivery, it is important to remember that newborn infants can acquire an infection in other ways beyond intrauterine maternal-fetal transmission (Schwartz and Graham, 2020).

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