Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

RBMO

COMMENTARY

After corona: there is life after the pandemic

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ABSTRACT

The current pandemic of Coronavirus Disease 2019 (COVID-19) has focused the attention of medical-care providers away from non-life-threatening diseases, including infertility. Although infertility does not jeopardize the physical survival of infertile couples, it does jeopardize their future quality of life. Human infertility can be caused by a number of factors, some of which are age-dependent, and their effects may become irreversible if appropriate measures are not taken in time to prevent irreversible childlessness. Accordingly, each case of infertility should be evaluated comprehensively to establish its position of priority. Assisted reproductive technology (ART) makes it possible to separate fertilization and pregnancy in time. Whereas pregnant women infected with coronavirus may have an increased risk of adverse neonatal outcomes, gametes do not transmit COVID-19. Thus, performing ovarian stimulation and fertilization without delay, freezing the resulting embryos and delaying embryo transfer until the end of the pandemic appears to be the best strategy at present.

BACKGROUND

An outbreak of febrile respiratory illness of unknown cause was first detected in the city of Wuhan in China in December 2019 (*Hui et al., 2020*). The infectious agent responsible for this disease was subsequently identified as a new type of coronavirus. The virus and the disease it causes have been named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (*Gorbalenya et al., 2020*) and Coronavirus Disease 2019 (COVID-19) (*Hui et al., 2020*), respectively. On 11 March 2020, the rapid spread of the disease across the world led the World Health Organization (WHO) to declare COVID-19 as a pandemic. A series of preventive measures, aimed at restraining COVID-19 propagation, have subsequently been taken in most countries.

SARS-CoV-2, the causative agent of COVID-19, is a member the Coronaviridae family, characterized as positive-sense, single-stranded RNA viruses (*Gorbalenya et al., 2020*). Human coronaviruses are endemic in the human populations, causing 15–30% of respiratory tract infections each year and, prior to the outbreak of the highly pathogenic Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), between 2002 and 2003, followed by that of Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV), between 2012 and 2015, they were only believed to cause mild, self-limiting respiratory infections in humans. Though belonging to the same Coronaviridae family as SARS-CoV and MERS-CoV, and showing some similarities with them, SARS-CoV-2 shows a number of features that are distinct from both of them. Genome sequencing of SARS-CoV-2 showed 79.6% similarity in genetic sequence to SARS-CoV (*Zhou et al., 2020*), and the sequence was made available to the WHO on 12 January 2020 (*Hui et al, 2020*). These data have made it possible to produce specific diagnostic polymerase chain reaction (PCR) tests and will be useful in the future development of an efficient vaccine.

VIRUS TRANSMISSION

Like the coronaviridae responsible for the two previous major respiratory disease outbreaks, SARS-CoV and MERS-CoV, SARS-CoV-2, shows a marked predilection for alveolar epithelial cells of the human lung, using angiotensin-converting enzyme 2 (ACE2) as the entry point (*Zhou et al., 2020*). However, unlike its two major predecessors, it cannot penetrate into cells via other known coronavirus entry points (receptors), such as aminopeptidase N (APN) and

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dipeptyl peptidase 4 (DPP4) (*Zhou et al., 2020*). Consequently, SARS-CoV-2 cannot enter cells that do not carry ACE2 on the surface. This appears to be the case for both mature human spermatozoa and oocytes, although ACE2 was reportedly detected in Leydig and Sertoli cells and spermatogonia of the human testis (*Wang and Xu, 2020*) as well as in theca and granulosa cells of the human ovary (*Reis et al., 2011*). If spermatozoa and/or oocytes could become vectors of virus transmission, they would inevitably contribute to vertical disease transmission from parents to children. In this context, it is of note that no vertical disease transmission from parents to children was reported for the previous SARS outbreak, in 2002–2003, caused by the closely related virus SARS-CoV which also use ACE2 as the main point of entry into cells (*Schwartz and Graham, 2020*).

CONCEPTION AND PREGNANCY

In view of the above, the risk of the current COVID-19 pandemic for conception is non-existent. On the other hand, the available published data on the potential maternal and neonatal outcomes from women infected with SARS-CoV-2 during pregnancy are inconclusive. While there is a consensus as to the virtual lack of risk of SARS-CoV-2 vertical mother-to-child transmission (*Schwartz and Graham, 2020*), the potential risk of maternal infection with SARS-CoV-2 during pregnancy for the health status of newborns is a matter of debate. One study reported various kinds of health problems in nine out of ten neonates born to mothers with SARS-CoV-2 pneumonia, leading to the death of one of them (*Zhu et al., 2020*). On the other hand, another study reported the birth of nine normal children, without any health problems to mothers with laboratory-confirmed COVID-19 (*Chen et al., 2020*). In both studies, the vertical transmission of SARS-CoV-2 infection from the mothers to the newborns was excluded. The differences between the neonatal outcomes reported in each of the two studies may be partly explained by the low number of cases analyzed. However, the clinical symptomatology of the mothers in the series reported by *Zhu et al. (2020)* appears to be more severe compared with those in the report by *Chen et al., (2020)*. Consequently, the worse neonatal outcomes reported in the latter study may have been due to factors related to the mothers' health status just before, and during, parturition, rather than to a specific cause related to SARS-CoV-2 infection. Whatever the case, it seems prudent to try to avoid pregnancy as long as the risk of SARS-CoV-2 infection remains high. It is of interest to note that despite the fact that viral infections can cause the same devastating effects on pregnancies resulting from spontaneous conception as on those resulting from ART, no government has recommended general contraception, as was the case with Zika virus.

ASSISTED REPRODUCTION: SEARCH FOR THE MOST SENSIBLE SOLUTIONS

One of the most outstanding achievements of ART is the ability to separate, in space and time, the act of fertilization from that of the establishment of pregnancy. The substantial improvement of embryo-freezing techniques has led to a seemingly paradoxical situation of today's ART paradigm, according to which frozen embryo transfer (FET) attempts are more efficient than those using fresh embryos in ovarian stimulation cycles (*Wei et al., 2019*). This is probably because of a negative impact of current ovarian stimulation protocols on uterine receptivity. Accordingly, contrary to popular belief, couples receiving ART treatment are not disadvantaged if all embryos resulting from an ovarian stimulation cycle are frozen and transferred later, following appropriate treatment focused on achieving optimal uterine receptivity rather than maximum oocyte yield.

Deferred FET is thus an ideal solution for women who cannot postpone their ovarian stimulation without incurring a risk of reducing their chance of success, such as women with extremely poor ovarian reserve and/or advanced age, or those who need an urgent intervention for fertility preservation, such as patients programmed for anticancer therapy. This is also the best choice for all those women who have already started their preparatory phase of ART treatment which can be as long as several months, especially in cases of customized protocols used in women with extremely poor ovarian reserve (*Tesarik, 2017*). Similar recommendations have been proposed in international reproduction guidelines, such as those issued by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). These guidelines have been highlighted and commented on in a recent paper by *La Marca et al. (2020)*.

GLOBAL CONCLUSIONS

The present COVID-19 pandemic should not bring about exclusion, even a temporary one, of women with urgent need for ART from efficient treatment options to achieve pregnancy and childbirth. Far from underestimating the impact of the current COVID-19 pandemic on different aspects of human life, we should nonetheless avoid falling into the trap of overacting. Pandemics come and go, and there is life thereafter. There will be 'after corona' life, too, and we should do the maximum to make it the best possible future for people in urgent need of help, such as women in search of motherhood, some who do not have time to be lost. Let us not allow any virus to spoil their life expectancies.

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