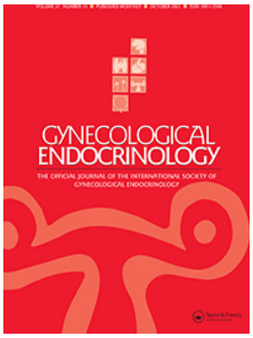

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ORIGINAL ARTICLE
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Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study

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ABSTRACT

Objective: No information exists in the literature regarding the effect of coronavirus disease 19 (COVID-19) infection on subsequent *in* vitro fertilization (IVF) cycle attempt. We, therefore, aim to assess the influence of COVID-19 infection on IVF treatments.
Design: An observational study.
Setting: A tertiary, university-affiliated medical center.
Patients and methods: All consecutive couples undergoing ovarian stimulation (OS) for IVF, before and after recovering from COVID-19 infection, and reached the ovum pick-up (OPU) stage. The stimulation characteristics and embryological variables of couples undergoing IVF treatments after recovering from COVID-19 infection were assessed and compared to their IVF cycles prior to COVID-19 infection.
Main outcome measures: Stimulation characteristics and embryological variables.
Results: Nine couples (seven with the female partner infection and two with the male partner) resumed IVF treatment 8–92 d after recovering from the COVID-19 infection (negative polymerase chain reaction [PCR]). No in-between cycles differences were observed in OS and embryological variables between the cycles before and after recovering from the COVID-19 infection, except for a significantly lower proportion of top-quality embryos.
Conclusions: COVID-19 infection did not affect patients' performance or ovarian reserve in their immediate subsequent IVF cycle, except for a reduced proportion of top-quality embryos (TQEs). We therefore suggest, to postpone IVF treatment for a least 3 months (duration of folliculogenesis and spermatogenesis) after recovering from COVID-19 infection, aiming to recruit healthy gametes that were not exposed to COVID-19 infection during their development.

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Introduction

In December 2019, a new infectious respiratory disease emerged in Wuhan, Hubei province, China [1]. The disease, now termed coronavirus disease 19 (COVID-19) rapidly spread within China, affected millions of people worldwide, with more fatalities compared with the SARS and MERS coronavirus epidemics combined.

When considering the relationship between COVID-19 infection and infertility or infertility treatments, the ASRM Coronavirus/COVID-19 Task Force [2] mainly concentrated on patients and staff responsibilities to minimize the transmission of the disease, mental health, and COVID-19 and the effect of COVID-19 on pregnancy.

Moreover, while the ASRM Coronavirus/COVID-19 Task Force emphasized that the existing evidence suggests that 'the virus likely does not infect gametes [3,4] or embryos,' no information exists in the literature regarding the influence of COVID-19 infection on laboratory/embryological variables nor ovarian stimulation (OS) during the subsequent *in* vitro fertilization (IVF) cycle attempt – which is considered the 'most reliable sign of decrease ovarian reserve' [5].

Prompted by the aforementioned information, we aimed to assess the influence of COVID-19 infection on OS characteristics and the embryological variables during the IVF treatment post-COVID-19 infection, in order to aid both fertility specialists counseling and their patients in their decision-making process.

Patients and methods

The study population consisted of all consecutive couples undergoing OS for IVF, before and after recovering from COVID-19 infection, and reached the ovum pick-up (OPU) stage. COVID-19 infection was diagnosed by approved molecular assay for SARS-CoV-2 RNA. The study was approved by the institutional research ethics board of Sheba Medical Center.

Data on patient age and infertility-treatment-related variables were collected from the files. Embryological/laboratory variables of the IVF cycles were assessed and compared between the patients' IVF cycle before and after recovering from the COVID-19 infection. Embryos classification was based on the individual embryo scoring parameters according to pre-established definitions [6]. A top-quality embryo (TQE) was defined as seven or

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Table 1. Patients' baseline clinical characteristics and OS variables pre/post-Covid-19 infection.

	Female infection			Male infection		
	Pre-infection	Post-infection	*p* Value	Pre-infection	Post-infection	*p* Value
Number of patients	7		–	2		–
Mean interval between OPU cycles (months)	7.57 ± 5.42		–	3 ± 0		–
Mean interval between Covid 19 test to post-infection OPU cycle (days)	46.4 ± 29.3		–	66 ± 15		–
Maternal age, years (mean ± SD)	34 ± 7.1	34.5 ± 7.4	NS	40.5 ± 1.2	40.5 ± 1.2	NS
Maternal BMI, kg/m^2 (mean ± SD)	22.9 ± 0.1	23.6 ± 4.9	NS	39.4 ± 2.9	39.4 ± 2.9	NS
Mean basal FSH IU/L (mean ± SD)	7 ± 3.6		–	10.5 ± 2.8		–
Mean basal LH IU/L (mean ± SD)	3.7 ± 2.4		–	5.5 ± 0.4		–
Maternal smoking (%)	0		–	0		–
OS characteristics						
Duration of stimulation (days)	10.8 ± 2.4	9.4 ± 3.1	NS	9.5 ± 0.4	9 ± 1.6	NS
Range	8–14	3–14		9–10	7–11	
Total FSH dose used, IU (mean ± SD)	3384 ± 1367	2697 ± 1700	NS	2550 ± 244	3750 ± 489	NS
Range	1575–5850	675–6300	–	2250–2850	3150–4350	–
Mean peak estradiol levels pmol/L (mean ± SD)	7956 ± 7736	5122 ± 3799	NS	2056 ± 239	1800 ± 90	NS
Range	1292–25,433	1252–13,697	–	1763–2350	1690–1911	–
Mean peak progesterone levels nmol/L (mean ± SD)	2.1 ± 0.8	2 ± 1.3	NS	1 ± 0.1	0.9 ± 0.1	NS
Range	0.6–3.4	0.8–4.9	–	0.9–1.1	0.7–1.1	–

more blastomeres on day 3, equally-sized blastomeres and ≤10% fragmentation.

Statistical analysis was performed with paired student's *t*-test and Chi-square, as appropriate. Results are presented as means ± standard deviations; *p* qu.05 was considered significant.

Results

Of all couples who underwent IVF cycle treatments in our center before the COVID-19 pandemic, in 22, one of the partners was infected by COVID-19. Of whom, nine couples (seven with the female partner infection and two with the male partner) resumed IVF treatment after recovering. The interval between recovering from the COVID-19 infection (negative polymerase chain reaction [PCR]) and the subsequent IVF cycle was 8–92 d.

Patients clinical characteristics and the details of their IVF cycle attempts, before and after the COVID-19 infection, are shown in Table 1. There were no differences between the cycles in the length of OS, total dose of gonadotropin used, nor the peak estradiol and progesterone levels (Table 1).

Furthermore, while no differences were observed in the number of oocytes and mature oocytes retrieved, fertilization rate or semen analyses, the ratio of TQEs per number of 2PN were significantly lower post COVID-19 infection (Table 2).

Discussion

In this study, we observed no influence of COVID-19 infection on patients' performance during their immediate subsequent IVF cycle, except for the ratio of TQEs per fertilized oocytes, reflecting a detrimental effect of the COVID-19 infection on the developing gametes/embryos.

To date, damage to the female reproductive system in COVID-19 patients has not been reported. There is indirect evidence that COVID-19 might affect female fertility by attacking ovarian tissue and granulosa cells, and decreasing ovarian function and oocyte quality. Moreover, COVID-19 might damage endometrial epithelial cells and affect early embryo implantation [7–10].

Regarding the effect of COVID-19 on the male reproductive system, this issue is even more controversial. While five studies failed to detect the presence of COVID-19 viral RNA in the semen samples of patients with active or resolving infection [11–15], one study identified COVID-19 RNA in 15.38% of the semen samples [16] and another study [15] demonstrated that patients with moderate infection had significantly reduced sperm quantity and quality, compared to patients with mild infection or normal controls.

Folliculogenesis and spermatogenesis are complex and dynamic processes involving multiple endocrine cells and numerous signals that have been estimated to span >3 months [17,18]. The COVID-19 infection, by its known ability to activate the release large amounts of pro-inflammatory cytokines and precipitate and sustain an aberrant systemic inflammation [19], might also interfere with these processes, resulting in abnormal gametes (oocytes and sperms), with the consequent production of low-quality embryos.

In this study, we could not demonstrate any detrimental effect of COVID-19 on ovarian reserve/oocytes pool, as reflected by the similar response to OS – which is considered the 'most reliable sign of decrease ovarian reserve.' However, we did notice a significant decrease in the proportion of TQEs in patients IVF treatment attempt post-COVID-19 infection. Since the IVF treatment attempts were conducted 8–92 d post-infection, it might be assumed that the retrieved gametes during these cycles were exposed to the COVID-19 induced systemic inflammation during their development, i.e. the inflammatory environment detrimentally interferes with the intricate complex processes of folliculogenesis and spermatogenesis.

The limitations of our study are the small sample size and the short period of follow-up.

In conclusion, COVID-19 infection did not affect patients' performance or ovarian reserve in their immediate subsequent IVF cycle, except for a reduced proportion of TQEs. We therefore suggest, to postpone IVF treatment for a least 3 months (duration of folliculogenesis and spermatogenesis) after recovering from COVID-19 infection, aiming to recruit healthy gametes that were not exposed to COVID-19 infection during their development. Future larger studies with longer follow-up will be needed to validate our observations.

Ethical approval

The study was approved by our institutional review board (SMC-7901-20).

Table 2. IVF cycle laboratory characteristics according to pre/post-Covid-19 infection.

	Female infection			Male infection		
	Pre-infection	Post-infection	*p* Value	Pre-infection	Post-infection	*p* Value
Mean # of oocytes per OPU (mean ± SD)	10 ± 7	11.4 ± 7	NS	3.5 ± 1.5	5.5 ± 1.5	NS
Mean # of MII per OPU (mean ± SD)	9.57 ± 7	9.1 ± 6.3	NS	3.5 ± 1.5	4.5 ± 0.5	–
Mean # of MII/# of oocytes retrieved (mean ± SD)	0.93 ± 0.1	0.84 ± 0.1	NS	1	0.85 ± 0.1	NS
Mean # of 2PN per OPU (mean ± SD)	8.5 ± 6.9	6.6 ± 6.3	NS	2.5 ± 0.5	3.5 ± 0.5	NS
Mean # of 2PN/# of oocytes retrieved (mean ± SD)	0.81 ± 0.1	0.73 ± 0.3	NS	0.8 ± 0.2	0.8 ± 0.2	NS
Mean # of TQE per OPU (mean ± SD)	6.1 ± 5.2	3 ± 3.3	NS	1.5 ± 0.5	1 ± 1	NS
Mean # of TQE/# of 2PN (mean ± SD)	0.58 ± 0.2	0.26 ± 0.2	.03	0.66 ± 0.3	0.33 ± 0.2	<.001
Pre-wash total motile sperm count, millions (mean ± SD)	74 ± 70	56 ± 47	NS	245 ± 7	154 ± 10	NS

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

R.O. designed the study, wrote the first paper draft, edited it, proof read the article, and took part in discussions regarding the results. A.S.Z. retrieved the data, proof read the article and took part in discussions regarding the results. A.A. designed the study conducted the embryological work and retrieved the data, proof read the article, and took part in discussions regarding the results. The author(s) read and approved the final manuscript.

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