

# Prior COVID-19 infection increases degenerated oocytes but does not affect IVF outcomes: A Prospective Cohort Study

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## Abstract

**Objective:** To investigate whether prior COVID-19 infection and time interval after infection affect the in vitro fertilization (IVF) outcomes. **Design:** A prospective observational cohort. **Setting:** Reproductive center in China. **Population:** Participants recovered from COVID-19 and healthy controls. **Methods:** All participants received normal IVF treatment. The oocyte and embryo quality as well as pregnancy outcome data were collected and analyzed. **Main outcome measure:** Oocytes and embryo quality, clinical pregnancy outcomes. **Results:** The oocyte and embryo quality were comparable between the two groups, including the number of oocytes, 2PN zygotes, fertilization rate, cleavage embryos, day 3 good-quality embryos, blastocyst formation rate, and good-quality blastocysts. Nevertheless, the study group exhibited more degenerated oocytes ( $0.15 \pm 0.40$  vs.  $0.10 \pm 0.33$ ,  $P=0.035$ ). Further regression analysis indicated that prior COVID-19 infection is positively related to the number of degenerated oocytes (Adjusted  $\beta$ : 0.06, 95% confidential interval (CI): 0 -0.10,  $P=0.032$ ). No significant differences were observed in clinical pregnancy rate, implantation rate, early miscarriage rate, ectopic pregnancy rate, and ongoing pregnancy rate. Similarly, we observed no difference in oocyte and embryo quality as well as pregnancy outcomes across various post-infection time intervals. **Conclusions:** Preceding COVID-19 could increase the number of degenerated oocytes. However, it does not affect subsequent pregnancy outcomes. Additionally, post-infection time interval plays no significant role in IVF outcomes.

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**Conclusions:** Preceding COVID-19 could increase the number of degenerated oocytes. However, it does not affect subsequent pregnancy outcomes. Additionally, post-infection time interval plays no significant role in IVF outcomes.

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### Keywords

Post-COVID-19, oocyte quality, embryo quality, pregnancy outcomes, time interval

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## Introduction

The global health crisis of coronavirus disease 2019 (COVID-19) continues to impact people of all age groups worldwide, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). Recent studies increasingly support that COVID-19 infection may affect reproductive function, as the female reproductive system expresses relevant receptors such as angiotensin-converting enzyme 2 (ACE2), and transmembrane serine protease 2(1).

The COVID-19 infection detracts the pregnancy process (both maternal and fetal) in many cases. Several meta-analyses have shown a higher likelihood of preeclampsia, preterm birth, stillbirth, gestational diabetes, and low birth weight in pregnant individuals with SARS-CoV-2 infection compared to those without the infection (2-4).

Furthermore, many studies documented female reproductive function alteration after the COVID-19 infection. The most obvious alteration is the upsurge of menstrual abnormalities such as prolonged cycles and decreased volume of menstruation (5). Others also stated a shortened or disordered menstrual cycle as well as an increased volume of menstruation (6). It was subsequently reported that the sex hormone, ovarian reserve, and endometrium were also affected by the COVID-19 infection (7). In addition, the infection of COVID-19 worsened the symptoms of endometriosis which was the key factor in the causes of infertility (8). And the genes related to endometrial receptivity were changed (9). Thus, these alterations in the female reproductive system impair reproductive functions. Clinical evidence has emerged progressively to confirm the actual impact of SARS-CoV-2 infection on reproductive function.

In a small-sample-sized observational study, the proportion of top-quality embryos is decreased in women after COVID-19 infection (10). A slight decrease in the blastocyst formation rate in the case group is also recorded (11). However, Soha Albeitawi et al. found no difference in oocyte and embryo quality as well as pregnancy outcomes (12), which is consistent with the results of other researchers (11, 13). However, the opposite opinion shows that the clinical and ongoing pregnancy rates are significantly lower in frozen embryo transfer cycles of patients with past SARS-CoV-2 infection (14). Unfortunately, current evidence is hard to prove the impact of COVID-19 on in-vitro fertilization (IVF) outcomes due to the inconsistent results as well as the limited evidence provided by these relatively small-sample-sized studies as indicated by a recent meta-analysis (15). Hence, we carried out this prospective cohort study with larger sample size to investigate the impact of COVID-19 infection and the time interval on the IVF outcomes in women who receive ovarian stimulation.

## Materials and methods

### Ethics and written consent

A prospective observational cohort study was performed to explore the effect of post-COVID-19 and time intervals on women undergoing IVF treatment. This study was approved by the Ethics committee of the reproductive and genetic hospital of CITIC-Xiangya (approval number: LL-SC-2023-012) and written consent was obtained from all participating patients.

### Participants

Patients were screened during the consultation step and those who met the inclusive and exclusive criteria were eligible and enrolled for our study. The study group comprises individuals who have recovered from COVID-19 after being infected, while the control group consists of individuals who remained uninfected by COVID-19.

Inclusion criteria were: (1) age between 20 and 45 years old, (2) received ovarian stimulation, (3) women infected with COVID-19 before the treatment and the infection was confirmed by nucleic acid testing and/or antigen testing were enrolled in the study group, (4) women who never infected COVID-19 (confirmed by nucleic acid testing and/or antigen testing or never had similar COVID-19 infection symptoms such as fever, sore throat, running nose, etc.) were enrolled in the control group.

Exclusion criteria were as follows: (1) women with suspicious COVID-19 symptoms (such as fever, sore throat, back pain, headache, etc.) but did not confirm by nucleic acid testing and/or antigen testing, (2) oocyte donation, (3) intrauterine insemination, (4) oocyte cryopreservation, (5) other conditions not applicable for assisted reproductive technology.

#### Calculation of sample size

We set up a matching ratio between the study and control groups as 2:1, due to a decrease in the proportion of eligible participants in the control group after December 2022, when the Chinese government released “a circular on further optimizing the COVID-19 response”. The hypothesized clinical pregnancy rate difference across both groups is 10%. With a test efficacy of 90% and a significance level ( $\alpha$ ) set at 0.05, the calculated enrollment requirements are 760 individuals for the study group and 380 for the control group. After factoring in a 5% dropout rate, the final targeted enrollment is set at 800 individuals for the study group and 400 for the control group, resulting in a total of 1200 participants.

#### Ovarian stimulation protocol

Controlled ovarian stimulation was conducted using gonadotropin-releasing hormone (GnRH) agonist protocol, GnRH-antagonist protocol, progestin-primed ovarian stimulation protocol, and others such as mild stimulation, etc. The initial gonadotropin dosage was primarily determined by female age, body mass index (BMI), including anti-Müllerian hormone (AMH), antral follicle count (AFC), and basal follicle-stimulating hormone (FSH) levels. Throughout the stimulation process, follicular development was monitored through transvaginal ultrasound and serum hormone measurements, with adjustments made to the gonadotropin dosage as needed. Ovulation was triggered by administering human chorionic gonadotropin (hCG) after confirming adequate follicle stimulation by ultrasound and hormone concentrations.

Patients were slated for oocyte retrieval 35–36 hours after hCG administration. The procedures for oocyte retrieval, oocyte and embryo culture, insemination, intracytoplasmic sperm injection (ICSI), and embryo transfer were determined by the standard practices of the center, which holds ISO 9001 Certification.

#### Outcome measurement

The primary outcomes in the present study were: oocytes and embryo quality. The secondary outcomes were: clinical pregnancy outcomes. The clinical pregnancy was identified as the presence of gestational sac(s) exhibiting fetal heart activity through ultrasound in the fourth week following embryo transfer. The implantation rate was calculated by dividing the total number of embryos transferred by the number of sacs. Subsequently, miscarriage was characterized as the loss of intrauterine pregnancy after the confirmation of gestational sacs (16). Pregnancy outcomes were followed up to three months after embryo transfer.

#### Data analysis:

Statistical Package for Social Sciences for Windows, version 25.0 (SPSS Inc, Chicago, IL, USA) was used to perform data analyses. The flowchart was generated using Edraw Max, version 9.2 (Shenzhen, China), and graphs were created using GraphPad Prism 8 (GraphPad Software, San Diego, USA). Homogeneity of variance and normality of data were estimated using the Shapiro–Wilk, Kolmogorov–Smirnov, and Lilliefors tests, respectively. Values were expressed as means  $\pm$  standard deviation, or frequency (%). A comparison of quantitative variables (also continuous variables) between groups was performed using the Kruskal–Wallis test or ANOVA according to the normality. Qualitative variables (also categorical variables) were compared by the Chi-square ( $\chi^2$ ) test or Fisher’s exact test. Multivariate logistic regression analysis was performed

to figure out the risk factors of pregnancy outcomes. Data were considered statistically significant with a two-sided  $P < 0.05$ .

## Results

A total of 1300 infertile women were recruited in our study. Finally, there were 781 women recovered from COVID-19 and 388 women uninfected with COVID-19, a total of 1169 persons enrolled. The reasons for other participants' exclusion were detailed and stated in our flow chart (Supplementary figure S1). As for embryo transfer, 215 post-COVID-19 and 113 control women were performed and all of them were followed by three months after embryo transfer to collect the data on pregnancy outcomes for further analysis. Reasons for embryo transfer cancellation are as follows: 1) ovarian hyperstimulation syndrome ( $n=36$ ), 2) no oocytes ( $n=8$ ), 3) no transferrable embryo ( $n=79$ ), 4) preimplantation genetic test ( $n=299$ ), 5) asynchrony in embryo and endometrium ( $n=311$ ), 6) personal reasons ( $n=108$ ).

There is no significant difference in participants' demographic information between the two groups on many levels, such as age, infertility duration, BMI, AMH, and AFC, while the waist-to-hip ratio is slightly higher in controls. In addition, no significant difference is observed in the basal levels of FSH, luteinizing hormone (LH), estradiol (E2), and progesterone (P) between the two groups (Table 1). We also tested some endocrine markers to evaluate the impact of COVID-19 infection on the endocrine function. Interestingly, the fasting glucose is lower in the study group (5.18 (4.3, 5.43) vs. 5.24 (5.02, 5.52),  $P=0.001$ ) while the free thyroxine (T4) is higher (0.99 (0.92, 1.09) vs. 0.97 (0.90, 1.07),  $P=0.044$ ). No difference is observed in blood pressure, blood cells, and coagulation function. The proportion of male partners with previous confirmed COVID-19 infection is significantly higher in the study group (54.93% vs. 9.07%,  $P<0.001$ ) (Table 1).

The proportion of women treated with different stimulation protocols between the two groups is similar. The dose of stimulation drugs, stimulation duration, and hCG for triggering, have no significant difference in whether the patients suffered from COVID-19 before or not. On hCG day, the levels of E2, P, LH, and follicles are alike in two groups. Besides, the oocyte and embryo quality are also parallel between the two groups, such as different stages of oocytes, the number of 2 pronuclei (2PN) zygotes, fertilization rate, cleavage embryos, the number of day 3 good quality embryo, blastocyst formation rate, and the number of good-quality blastocyst. However, the number of degenerated oocytes is higher in the study group ( $0.15 \pm 0.40$  vs.  $0.10 \pm 0.33$ ,  $P=0.035$ ) (Table 2). Further regression analysis shows that COVID-19 affection before is positively related to the number of degenerated oocytes (Adjusted  $\beta$ : 0.06, 95% confidential interval (CI): 0 -0.10,  $P=0.032$ ) (Table 3).

In women who received embryo transfer, there is no difference in the endometrial thickness before transfer, the number of embryos transferred, and the number of good-quality embryos transferred. Similarly, no difference is observed in the pregnancy outcomes such as clinical pregnancy rate, implantation rate, early miscarriage rate, ectopic pregnancy rate, and ongoing pregnancy rate (Table 2). Further regression analysis also shows that COVID-19 infection or not is not related to clinical pregnancy, embryo implantation, and ongoing pregnancy (Table 3).

Our participants are divided into four groups according to the time interval from COVID-19 infection to the IVF/ICSI treatment to illustrate whether recovery time plays a role in IVF/ICSI performance. Group 1 represents recovery time within 60 days ( $n=72$ ), Group 2 represents recovery time between 60-120 days ( $n=557$ ), group 3 is for recovery time between 120-180 days ( $n=107$ ), and group 4 is over 180 days ( $n=45$ ). The blastocyst formation rate differs among these groups either compared with or without controls but with no trend. However, no difference was observed in oocyte and embryo quality as well as pregnancy outcomes in women experiencing different time intervals (Table 3, 4).

## Discussion

### Main findings

In the present study, we investigated the impact of COVID-19 infection on the IVF/ICSI performance in infertile couples. However, even more degenerated oocytes in post-COVID women, there is no difference in

the embryo quality, as well as pregnancy outcomes in women with or without previous COVID-19. Moreover, we also illustrated that the time interval between COVID-19 infection and IVF/ICSI treatment does not affect the outcomes.

## Interpretation

As the main receptor of SARS-CoV-2, ACE2-mediated signaling cascades can regulate ovarian steroidogenesis, follicular development, oocyte maturation, ovulation, and atresia in females(17). Additionally, the ACE2/Ang 1–7/Mas axis facilitates the meiotic resumption of oocytes, a process intricately controlled by the LH(18). Unfortunately, SARS-CoV-2 infection can down-regulate ACE2 receptors, leading to reduced synthesis of Ang 1–7, which impairs normal reproductive physiology(1). Correspondingly, we found a significantly higher number of degenerated oocytes in women with prior SARS-CoV-2 infection, which indicates the long-lasting effects of COVID-19 infection on reproductive function.

It was observed that certain individuals with COVID-19 exhibited abnormal levels of sex hormones. Women with COVID-19 showed disproportionately elevated concentrations of FSH and LH (7). They may also experience ovarian damage, including a reduction in ovarian reserve (AMH) and reproductive endocrine disorders such as testosterone and prolactin, indicating an ovarian injury (19). However, we observed no difference in sex hormones and ovarian reserve markers such as AMH and AFC in the present study. Similarly, Kezhen Li et al. found the same results in their study as ours (20). Besides, we could not find any difference in the pregnancy outcomes in our study, which is in accordance with other studies demonstrating that prior SARS-CoV-2 infection in females had no adverse influence on subsequent IVF treatment (21, 22). In general, the potential impact of SARS-CoV-2 infection on ovarian reserve as well as embryo quality remains a matter of controversy, and additional investigations are needed to address this issue conclusively.

COVID-19 is accounted to cause consequences on diabetes and the endocrine glands, such as the adrenals, thyroid, and pituitary, along with conditions like hyponatremia and hypogonadism (23). It is also linked to both new and persistent hyperglycemia, leading to the possibility of new-onset diabetes even in individuals with initially normal HbA1C levels (24). However, we observed the opposite result that women after COVID-19 recovery have even lower fasting glucose levels than controls. Moreover, one proposed mechanism for subacute thyroiditis in COVID-19 involves an exaggerated immune response to the virus and direct viral infection of the gland (25). This condition typically progresses through an initial hyperthyroid phase, followed by a hypothyroid phase, with eventual recovery to either a euthyroid state or hypothyroidism. Additionally, another mechanism contributing to thyroid pathology is non-thyroidal illness syndrome, marked by low or normal plasma T4 despite the presence of normal or slightly decreased thyroid-stimulating hormone (TSH) (26). Surprisingly, there is an obvious higher free T4 and normal TSH level in women after COVID-19 infection, indicating the long-lasting effects of COVID-19 on the thyroid function. Whether this slight alteration affects oocyte degeneration is unknown and needs further investigation. What's more, it is still unclear how thyroid dysfunction progresses after COVID-19 over time and the pattern of its development. Luckily, it seems that the slight alteration in thyroid function does not affect the IVF/ICSI pregnancy outcomes.

Additionally, studies also reported that COVID-19 leads to coagulopathy as it directly induces the production of endogenous chemical substances that promote the alteration of vascular hemostasis (27). A higher D-dimer level, prothrombin time, fibrinogen, and thrombin time were reported in studies (28, 29). Quantitative hematologic abnormalities are also described in some studies including lymphocytopenia, neutrophilia, eosinopenia, and mild thrombocytopenia (30, 31). While certain changes returned to normal values after recovery, others endured for months, illustrating the lasting impact of COVID-19 on the body (32). However, we did not notice any change in coagulation function and blood cells in our participants.

Women who recovered from COVID-19 and received frozen embryo transfer within 60 days exhibited a significantly lower pregnancy rate than controls. Conversely, when the time interval was above 60 days, the difference disappeared (14). To ensure the recruitment of healthy gametes not exposed to COVID-19 during their development, it is recommended for infertile women to delay IVF treatment for at least 3

months (the duration of folliculogenesis and spermatogenesis) after recovering from a COVID-19 infection (10). Nevertheless, a recent study shows that the time interval following infection does not affect IVF/ICSI outcomes (21). Unfortunately, the sample size in the above three studies is relatively small to provide validated evidence. We also explored the time difference in women after COVID-19 infection to IVF/ICSI treatment in our present study. However, there is no influence of time difference in IVF performance as shown by our results. Hereby, we suggested infertile women after COVID-19 infection to received their assisted reproductive treatment as soon as possible once they are prepared. There is no need to delay their attempt to get pregnant.

### Strength and limitations

To the best of our knowledge, this is the first study that combined endocrine function and IVF/ICSI outcomes with prior COVID-19 infection. Despite the large sample size and good design of our study, limitations also exist. One of the limitations is that the sample size of women who received fresh embryo transfer is small, which restricts the test efficacy, especially in the time interval after COVID-19 analysis. Secondly, there is a lack of long-term pregnancy outcomes in our study. Pregnancy outcomes within three months were followed up in our study so far and the long-term outcomes are still ongoing following in our other study. What's more, no current published evidence focusing on pregnancy complications and neonatal outcomes in IVF/ICSI in women with prior COVID-19 infection. Hence, studies with large sample sizes and long-term outcomes are needed to further illustrate the impact of COVID-19 on IVF performance.

### Conclusions

Preceding COVID-19 could increase the number of degenerated oocytes. However, females with prior COVID-19 infection did not exhibit detectable negative impacts on subsequent pregnancy outcomes. Additionally, post-infection time interval plays no significant role in IVF outcomes. There is no need to postpone the IVF treatment after the COVID-19 infection.

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### Disclosure of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### Contribution to Authorship

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### Details of Ethics Approval

The procedures of the study received ethics approval from the Ethics committee of the reproductive and genetic hospital of CITIC-Xiangya (approval number: LL-SC-2023-012) responsible for human experimentation on April 3, 2023.

### Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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