Original Article

The Covid-19 Infection Effect on Assisted Reproductive Method Outcomes

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Received April 2024; Revised and accepted June 2024

Abstract

Objective: COVID-19 can have potential pathogenic effects on the oocyte and embryos, but there is limited data about its impact. This study aimed to investigate the COVID-19 impact on the outcome of Assisted Reproduction Techniques (ART) methods.

Materials and methods: This case-control study was conducted on 190 infertile women who underwent oocyte retrieval at Yas Hospital in vitro fertilization (IVF) department affiliated to Tehran University of Medical Sciences, from October 2021 to October 2022. The case group was defined as women whose PCR test was positive on puncture day and the control group was women with COVID-19 negative tests on puncture day. The study outcome measurements included the number of oocytes retrieved and the number and quality of embryos. Finally, the data were analyzed by SPSS 24.

Results: The mean age of the participants was 32.89 ± 5.58 years with an age range of 18-49 years. No significant difference was observed between the two groups regarding baseline variables. The mean number of oocytes was significantly (p =0.001) lower in the case (6.68±4.25) group versus the control (9.07±4.10) group. While there was no statistically significant difference regarding the mean number of embryos in the study groups, No grade A embryos were observed in more than half (57.5%) of the women in the case group. Furthermore, the frequency of grade C embryos on average was 1.08±1.11 in the case group and 0.57±0.75 in the control group, with a statistically significant difference (p =0.010).

Conclusion: The findings of this research highlighted that women infected with COVID-19 on the puncture day have a lower number of oocytes and also good-quality embryos.

Keywords: In Vitro Fertilization; COVID-19; Embryo Transfer; Oocyte Retrieval

Introduction

In December 2019, the first outbreak of COVID-19 appeared in China and quickly spread to the world (1, 2). The clinical spectrum of the disease varies from a mild condition to severe symptoms. The mild presentation is observed in 81% of cases; while 14% develop the severe form of the disease characterized by dyspnea, and hypoxia, around 5% of patients may show a very severe and critical condition presenting with respiratory failure, shock, or multiple organ dysfunction (3, 4).

During epidemics of infectious diseases, pregnant women are at a higher risk of premature labor, fetal

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growth restriction, fetal distress, preeclampsia, and the need for cesarean section delivery. These risks are particularly exaggerated in women hospitalized with pneumonia (5-9).

The SARS-CoV-2 virus penetrates its target cells by binding to the angiotensin-converting enzyme (ACE2) and modulates the expression of this enzyme in host cells. Evidence shows that ACE2 is widely expressed in the ovary, uterus, vagina, and placenta, suggesting that besides through droplets- and contact-mediated transmission, this virus can also spread through mother-to-child and sexual transmission. Angiotensinogen II (Ang II), ACE2, and Ang regulate follicular growth and ovulation, modulate angiogenesis and luteolysis, and affect endometrial histological changes and fetal development. Therefore, COVID-19 may interfere with women's reproductive functions through regulating the ACE2 pathway (10).

According to the above-mentioned, it is logical to consider that COVID-19 can have potential pathogenic effects on the oocyte and embryos. Therefore, this study aimed to investigate the COVID-19 impact on the outcome of ART methods.

Materials and methods

This case-control study was conducted on 210 infertile women who underwent oocyte retrieval at Yas Hospital IVF department affiliated with Tehran University of Medical Sciences, Tehran, Iran from October 2023 to January 2024.

Infertile women aged 18 to 40 years who were candidates for the FET cycle and were willing to participate were enrolled in the study. According to our IVF department, during the COVID-19 pandemic, for all cases who enrolled in the operation room, COVID-19 PCR tests have to be done. The case group was defined as women whose PCR test was positive at puncture day and the control group was women with negative test at puncture day.

According to a value reported in the previous study, the sample size was calculated as 40 women in each group. To increase the power of the study, the control group cases were increased to 150 women, so the total sample size was 190. The subjects were recruited by convenience sampling method.

Patients' demographic and clinical data, including age, body mass index (BMI), comorbidities, symptoms at the onset of the disease, the individual's epidemiological history, blood group, and type and duration of infertility, were recorded in a pre-prepared questionnaire. The information required was obtained by interviewing the patient, clinical examinations, and reviewing laboratory results and embryology and ultrasound reports. The study outcomes were the number of oocytes retrieved and the number and quality of embryos.

To analyze the quantitative data, the Mann-Whitney U test (for variables with non-normal distribution) or the independent t-test (for variables with normal distribution) was used. The Chi-square test was used to compare qualitative variables between the two study groups. The statistical significance level for all tests was considered less than 0.05.

The guidelines of the Declaration of Helsinki were observed throughout the study. The study's protocol was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences and received the ethics code of IR.TUMS.MEDICINE.REC.1400.1226.

Results

Totally190 individuals participated in this study, of whom 150 belonged to the control group and 40 were included in the case group. The mean age of the participants was 32.89 ± 5.58 years with an age range of 18-49 years. No significant difference was observed between the two groups regarding baseline variables.

In the case group, the most prevalent COVID-19 symptom was cough (40%), followed by fever (30%) and then sore throat (27.5%), and rhinorrhea (22.5%). Other symptoms attained a frequency of < 10%.

The comparison of the mean number of oocytes showed a significant difference between the case (6.68 ± 4.25) and control (9.07 ± 4.10) groups (p =0.001). The mean number of embryos was 2.98±1.42 in the case group and 2.76 ± 0.71 in the control group, indicating no statistically significant difference between the two groups (p =0.360).

The frequency of grade A embryos was compared in the case and control groups. It was 0.97 ± 0.85 in the case group and 0.95 ± 0.261 in the control group with no significant (p =0.937) difference; however, no grade A embryos were observed in more than half (57.5%) of the women in the case group.

The mean frequency of grade B embryos was 0.93±1.09 in the case group compared to 1.23 ± 0.72 in the control group, with no significant difference (p =0.106). The mean frequency of grade C embryos was 1.08 ± 1.11 in the case group and 0.57 ± 0.75 in

the control group, with a statistically significant difference (p =0.010).

Discussion

The results of the present study showed that the mean numbers and quality of oocytes and embryos retrieved from infertile women with Definite Diagnosis of COVID-19 were significantly different from non-infected women. The frequency of grade C embryos was significantly (p-value=0.010) higher in the case group and more than half (57.5%) of the women in the group failed to have grade A embryos.

Covid-19 is a serious and dreadful infectious disease commonly presenting with symptoms such as fever, cough, and fatigue. It has also been postulated that the Covid-19 disease can have adverse effects on reproductive health. At the beginning of the COVID-19 pandemic, the American Society of Infertility published a guideline that recommended the cessation of all non-emergency infertility treatment producers except for those who would need emergency oocyte or embryo freezing (such as cancer patients) (11).

Yet our knowledge about the effects of COVID-19 is limited. The SARS-CoV-2 virus penetrates host cells primarily by binding to ACE2, a phenomenon that can be facilitated by the proteolytic cleavage and activation of transmembrane protease, serine 2 (TMPRSS2) (12). Several studies have asserted that these essential receptors are not expressed on sperms (13), oocytes (14), and embryos (15); however, gamete infection is still possible during IVF procedures though it is highly improbable.

Other studies have suggested a key role of oxidative stress in COVID-19 pathogenicity at the molecular level. On the other hand, oxidative stress facilitates the development of female reproductive disorders and infertility (16) by causing epigenetic changes in oocytes (17), and therefore, exerting adverse effects on the quality of oocytes (18) as one of the important contributors to the rapid development of blastocysts. However, ACE2 receptors have been detected on mice follicles before ovulation (19), as well as on human ovaries (20) and germ cells. Therefore, it cannot be ruled out the indirect adverse effects of the COVID-19 virus on the fetus (21).

The COVID-19 pandemic has also changed the attitudes of infertile couples toward fertility, fertility counselors, and fertility clinics (22, 23). The psychological impact of fertility treatment cessation during the COVID-19 crisis should be considered a contributor to this event (24). Many fertility clinics were forced to close during the pandemic (25). In the post-Covid-19 era, vaccination against the SARS-CoV-2 virus become an obligation in many countries (26), raising ongoing concerns over the effects of vaccines on fertility. Nonetheless, currently, there is no evidence showing that vaccines can have adverse effects on fertility (27).

In a study by Wang et al., the effects of asymptomatic or mild SARS-CoV-2 infections were assessed on women's fertility and the laboratory and clinical outcomes of ART treatments. Patients undergoing ART treatment at the Reproductive Health Center of Tongji Hospital, Wuhan, China, from May 2020 to February 2021 were assessed in the study. Anti-SARS-CoV-2 antibodies were identified in the sera of 70 individuals, for which 3973 patients had negative results. There were 65 women in the case group and 195 women in the control group. Ovarian reserves and ovarian responses were similar between the two groups after matching. Despite a slight decrease in the rate of blastocyst formation in the case group, the proportion of mature oocytes, impaired oocytes, fertilized oocytes, cleavage embryos, top-quality embryos, and frequency of blastocysts was similar between the two groups. In addition, there was no significant difference in terms of biochemical pregnancy rate, clinical pregnancy rate, early abortion rate, or implantation rate. Finally, the results of this study provided no evidence that a history of asymptomatic or mild SARS-CoV-2 infection in women could adversely affect the fertility rate or the laboratory, clinical, and fetal outcomes of ART treatment (28). In contrast, the results of our study showed that the case group had significantly higher rates of grade C embryos and a significantly lower number of oocytes compared to their peers in the control group.

In a review study by Mahabadi et al., the effects of the COVID-19 disease were investigated on sperm quality parameters and male fertility, and reported that COVID-19 infection might predispose men to infertility. The SARS-CoV-2 virus uses ACE2 as a receptor to penetrate human cells. It has been shown that ACE2 is expressed in the lungs, as well as in testes, and especially in Leydig and Sertoli cells. Also, the expression of proteases such as TMPRSS12, TMPRSS11B, and TMPRSS2 can facilitate the fusion of the virus to the host cell. Since the exact virulence mechanisms exploited by this virus are incompletely understood, and no specific medications or vaccines

with complete protection have been developed so far, the most important step for curbing the spread of the virus is to disrupt its transmission cycle. The symptoms of COVID-19, such as fever, lead to andrological effects, which should become the center of attention. Finally, it can be concluded that the SARS-CoV-2 virus may be able to infect testicular cells through ACE2 and exert adverse effects on the male reproductive system; nevertheless, more studies are required in this area (29).

However, most studies suggest that SARS-CoV-2 infection is unlikely to have long-term adverse effects on the female reproductive system (14). A recent cross-sectional study that hormones involved in reproductive functions, such as FSH and AMH, were comparable between patients with or without Covid-19 infection. Well-designed studies presenting direct evidence on the possible effects of the SARS-CoV-2 virus on gametes, embryos, and female fertility are limited (30) and have mostly spared investigations on hormones related to reproductive function.

Besides possible effects on gametes and embryos, evidence shows that contracting COVID-19 infection by pregnant women can influence the outcome of pregnancy and result in complications such as premature birth, a low Apgar score, and low birth weight. In this regard, Chen et al.'s study (2020) on 9 pregnant women infected with COVID-19 showed an incidence rate of 44.4% for premature birth in these women, indicating an unusually high rate (5). Nevertheless, obstetric and neonatal complications were not addressed in this study.

One of the limitations of this study was the lack of assessing the possible effects of factors such as stress, anxiety, and individual differences on the study's outcomes was beyond the power of the researcher; however, we made tremendous efforts to reduce participants' stress by talking to them and providing emotional support.

Conclusion

The findings of this research highlighted that women who infected with COVID-19 on the puncture day have a lower number of oocytes and good-quality embryos.

Conflict of Interests

Authors declare no conflict of interests.

Acknowledgments

This study was extracted from the Obstetrics& Gynecology residency thesis of the first author under the supervision of the corresponding author.

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Citation: Poursaadat N, Nazemi P, Shams Zamenjani S, Pourmand N, Mohammadkhani R, Akbari Asbagh F. **The Covid-19 Infection Effect on Assisted Reproductive Method Outcomes.** J Family Reprod Health 2024; 18(2): 85-9.