

# Could Assisted Reproductive Technology Be a Predisposing Risk Factor for COVID-19 Infection in Women?

## Yardımcı Üreme Teknolojileri Kadınlarda COVID-19 Enfeksiyonu için Predispozan Bir Risk Faktörü Olabilir Mi?

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### ABSTRACT

**Introduction:** The treatment agents used in assisted reproductive technology (ART) treatments could cause supra-physiologic hormone levels. We aimed to show if the ART could be a predisposing risk factor to be positive for Coronavirus Disease 2019 (COVID-19).

**Methods:** The data of the 43 infertility patients who were treated with ART between 1 March and 1 December 2020 at a Reproductive Endocrinology and Infertility Unit of a tertiary center were collected retrospectively. These patients were phoned and asked if they wanted to participate in the study; they were positive for COVID-19 or had a symptom of the illness.

**Results:** It was found that only 1 (2.4%) case had COVID-19 after the ART treatment, had a loss of smell and taste. The remaining treated 42 cases had no symptoms of COVID-19 or a diagnosis with COVID-19.

**Conclusion:** When turning to normal practice life, all patients should be evaluated for COVID-19 during pre, per, and post-treatment time in order to stop the ART and protect against the cases from the possible side effects of assisted reproductive treatments, especially the possible, but undefined, predisposition factor to COVID-19.

**Keywords:** Covid-19, assisted reproductive technology, risk factors, prognosis

### ÖZET

**Giriş:** Yardımcı üreme teknolojisi (YÜT) tedavilerinde kullanılan tedavi ajanları, suprafizyolojik hormon seviyelerine neden olabilir. YÜT'ün Koronavirüs Hastalığı 2019 (COVID-19)'na yakalanmak için bir risk faktörü olup olmadığını göstermeyi amaçladık

**Yöntemler:** 1 Mart - 1 Aralık 2020 tarihleri arasında üçüncü basamak bir merkezin Üreme Endokrinolojisi ve İnfertilite Ünitesi'nde YÜT ile tedavi edilen 43 infertilite hastasının verileri geriye dönük olarak tarandı. Bu hastalara telefonla ulaşıldı, araştırmaya katılmak isteyip istemedikleri; COVID-19 tanısı alıp almadıkları veya hastalık semptomu taşıyıp taşımadıkları soruldu.

**Bulgular:** Görüşme sırasında sadece 1 (% 2,4) vakanın tedavi sonrası dönemde COVID-19'a yakalandığı tespit edildi ve o kişide koku ve tat kaybı hala devam ediyordu. Geri kalan tedavi alan 42 hastada COVID-19 semptomu yoktu veya COVID-19 için pozitif bir test sonucunun olmadığı saptandı.

**Sonuç:** Normal çalışma hayatına dönerken, YÜT'ü durdurmalı ve özellikle mümkün olan yardımcı üreme tedavilerinin olası yan etkilerinden vakaları korunmak için tüm hastalar tedavi öncesi, sırası ve sonrası dönemde COVID-19 açısından değerlendirilmelidir.

**Anahtar Kelimeler:** Diyabetes mellitus, depresyon, anksiyete

### INTRODUCTION

The World Health Organization (WHO) declared the Coronavirus Disease 2019 (COVID-19) pandemic on 11 March 2020 and alerted all governments to prepare emergency plans for COVID-19. After this important

notice, almost all health societies published their recommendations to guide patients and clinicians in how to behave during the pandemic. On 17 March 2020, the American Society for Reproductive Medicine (ASRM) recommended that all assisted reproductive

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technology (ART) treatments and non-urgent diagnostic procedures should be postponed except for some cases which are currently "in-cycle" or who require urgent stimulation and cryopreservation because of the unknown effect of COVID-19 on fertility, pregnancy, and fetus (1). The European Society of Human Reproduction and Embryology (ESHRE) suggested similar recommendations to the ASRM on 19 March 2020 (2). In Turkey, the first case was detected and declared on 10 March 2020. Due to these societies' recommendations and being a part of the pandemic, many fertility centers in Turkey did not start any type of new ART treatment.

The updated version of the recommendations for ART has been published since March 2020. The latest version of ESHRE's guidelines recommended restarting ART under some rules and conditions (2). Although the advice to return to normal daily practice has been offered, the risk of infection during the delivery of reproductive care, the possibility of COVID-19 contamination, and the effect of COVID-19 on the fetus and neonate are still unclear.

The treatment agents used in ART modalities could cause supraphysiologic hormone levels that may be related to new clinical effects on a woman's body. According to knowledge, there are no reports about whether or not this high level of hormones due to the ART is a predisposing or prognostic factor for COVID-19. In this report, We aimed to show if the ART could be a predisposing risk factor to be positive for Coronavirus Disease 2019 (COVID-19).

## **MATERIALS AND METHODS**

After the ethical committee's approval and the permission from the Republic of Turkey Ministry of Health, the data of 43 infertility patients who were treated with ART between 1 March and 1 December 2020 at a Reproductive Endocrinology and Infertility unit of a tertiary center were collected retrospectively. These patients were contacted and asked if they

wanted to participate in the study and if they were positive for COVID-19 or had a symptom of the illness. All of the patients agreed to participate and answered the questions.

The SPSS 21.0 program was used in the statistical analysis of the data. The variables were expressed as mean  $\pm$  standard deviation ( $X \pm SD$ ), and the percent (%) value was calculated for variables determined by count. The "p" significance value was taken as 0.05 in all the statistical analyses.

## **RESULTS**

In the present study, 43 infertile women who were treated with ART at the fertility center between 1 March and 1 December 2020 were contacted, and all agreed to be included in the study. All of the treatments for the patients were initiated before the declaration of the Covid-19 outbreak. New cycles had not been initiated due to the recommendations of the international and national societies. The mean age of the patients was  $33.25 \pm 4.74$  (minimum 23; maximum 42) years old, and the duration of infertility was  $5.02 \pm 4.69$  (minimum 1; maximum 18) years. The mean time of interview after the end of ART was  $46.7 \pm 18.3$  days. As seen in Table 1, ovarian stimulation, oocyte pick-up, and intracytoplasmic sperm injection (ICSI) were used for all patients. Embryo transfer was performed on 27 (62.7%) patients, and clinical pregnancy was detected in 10 of the 27 patients after the ART procedure. At the time of the interview, none of the infertile women had any symptoms of COVID-19, such as fever, cough, headache, myalgia, fatigue, sore throat, diarrhea, acute loss of smell or taste, or a confirmed diagnosis from a positive test result for COVID-19 nucleic acids by real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR). 1 (2.4 %) COVID-19 case was detected in the study group. There was a loss of smell or taste on 1 (2.4 %) patient in the study group.

**Table 1.** Clinical characteristics of the participants.

		n	%
<b>OPU</b>	Performed	41	95.3
	Canceled	2	4.7
<b>ET</b>	Performed	27	62.7
	Canceled	16	37.3
<b>Clinical Pregnancy Rate / Embryo transfer</b>		10	40.7
<b>Known as positive for COVID-19 after ART</b>	Yes	1	2.4
	No	42	97.6
<b>Any symptom of COVID-19 after ART</b>	Yes	1	2.4
	No	42	97.6

**Abb.** ART; Assisted reproductive treatment, COVID-19; Coronavirus Disease 2019, ET; Embryo transfer, OPU; Oocyte pick-up, ICSI; Intracytoplasmic sperm injection.

## DISCUSSION

It is still unknown whether or not ART could be a potential risk or prognostic factor for COVID-19. It has been shown that women are less likely to be positive for COVID 19 and that their mortality rate is less than men's (3). It has also been hypothesized that this statistically significant difference has been caused by the role of the protective effect of estrogen (4). Furthermore, the use of conjugated equine estrogens has been proposed to regulate the immune response to COVID-19 by activating the estrogen receptors (4). These receptors are known as transcription factors regulating the development of immune cells and the pathways of the immune system (5). Despite the recommendation concerning the use of estrogen for the treatment of COVID-19, the beneficial or harmful estrogen level is undetermined. The estrogen and progesterone levels in a stimulated cycle could be ten times greater than the hormone levels in natural menstrual cycles (6). It is doubtful that such a high level of hormones may still have an immunomodulatory role. To evaluate this relationship, the patients, who had been treated with ART recently, could provide a great opportunity to gain insight into the association between ART and COVID-19.

Di Mascio et al. reviewed and concluded that pregnant women are not at higher risk of Coronavirus spectrum infections compared with the general population (7). According to our knowledge, there are only two reports about pregnant after ART has been reported as diagnosed with COVID-19 (8,9). Hantoushzadeh et al. reported that seven pregnant women died due to severe COVID-19 disease, and one of these cases achieved pregnancy with ART due to age-related infertility (8). In another study, 88 women ongoing pregnancies achieved by ART were phoned. It was found that ten patients (11.3 %) had symptoms related to COVID-19; the COVID PCR test was performed on 5 out of the ten female-patients with symptoms. Two of them were positive (40 %) and three negatives (60 %) (9). In our study, the 43 infertile couples who applied for infertility treatment between 1 March and 1 December 2020 were evaluated, contacted, and asked if they were positive for COVID-19 or had any symptoms of the virus. While we were talking to all cases, only 1 (2.4%) case has been identified COVID-19. This result cannot show whether ART treatment may be a predisposing or prognostic factor for COVID-19. In addition, the patients who achieved pregnancy by ART treatment did not have any medical problems related to COVID-19. Almost all patients were below 42 years old, and it is

well known that COVID-19 especially affects people who are older. It may be speculated that the women did not show any significant signs of COVID-19 due to the young ages in our study. All pregnancies were almost in the first trimester, so it could not be said whether pregnant women may or may not be at a higher risk of COVID 19 at different stages of the pregnancy period.

The first limitation of this study was that these results are only from a single fertility center, and the number of participants is very low. The second limitation was that at the time when we reached the patient, she might have been in the incubation period of COVID-19, so the case of a positive COVID-19 diagnosis would have been after the interview.

## CONCLUSION

In conclusion, there are only four pregnant achieved by ART and diagnosed with COVID-19 in the literature. It is possible that number of these cases could be more. So, we want to bring attention to the potential risk of COVID-19 infection in patients who have been treated with ART. With the return to normal practice life, all fertility societies' guidelines should be followed carefully; all patients should be evaluated for COVID-19 during pre, per and post-treatment time for continuing ART treatments and protecting the patients from the side effects of ART, especially with the possible, but undefined, predisposition factor to COVID-19

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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