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CoronaVac vaccine does not affect ovarian reserve

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ABSTRACT

Objectives: In this study, our aim is to investigate the effect of CoronaVac vaccine on ovarian reserve in female patients followed up for infertility.

Material and methods: Our study is a retrospective study. Forty-six infertile patients who received two doses of CoronaVac vaccine one month apart and had not had a previous Covid 19 infection were included in the study. Anti-müllerian hormone (AMH) and folliculometry of 46 patients one month before CoronaVac vaccine and one month after the second dose of vaccine were compared.

Results: There was no statistically significant difference in the change of AMH level and follicle number before and after vaccination (respectively p = 0.366; 0.610).

Conclusions: Considering that having a COVID-19 infection has a negative effect on female fertility and causing ovarian damage in recent studies, vaccination is a rational and cost-effective approach to protect ovarian reserve. Knowing that the vaccine does not have a negative effect on fertility may increase the application of the vaccine in women of reproductive age.

Key words: anti mullerian hormone; CoronaVac; infertility; ovarian follicle; vaccination

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INTRODUCTON

Cases of pneumonia of unknown etiology were first reported in December 2019 in Wuhan, China [1]. It was announced to the world in January 2020 that a new type of coronavirus (SARS-CoV-2) was isolated by the Chinese Government; Due to the rapidly spreading epidemic affecting the whole world, it was declared a pandemic by the World Health Organization (WHO) [2, 3].

Although mortality rates vary by country, the average mortality rate has been reported as 1.4% [4].

Many vaccine studies have been carried out since the first day of the epidemic [5].

CoronaVac vaccine, an inactivated vaccine against COVID-19 containing inactivated SARS-CoV-2, is a Chinese vaccine developed by Sinovac Life Sciences (Beijing, China). Randomized, double-blind, placebo-controlled phase I/II clinical trials have demonstrated the safety, tolerability, and immunogenicity of the CoronaVac vaccine in healthy adults aged 18 years and over [6, 7].

CoronaVac vaccine phase III clinical trials were conducted in Turkey. The Republic of Turkey Ministry of Health General Directorate of Pharmaceuticals and Pharmacy approved the CoronaVac COVID-19 vaccine for the emergency use of the disease on January 13, 2021 [6, 8]. Vaccine application has started in our country.

Women of reproductive age are also among the population infected with COVID-19 [9, 10].

COVID-19 doesn't just cause respiratory symptoms. It can also cause damage to the nervous system, immune system, liver and, according to limited reports, the male reproductive system [11–16].

For this reason, it was thought that ovarian tissue in women may also be the target of COVID-19 infection, and studies have been conducted on this [17, 18]. As a result of the studies, it was shown that COVID-19 infection causes ovarian damage [18].

Ovarian reserve is defined as the number of oocytes remaining in the ovary, or oocyte quantity (oocyte number) [19]. The best evaluation method of ovarian reserve is AMH level and antral follicle count [20].

In this study, we aimed to investigate the effect of CoronaVac vaccine on ovarian reserve.

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Objectives

COVID-19 vaccines can protect patients from ovarian damage caused by COVID-19 infection. However, the effect of CoronaVac vaccine on ovarian reserve is unknown. In this study, our aim is to investigate the effect of Coronavac vaccine on ovarian reserve in female patients followed up for infertility.

MATERIAL AND METHODS

Participants

Our study is a retrospective study. Between January 2020 and April 2021, there were 256 patients who applied to our clinic due to infertility.

Inclusion criteria were to have never had a COVID-19 infection before, to have received two doses of CoronaVac vaccine, and to have the AMH level measured before the first dose of the vaccine and one month after the second dose. Exclusion criteria were to have had a COVID-19 infection, to have undergone ovarian surgery, and to be pregnant. Patient data were searched according to these criteria.

The records of 124 patients whose AMH measurements and folliculometry were performed were checked to see if they had COVID-19 infection and whether they had CoronaVac vaccine. Fifty-two patients who did not have COVID-19 infection and received two doses of CoronaVac vaccine were identified. Six patients who had undergone ovarian surgery were excluded from the study. The remaining 46 patients were included in the study.

Since no similar study has been conducted before, the standardized effect size for the difference in AMH levels was accepted as 0.4, and the sample size was calculated as 41 individuals for $\alpha = 0.05$ and $1 - \beta = 0.80$.

As a result of the patient records scanning, it was seen that 46 patients who met the inclusion criteria in our study provided sufficient sample size for the study. By taking all these 46 patients, the 1-β of the study increased to 0.845.

Data collecting

Our hospital has a database with demographic data, laboratory and imaging records for each patient. The data of the patients were accessed using this database. Anti-mullerian hormone (AMH) level taken within one month before CoronaVac vaccination of the patients and basal antral follicle counts with ultrasound were recorded. AMH and basal antral follicle counts performed one month after the second dose of CoronaVac were recorded.

AMH and folliculometry

To measure the AMH level of the patients, blood was taken from the patients and the blood was centrifuged at 4000 rpm for 10 minutes. Serum was used as the sample type, AMH levels of the patients were measured by the electrochemiluminescent method with the Roche Cobas 6000 series E601 module. For folliculometry, the basal antral follicle numbers were counted by the same obstetrician and gynecologist during the menstrual period of the patients with the transvaginal probe of Toshiba Aplio 500 ultrasound.

Statistical analysis

Anti-mullerian hormone (AMH) and folliculometries of 46 patients, one month before CoronaVac vaccine and one month after the second dose of the vaccine were compared.

The conformity of the variables to the normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov Smirnov test). The numerical data collected in the study are mean, median, standard deviation, minimum-maximum values; Categorical data were expressed by descriptive methods such as numbers and percentages. Wilcoxon test was used to compare the changes in follicle count and AMH values before and after vaccination. Values with a P value below 0.05 were considered statistically significant. SPSS Statistics Version 22.0 was used for all statistical analysis and calculations.

RESULTS

The mean age of 46 patients participating in the study was 36.4 ± 4.9 years, and the mean body mass index (BMI) was 25.3 ± 4.7 kg/m^2. 34 (73.9%) of the patients had no additional disease. Additional diseases were diabetes, hypertension and hypothyroidism. 37% of the patients stated that they used to smoke. When obstetric and gynecological history were evaluated, it was determined that the mean age of menarche was 13.2 ± 1.6 years, and the median of gravida and parity was 1. 11 (24%) patients were primary infertile and 35 (76%) patients were secondary infertile (Tab. 1).

Four of the patients (8.7%) had PCOS and 2 (4.3%) had myoma. Before vaccination, 9 (19.6%) of the patients had menstrual irregularity (Tab. 2).

The median AMH of the participants was 1.22 (0.01–8.21) ng/mL before vaccination and 1.47 (0.01–8.99) ng/mL after vaccination. The median number of follicles before vaccination was 15 (3–37) and the median number of follicles after vaccination was 17 (3–35). There was no statistically significant difference in the change of AMH value and follicle number before and after vaccination. (respectively $p = 0.366$; 0.610) (Tab. 3).

DISCUSSION

Many viruses can adversely affect reproductive health in women. For example, menstrual disorders are common in women with HBV or HCV infection, and reproductive dysfunction such as pregnancy loss and infertility has also been identified [21]. An earlier onset of menopause has been found in women with human immunodeficiency virus [22].

Table 1. Demographic characteristics of the patients

	Mean ± SD	Median (min–max)
Age [year]	36.4 ± 4,9	37.5 (24–41)
BMI [kg/m^2]	25.3 ± 4–7	25.4 (16.9–36.9)
Gravidity	1.7 ± 1.4	1 (0–7)
Parity	1.1 ± 0.8	1 (0–3)
Age of menarche [year]	13.2 ± 1.6	13 (11–17)
	n (%)	
Smoking		
No	29 (63)	
Yes	17 (37)	
Chronic disease		
No	34 (73.9)	
Hypothyroidism	5 (10.9)	
Diabetes	3 (6.5)	
Hypertension	2 (4.3)	
Diabetes + Hypertension	1 (2.2)	
Hypertension + Hypothyroidism	1 (2.2)	
Primer infertility	11 (24)	
Sekonder infertility	35 (76)	

BMI — body mass index; SD — standard deviation

Table 2. Clinical characteristics and laboratory parameters of the patients

	n (%)
Pre-vaccination menstrual cycle	
Regular	9 (19.6)
Irregular	37 (80.4)
History of oral contraceptive use	
No	42 (91.3)
Yes	4 (8.7)
Gynecological disease	
No	40 (87)
PCOS	4 (8.7)
Uterine fibroid	2 (4.3)

PCOS — polycystic ovary syndrome

Sustained infection by hantavirus has been confirmed to affect female fertility in animal experiments [23].

The known effects of viral infections on fertility suggested that COVID-19 infection may also affect fertility. The results of the study by Stanley et al. [24] showed that COVID-19 infection had no long-term effects on male and female reproductive function.

According to a study by Fu et al. [25], they stated that COVID-19 infection acts on ACE 2 receptors and these receptors are also found in large numbers in testicular tissue, so it can seriously harm male sexual development in younger men and cause infertility in an adult male.

Illinois et al. [26] claimed that COVID-19 infection can damage Sertoli and Leydig cells, again via ACE 2 receptors.

Khalili et al. [27] in a systematic review, it was stated that male gonads may be the target of COVID-19 infection.

Studies have been carried out to show whether COVID-19 infection, which affects male fertility, has an effect on female fertility. According to the results of the study conducted by Li et al. [17] in 237 women of reproductive age with COVID-19 infection, they showed that follicle stimulating hormone (FSH), Luteinizing hormone (LH) and AMH values did not change significantly. Oligomenorrhea and hypomenorrhea were observed in one-fifth of the patients. In a subgroup analysis of patients with menstrual changes, they showed that COVID-19 infection causes suppression of ovarian function and may be the result of transient sex hormone changes that persist after recovery.

However, in a recent study by Ding et al. [18], they showed lower levels of AMH and higher levels of testosterone and prolactin in women with COVID-19 infection compared to the normal population. They concluded that women with COVID-19 may experience ovarian damage, including reduced ovarian reserve and reproductive endocrine disorder.

According to a survey of women of reproductive age in Texas, only one-third of 342 women agreed to get vaccinated as soon as possible. The vast majority of those who did not want to be vaccinated doubted its safety and efficacy [28].

Table 3. Comparison of AMH and follicle counts before and after vaccination

		Mean ± SD	Median (min–max)	p value
AMH	**Pre-vaccine**	1.86 ± 1.7	1.22 (0.01–8.21)	0.366
	Post-vaccine	1.96 ± 1.9	1.47 (0.01–8.99)	
Follicle counts	**Pre-vaccine**	16.8 ± 7.04	15 (3–37)	0.610
	Post-vaccine	16.98 ± 6.26	17 (3–35)	

AMH — anti-mullerian hormone

The results of a study by Orvieto et al. [29] in 36 IVF-treated couples showed that the mRNA SARS-CoV-2 vaccine did not affect patients' performance or ovarian reserve in the immediate next IVF cycle. In our study, in parallel with the results of this study, the AMH levels and follicle numbers of the patients were not affected after vaccination.

Bowman et al. [30] in his study, they investigated the BNT162b2 vaccine developed in response to the COVID-19 pandemic. To support its use in women of childbearing potential, they performed a developmental and reproductive toxicity study in rats according to regulatory guidelines. A full human dose of BNT162b2 of 30 μg mRNA (> 300 times the human dose on a mg/kg basis) was administered intramuscularly to female rats twice before mating and twice during pregnancy. A strong neutralizing immune response was confirmed before mating and at the end of pregnancy and lactation. Neutralizing antibodies were also confirmed in fetuses and pups. It was observed that BNT162b2 had no effect on female mating performance, fertility, or ovarian or uterine parameters [30]. In our study, as in this animal experiment, no statistically significant difference was found when the ovarian reserve was compared before and after vaccination.

As a result of this information in the literature, based on the conclusion that COVID-19 infection may affect female fertility, we focused on how female fertility can be preserved in our study and investigated the change in ovarian reserves of women who have been vaccinated with CoronaVac in our country. We did not find a significant difference between the AMH and folliculometry before the first dose of the vaccine and the AMH and folliculometry one month after the second dose of the vaccine. As a result of our study, which supports the studies in the literature, post-vaccine ovarian reserve was not affected.

Our study has limitations. Our study was retrospective and was conducted on a small number of patients. Another limitation is the lack of long-term results of the patients. However, the absence of a study similar to our study in the literature is the advantageous aspect of the study.

CONCLUSIONS

In conclusion, considering that having a COVID-19 infection has a negative effect on female fertility and causing ovarian damage in recent studies, vaccination is a rational and cost-effective approach to protect ovarian reserve. Knowing that the vaccine does not have a negative effect on fertility may increase the application of the vaccine in women of reproductive age. However, there is a need for similar studies with a large number of patients on vaccines produced with other technologies to support this result.

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Authors' contributions

Conceptualization: Ayşe Rabia Şenkaya, Deniz Can Öztekin;
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Ethics approval

Approval was obtained from the local ethics committee. Decision number is 829.

Conflicts of interest

The authors declare that they have no conflict of interest.

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