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Does the SARS-CoV-2 mRNA vaccine damage the ovarian reserve?

Elif Yildiz, MD[a], Burcu Timur, MD[a], Gurhan Guney, MD[b,*], Hakan Timur, MD[c]

Abstract

To search whether or not the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) messenger ribonucleic acid (mRNA) vaccine affects the fertility of women at the 6th months by using AMH, which is an ovarian reserve test. Our study, designed as a prospective case-control study, included 104 women who presented to the GOP EAH obstetrics and gynecology outpatient clinic in January and February 2022. The study group included 74 women who presented to the outpatient clinic and planned to be vaccinated and 30 women who refused to be vaccinated as the control group. Anti-COVID-19 antibody levels in all participants were checked before participation in the study, and participants who were positive were excluded from the study. Blood was taken from the participants in both control and study groups to evaluate their AMH levels before the 2 doses of vaccination. After 2 doses of the vaccine, they were called for follow-up, and serological tests were performed to check whether they were positive for anti-COVID-19 antibodies. Participants in both groups were referred for follow-up after 6 months, samples were taken again for AMH, and the data were recorded. The mean age of the study group was 27.6 ± 5.3 years, and the mean age of the control group was 28.65 ± 5.25 years (*P* = .298). There was no statistically significant difference between the vaccinated and nonvaccinated groups in terms of AMH levels measured at the 6th month (*P* = .970). When the vaccinated group was compared in terms of AMH values at the first visit before vaccination and at the 6th month after vaccination, no statistically significant difference was found between them (p:0.127) mRNA vaccination to protect against SARS-CoV-2 does not adversely affect ovarian reserve, which is an indirect indicator of fertility. mRNA vaccines continue to be the most important method of protection against epidemics. Carefully and accurately informing women who are hesitant to get vaccinated is of great importance for the success of the fight against the epidemic.

Abbreviations: ACE2 = angiotensin-converting enzyme 2, AMH = anti-mullerian hormone, COVID-19 = coronavirus disease 2019, mRNA = messenger ribonucleic acid, SARS-COV-2 = severe acute respiratory syndrome corona virus-2.

Keywords: anti-mullerian hormone, fertility, mRNA vaccine, ovarian reserve, SARS-CoV-2

1. Introduction

Coronavirus disease 2019 (COVID-19) first appeared in Wuhan, China, in December 2019, and was recognized as a pandemic by the World Health Organization due to the rapid global spread of the infection.[1] The noisy picture at the emergence of the clinic, the existence of cases that could result in death, the emergence of the need for intensive care, and the heavy measures taken due to these started a tense process all over the world and created intense pressure on the scientific world regarding treatment and prevention methods.[2] The emergence of variant virus strains that are more contagious due to gene mutations and the absence of an antiviral agent has further increased the urgent need to develop an effective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.[3] One of the most effective and least costly methods for epidemic prevention is vaccination. According to World Health Organization reports, more than 20 life-threatening diseases are prevented with the vaccines developed, and 2 to 3 million deaths are prevented every year.[1,2] For these reasons, effective vaccination against Covid 19 becomes vital for public health. However, people`s reluctance to be vaccinated due to lack of information, misdirection or anti vaccine views may act as a barrier to vaccination which is the most important method to prevent the spread of infection.[4–6] To promote vaccination against COVID-19, we need to know why people do or do not want COVID-19 vaccines, and the most reliable sources of information for decision-making. The literature cites the rapid pace of vaccine development and concerns about COVID-19 vaccine safety as the primary causes of vaccine hesitancy.[7] The first concern is that vaccines may have negative effects. Particularly in developing countries, the

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[a] *Department of Obstetrics and Gynecology, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, Istanbul, Turkey,* [b] *Department of Obstetrics and Gynecology, Ordu University Training and Research Hospital, Ordu, Turkey,* [c] *Department of Reproductive Endocrinology and Infertility, Balikesir University Medical Faculty, Balikesir, Turkey.*

* *Correspondence: Gurhan Guney, Balikesir University School of Medicine, Department of Reproductive Endocrinology and Infertility, 10145, Çağış Kampüsü, Balıkesir, Turkey (e-mail: gurhanguney@yahoo.com).*

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concern that fertility will be negatively affected is one of these negative impact expectations.[8] Successful reproduction is essential for the survival of all species. Reproductive health in humans encompasses a range of factors and processes, including physical, mental, and social health, and it requires wellness. This is important for successive generations in order to maintain good health.

Although the respiratory system was thought to be the only system affected by COVID-19, studies have reported that many tissues and systems are affected. Many studies have shown that the virus uses the angiotensin-converting enzyme (ACE)-2 receptor to enter the cell, and that all tissues with these receptors can be affected.[9] One of the tissues where these receptors are concentrated outside the respiratory system is the ovarian tissue, and ACE 2 enzyme plays an important role in reproductive functions by interacting with ACE 2 receptors. Both the SARS CoV 2 virus and messenger ribonucleic acid (mRNA) vaccine use the S protein in their own structure while they enter the cell, in other words, while binding to ACE2 receptors. This raises the concern that both the virus and vaccine may damage ovarian tissue.[10]

The most current marker used in the evaluation of damage to ovarian tissue, in fact, the loss of fertility, is the anti-Mullerian hormone (AMH). AMH is a glycoprotein produced by granulosa cells in the preantral and small antral follicles of the ovaries of women. Unlike other reproductive hormones, its levels are not affected by the day of the menstrual cycle and show ovarian reserves quite well.[11]

Vaccination remains the most effective method of protection against epidemics. Accordingly, there is a need to both obtain more information about vaccines and remove the obstacles to getting vaccinated, with the increase of confidence in the vaccine by providing the right information to people. In our study, we aimed to examine how the fertility of immunized women was affected by the vaccine over 6 months and the change in ovarian reserve with AMH.

2. Subjects and methodology

2.1. Study design

GPower 3.1 software (Universitat Kiel, Kiel, Germany) was used to calculate the number of people to be included in the group and the sample size was calculated. Wilcoxon-Mann–Whitney U test was used to calculate the difference between the means of 2 independent groups (vaccinated - unvaccinated). In the sample size calculation made by establishing a 1-way hypothesis, it was concluded that a total of 56 samples (Vaccinated group:28, unvaccinated group:28) should be taken in the sample size calculated with a medium effect size (dz: 0.7), 80% power (1-β) and 5% margin of error (α). This prospective case-control study was conducted with 104 participants who presented to the GOP EAH obstetrics outpatient clinics in January and February 2022. The participants were invited to participate in the study. All participants were provided detailed information, and written informed consent was obtained before inclusion in the study. Before starting the study, approval was obtained from the ethics committee of Gaziosmanpaşa Training and Research Hospital (approval date: January 5, 2022, Approval No.:362), and the trial was registered (NCT04748172).

2.2. Participants

Women who were older than 18 years and younger than 44 years of age, who presented for routine outpatient follow-up, had not yet been vaccinated, and had no infection were included in the study. Pregnant women, those younger than 18 years of age and older than 45 years, those with a diagnosis of cancer, women who had undergone surgery that might affect ovarian reserve, those with a diagnosis of endometrioma, women using oral contraceptive dose, those in menopause and with premature ovarian failure, women who had COVID 19, and those who had been vaccinated before, even in a single dose, were excluded from the study. Antibody tests and nasopharyngeal swab samples were obtained from patients who met the eligibility criteria and agreed to participate in the study. Women who were positive in any of the test results were excluded from the study. Thus, at the beginning of the study, it was recorded that the participants did not have an infection, were not vaccinated, and did not have active infections in the last 3 months.

Women plans for vaccination were also questioned. Seventy-four women who planned to be vaccinated were included in the study group and 30 women who refused to be vaccinated were included in the control group. All participants underwent complete physical and pelvic examinations. Gynecological and general medical histories were obtained, and demographic characteristics were recorded for each patient. Blood samples for AMH were taken from the participants in the study group before vaccine administration, and the first dose of the vaccine was administered on the same day.

2.3. Laboratory studies

Blood samples were centrifuged at 10,000 rpm for 10 minutes, and serum samples were separated, transferred to sterile Eppendorf tubes, and stored at −80°C until use.

The study group received a second dose of the vaccine 21 days after the first dose. Antibody responses to the vaccine were assessed at 3 months. Blood samples were collected for the analysis of anti-COVID-19 antibody levels. All patients had increased anti-COVID-19 antibody levels in response to the vaccine. After the second dose of the vaccine, blood samples were taken for AMH levels by being called for follow-up again in the 6th month. In the control group, AMH samples were collected during the first examination of 30 women who refused vaccination. The samples were stored under appropriate conditions. After 6 months, the study participants were called again, for the AMH test follow-up. All blood samples were stored as plasma and run at the same time, in the same laboratory by using the same electrochemiluminescence immunoassay method (AMH assay, Roche Diagnostics International Ltd. Switzerland) with Abbott architect I1000 SR immune assay analyzer (Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL). The AMH detection range was set at 0.01 to 30 ng/mL, and the minimum detectable dose of this kit was 0.01 ng/mL.

2.4. Statistical analysis

The IBM SPSS 25 package was used for all analyses. A normality check of continuous variables was performed using the Shapiro–Wilk test. Nonparametric analysis methods were used because the variables did not conform to a normal distribution. The Mann–Whitney U test was used to compare the differences between the vaccinated and unvaccinated groups. The difference between the first and second measurements was evaluated using Wilcoxon test. Categorical data were analyzed using the chi-squared test and Fisher exact test.

3. Results

A total of 104 women were included in the study, and full follow-up was achieved in all (100%) of them. All the women in the case group completed 2 vaccinations. The study group consisted of 74 women who had received the mRNA vaccine twice. There were no statistically significant differences between the 2 groups in terms of age, height, weight, BMI, gravidity, and parity ($P > .05$) (Table 1). Again, there were no statistically significant differences between the 2 groups in terms of menstrual cycle regularity, giving birth, delivery type, education level,

Table 1

Demographic data of the patients.

	Vaccination (−)	Vaccination (+)	*P* value
Age	27.6 ± 5.3	28.65 ± 5.25	.298
Size	163.13 ± 4.87	162.07 ± 6.55	.674
Weight	64.33 ± 9.68	64.15 ± 11.01	.707
BMI	24.23 ± 3.99	24.48 ± 4.56	.958
Gravida	2.16 ± 2	1.95 ± 1.5	.663
Parity	2.14 ± 1.5	1.75 ± 1	.439
Abort	1.33 ± 1	1.22 ± 1	.765

p: Mann–Whitney U test.
$P < .05$ accepted as statistically significant.
BMI = body mass index.

Table 2

Analysis of the relationships between the groups and certain characteristics.

		Vaccine (−)		Vaccine (+)		Total		
		n	%	n	%	n	%	*P*
Menstrual cycle	Regular	24	80.0	54	76.1	78	77.2	.666
	Irregular	6	20.0	17	23.9	23	22.8	
Marital status	Single	13	43.3	22	31.0	35	34.7	.233
	Married	17	56.7	49	69.0	66	65.3	
Birth	None	14	46.7	32	45.1	46	45.5	.460
	Normal delivery	14	46.7	28	39.4	42	41.6	
	Cesarean section	2	6.7	11	15.5	13	12.9	
Education	Primary school	6	20.0	7	9.9	13	12.9	.486
	Middle school	3	10.0	10	14.1	13	12.9	
	High school	4	13.3	14	19.7	18	17.8	
	University	17	56.7	40	56.3	57	56.4	
Contraception	RIA	23	76.7	38	53.5	61	60.4	.243
	Ox	4	13.3	14	19.7	18	17.8	
	Traditional	2	6.7	8	11.3	10	9.9	
	Barrier	1	3.3	10	14.1	11	10.9	
	None	0	0.0	1	1.4	1	1.0	

p: Chi-square test * Fisher's exact test.
$P < .05$ accepted as statistically significant.

marital status, and contraception methods ($P > .05$) (Table 2). These groups were independent and homogeneous in terms of their specific characteristics. The mean AMH levels were 3.37 μg/L (±SD 2.23) and 3.40 μg/L (±SD 2.26) at baseline and 6 months, respectively in the vaccinated group ($P = .127$). The control group comprised 30 women who had never been vaccinated. The mean AMH levels were 3.17 μg/L (±SD 2.17) and 3.32 μg/L (±SD 2.13) at baseline and 6 months, respectively in unvaccinated group ($P = .166$) (Table 3). In the unvaccinated group, the first and second AMH measurements did not differ according to age groups (p:0.106 and p:0.066, respectively), as shown in Table 4. AMH subanalyses were performed for 3 age groups: <30 years, 30 to 34 years, and >35 years. In the vaccinated group, the AMH values of those aged 35 years and older were lower than those of those aged under 30 years ($P < .001$). The AMH values of those aged 35 years and older were also lower than those of those aged 30 to 34 years ($P < .001$), as shown in Table 4.

4. Discussion

In our study, we observed that plasma AMH levels did not change significantly after 6 months in women who received 2 doses of the mRNA vaccine compared to the unvaccinated group. Regardless of the baseline AMH levels and age, AMH levels did not change before and 6 months after vaccination. We also performed a subgroup analysis of age groups and observed that pre-vaccination AMH levels were lower in the group over 35 years of age than in the others, but the change after 6 months was not statistically significant. Our study is the first to evaluate the change in AMH levels 6 months after vaccination, adding to the growing evidence that COVID-19 vaccines do not affect fertility and ovarian reserve.

Although the respiratory system is the main system affected by Covid 19 infection (Covid 19), studies have shown that the genital system might also be seriously affected.[12] While the virus enters the cell, it also enters the cell by binding to the ACE2 receptor system, and many studies have shown that the ACE2 receptor system plays an active role in the regulation of female reproductive functions.[10] Therefore, it is thought that reproductive functions may be impaired in COVID 19, and various studies have been carried out to investigate this impairment.[13] For example, Barragan et al[14] performed controlled ovarian stimulation in 2 patients with a previous SARS COV 2 positive PCR result and did not detect viral RNA in the ovarian follicle fluid. The very small number of patients, presence of other proteins in oocytes apart from viral RNA, and asymptomatic nature of the patients in Barragan et al`s study require more comprehensive studies to confirm the absence of viral RNA. In a comprehensive study conducted by Orvieto et al,[15] 9 in-vitro fertilization couples documented with Covid 19 were evaluated in terms of embryo quality, and it was determined that there was a decrease in good quality embryos due to Covid 19.[14] Similarly, Fangyuan et al,[16] as a result of their comprehensive systematic review and meta-analysis, showed that Covid 19 negatively affects fertility in women, mainly by reducing ovarian reserve. Many studies have shown that while SARS-CoV-2 attacks human cells, it binds to ACE receptors in human cells via its own viral S protein.[17] Since this S protein is used as the host antigen in mRNA vaccines, the question arises as to whether vaccines interact with this pathway and negatively affect fertility.[18] In the evaluation of fertility, besides the number of oocytes, the determination of serum AMH levels is also a good option as the most objective indirect indicator of ovarian reserve, which is not affected by the menstrual cycle. Based on this relationship, Kolotorova et al[19] evaluated AMH values in 25 healthy women after 3 doses of vaccination, and the results at 2 to 4 months were examined. They showed that the level of AMH was not affected in the short term after 3 doses of vaccination, emphasizing that vaccination was not the thing to be afraid of but rather the infection itself. In another study conducted by Sasson et al,[18] 129 women with 2 doses of Covid 19 mRNA vaccine were compared in terms of AMH levels before and at the 3rd month after vaccination, and no significant difference was observed. Although the number of patients was high, the limitations of the study were that they did not choose unvaccinated individuals as the control group and evaluated their AMH levels as soon as the 3rd month after vaccination. Although the number of patients in our current study was less than this study, the fact that our control group consisted of individuals who could not be vaccinated and that we evaluated pre- and post-vaccine AMH levels at the end of a longer period of 6 months are the positive aspects of our study. Similarly, in a study performed by Soysal et al,[20] 30 mRNA-vaccinated patients and 30 non-vaccinated patients were compared in terms of AMH levels before vaccination and on the 90th day after vaccination, and no significant difference was found. Although the short duration of the study and the evaluation of fertility only with AMH are considered limitations of this study, the low number of studies investigating the relationship between covid 19 vaccine and fertility makes both studies very valuable. Fertility depends not only to AMH levels. ACE receptors, which are the main receptors that transport the S protein used in the mRNA vaccine into the

Table 3

Comparisons of the groups in terms of AMH levels.

	Vaccine (–)			Vaccine (+)			
	Mean ± SD	median [IQR]	Min-Max	Mean ± SD	median [IQR]	Min-Max	p_{group}
AMH at first visit	3.17 ± 2.17	3.08 [1.52–4.49]	0.07–9.73	3.37 ± 2.23	2.93 [1.6–5.24]	0.08–9.76	0.637
AMH at the sixth mo	3.32 ± 2.13	3.3 [1.9–4.87]	0.03–9.7	3.4 ± 2.26	2.9 [1.8–4.94]	0.03–9.7	0.970
AMH _difference	0.15 ± 1.17	−0.07 [−0.21 to 0.03]	−1.74 to 3.38	0.03 ± 0.86	−0.07 [−0.23 to 0.1]	−1.74 to 3.01	0.964
p_{time}	0.166			0.127			

p_{time}: Wilcoxon test, Comparison of vaccinated and non-vaccinated individuals within itself in terms of AMH levels at baseline and at 6 mo.
p_{group}: Mann–Whitney U test, Comparison of vaccinated and non-vaccinated 2 groups in terms of AMH levels.
P < .05 accepted as statistically significant.
AMH = Anti-Mullerian Hormone.

Table 4

Age-related change in AMH.

Unvaccinated group	Age < 30 (n = 20)	Age 30–34 (n = 6)	Age ≥ 35 (n = 4)	*P* value
AMH 1	5.66 ± 5.33	3.99 ± 3.78	2.55 ± 2.01	.106
AMH 2	4.98 ± 4.96	4.31 ± 4.19	2.7 ± 2.2	.066
Vaccinated group	Age < 30 (n = 45)	Age 30–34 (n = 17)	Age ≥ 35 (n = 9)	
AMH 1	4.41 ± 4.07	2.8 ± 2.27	0.92 ± 0.43	<.001
AMH 2	4.34 ± 4.05	3.03 ± 1.99	0.81 ± 0.19	<.001

p: Kruskal-Wallis test, AMH (Mean ± SD).
AMH 1: Amh at the first visit.
AMH 2: Amh levels at the sixth mo.
AMH = Anti-Mullerian hormone.
P < .05 accepted as statistically significant.

cell, are also present in the endometrium.[21] Endometrial thickness, endometrial morphology, subendometrial blood flow, uterine spiral artery blood flow, and menstrual patterns are also determinants of fertility that affect uterine receptivity.[22] In a comprehensive prospective study conducted by Wang et al,[23] it was shown that the Covid 19 mRNA vaccine causes a short-term prolongation of menstrual cycle times. For this reason, Wang et al concluded that the immune response after vaccination might temporarily affect the hypothalamic-pituitary-ovarin and endometrial parts. Similar to Wang S et al 's study, Male V., the lecturer reproductive immunologist, stated in her editorial comment that menstrual irregularities occur following the Covid 19 mRNA vaccine, similar to the HPV vaccine, and that this is due to the response of the immune cells in the uterus to the vaccine. Male V. also stated that the relationship between the Covid 19 mRNA vaccine and menstrual irregularities should be confirmed with more studies to be conducted, since this response, albeit physiologically, may be understood pathologically by the patients and may cause vaccine opposition.[24] In our study, we did not observe any differences in menstrual cycle patterns between vaccinated and unvaccinated patients. Currently, the effects of SARS-CoV-2 infection or vaccination on fertility, menstruation, ovarian reserve, and pregnancy are not fully known. New studies are being conducted by many centers on this subject; however, more studies are still needed.[25]

In our study Amh values were between the range of 1.14-5.60 and there were many subjects with abnormally low AMH values which explained this such broad standart deviation relevantly. Since the standard deviation range is wide, we also added the median, minimum and maximum AMH values to Table 3. In a study by Dayal M et al[26] normal range of AMH was showed as between the range of 2-6.8 which had similar to our results. Although, we selected our patients randomly, restrictions such as the ban on going out during the Covid 19 pandemic period may have changed the characteristics of the patients coming to the clinic and may have resulted in the heterogeneous formation of the sample group. Such heterogeneity of sample groups may be considered as a limitation of our study, and our results should be confirmed by studies to be conducted with more homogeneous and larger numbers of patients.

Any study that increases our knowledge of vaccine safety and removes the barrier for people to get vaccinated is valuable, and our study provides more evidence in this direction, in line with the literature. Our study was performed before and after vaccination in healthy and infertile women. Our study evaluated longer-term effects compared with studies performed before and after vaccination, both in healthy volunteers and infertile in-vitro fertilization candidates. To the best of our knowledge, our study is the first to evaluate these effects at 6 months. The SARS-CoV-2 vaccine did not adversely affect the ovarian reserve, supporting the literature and contrary to popular beliefs. Vaccination continues to be the most important method of protection during pandemics. Carefully and accurately informing women who are hesitant to get vaccinated is of great importance for the success of the fight against COVID-19. Larger studies with more participants are needed to confirm our results.

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Author contributions

Conceptualization: Elif Yildiz, Burcu Timur.
Data curation: Elif Yildiz, Burcu Timur, Gurhan Guney, Hakan Timur.
Formal analysis: Elif Yildiz, Burcu Timur.
Funding acquisition: Elif Yildiz, Burcu Timur.
Investigation: Elif Yildiz, Burcu Timur.
Methodology: Elif Yildiz, Burcu Timur, Gurhan Guney, Hakan Timur.
Project administration: Elif Yildiz, Burcu Timur.
Software: Gurhan Guney, Hakan Timur.
Supervision: Elif Yildiz, Gurhan Guney.
Writing – original draft: Elif Yildiz, Gurhan Guney.
Writing – review & editing: Elif Yildiz, Gurhan Guney.

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