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# The effect of COVID-19 infection on anti mullerian hormone

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## ABSTRACT

**Aim**: The possible impact of COVID-19 infection on female reproductive system is a controversial issue. The aim of this study was to investigate the effect of COVID-19 infection on anti mullerian hormone (AMH) as a predictor of ovarian response to ovarian stimulation.

**Material and Method**: This prospective study was conducted at a university-affiliated tertiary medical center between June 2021–February 2022. The study population included 79 reproductive-aged women (22-34 years) with COVID-19 infection. Blood samples were collected for AMH levels before COVID-19 infection and after three months of COVID-19 disease.

**Results:** The mean age of the study group was 28.11±3.49 years. Estradiol and Luteinizing Hormone (LH) was found to be lower after three months of COVID-19 disease ($p<0.05$). Follicle Stimulating Hormone (FSH) was significantly higher in post-COVID-19 group ($p<0.05$). Free T4 (FT4) and body mass index (BMI) were found to be higher after three months of COVID-19 disease but not significant ($p>0.05$). There was a statistically significant association between Pre-COVID-19 and Post-COVID-19 in terms of AMH ($p<0.05$). AMH values have decreased after COVID-19 infection in patients. There was a statistically significant association between menstrual volume and COVID-19 disease ($p<0.05$). According to the findings, menstrual cycle irregularity has increased after being infected with COVID-19.

**Conclusion**: In conclusion, the results showed that COVID-19 could adversely affect the AMH level and the female reproductive system.

**Keywords**: COVID-19, women's fertility, anti mullerian hormone, ovarian reserve

## INTRODUCTION

In late 2019, a new virus (COVID-19) was first observed in China. On January 30, 2020, the World Health Organization (WHO) considered it an international threat to public health. COVID-19 became prevalent all over the world in a short time (1). At the global level, 591 million cases of COVID-19, including 6.5 million deaths have been confirmed since 16 August 2022, as reported by the WHO (2). Considering the power and spread of this virus, the WHO declared an emergency and recommended that the countries should reduce the personal transmission of this disease by reducing the contact rate and control its global spread (3). Several countries had to impose isolation in their cities. In the modern world, no virus had an extensive global impact as much as COVID-19. In addition, researchers have conducted several studies on the effects of this virus on people in the last three years (4).

The effects of the COVID-19 virus are evident in some dimensions and still unknown in some dimensions. Certainly, COVID-19 and its effects on various dimensions of human life have been studied by researchers for years. The effects of COVID-19 on the reproductive system, particularly on women, are highly important (5). Since it plays an important role in survival of the species, several researchers argue that one of the most important systems in the whole body is the reproductive system (6). It appears that COVID-19 leaves adverse effects on the female and male reproductive system. Particularly, the virus's potential pathogenicity on the granulosa cells and the ovarian and testicular tissues may impact ovarian and testicular function, oocyte quality, and spermatozoa with pregnancy outcomes (7). Consider the COVID-19 pandemic scale, there may be a potential decrease in fertility (8). For this reason, it is very important for women who plan to become pregnant in the future to carefully examine the effects of COVID-19.

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Anti mullerian hormone (AMH) is a glycoprotein dimer and a member of the transforming growth factor-beta family (9,10). This substance is secreted from the granulosa cells of primary, pre-antral, and small antral follicles (4-6 mm) of the ovary (11). AMH serum concentration depends on the number of small follicles and their ovarian reserves (12). AMH has always been considered as a marker to investigate ovarian function. AMH plays an important role in primary follicle growth (13).

Unlike other reproductive hormones, the state of the menstrual cycle does not affect the AMH levels. The serum AMH assay has recently played an increasingly important role in female fertility management (12).

Several studies have been conducted to evaluate the effect of the COVID-19 virus on women's fertility (14-16). In the present study, the effect of COVID-19 on AMH levels was assessed. The present study is significant for identifying the effects of COVID-19 on women's fertility and providing preventive treatments. Physicians can provide more effective treatments for pregnant women with a history of COVID-19 infection by determining the exact effects of COVID-19 infection in women. This study aims to investigate the effect of COVID-19 on AMH levels.

## MATERIAL AND METHOD

This prospective study was carried out with the permission of Gümüşhane University Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: 2021/3). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Seventy nine women participated in this study during June 2021–February 2022.

The study population included 79 reproductive-aged women (22–34 years) with COVID-19 infection. The study excluded women during pregnancy, under fertility treatments, with ovarian failure, previous COVID-19 infection, or vaccinated women.

All respondents filled out an automatic questionnaire on gynecological, general medical and obstetrical background during recruitment and after three months. We took blood samples at AMH plasma levels during recruitment. The patients who applied to the clinic between the dates of the study and met the admission criteria were given detailed information about the purpose and scope of the study. Informed consent forms were signed by the patients who accepted to participate in the study, and a routine clinical procedure (history, physical examination, blood analysis, etc.) was performed. Serum samples were obtained by centrifuging the venous blood samples for 10 minutes at 4000 rpm for 10 minutes after the 30-minute coagulation period. Serum samples collected for biochemical and hormonal evaluation were examined in our hospital's biochemistry and hormone laboratory. Anti-mullerian hormone (AMH), prolactin, follicle stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and free T4 (FT4) values were recorded. The scale for measuring hormones was nanograms per milliliter (ng/ml).

A polymerase chain reaction (PCR) test for COVID-19 was employed to analyze individuals infected with SARS-CoV-2, the virus that causes COVID-19. The PCR test's positive result was considered a COVID-19 infection.

**Statistical Analysis**

The Kolmogorov-Smirnov test performed to check the normality, and based on the test results, A Wilcoxon signed-rank test and Paired t-test were used to check statistical significance. Median, range, mean and standard deviations (SD) measured to check each continuous variable, including age, BMI, AMH, FSH, E2, LH, prolactin, FT4, and TSH. Pearson's chi-squared test is used to determine whether there is a statistically significant difference between menstrual volume and COVID-19 infection. The Paired Samples Z-Test was used to determine the significance of menstrual volume after COVID-19 infection. SPSS v26 used for statistical analyses. A value of p-value $< 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two groups' total mean was measured based on the Mann-Whitney test with the power of 85%, effect size of 31%, and 0.05 type 1 error for at least 77 patients (17).

## RESULTS

This study included seventy nine age ($28.11 \pm 3.49$) and BMI ($25.32 \pm 4.12$) women. **Table 1** shows descriptive statistics of study parameters. **Table 2** shows the comparison of pre-COVID-19 and post-COVID-19 groups on the study parameters. As stated in Table 2, a Mann-Whitney test did not find a statistically significant association between pre-COVID-19 and post-COVID-19 in regard to BMI ($p> 0.05$). There was a statistically significant difference between groups in regard to FSH, estradiol and LH ($p<0.05$). There was not a statistically significant difference between pre-COVID-19 and post-COVID-19 in regard to PRL ($p=0.471$), FT4 ($p=0.053$) and TSH ($p=0.866$).

**Table 1.** Descriptive statistics of study parameters (n=79)

| Study parameters | median (range) | mean ± SD |
|---|---|---|
| Age | 28 (22-34) | 28.11±3.49 |
| BMI | 25 (17.3-40.8) | 24.84±4.12 |
| AMH | 1.6 (0.8-3.7) | 1.75±0.7 |
| FSH | 5.85 (1.79-10.1) | 5.74±1.85 |
| Estradiol | 41.5 (6.98-330.9) | 59.68±54.76 |
| LH | 5.34 (1.68-22.8) | 6.45±3.62 |
| Prolactin | 20.255 (4.42-143) | 23.55±15.19 |
| FT4 | 1.045 (0.52-8.03) | 1.26±0.96 |
| TSH | 1.61 (0.47-4.96) | 1.81±0.87 |

SD, standard deviation.

**Table 2.** Comparison of pre- COVID-19 and post- COVID-19 groups

| Study parameters | Pre-COVID (n=79) M±SD | Post-COVID (n=79) M±SD | p value |
|---|---|---|---|
| BMI | 24.71±1.96 | 24.94±4.01 | 0.074 |
| AMH | 2.01±0.7 | 1.49±0.61 | <0.001* |
| FSH | 5.42±1.71 | 6.06±1.94 | 0.034** |
| Estradiol | 66.06±58.34 | 53.3±50.48 | 0.016* |
| LH | 7.68±4.3 | 5.22±2.2 | <0.001* |
| Prolactin | 24.76±18.85 | 22.34±10.31 | 0.471* |
| FT4 | 1.22±0.94 | 1.3±0.97 | 0.053* |
| TSH | 1.83±0.82 | 1.79±0.92 | 0.866* |

M, Mean; N, number of subjects; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FT4, Free Tiroksin; TSH, thyroid-stimulating hormone. *A Wilcoxon signed-rank test. ** Paired t-test

There was a statistically significant difference between pre-COVID-19 and post-COVID-19 in regard to AMH ($p<0.05$). The post-COVID-19 group had significantly lower value than the pre-COVID-19 (M=1.49; SD=0.61 vs. M=2.01; SD=0.7).

As stated in **Table 3**, a chi square test found that there was a statistically significant association between the menstrual volume and COVID-19 infection ($p<0.05$). The Pairwise Z-Tests found that the percentage of women with the fixed menstrual volume was significantly higher for the pre-COVID-19 period (43% from n=34) than three months after COVID-19 infection. The percentage of women with decreased menstrual volume was significantly higher for the post- COVID-19 period (78.5% from n=62) than before the COVID-19 illness.

**Table 3.** The relationship between menstrual volume and COVID-19 infection

| Variable | Pre-COVID (n=79) n (%) | Post-COVID (n=79) n (%) | p value |
|---|---|---|---|
| Menstrual volume | | | <0.001† |
| It has fixed | 34 (43) †† | 12 (15.2) | |
| It has decreased | 35 (44.3) | 62 (78.5) †† | |
| It has increased | 10 (12.7) | 5 (6.3) | |

†A Chi-square test. †† Pairwise Z-Tests

In this study, four groups were considered for the menstrual cycle (patients with a menstrual cycle shorter than 28 days, cycles between 28 and 35 days, cycles longer than 35 days, and prolonged menstrual cycles). According to research findings, 32/79 (42%) women have faced menstrual cycle irregularity after being infected with COVID-19.

**Figure 1** shows that the women's AMH decreases after the COVID-19 infection. Values of E2 and LH have also reduced. However, BMI and FSH have increased in women in the time period.

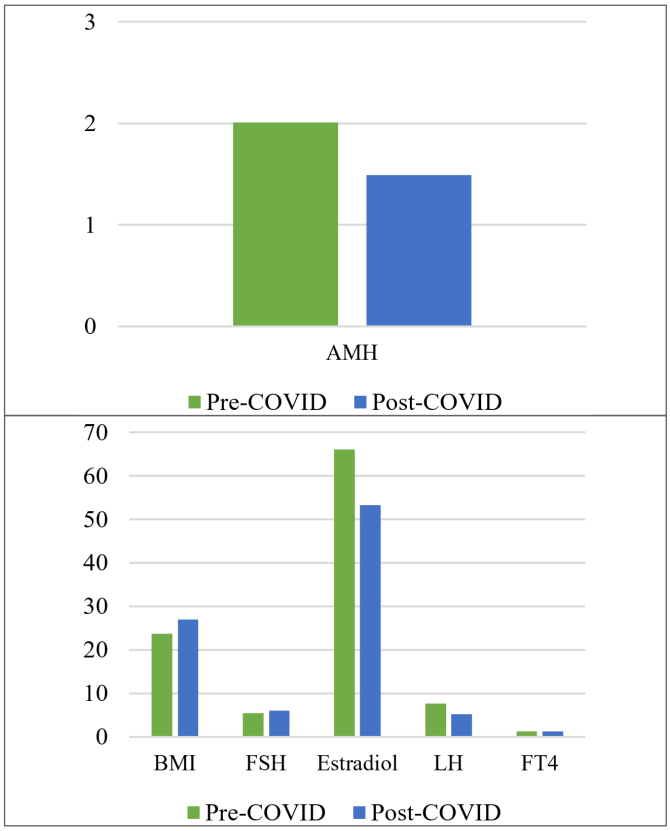


**Figure 1.** The effect of COVID-19 disease on study parameters

## DISCUSSION

In our study, we investigated the impact of infection with COVID-19 on female reproductive system. AMH levels as a marker for predicting ovarian response were significantly lower in the post-COVID-19 group. AMH levels decreased 25% after COVID-19 infection in women. FSH and FT4 were significantly higher in the post-COVID-19 group. E2 and LH were significantly lower in the post-COVID-19 group. Menstrual volume decreased significantly in the post-COVID-19 group. In the post-COVID-19 group, 42% had changed menstrual cycle.

The COVID-19 pandemic caused the prevalence of depression, stress, and anxiety among women in general. Many studies reported shorter or longer menstrual cycles and irregular menstrual volume because of psychological pressure in pandemics (18-21) and COVID-19 vaccination (22,23). A few studies assessed the effects of COVID-19 infection on menstrual cycle and volume in women of

reproductive age. Khan et al. (24) demonstrated alterations in menstrual patterns and increased irregular periods because of infection by COVID-19 in women of reproductive age. Their study reported irregular periods (60%), increased cycle length (35%), and alterations of menstrual pattern (16%). Li et al. (25) reported menstrual abnormalities, altered menstrual flow (25%), and alterations in menstrual cycle pattern (28%) in COVID-19 positive women accepted in Wuhan hospital. Patients who were more severely ill encountered longer menstrual cycles. Vast of the majority of women returned to their regular cycle after months. Ding et al. (26) noted the effect of COVID-19 infection on two groups of mild and severe cases. The more severe patients encountered irregular menstruations, increased dysmenorrhea, more frequent amenorrhea and higher flow. Our study approves of these results. The current study showed that the menstrual volume and menstrual cycles of post-COVID-19 patients were adversely affected.

According to Li et al. (25), the reproductive aged women diagnosed with COVID-19 had AMH levels and sex hormone concentrations comparable to those of the controls. Kolanska et al. (14) reported no mid-term and long-term effects of COVID-19 infection on AMH levels. Their study demonstrated there was not association between mild COVID-19 infection and ovarian reserve as evaluated by AMH levels in women of reproductive age. Herrero et al. (27) demonstrated that number of retrieved oocytes and oocyte maturity rate in women undergoing assisted reproductive technology procedures for confirmed COVID-19 infection were decreased compared with controls. Our study disapproves of these results. In the present study, we indicated that AMH levels from post-COVID-19 patients decreased compared with before COVID-19 infection. In contrast Orvieto et al. (28) reported no statistically significant difference in fertilization rate and number of oocytes obtained in 9 women included to their study. However, their study showed the top-quality embryos rate were significantly lower after COVID-19 infection.

As a limitation of the present study, we analyzed the enrolled patients three months after infection with COVID-19. Consequently, further studies should be done to investigate if one can revert these ovarian alterations after a long time allowing physicians to design an optimized fertility protocol for those recovering from COVID- 19 and prevent the possible complications. More definite evidence can be given about the reproductive performance of female patients recovering from COVID-19 through studies with larger populations.

## CONCLUSION

The results described this evidence that infection with COVID-19 could damage ovarian reserve, alter the AMH level and potentially affect reproductive outcomes. More researches are needed to estimate the effect of COVID-19 on women's reproductive system. These results can be used to straighten the public health policies and improve the clinical interventions. In the end, the present study gives a solid ground for more research to assess the possible effects of the COVID-19 on the women's fertility.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Gümüşhane University Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: 2021/3).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement**: The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

## REFERENCES

1. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020; 50: 620-32.
2. WHO. WHO Coronavirus (COVID-19) Dashboard 2022.
3. Gürbüz T, Gökmen O, Dokuzeylül Güngör N. COVID-19 infection mimicking Postpartum Pulmonary Embolism: A Case Report. J. Exp. Clin. Med 2022; 39: 577-8.
4. Gürbüz T, Gökmen O, Kaptan G, et al. Investigating anxiety, depression and obsessive-compulsive disorders among the pregnant women during COVID-19 pandemic. J Health Sci Med 2021; 4: 7-12.
5. Karlı P, Gürbüz T, Şentürk M. COVID-19 pandemic and the quality of couples' sexual relationships. Anatolian Curr Med J 2021; 3: 104-8.
6. Bechmann N, Maccio U, Kotb R, et al. COVID-19 infections in gonads: consequences on fertility? Horm Metab Res 2022; 54: 549-55.
7. Biviá-Roig G, Boldó-Roda A, Blasco-Sanz R, et al. Impact of the COVID-19 pandemic on the lifestyles and quality of life of women with fertility problems: a cross-sectional study. Front Public Health 2021; 9: 686115.
8. Li F, Lu H, Zhang Q, et al. Impact of COVID-19 on female fertility: a systematic review and meta-analysis protocol. BMJ Open 2021; 11: e045524.
9. Yurci A, Gungor ND. Low antimullerian hormone levels improve fertility outcome in patients with polycystic ovary syndrome. Gynecol Reprod Health 2021; 5: 1-5.

10. Gungor ND, Gurbuz T. Prediction of the number of oocytes based on AMH and FSH levels in IVF candidates. J Surg Med 2020; 4: 733-7.
11. Gungor ND, Gurbuz T. Pregnancy Outcomes of Intrauterine Insemination in Age-Matched Young Women According to Serum Anti-Mullerian Hormone Levels. J Reproduct Med JRM 2021; 66: 195-202.
12. Gurbuz T, Gungor ND, Okcu NT, Tosun SA. Correlation between Anti-Mullerian Hormone Levels and Sexual Dysfunction in Infertile Women. ARJGO 2020; 4: 10-16.
13. Grynnerup AG, Lindhard A, Sørensen S. The role of anti-müllerian hormone in female fertility and infertility - an overview. Acta Obstet Gynecol Scand 2012; 91: 1252-60.
14. Kolanska K, Hours A, Jonquière L, et al. Mild COVID-19 infection does not alter the ovarian reserve in women treated with ART. Reprod Biomed Online 2021; 43: 1117-21.
15. Dewailly D, Laven J. AMH as the primary marker for fertility. Eur J Endocrinol 2019; 181: D45-D51.
16. Carp-Veliscu A, Mehedintu C, Frincu F, et al. The effects of SARS-CoV-2 infection on female fertility: a review of the literature. Int J Environ Res Public Health 2022; 19: 984.
17. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009; 41: 1149-60.
18. Takmaz T, Gundogmus I, Okten SB, Gunduz A. The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers. J Obstet Gynaecol Res 2021; 47: 3241-9.
19. Sharp GC, Fraser A, Sawyer G, et al. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. Int J Epidemiol 2022; 51: 691-700.
20. Todić I, Mihajlović S. Impact of SARS-CoV-2 pandemic on menstrual cycle in young women. Medicinski podmladak 2022; 73: 47-53.
21. Hashmi N, Ullah I, Tariq SR, et al. How is the COVID-19 pandemic affecting women's menstrual cycles and quality of life? A view from South Asia. BJPsych Advances 2022; 28: 274-7.
22. Wong KK, Heilig CM, Hause A, et al. Menstrual irregularities and vaginal bleeding after COVID-19 vaccination reported to v-safe active surveillance, USA in December, 2020-January, 2022: an observational cohort study. Lancet Digit Health 2022; 4: e667–75.
23. Male V. Menstrual changes after COVID-19 vaccination. BMJ 2021; 374: 2211
24. Khan SM, Shilen A, Heslin KM, et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. Am J Obstet Gynecol 2022; 226: 270-3.
25. Li K, Chen G, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. Reprod Biomed Online 2021; 42: 260-7.
26. Ding T, Wang T, Zhang J, et al. Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in Wuhan, China: an observational study. Front Med (Lausanne) 2021; 8: 635255.
27. Herrero Y, Pascuali N, Velázquez C, et al. SARS-CoV-2 infection negatively affects ovarian function in ART patients. Biochim Biophys Acta Mol Basis Dis 2022; 1868: 166295.
28. Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. Gynecol Endocrinol 2021; 37: 895-7.