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Post COVID-19 effect of ovarian reserve

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Abstract

Introduction: The SARS-CoV-2 infection's rise in circulating Ang II can change ovarian function, affect how oocytes develop and mature biologically, affect the quality of oocytes produced, and eventually reduce reproductive function

Aim of the study: to evaluate how COVID-19 infection affects women undertaking assisted reproductive technology (ART) treatment for primary or secondary infertility.

Subjects and Methods: A cross-sectional analytical study conducted at the Gynecology and Obstetrics department at Fayoum University Hospital saw 120 infertile (primary or secondary infertility) women who had verified prior COVID-19 infection as part of this cross-sectional analytical study. For all the study's female participants

Results: In the current study, we included 120 infertile women with confirmed COVID-19 infection who had an average age of (26.96 ± 5.68) years, an average BMI of (21.8 ± 7.62) kg/m2, an average duration of (3.95 ± 1.16) months, a mild form of the disease reported by 86 (71.7%), a severe form reported by 30 (25%), and only a moderate form reported by four women (3.3%). According to the severity of the disease, the AMH, AFC, FSH, and LH mean serum levels measured after COVID-19 infection did not differ statistically significantly from the mean serum levels examined before COVID-19 infection ($P > 0.05$). before COVID-19 infection in the three groups according to disease severity ($P > 0.05$).

Conclusions: The results of the study demonstrated that the COVID-19 virus had no impact on ovarian reserve; nevertheless, changes in menstruation status may be brought on by the severe inflammatory reaction and immune response of the COVID-19 disease or by psychological stress and anxiety.

Key words: COVID-19; Ovarian Reserve; AMH; AFC; FSH; LH.

1. Introduction

The COVID-19 epidemic has been affecting the entire planet since December 2019. Infection with COVID-19 raises concerns regarding both short- and long-term impacts on general health, in addition to its impact on mortality. The clinical signs and symptoms of COVID-19 infection are highly diverse and affect numerous organs [1]. There was a contentious discussion about the effect of virus infection on human reproduction during the COVID-19 crisis. According to research, infected males had changed semen characteristics, which raised the serum level of the hormone luteinizing hormone (LH) [2]. Furthermore, a previous study found no connection between viral infection and obstetric problems [3]. In contrast, numerous other studies have centered on the possibility that sperm and oocyte function could be affected by the SARS-CoV-2 infection [4, 5].

The SARS-CoV-2 virus infects human cells by directly engaging with the angiotensin-converting enzyme 2 (ACE2) receptors present on the cell surface (6). The testes [1, 7, 8] and ovarian tissue [5, 9] both have ACE2 receptors [10]. In the ovary, ACE2 contributes to the control of steroidogenesis, the response to gonadotrophins, follicle growth, angiogenesis, and degeneration [5].

Despite the abundance of recent papers on the subject, the outcomes of in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and many other assisted reproductive technology (ART) procedures are still not entirely understood. However, because there are not enough acceptable samples and controls, the majority of the present studies on this topic are speculative and have a low grade in the evidence hierarchy.

ACE2, Ang II, and Ang-(1–7) may regulate follicular development and ovulation, corpus luteum angiogenesis and degeneration, and endometrial tissue development. Ovarian reserve is an essential factor impacting female fertility. A decreased ovarian reserve may affect fertility by reducing egg quality. Moreover, the ovaries have a high expression of ACE2 [11].

The SARS-CoV-2 infection's rise in circulating Ang II can change ovarian function, affect how oocytes develop and mature biologically, affect the quality of oocytes produced, and eventually reduce reproductive function [12]. Moreover, Ang II recruitment raises oxidative stress, which may trigger inflammatory responses and alter ovarian physiology and fertility [5, 13].

The ovarian reserve function should therefore be the leading observational indicator for the impact of COVID-19 on female fertility. E2, testing for AMH, a basal FSH or LH concentration, and an assessment of AFC are examples of frequently utilized ovarian reserve markers. The common consensus is that women start losing their ability to conceive at age 49 and that fertility begins to decline at age 13 [14]. Female fertility naturally decreases with age. Women's fertility declines gradually and steadily between the ages of 30-35; however, after the age of thirty-five, ovarian reserve and oocyte quality reductions cause the fall to accelerate more quickly [15].

So, the current study aimed to assess COVID-19's impact on the fertility of women aged 35 and older. This study's objective was to evaluate how COVID-19 infection affects women who have had assisted reproductive technology (ART) due to primary or secondary infertility.

2. Subjects and methods

2.1. Subjects

After receiving approval from the Scientific Research Ethics Council of the Faculty of Medicine, Fayoum University, the current cross-Sectional analytical study was carried out during a six-month period at the Obstetrics and Gynecology Department of the hospital (from February 2022 to August 2022).

Inclusion criteria

That included patients aged between the ages of 18 and 40, and with a PCR and/or CT verified recent COVID-19 infection history. Individuals without any other illness concomitant, infertile females with COVID-19 history were recruited after giving their informed consent and agreed to participate in the study.

Exclusion criteria

That included patient's opposition, borderline ovarian insufficiency and PCO (premature ovarian failure), related medical illnesses such as hypo- or hyperthyroidism, autoimmune disorders, and chronic incapacitating diseases, including diabetes mellitus, and when the ovarian vasculature is impacted by prior pelvic surgery.

Sample size

This calculation estimates a total sample size of 120 participants for 85% power, a 0.05 error probability, and a 10% follow-up dropout rate.

2.2. Methods

The following steps were applied in the current study:

- Previous obstetric and medical history was gathered at the time of study entry. Data from their hospital records were collected; they underwent testing of their reproductive function in the early follicular phase (AMH, FSH, LH).
- All participants baseline information, including age, body mass index (BMI) (kg/m2), and tobacco use were noted.
- Infertility type and duration were reported.
- Confirmation of earlier COVID-19 infection: The study participants were questioned about their COVID-19 status using the Ministry of Health data system. Real-time reverse-transcriptase polymerase chain reaction (PCR) analysis of throat swab samples produced a positive finding for COVID-19 illness. The severity of COVID-19 disease was divided into three categories by the American Thoracic Society/Infectious Diseases Society of America guidelines: mild, moderate, and severe illness. The 120 participants had COVID-19 infection, which was ultimately discovered after this investigation. Positive PCR test findings for every participant were recorded.
- Infection period of COVID-19 was noted.
- A thorough examination of the abdomen.
- Transvaginal 9-MHz ultrasound probes were used by certified gynecological sonographers between days 3 and 5 of a woman's menstrual cycle to evaluate the

ovarian reserve. Total antral follicle count (AFC) includes antral follicles that are 2 to 10 mm in diameter from both the left and right ovary.

- Serum laboratory tests: To assess serum AMH Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (LH).

Study outcomes

The proportion of women with impaired fertility following COVID-19 infection was the study's main finding. The following signs of healthy ovarian reserves: Anti-Müllerian hormone, first (AMH). (2) Baseline concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the ratio of FSH to LH.

2.3. Statistical data analysis

Data collection, analysis, and coding took place using IBM SPSS version 20. where the mean, standard deviation, and range of parametric and quantitative data were displayed. In order to present qualitative data, numbers, and percentages were used. The Fisher exact test was used in place of the Chi-square test when predicted cell counts were less than 5. The independent sample t-test was used to compare two independent groups using numerical data and parametric distribution. The Mann-Whitney U test was used to compare two independent groups with numerical data and a non-parametric distribution. $P > 0.05$, $P < 0.05$, and $P < 0.001$ indicated non-significant, significance, and strong significance, respectively; each had a 5% margin of error and a 95% confidence range.

3. Results

The length of the COVID-19 infection ranged from 2–8 months, with an average of 3.95 months. In terms of COVID-19 severity, the majority of the women (71.7%) reported mild cases, while 25% reported severe cases, and only 3.3% reported intermediate cases (Table 1).

Table 1: The duration and severity of COVID-19 infection.

Variables		**Descriptive statistics**
Duration since COVID-19 infection	Range (Min – Max)	2.0 - 8.0
	Mean ±SD	3.95 ±1.16
COVID-19 Severity	Mild	86 (71.7%)
	Moderate	4 (3.3%)
	Sever	30 (25.0%)

63.3% of the women in the study reported no changes to the length of their menstrual cycles, (25.8%) reported longer cycles, and (10.3%) reported shorter cycles (Table 2).

There were non-statistically significant changes in menstrual regularity in the three studied groups ($P < 0.05$) (Table 3).

Table 2: Change in menstrual cycle post-COVID-19 according to disease severity; (N= 120).

Variables	**COVID-19 Severity**			**Total N= 120**	***P-value***
	Mild N= 86	**Moderate N= 4**	**Severe N= 30**		
No Change	54 (62.8%)	3 (75.0%)	19 (63.3%)	76 (63.3%)	0.874
An increased cycle length	23 (26.7%)	1 (25.0%)	7 (23.3%)	31 (25.8%)	
A decreased cycle length	9 (10.5%)	0 (0.0%)	4 (13.3%)	13 (10.8%)	

Table 3: Comparison of menstrual cycle regularity pre- and post-COVID-19 infection according to disease severity.

Variables	**Mild (N=86)**			**Moderate (N=4)**			**Severe (N=30)**		
	Pre-	Post-	*P-value*	Pre-	Post-	*P-value*	Pre-	Post-	*P-value*
Regular	58 (65.9%)	54 (61.4%)	0.319	1 (50%)	1 (50%)	0.833	17 (56.7%)	14 (46.7%)	0.303
Irregular	30 (34.1%)	34 (38.6%)		1 (50%)	1 (50%)		13 (43.3%)	16 (53.3%)	

4. Discussion

Several studies have looked into how COVID-19 affects infertility and menstrual cycles, but the issue is still up for debate and needs more investigation, emphasizing the significance of our work. The current study's goal was to assess how 120 infertile women who were undergoing an assisted reproductive technology (ART) program were affected by COVID-19 infection in their ovarian reserve (women with primary or secondary infertility). Anti-Mullerian hormone (AMH), a biomarker for ovarian reserve, is thought to be the most accurate and early predictor of ovarian reserve Although AMH levels were marginally reduced between the pre- and post-COVID-19 periods in the current investigation, this change was not statistically significant. Reproductive hormones (FSH and LH) also underwent a number of modifications, but these changes did not differ in a way that was statistically significant. Also, the post-COVID-19 infection AFC was contrasted with the baseline AFC, and the results revealed non-statistically significant differences between the three examined groups in terms of COVID-19 severity.132 young women between the ages of 18 and 40 who were evaluated for reproductive function in the early follicular phase before and after COVID-19 disease came to the same conclusions. The serum concentrations of AMH did not differ between pre-and post-treatment (P = 0.097), and there was no statistically significant difference between pre-and post-illness, according to the investigators [16]. Li et al. (2021) found no evidence that the disease had any effect on blood AMH concentrations when they examined the levels of sex hormones such as FSH, LH, estradiol, progesterone, and testosterone in 91 women with COVID-19 who were of reproductive age compared to 91 healthy women. Also, they discovered no proof that the SARS-CoV-2 virus affected ovarian reserve or sex hormone levels in any way [17]. According to the current investigation, the serum FSH and LH concentrations of the patients before and after the COVID-19 illness were comparable in the same patients. Ding et al. (2021) found that there were no differences in FSH, AMH, or the number of antral follicles (AFC) between the 195 women in the control group (negative IgG) and the 65 women with positive SARS-CoV-2 IgG [18].

Contrary to our findings, (1132) patients undergoing IVF between April and September 2020 had significantly higher FSH levels at the beginning of the cycle than before the pandemic, and the heightened level of FSH has been associated with lower pregnancy rates [19]. Ding et al. (2021) investigation into the hormonal state of the ovaries produced different findings [18]. They claimed that the COVID-19 infection might have a negative effect on ovarian reserve and endocrine function because the serum AMH concentrations of 78 COVID-19 patients (17 of whom had severe illness) were significantly lower than those of 51 healthy women [18]. Angiotensin-converting enzyme 2 (ACE2), they hypothesized, is responsible for the SARS-CoV-2 virus's entry into cells [20].

Results from different studies on the impact of COVID-19 on menstrual cycles may vary due to different study groups, research techniques, and sample sizes. In the current study, 63.3% of women reported no changes in their menstrual cycle length, while 25.8% and 10.3% reported lengthening and shortening cycles, respectively. However, these changes were not statistically significant. Another cross-sectional online questionnaire study found that 25% of 749 women had longer cycles, 20% had shorter cycles, and more than 50% experienced psychosocial menstrual symptoms. About 17% of women felt stressed about their altered menstrual cycle, and they had normal menstrual cycles prior to COVID-19 with at least nine menstruations or withdrawal bleedings [21]. Malloy et al. (2021) found that 87% of 12,302 women in their cross-sectional online questionnaire study reported menstrual cycle irregularities, with 29% reporting additional symptoms and 27% reporting increased bleeding [22]. A study of 177 women who had recovered from COVID-19 found that 28% had changes in their menstrual cycle patterns, with 25% experiencing altered menstrual flow, mostly longer cycles with decreased flow. Women with systemic issues were more likely to experience these abnormalities, and those with severe illnesses had longer menstrual cycles [17]. We require a deeper comprehension of how the menstrual cycle may be impacted by COVID-19 infection, which processes are involved, and the cause of these alterations. This is based on the findings of the current study and the previous studies. as the site of implantation; the endometrium plays a significant role in human-assisted reproductive technologies.

Stress can affect the menstrual cycle, and with the current pandemic leading to increased stress levels, it is important to consider the possibility of menstrual abnormalities. The present study has certain limitations. To start, only four of the very few women included in the analysis had mild COVID-19 illnesses. Second, just one center was used to conduct this study. Finally, we were unable to examine this because not all study participants had pre-COVID-19 serum levels of progesterone, testosterone, or prolactin. Lastly, if an autopsy or ovarian biopsy sample is available, the SARS-CoV-2 virus should be studied to assess its long-term effects on the ovary.

Conclusion

Based on the given information, we concluded that SARS-COV-2 infection didn't not harm the ovaries responsible for creating eggs in women. Also, the menstrual cycle abnormalities might be caused by the body's inflammatory response and immune system reaction to COVID-19, as well as related stress and anxiety. However, these changes usually disappear within a few months after recovering from the virus. Although more patients had irregular periods after contracting COVID-19, the menstrual cycle abnormalities were not statistically significant in the current study's findings, especially when compared to the severity of the infection. Nevertheless, more extensive research and larger sample sizes are required to confirm these results.

Ethical approval:

The research ethics committee for the faculty of medicine at Fayoum University gave its clearance after the study complied with all the administrative rules (Number M757). The consent to the right to decline or leave the study without providing a reason was explained to participants, and they were also assured of anonymity and confidentiality.

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