COVID-19 disease effect on ovarian reserve in women of reproductive age: an analytical before-and-after COVID-19 study

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Abstract

Background: COVID-19 is a serious pandemic that affected multiple systems in the human body. Its effect on female fertility is not widely evaluated.

Objective: to evaluate the effect of COVID-19 infection on the ovarian reserve and menstrual cycle in infertile women undergoing an assisted reproductive technology protocol.

Study design: A cross-sectional analytical study was conducted on 120 infertile (primary or secondary infertility) women attending the Gynecology and Obstetrics Department at Fayoum University Hospital with confirmed previous COVID-19 disease. The ovarian reserve in this group was studied using AMH, AFC, and serum FSH, LH. The menstrual cycle length was evaluated before and after infection.

Results: We studied 120 infertile women with confirmed COVID-19 infection. The average age was 26.96 ±5.68 years. Out of the 120 cases, 86 cases (71.7%) were diagnosed as mild COVID-19 infection, while severe cases were reported in 30 (25%), and only four women (3.3%) reported a moderate form of the infection. AMH, AFC, FSH and LH mean serum levels tested post-COVID-19 showed non-statistically significant difference in pre and post covid with infection (p-values > 0.05). A great proportion of the patients reported no change in the cycle length (63.3%) with insignificant difference reported between patients with mild, moderate, and severe infection (P value 0.874).

Conclusion: It was found that COVID-19 has no effect on ovarian reserve.

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

Introduction

There has been a global pandemic of COVID-19 since December 2019. Concerns about the short- and long-term repercussions of COVID-19 infection extend beyond the virus's impact on mortality rates. Many different organs may be involved in the wide variety of clinical symptoms caused by SARS - COVID-19 (1).

Human fertility and the effects of the COVID-19 virus were at the center of a heated discussion during the pandemic. Studies have suggested that higher serum luteinizing hormone (LH) level is linked to changes in semen parameters in infected males (2, 3). Others have investigated the potential effect of SARS-CoV-2 infection on sperm and oocyte function (4, 5, 6). By directly interacting with surface angiotensin-converting enzyme 2 (ACE2) receptors, the SARS-CoV-2 virus is able to infect human cells (7). Both ovarian (6,7,8) and testicular tissues have ACE2 receptors (9-11); therefore, follicle growth, angiogenesis, and degeneration, as well as the reaction to gonadotrophins, would be impacted by ACE2 (7, 8, 11).

In addition to influencing the formation of endometrial tissue, ACE2, Angiopoietin II (Ang II), and Angiopoietin 1-7 (Ang 1-7) may control the angiogenesis and degeneration of the corpus luteum and the follicular and ovarian follicles, as well as the timing of ovulation. The ovarian reserve of a woman is a major factor in her ability to have children. Fecundity may be negatively impacted by diminished ovarian reserve due to decreased egg quality (11). More importantly, ACE2 is abundantly expressed in the ovary (12). Additionally, there has been concerns about the menstrual changes that were reported by some patients as change in duration, change in menstrual bleeding pattern, and altered pain which indicated further evaluation (13).

Alterations in ovarian function, the biological process of oocyte formation and maturation, oocyte quality, and fertility function may result from a decrease in ACE2 activity caused by SARS-CoV-2 infection, which can increase circulating Ang II (14). Also, the recruitment of Ang II promotes oxidative stress (6), causes inflammation, which might hamper ovarian function and fertility (15).

Therefore, indicators of the effect of COVID-19 on female fertility should focus primarily on the ovarian reserve function. Ovarian reserve is often measured by measuring a patient's basal FSH or LH concentration, as well as E2, AMH, and an assessment of ovarian function capacity. Accordingly, the primary objective of this study was to evaluate the effect of COVID-19 infection on ovarian reserve among infertile women. A secondary objective was to evaluate the effect of infection on the menstrual cycle length.

Methods

This was a cross-sectional study conducted on infertile (primary or secondary infertility) women attending the Gynecology and Obstetrics Department at Fayoum University Hospital (from March 2022 to September 2022). According to findings from a previous study (16), the global prevalence of infertility is estimated to be around 9%. Using Power Analysis and Sample Size Software (PASS 2020) "NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass", we estimated that 120 participants are needed in order to achieve 85% power, - error probability 0.05, and a 10% dropout rate during follow up.

Women aged from 18 to 35 years old, with history of confirmed COVID-19 infection by PCR and / CT, with no coexisting medical disorders were included in this study. While those with PCOS or border line ovarian insufficiency (premature ovarian failure), and associated medical conditions (hypothyroidism or hyperthyroidism, auto immune disease, chronic diseases such as DM and those with previous pelvic surgery

potentially affecting ovarian vasculature) were excluded.

The diagnosis of SARS-CoV-2 infection was done using a real-time reverse-transcriptase polymerase chain reaction (PCR) assay of throat swabs (17). SARS-CoV-2 cases were classified as either "mild," "moderate," or "severe" according to criteria established by the American Thoracic Society and the Infectious Diseases Society of America (18). All positive PCR test dates of the participants were noted. Information on ovarian function (AMH, FSH, LH and AFC), prior to COVID-19 infection was obtained from hospital records between January 2019 and April 2021.

At study entry, baseline demographic was recorded, including age, body mass index (BMI) (kg/m^2), tobacco smoking, as well as type and duration of infertility. Past obstetric and medical histories were collected first from all patients included in the study. Time from SARS-CoV-2 infection was recorded.

Ultrasound assessment of ovarian reserve:

Qualified gynecological sonographers performed pelvic ultrasound assessments between days 3 and 5 of the menstrual cycle, using a transvaginal 9-MHz ultrasound probe (Voluson S10, GE). The recorded antral follicle count (AFC) represents the combined total antral follicles between 2 and 10 mm from the left and right ovaries.

Laboratory tests: Serum samples were taken for the measurement of AMH, basal follicle-stimulating hormone (FSH), and basal luteinizing hormone (LH). All samples and ultrasound evaluations were done 3- 6 months after cured infection.

The patients were asked to report their menstrual cycle length (average length of 24-38 days) (19) before and after infection.

The primary outcome of the current study was the proportion of women with decreased fertility post SARS-CoV-2 infection according to the following indicators of ovarian reserve function (AMH, basal FSH, basal (LH) and AFC). A secondary outcome measure was to evaluate the effect of COVID-19 infection on the menstrual cycle length.

Ethical approval: The ethical committee of Fayoum University's Faculty of Medicine approved the current study on 13/2/2021, approval number: (M 575). Before enrolling in the study, all women gave a written informed consent after clarifying the study's goals. The confidentiality of the data base was ensured.

Statistical Data Analysis:

Data were collected, reviewed, coded, and entered into IBM version 21 of SPSS (Statistical Package for the Social Sciences). Quantitative data were presented as means, standard deviations, and ranges when their distribution was found to be parametric, while qualitative data were shown as counts and percentages. The Chi-square test was used to compare two groups based on qualitative data, whereas the Fisher exact test was used in place of the Chi-square test whenever the predicted count in any given cell was less than 5. Independent sample t-test was used to evaluate differences between the two groups, both of which had quantitative data with a parametric distribution. The Mann-Whitney U test was used to compare two unrelated groups based on quantitative data with a non-parametric distribution. The margin of error was approved at 5%, and the confidence interval was set to 95%. $P > 0.05$ was considered not significant, P 0.05 or less was thought to be significant, and P 0.001 was deemed to be highly significant. Basic graphs were used to present some data.

Results

One hundred thirty- three women were eligible for the study. Upon evaluation of the hospital records, laboratory results were not available for 13 patients, leaving 120 patients for the final analysis.

Table (1) presents the baseline data of the 120 women included in the current study. Their ages ranged from 18 to 38 with an average age of 26.96 ±5.68years, their BMI ranged from 19.8 to 23.4 with an average BMI of 21.8 ±7.62kg/m2. The infertility duration ranged from 2 to 8 years with an average of (3.78 ± 2.32) years. The time frame of COVID-19 infection ranged from 2 to 8 months with an average duration of 3.95 ± 1.16 months. Regarding COVID-19 severity, most women reported a mild form of the disease (86 71.7%), while severe cases were reported by 30 (25%), and only four women (3.3%) reported a moderate form of the disease.

Figure (1) shows the change in menstrual cycle post-COVID-19 according to disease severity. Most of the women reported no changes in menstrual cycle length (63.3%), 25.8% reported an increased cycle length, and 10.3% reported a decreased cycle length. There was no significant difference in menstrual cycle length change among women with mild, moderate, and severe infection (P value 0.874). A comparison of menstrual cycle regularity pre- and post-COVID-19 infection, according to disease severity, revealed non-statistically significant changes in menstrual regularity in the three studied women groups (p-values <0.05).

According to SARS-CoV-2 severity, Table (2) shows a comparison of the reproductive function and ovarian reserve between the studied population. The mean concentration of AMH tested during ART treatment post-COVID-19 infection was slightly decreased but not significantly different as compared with the mean concentration of AMH tested before COVID-19 infection in the three groups. Similarly, FSH and LH mean serum levels tested post-COVID-19 showed non-statistically significant difference as compared with the mean serum levels tested before COVID-19 infection in the three groups according to disease severity: (p-values >0.05). The basal antral follicle count (AFC) showed non-statistically significant difference in the three studied groups according to SARS-CoV-2 severity: (p>0.05).

Discussion

The inflammatory effects of COVID19 infection, known as chronic COVID syndrome, can linger for months after the initial infection. It is hypothesized that COVID19 exerts its effects on the ovary because of this prolonged COVID condition characterized by persistent inflammation and also by the direct binding of SARSCoV2 to the ovary.

The ACE2 system, the main component of the renin-angiotensin-aldosterone pathway, is the primary host receptor for the SARS-CoV-2 virus. By binding to ACE2 and altering ACE2 expression in host cells, the virus can infect its intended host cell. Since it is expressed and has a regulatory influence on follicle formation and ovulation, there is concern that the virus may hinder female reproductive activities by modulating ACE2. This has been investigated by numerous studies.

After analyzing the effect of COVID-19 on fertility, Li et al. noted that the virus's potential pathogenicity on testicular and ovarian tissues and on granulosa cells could affect testicular and ovarian functions, spermatozoa, oocyte quality, and pregnancy outcomes (20). For this reason, they stressed the importance of future fertility assessments for persons with COVID-19 infections. Jing et al., showed that in SARS-CoV-2, the expression of ACE2 allows the virus to infect the placenta as well as the uterine lining, which can lead to infertility, monthly abnormalities, and fetal discomfort in pregnant women (6).

Several studies have shed light on the effects of COVID19 on fertility and menstrual cycles, however, there is no clear evidence. This cross-sectional study of 120 infertile women (those with primary or secondary

infertility who were participating in an assisted reproductive technology (ART) regimen) investigated the impact of SARS-CoV-2 on ovarian reserve.

In the current investigation, although there was a trend toward lower AMH levels between the pre- and post-COVID-19 periods, the difference was not statistically significant. Similarly, there was a trend toward lower FSH and LH levels, but the difference was not statistically significant. There was also no statistically significant difference between the three groups tested according to COVID-19 severity.

In line with these findings, a study of 132 young women aged 18 to 40 years, found no statistically significant variation in the blood concentrations of AMH between pre- and post-illness (P = 0.097), suggesting that reproductive function in the early follicular phase was not affected by COVID-19 disease (21, 22). Comparing the levels of sex hormones like FSH, LH, oestradiol, progesterone, and testosterone in 91 women with COVID-19 who were of reproductive age and 91 healthy women, the lack of an effect on ovarian reserve or sex hormone concentrations by SARS-CoV-2 was also confirmed by Li et al. (20). Similar to the present study, previous research has shown no difference between patients' pre- and post-COVID-19 illness blood FSH and LH concentrations.

Wang et al. also reported no changes in FSH, AMH, and the number of antral follicles (AFC) between women who had SARS-CoV-2 Ig-G and those who did not. Their study comprised 65 women with positive SARS-CoV-2 Ig-G and 195 women as the control group (-ve Ig-G) (23).

In a study by Kolanska et al., the AMH levels of the 14 women who tested positive for SARS-CoV-2 (all with moderate disease) were comparable to those of negative SARS-CoV-2 in the control (24). Similar results were obtained in a study that compared AMH levels in hospitalized women with and without COVID-19 (20).

Contrary to our findings, among 1132 individuals who underwent IVF between April and September 2020 (compared to a pre-pandemic study), FSH levels were considerably higher at the beginning of the cycle than before the pandemic, a finding associated with decreased pregnancy rates (25).

Contradictory findings regarding ovarian hormone levels were reported by Ding et al., who found that serum AMH concentrations of 78 COVID-19 patients (17 of whom had severe illness) were significantly lower than the serum AMH concentrations of 51 healthy women, leading them to conclude that COVID had a potentially detrimental impact on ovarian reserve and endocrine function (26, 27). This disagreement in findings between these different studies could be due to several factors, including the use of different groups, the use of different study methods, or the use of a relatively small sample size.

In the process of embryo implantation, the endometrium plays a crucial function. Based on their findings, Henarejos et al., in a meta-analysis of COVID-19 effects on the uterine lining, established that the endometrium is protected from SARS-CoV-2 infection via TMPRSS2 due to its low ACE2 and medium TMPRSS2 levels. However, towards the middle of the secretory process, upregulation of TMPRSS4 was found to be linked to that of Cathepsin L (CTSL), CTSB, FURIN, and MX1. Consequently, during the early and middle secretory phases, the endometrium may be vulnerable to SARS-CoV-2 infection via TMPRSS4. BSG (potential additional host receptor for viral entry) was an alternative receptor whose expression, like that of ACE2 (a protein on the surface of many cells, it is an enzyme that generates small proteins) and TMPRSS2 (a cell service protein primarily expressed by endothelial cells across the respiratory and digestive tracts), changed over the menstrual cycle. It

was discovered that the S protein cleavage factor FURIN strongly activates BSG. In addition to ACE2, increased BSG expression may explain SARS-CoV-2 infection (28, 29).

A cross-sectional online questionnaire study by Malloy et al. (12,302 women) found that 87% of the women had experienced disruptions in their menstrual cycle pattern, 29% had experienced more severe menstrual symptoms (abdominal pain, back pain, discharge changes), and 27% had experienced heavier menstrual bleeding (30).

In the cross-sectional study by Li et al., 25% of infected women experienced altered menstrual flow (most commonly lower flow), and 28% experienced changes in their menstrual cycle pattern after contracting COVID-19 (mainly longer cycle). In patients with systemic problems, menstrual irregularities were most common. Longer menstrual cycles were observed in women with severe illnesses (20).

Conclusion

SARS-CoV-2 virus have no effect on ovarian reserve; however, menstrual changes were found.

Conflict of interest

The authors report no conflicts of interest..

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Table (1): Baseline data of the studied women; (N= 120):

		Descriptive statistics
Age	Range (Min – Max)	18.0 - 38.0
	Mean ±SD	26.96 ±5.68
BMI (kg/m^2)	Range (Min – Max)	21.8 ±7.62
	Mean ±SD	19.8 - 23.4
Infertility Type; N (%)	Primary	58 (48.3%)
	Secondary	62 (51.7%)
Duration of infertility	Range (Min – Max)	1.0 - 12.0
	Mean ±SD	3.78 ±2.32
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%)

Table (2): Comparison of the reproductive function and ovarian reserve between the studied population according to COVID-19 severity; (N= 120):

	Mild N= 86	p-value	Moderate N= 4	p-value	Severe N= 30	p-value
AMH ng/ml (before)	2.11 ±1.11	0.071	1.99 ±0.43	0.999	1.82 ±0.84	0.081
AMH ng/ml (after)	2.07 ±1.10		1.99 ±0.45		1.74 ±0.84	
FSH IU/L (before)	5.67 ±2.33	0.063	6.65 ±0.95	0.817	6.50 ±2.26	0.659
FSH IU/L (after)	6.65 ±2.18		6.56 ±1.38		6.61 ±1.66	
LH IU/L (before)	5.55 ±2.74	0.551	5.05 ±2.72	0.693	5.78 ±2.07	0.576
LH IU/L (after)	5.36 ±1.94		4.64 ±1.76		5.88 ±1.83	
AFC (before)	7.85 ±2.03	0.587	8.75 ±4.11	0.769	10.03 ±1.69	0.821
AFC (after)	7.78 ±2.14		8.25 ±1.50		9.97 ±2.62	

Figure 1: Change in menstrual cycle post-COVID-19 according to disease severity.