



RESEARCH ARTICLE

Evaluation of AMH, FSH and LH on group of patient infected with COVID-19 fertile and infertile female in Baghdad.

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| Article Info. | Abstract |
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| Article history: | Extreme Acute Respiratory disaster SARS-CoV-2, a pathogenic and highly transmissible coronavirus, is the cause of Coronavirus Disease 19 (COVID-19). A significant number of individuals lost their lives as a consequence of the SARS-CoV-2 global pandemic. Despite enormous efforts made in practically every country since its first report in December 2019, this disease spread globally, especially in most of Europe, Iran, and the United States. The spread of SARS-CoV-2 has created a major threat to world health. This study examined several indicators of hormonal parameters in an effort to assessment the collected scientific data and demonstrate the effect of COVID-19 on female fertility. Out of the 180 patients, 110 were infertile and 70 were fertile COVID-19-positive female patients who were admitted to the Kamal al-Samarrai and Fatima Al-Zahraa hospitals in Baghdad between April 2022 and November 2022. The control group consisted of 70 patients. The results of the study showed that there was a statistically significant (<.001) difference in anti Müllerian hormone (AMH) between the patient and control groups. Follicular stimulating hormone (FSH), luteinizing hormone (LH) were statistically significant differences and showed elevated level between the patient and control groups. The results showed that COVID-19 infection may alter AMH levels, reduce ovarian reserve, affect the immune system, and potentially alter the course of reproduction. Pituitary gonadotropin and ovarian hormone secretion also seem to be impacted by COVID-19 disease. |
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1-Introduction

The term "coronaviruses" (CoVs) refers to a class of ribonucleic acid (RNA) viruses that are members of the family Coronaviridae, subfamily Coronavirinae, and order Nidovirales. The HCoV-229E strain was one of the first CoVs to infect humans and affect their respiratory system, another strain, HCoV-OC43, was found to be present in the human upper respiratory tract. Patients with both strains of the infection displayed the typical cold symptoms, including headaches, sneezes, and sore throats (1). Aerosol and airborne transmission are two ways that the pathogen known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can spread from person to person (2). The lung is the principal site of viral infection within the respiratory system (3). Numerous profound effects of COVID-19 have been felt by humanity leading to significant instability in the social, medical, political, and economic domains. Acute respiratory distress of severe magnitude coronavirus 2 (SARS-CoV-2) infection modifies the body's typical immune response while causing localized and systemic harm to organs and tissues (4). The respiratory tract gets infected as soon as the virus enters the body. SARSCoV-2 infection occurs in three stages: I asymptomatic incubation period in which the virus may or may not be detectable; II is a no severe symptomatic period in which the virus is present; and III is a severe respiratory symptomatic stage with a high viral load. Extra pulmonary lesions unique to COVID-19 includes hepatocellular lesions, neurological disorders, myocardial dysfunction and arrhythmia, gastrointestinal disorders, and genital impairment, Acute renal lesions/acute kidney damage are also included (5). The ovaries have a higher number of IV angiotensin-converting enzyme 2 (ACE2) receptors, which may impair the female reproductive system. There's no antiviral medication that has been clinically approved to treat COVID-19. However, fewer antiviral medications with a broader spectrum of activity have been tested in clinical trials against COVID-19, with encouraging outcomes. However, studies have also revealed signs of other organs and systems, including the heart, kidneys, and reproductive system (6). Women are also more vulnerable to viral infections than men are, which raises the risk of reproductive system impairment for all women, particularly those who are childbearing age. Given this, the COVID-19 needs to give more attention to female fertility and related reproductive health care (7). The ovaries could be

the target of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (8). Sexual hormones such as follicle-stimulating hormone and luteinizing hormone, along with anti-Müllerian hormone (AMH) and basal antral follicle count, are the most widely used indicators of ovarian reserve (9).

The measurement of female fertility is based on ovarian reserve. Moreover, irregular menstruation may also be a sign of low ovarian reserve in women who are of reproductive age (10). Women who are infected may be susceptible to COVID-19-related ovarian damage, such as hormone disruption and decreased ovarian reserve (11).

2- Materials and Methods

2-1 Study design

This study was a hospital-based cross sectional, case-control study which was done on Iraqi population from Baghdad city. Blood samples were collected from a total of No.180(volunteers in a period from April 2022 till November 2022 from Kamal al-Samarrai hospital, and Fatima Al-Zahraa hospital in Baghdad city. The (No.180) volunteers were classified to patients group (No.110) which include (No.40) fertile infected with COVID-19, (No.40) infertile infected with COVID-19 (No.40), and infertile uninfected with COVID-19 (No.30). The control group (No.70) apparently healthy individuals without symptoms or chronic disease and fertile female and uninfected with COVID-19 at the time of collected sample. Serum sample into aliquots was stored at (-20°C) until needed for studied parameters investigation.

2-2-1 Inclusion criteria:

Criteria for inclusion: All patients between the ages of 18 and 40 were included in the study. the first group suffers from secondary infertility, While the second group of women has children within the last five years. She previously gave birth naturally that is without the use of artificial insemination or IVF. she has never received fertility treatment before for the past six months, she has not received the Covid-19 vaccination.

2-2-2 exclusion criteria

primarily infertile females. women who were not overexposed to ionizing radiation, pesticides, lead, cadmium, mercury, or other physical, biological, chemical, or environmental factors that have an impact on female fertility. Do not have any gonadal injuries from radiation therapy to the abdomen or pelvis or from high-dose chemotherapy with alkylating agents.be excluded if they have severe thyroid dysfunction or other conditions that impair female fertility. She's had miscarriages in the past. Her family has a history of infertility issues. severe obesity. women who are pregnant or taking birth control pills. subjects who declined to take part in the research.

2-3 Statistical analysis

The statistical analysis for the study was done using the social sciences statistics program. (SPSS Version 21). For the quantitative variable, data were shown as Mean±SD so that study groups' means could be compared to one another. ROC Curve was used to study relations.

3- Results

Fertility and COVID_19 were used as the variables in an analysis of variance (ANOVA) to determine if there were any significant differences in Anti-Müllerian Hormone (AMH) levels. According to Table 1, there were notable variations in AMH between the various levels of COVID-19 and fertility, as indicated by the highly significant ANOVA results ($p < .001$). Additionally, the highly significant interaction effect between COVID_19 and fertility revealed significant variations in AMH for each combination of COVID_19 and fertility factors ($p < .001$).

Table (1): - Analysis of Variance for AMH, FSH, LH by Fertility and COVID_19 in studied groups.

| variable | Term | SS | df | F | p | η_p^2 |
|----------|--------------------|----------|----|--------|--------|------------|
| AMH | Fertility | 238.35 | 1 | 576.36 | < .001 | 0.77 |
| | COVID_19 | 103.44 | 1 | 250.15 | < .001 | 0.59 |
| | Fertility:COVID_19 | 61.92 | 1 | 149.74 | < .001 | 0.46 |
| FSH | Fertility | 1,042.78 | 1 | 279.12 | < .001 | 0.61 |
| | COVID_19 | 1,500.11 | 1 | 401.53 | < .001 | 0.70 |
| | Fertility:COVID_19 | 277.83 | 1 | 74.37 | < .001 | 0.30 |
| LH | Fertility | 412.43 | 1 | 200.57 | < .001 | 0.53 |
| | COVID_19 | 605.75 | 1 | 294.59 | < .001 | 0.63 |
| | Fertility:COVID_19 | 14.60 | 1 | 7.10 | .008 | 0.04 |

The main effect of Fertility was found to be significant, $p < .001$ suggesting noteworthy differences in AMH based on Fertility levels. Similarly, the main effect of COVID_19 was significant, as indicated by $p < .001$ signifying substantial differences in AMH based on COVID_19 levels table (1).

Table (2): - Descriptive statistics of anti Müllerian hormone by the studied groups.

| Marker | Groups | Variable | $M \pm SD$ | No. | Median | p |
|--------|---------------------|-----------------|-----------------|-----|--------|--------|
| AMH | Infected COVID-19 | Fertile | 2.05 ± 0.56 | 40 | 2.02 | < .001 |
| | | Infertile | 0.86 ± 0.46 | 40 | 0.85 | |
| | uninfected COVID-19 | Infertile | 1.22 ± 0.30 | 30 | 1.22 | < .001 |
| | | Healthy control | 4.87 ± 0.85 | 70 | 4.78 | |

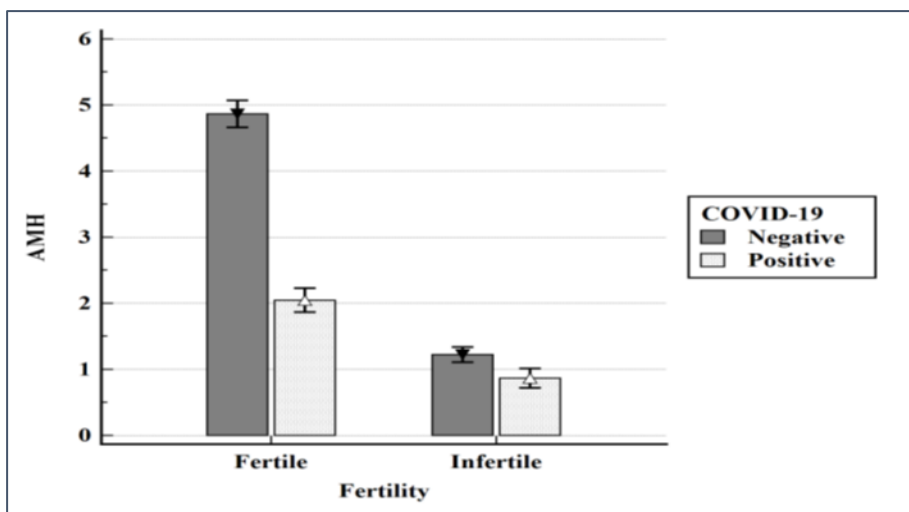


Figure (1): - Means of Anti-Müllerian Hormone (AMH) by Fertility and COVID-19 infection with 95.00% CI Error Bars.

The mean AMH level for the combination of Fertile and Negative infection (healthy control) (4.87 ± 0.85) was significantly higher than for Fertile and Positive (2.05 ± 0.56), $p < .001$, in the same way for the interaction effect between Fertility and COVID_19. Furthermore, with regards to the interaction effect between COVID_19 and fertility, the combination of being both healthy control (4.87 ± 0.85) had a mean AMH level that was significantly higher than that of being both infertile and positive (0.86 ± 0.46), with a p-value of less than .001. In contrast, the mean AMH level for the combination of Infertile and Absent infection (1.22 ± 0.30) was significantly lower than for Fertile and Positive (2.05 ± 0.56), $p < .001$, for the interaction effect between Fertility and COVID_19.

The mean AMH level for the combination of Fertile and Positive (2.05 ± 0.56) was significantly higher than for Infertile and Positive (0.86 ± 0.46), $p < .001$, for the interaction effect between Fertility and COVID_19, as shown in table (2).

Follicle-stimulating hormone (FSH) and luteinizing hormone levels were compared to the variables COVID-19 and fertility using an analysis of variance (ANOVA) to see if any significant differences existed.

Table (3): - Descriptive statistics of fertility hormone by the studied groups.

| Parameter | Groups | Variable | No. | $M \pm SD$ | Median | SE_M | p |
|-----------|---------------------|-----------------|-----|------------------|--------|--------|--------|
| FSH | Infected COVID-19 | Fertile | 40 | 18.87 ± 1.96 | 19.30 | 0.31 | < .001 |
| | | Infertile | 40 | 21.31 ± 2.68 | 20.65 | 0.42 | |
| | uninfected COVID-19 | Infertile | 30 | 17.86 ± 1.61 | 17.90 | 0.29 | < .001 |
| | | Healthy control | 70 | 10.21 ± 1.49 | 10.00 | 0.18 | |
| LH | Infected COVID-19 | Fertile | 40 | 10.27 ± 1.29 | 10.40 | 0.20 | < .001 |
| | | Infertile | 40 | 12.84 ± 2.00 | 12.71 | 0.32 | |
| | | Infertile | 30 | 9.60 ± 1.34 | 9.61 | 0.24 | < .001 |

| | | | | | | | |
|--|------------------------|--------------------|----|------------|------|------|--|
| | uninfected COVID-19 | Healthy control | 70 | 5.83± 1.14 | 5.83 | 0.14 | |
|--|------------------------|--------------------|----|------------|------|------|--|

The ANOVA results showed significant results (Table 1). A significant difference in FSH was observed across the different levels of COVID-19 and Fertility ($p < .001$). Moreover, there was a significant interaction effect between COVID-19 and fertility, with $p < .001$. This indicates that FSH levels were significantly impacted by the combined effects of COVID-19 and fertility. This interaction effect is crucial because it indicates that there is more going on than just additive interaction between these two factors and FSH levels.

Furthermore, the main effect of fertility was found to be significant, with $p < .001$ indicating significant differences in FSH according to fertility levels. Similarly, the primary impact of COVID-19 was found to be statistically significant, with $p < .001$ signifying noteworthy variations in FSH according to COVID-19 concentrations. table (1). Detailed descriptive statistics can be found in (Table 3)

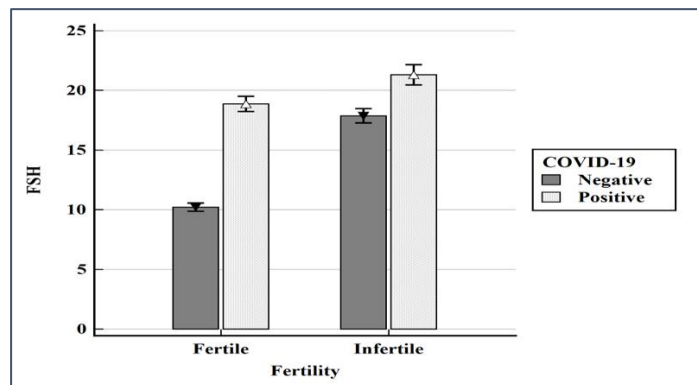


Figure (2): - Means of Follicle-Stimulating Hormone (FSH) by Fertility and COVID-19 infection with 95.00% CI Error Bars.

Statistical significance was demonstrated by the ANOVA analysis results, with $p < .001$. The data presented in Table (1) indicates that there are significant differences in the levels of luteinizing hormone between the COVID-19 and fertility categories. Furthermore, a significant interaction between COVID-19 and fertility was observed, with $p = .008$. As indicated by the interaction term, this shows that there were significant differences in LH for every combination of COVID-19 and fertility. Furthermore, $p < .001$ indicated significant differences in LH levels according to Fertility categories, indicating that Fertility had a significant influence. Likewise, significant differences in LH levels based on COVID-19 categories were highlighted by the significant impact of COVID-19 ($p < .001$) (Table 1). Detailed descriptive statistics can be found in (Table 3)

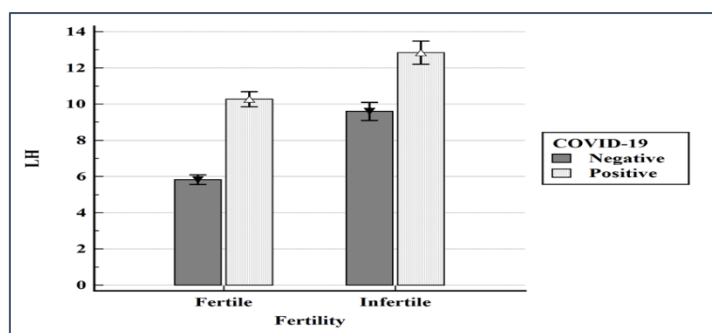


Figure (3): - Means of Luteinizing Hormone by Fertility and COVID-19 infection with 95.00% CI Error Bars.

4-Discussion

COVID-19 is a serious public health concern due to its extensive reach and widespread global distribution (12). Claim that SARS-CoV-2 infection disrupts normal immune responses, leading to systemic and localized tissue damage (13). the lower respiratory tract is primarily affected by local tissue damage, which manifests as pneumonia with fever, cough, expectoration, and hemoptysis (14). list the extra pulmonary damage caused by COVID-19 as acute kidney injury, hepatocellular injury, neurological disorders, myocardial dysfunction and arrhythmia, and gastrointestinal symptoms (15). Both direct and indirect evidence point to the possibility that COVID-19 may affect female fertility and this theory has received far more attention. a female's fertility is her ability and potential for reproduction. However, no comprehensive reviews

have been carried out to fully investigate the connection between female fertility and COVID-19. We will conduct a systematic review and meta-analysis to improve our understanding of the relationship between COVID-19 and female fertility and to enable individual and societal preventative measures (16).

The study will also ascertain the current general understanding of COVID-19 and female fertility in light of updated literature. Combining the available data on the association between female fertility and COVID-19 with clinical and public health implications, fertility preservation should be encouraged in these patients. The capacity of SARS-CoV-2 to bind to ACE2 and invade target cells may have an effect on female fertility. ACE2 regulates angiotensin II (Ang II) and Ang-(1-7) levels to fulfill its physiological functions, and it is expressed by the placenta, uterus, vagina, and ovaries (17). An important factor in determining a woman's fertility is her ovarian reserve. ACE2, Ang II, and Ang-(1-7) may control the growth of endometrial tissue, angiogenesis and degeneration of the corpus luteum, and follicular development and ovulation. Because of the decreased ovarian reserve caused by lower-quality eggs, fecundity may be affected (18). It is commonly known that a woman's fertility starts at (roughly) 13 years old and ends at age 49. Forty Naturally, as women age, their fertility declines. A woman's ovarian reserve and oocyte quality start to deteriorate around the age of 35, which accelerates the decline in her fertility (19).

Previous research suggests that organ function can be negatively impacted by factors other than viral attacks. Respiratory failure, direct SARS-CoV-2 virus infection of ovarian tissue, or the immunological reaction triggered by the COVID-19 infection itself have all been linked to ovarian dysfunction (20). The anti-Müllerian hormone (AMH) has the potential to be a valuable new marker of ovarian reserve because its levels are believed to reflect the size of the follicle pool at rest. Since anti-Müllerian hormone levels are not notably altered during the menstrual cycle, AMH measurements are more practical than other endocrine markers of ovarian reserve (9). Since anti-Müllerian hormone seems to be the best endocrine marker for assessing the age-related decline of the ovarian pool in healthy women, it has the potential to predict the reproductive lifespan (21). The current study's table (1) shows that there were highly significant differences in AMH depending on fertility levels; the main effect of fertility was found to be ($p < .001$). A significant main effect of COVID-19 was also observed, as shown by ($p < .001$), indicating significant variations in AMH according to COVID-19 levels. Furthermore, it appears that there were notable variations in AMH for every combination of COVID-19 and fertility factors, as indicated by a highly significant interaction effect ($p < .001$) between the two variables. The current results align with a 2022 study done in Turkey that discovered a statistically significant difference ($p < .001$) between AMH and female COVID-19 infections. The post-COVID-19 patient had a significantly lower AMH value. Women's AMH levels, a measure of ovarian response, were markedly reduced after contracting COVID-19 (22). The COVID-19 pandemic has increased the likelihood of anxiety, stress, and depression in women generally. Several researches discovered that irregular menstrual volume and shorter or longer menstrual cycles were caused by psychological stress during COVID-19 pandemics (23). a few studies assessing the effect of COVID-19 infection on the menstrual cycle and volume in women of reproductive age revealed that the virus altered menstrual patterns and increased irregular periods in these women (24). An additional study discovered that 35% of women had longer cycles, 60% had irregular periods, and 16 percent had altered menstrual patterns. Conversely, another study did not discover any statistically significant differences in the amount of oocytes obtained or the rate of fertilization among the nine women involved in their study (25). Another study found no effects of COVID-19 infection on AMH levels over the long or intermediate term. Their findings showed no association between mild COVID-19 infection and women of reproductive age's ovarian reserve as assessed by AMH levels (24).

Hypothalamic pituitary gonadal axis regulation of the human reproductive system is a major function. The anterior portion of the pituitary produces LH and FSH, whereas the gonads produce estrogen and testosterone (26). The hypothalamic pituitary gonadal axis regulates the menstrual cycle in females (27) claim that the ovarian follicles' preparation for ovulation and the uterus' preparation for implantation are caused by the positive feedback loop between estrogen and LH. The pituitary and hypothalamus, which both have ACE 2 receptors, are potential sites of infection for SARS-CoV-2 if it manages to enter the brain (28). SARS-CoV-2 may enter the brain through the olfactory pathway, which is thought to involve a porous cribriform plate (29). The virus may then enter through the blood-brain barrier near the hypothalamus, where it is permeable. Additionally, hypophysitis brought on by a hypothalamic infection may upset the hypothalamic-pituitary-gonadal axis, resulting in irregular menstruation and infertility (30). In the current study Table (1) indicates that the interaction effect between COVID-19 and fertility depending on FSH was also found to be highly significant with $p < .001$. This shows that there was a significant correlation between FSH levels, COVID-19, and fertility. The discovery of this interaction effect is noteworthy because it implies that there is more going on than just additive relationship between these two variables and FSH levels. This result is in line with a different study that discovered elevated follicle-stimulating hormone (FSH) levels in the presence of hormonal imbalance. Menstrual and ovulation issues brought on by this hormonal imbalance may lead to infertility (31). Severe COVID-19 may affect the health of female reproduction in part due to similar hormonal imbalances that have been linked to other viral infections (32). Furthermore, our research results align with those from Iran, where it was discovered that female COVID-19 patients exhibited moderately elevated FSH levels (33). Further studies on female COVID-19 patients showed that the most ill patients had more irregular menstrual flow and period, with decreased flow and longer cycles being the predominant features.

These results lend credence to the hypothesis that irregular menstrual cycles may result from hormonal imbalances in women (16). The statistical significance of LH (p value $< .001$) suggests that there are significant differences in luteinizing hormone levels between the different COVID-19 and fertility categories. Furthermore, a significant interaction effect between COVID_19 and fertility was observed ($p = .008$). The interaction term shows that there were significant variations in LH for every combination of COVID_19 and fertility table (1). Numerous recent Chinese studies have confirmed that females with basal-level COVID-19 infection had higher levels of leptin. According to another study, there may be a significant increase in the serum pituitary hormone (LH) level as a result of the direct effect on brain tissue. (16). Furthermore, a different study found that women with COVID-19 had higher serum LH levels than healthy controls during the follicular phase (34). In line with our results, FSH and LH levels increased in COVID-19 patients, according to another set of results from Indonesia (35). Another study done in China in 2022 found that in COVID-19-infected females of reproductive age, FSH hormone remained unchanged despite elevated LH levels. These findings are at odds with our own. There might not be a virus in the female reproductive system, based on new data. Furthermore, no virus was discovered in the vaginal fluid or the cervical exfoliated cells, which comprise the lower genital tract (36). This aligns with the minimal data bolstering the hypothesis of vertical disease transmission from progenitors to progeny (37). More research is necessary to confirm the virus's presence in the female reproductive system, specifically in the ovary. The results of this investigation align with the findings of the systematic review which also emphasized the necessity of conducting a more comprehensive investigation into the long-term effects of COVID-19 on female fertility (38). All of these findings highlight how important it is to understand the potential long-term

consequences of severe COVID-19 infection on women's reproductive health and how important it is to provide women recovering from the virus with the appropriate support and interventions.

Finally, direct viral attack of the pituitary gland and/or ovarian follicles, as well as an intensified inflammatory response to viral infection, may cause aberrant gonadotropin/gonadal hormone secretion and hypothalamic pituitary ovarian axis dysfunction (20).

Conclusion: Among the study's conclusions are the following: - The data indicated evidence of impaired ovarian reserve, changed AMH levels, and possible effects of COVID-19 infection on reproductive outcomes. Pituitary gonadotropin and ovarian hormone secretion appear to be altered in both fertile and infertile women with COVID-19 disease.

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Ethical Approval

The specimens of this study took the patient's approval for adult patients and the consent of the irrigation for young people as the law and directives of the human rights organizations with adequate information in an ethical manner.

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