Research Article

Journal of Biochemistry (ISSN 2995-6536)

Analysis of Sex Hormones and AMH Correlated With COVID-19 in Women of Reproductive Age: An Observational Study.

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Received Date : September 23, 2024
Accepted Date : September 24, 2024
Published Date : October 15, 2024

ABSTRACT

COVID-19 is currently one of the most widespread infectious diseases globally. The goal of this research is to present a new understanding regarding the connection between SARS-CoV-2 and ovarian activity among women of childbearing age. In this observational study, clinical information from 218 women who were infected with SARS-CoV-2 was analyzed retrospectively. The relationship between the severity of the disease and sex hormone levels is analyzed and compared. E2 and T levels showed a significant downward trend with the aggravation of COVID-19 disease, and the difference was significant (P=0.000286, P=0.009). FSH and LH were not significantly affected(P=0.184, P=0.129), although they appeared to decline with disease progression. There were no significant P-values for age, prolactin and progesterone, AMH levels, and FSH/LH in the three groups of patients, with P=0.096, P=0.341, P=0.12, P=0.542, P=0.636, respectively. The significantly reduced E2 and T levels in the severely infected group suggest that SARS-CoV-2 may affect glands and related hormones directly or indirectly. The AMH showed no significant change, indicating that comprehensive ovarian reserve function was not affected in the short term, but long-term follow-up observation is required.

Keywords : *COVID-19, Endocrine System, Ovarian function, SARS-CoV-2, Sex hormones.*

INTRODUCTION

Over few years since COVID-19 broke out in 2019, numerous investigations have explored the clinical and laboratory features, epidemiological, diagnostic methods and treatment approaches of COVID-19 sufferers(1).People with COVID-19 may experience typical symptoms such as fever, cough, fatigue, and difficulty breathing during infection(2). Moreover, complications were found occurred outside the respiratory system and even led to death in COVID-19 cases, indicating that the virus effects other organs at the same time(3-7). Research was performed to observed the influence of SARS-CoV-2 may to female reproductive function and fertility(8-15). Goad et presented that uterus,ovaries, and fallopian tube are unlikely to be susceptible to infection by COVID-19(10). In addition, studies have shown that 16% and 28% of COVID-19 female cases experiencing irregular menstruation(16, 17). Li et al. found that within 1-2 months after COVID-19 infection, menstrual cycles of 99% cases return to normal, suggesting that the impact of COVID-19 on menstruation is temporary(18). Therefore, a better understanding of the reaction of female patients to SARS-CoV-2 infection and the ramifications of

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COVID-19 on the female endocrine and reproductive systems, as well as long-term fertility, plays a critical role in promoting women's physical and mental health(19).

The deadly COVID-19 is primarily enters host cells by binding to angiotensin converting enzyme 2 (ACE-2) receptors. The ACE-2 receptors are predominantly found in the epithelial cells of various human organs, including the lungs, liver, heart, kidneys, gastrointestinal tract, and vascular endothelial cells. Based on current reproductive system evidence, ACE-2 has been found to be extensively expressed in the ovaries, uterus, and vagina of female reproductive system, as well as the placenta(14). According to microarray data, the human ovary, which expresses all the genes required for SARS-CoV-2 infection, may be vulnerable to such infection(13, 20).ACE-2 expression can be elevated in human ovulatory follicles following hCG administration, with cumulus cells exhibiting higher ACE-2 expression compared to granulosa cells. Additionally, hCG has been shown to enhance ACE-2 expression in primary human granulosa/lutein cells(hGLC) cultures, implying a possible involvement of ACE-2 in the ovulatory process(8, 21, 22).A pathological study involving a systematic autopsy of Chinese patients diagnosed with COVID-19 revealed the existence of SARS-CoV-2 RNA and virosome in the ovary, as detected by transmission electron microscopy, PCR, and immunohistochemical staining (23). After COVID-19 infection, 91.3% (42/46 cases) of follicular fluid collected by ART detected positive IgG for SARS -CoV-2. The higher the titer of IgG antibodies in follicular fluid, the fewer the number of retrieved oocytes as well as the material oocytes(7). Despite the significant expression of ACE-2 receptors in the ovaries, there is currently no conclusive evidence regarding the impact of COVID-19 infection on ovarian function and any potential long-term effects on female fertility(24). Further research is needed on the specific function and role of ACE-2 receptors in the female reproductive system, and their relationship with reproductive health and COVID-19 infection. The main pathological changes of organs directly infected by SARS-CoV-2 included interstitial edema of multiple organs; inflammatory cell infiltration of lymphocytes, monocytes and neutrophils; cell degeneration, and intimal inflammation(23). Furthermore, indirect damage caused by viral infection is also an important factor that cannot be ignored, which may be a systemic response induced by respiratory failure and multiple organ dysfunction, or an indirect effect of the "immune/ inflammatory storm" on ovarian function(25).Additionally, hormonal imbalances can exacerbate cytokine storms and subsequent organ dysfunction(26). Although various viral pathogenic mechanisms can lead to abnormal organ function, the extent and mechanism of ovarian function damage in female patients infected with COVID-19 remain an important issue that urgently needs to be explored.

Since December 2022, China has adjusted its management and control policy of COVID-19, and novel coronavirus infection has returned to Category B management. COVID-19 is spreading rapidly throughout the country. Most people show mild or asymptomatic symptoms after infection, and a small proportion develop into severe cases. During this period, the number of patients who visited the hospital due to COVID-19 infection increased significantly in both outpatient and inpatient. The number of patients seeking medical attention in gynecological clinics and wards due to abnormal ovarian function and irregular menstruation has also considerably increased.

The goal of our study is to implement a systematic investigation of the clinical features and sexual hormone changes in the sexual maturity of women affected by COVID-19 following the adjustment of epidemic control policies, as well as to determine the effect of viral infection on reproduction function. The study involved a retrospective study of the clinical data, AMH levels, and serum sex hormone indicators of the target population.

MATERIALS AND METHODS

Participants

From December 1, 2022 to February 28, 2023 in the First Affiliated Hospital Zhejiang University School of Medicine outpatient and hospitalized patients of reproductive age who were confirmed with COVID-19 conducted a single-center retrospective study. The inclusion criteria were women aged 20 to 45; Data on basic reproductive endocrine data is collected on the 2nd to 5th day of menstruation or at any time if amenorrhea had been excessive for 3 months. These patients have a regular menstrual cycle and no history of gynecological benign or malignant diseases. After COVID-19 infection, sex hormone tests were performed due to physical examination or menstrual problems. The abnormal menstruation after COVID-19 infection is the external manifestation of the changes in sex hormone levels，which are easily influenced by emotional and other factors. Therefore, this study did not include changes in menstruation in the statistical analysis.

Exclusion criteria were: (1) The drugs currently being treated do not contain any components that affect hormone levels. Internal medicine and surgical underlying diseases that affect ovarian function are excluded, including abnormal body mass index that affects menstruation. (2) pregnancy or lactation, Polycystic ovaries, hyperprolactinemia and other diseases that interfere with menstruation. (3) A history of ovarian dysfunction diagnosed within 6 months prior to onset: manifestations of delayed menstruation, irregular menstruation, or early menopause; (4) Previous hysterectomy or oophorectomy. (5) Examples of oral or transdermal products containing estrogen include birth control pills and menopausal hormone therapies. In the end, 218 patients

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were enrolled. All the patients recruited in this research were confirmed to have COVID-19 based on the diagnosis and treatment guidelines for SARS-CoV-2 infection (10th edition). The infection of SARS-CoV-2 was confirmed through PCR testing, combined with lung CT scans, and the evaluation of illness severity was based on the duration and severity of fever, and arterial partial pressure of oxygen data. Some patients with common infections were positive for virus-specific-antibiotics self-test-kit.

The COVID-19 sufferers were categorized into three groups based on the severity of their illness: common infection, mild infection, and severe infection. The definitions for each group were as follows:(i) In the common infection group, upper respiratory tract infections were the main manifestations, such as dry throat, sore throat, cough, fever, etc. Mild clinical symptoms, relieved after self rest, did not seek medical attention from fever clinics or infectious disease departments. (ii) Mild: continuous high fever>3 days or (and) chest tightness, cough, tachypnea, respiratory rate less than 30 times per minute, oxygen saturation levels above 93% while at rest and breathing room air, and had or did not have typical viral pneumonia CT imaging. (iii) Severe: "Severe infection" was defined as patients who presented with respiratory distress along with oxygen saturation levels equal to or less than 93%, respiratory rate higher than 30 breaths per minute, arterial blood oxygen partial pressure (PaO2) to inhale oxygen fraction (FiO2) equal to or below 300mmHg, respiratory failure under mechanical ventilation, shock, combined other organ failure requiring intensive care.

Data collection

Patient age, menstrual history, comorbidities, clinical symptoms, signs, fertility history, laboratory and radiological findings, progress, prognosis and treatment were obtained from the patient record system of First Affiliated Hospital of Zhejiang University School of Medicine. Sex hormones and AMH of corresponding patients were collected from our hospital test system. In total, 218 patients were enrolled in this study.

This study was approved by the Ethical Committee of the First Affiliated Hospital of Zhejiang University School of Medicine(No. 0439). All methods were performed in accordance with the relevant guidelines and regulations. Subject to compliance with regulations, the Ethics Committee approves exemptions from informed consent.

Female hormone and AMH assay

Serum testosterone (quantitative range 3.82~1862.27ng/dl), estradiol (quantitative range 10~1000 pg/ml), follicle stimulating hormone (quantitative range 0.05~150mIU/ml), LH (quantitative range 0.09~250mIU/ml), prolactin (quantitative range 0.6~200 ng/mL), and progesterone (quantitative range 0.1~40 ng/ml) were all detected using the Abbott ARCHITECT i4000 chemiluminescence immunoassay analyzer (Abbott Company), AMH (quantitative range 0.01-23ng/mL) was detected using Roche Cobas8000 e602 fully automated immune analyzer using the antibody sandwich method principle. The variability within and between measurements of all indicators is less than 10%.

Statistical analysis

Statistical analyses were performed using SPSS Statistics software (Version 27.0, IBM Corp., Armonk, NY, USA). Data normality and variance homogeneity were first assessed. Since the data did not meet the assumptions of normality and homogeneity of variances, non-parametric tests were used. The Kruskal-Wallis test was applied for comparisons of continuous variables across groups. For categorical variables, Fisher's exact test and the chi-square test were utilized. Continuous variables were summarized as mean and standard deviation if normally distributed, or as median and interquartile range (IQR) if not. Categorical variables were reported as frequencies and percentages. Spearman's rank correlation coefficient was used to assess associations between variables and the COVID-19 group. Main risk factors were analyzed using binary logistic and linear regression models. Statistical significance was set at $p<0.05$. GraphPad Prism (Version 8.4.3, San Diego, CA, USA) was employed for creating bar and box plots.

RESULTS

Clinical Features and Baseline of the COVID-19 Women

The baseline of the 218 COVID-19 women is shown in Table 1. The average age of the women included in this study was 32.6 years, with a standard deviation of 7.19 years. Five of 218 (2.29%) were diagnosed as a severe group. Twenty of 218 (9.17%) patients described mild infection, while 193 of 218 had common infection. The mean ± SD, minimum, and maximum values of all 7 sex hormones (including FSH/LH ratio) are shown in Table 1.

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Table 1. Baseline of female COVID-19 patients (mean ± standard deviation, maximum, minimum)

Index	mean±SD	minimum	maximum
Age	32.60±7.09	20	45
T	27.55±10.49	1.56	56.94
E2	53.43±51.74	0.00	349.79
FSH	7.80±9.72	0.73	88.48
LH	5.57±6.24	0.10	45.27
PRL	14.12±6.84	3.97	51.76
P	0.32±0.5	0.10	3.58
AMH	2.93±2.53	0.01	13.50
FSH/LH	1.87±1.42	0.26	16.6

Clinical features of the patients' symptoms

Symptoms and baseline information of common group, mild group, severe group were stated in Table 2. At admission, majority symptoms of common group were cough (125,64.8%), sore throat (113,58.5%), sputum production (83,43%), fever (44,22.8%) etc. The prominent symptoms of the moderate infection group were cough (13,65%), fever (10,50%), chest pain (3,15%) and sputum production (3,15%) etc. Among the 5 critically ill patients tested, all had fever symptoms, of which 3 had consciousness disorders (60%). The incidence of nausea and vomiting was 2 cases (40%), persistent hypotension was 1 case (20%), and chest pain was 1 case (20%). Possible severe disease states, consciousness disorders, and persistent hypotension mask the clinical symptoms of many mild symptoms in patients. The clinical symptoms of the three groups of patients are biased, and statistical analysis of clinical symptoms has not been conducted.

Table 2. Clinical characteristics and single factor analysis of indicators in different groups.

Index	Common Group (n=193)	Mild Group(n=20)	Severe Group (n=5)	P value
Symptoms				
No symptoms	15(7.7)	0	0	/
Disorder of consciousness	0	0	3(60)	/
Fever	44 (22.8)	10 (50)	5 (100)	/
Persistent hypotension	0	0	1 (20)	/
Chest pain	21 (10.9)	3 (15)	1 (20)	/
nausea and vomiting	6 (3.1)	1 (5)	2 (40)	/
Cough	125 (64.8)	13 (65)	0	/
Sore throat	113 (58.5)	2 (10)	0	/
Sputum production	83 (43)	3 (15)	0	/
Baseline				
Age	32.96±7.19	30.35±5.41	27.60±6.54	0.096
T	27.79±10.20	29.61±9.75	9.93±10.62	0.009
E2	56.31±53.18	36.33±29.51	<10	0.000286
FSH	8.03±10.21	6.48±4.21	4.35±2.61	0.184
LH	5.80±6.53	4.02±2.75	2.91±2.02	0.129
PRL	13.90±6.77	16.23±7.80	14.19±5.08	0.341
P	0.33±0.53	0.21±0.97	0.78±0.54	0.12
AMH	2.86±2.50	3.56±3.15	2.93±0.31	0.542
FSH/LH	1.86±1.47	1.93±0.85	1.93±0.99	0.636

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Sex-related hormones and AMH difference comparison by statistical analysis

Based on the statistical analysis, there was no statistical difference in the age of patients in the general infection group, moderate group, and severe group (age: P=0.096). T(P=0.009) and E2(P=0.000286) were statistically significant among the three groups. With the aggravation of the disease, T showed a trend of increasing first and then decreasing. E2 decreased significantly with the aggravation of the disease. FSH (P=0.184) and LH (P=0.129) showed a downward trend in the three groups, although there was no statistical difference. Given that this study collected basic female endocrine indicators on the 2-5 days of the menstrual cycle, P(P=0.12) did not have clinical significance. PRL(P=0.341) , AMH (P= 0.542), and FSH/LH(P=0.636) levels found no statistical difference among the three groups.

Due to the quantitative range of our estradiol assay being 10~1000 pg/ml, the estradiol levels of every severe COVID-19 patient fell below the lower limit of detection. Consequently, our statistical data accurately recorded as “less than 10” for each case.

In figure 1, the box chart of statistical analysis can more intuitively show the change trend of E2 and T in different COVID-19 severity conditions. FSH and LH showed a weak downward trend, without significant statistical differences. There was no significant change trend in other indicators such as age, P, PRL, and AMH between three groups.

Figure 1

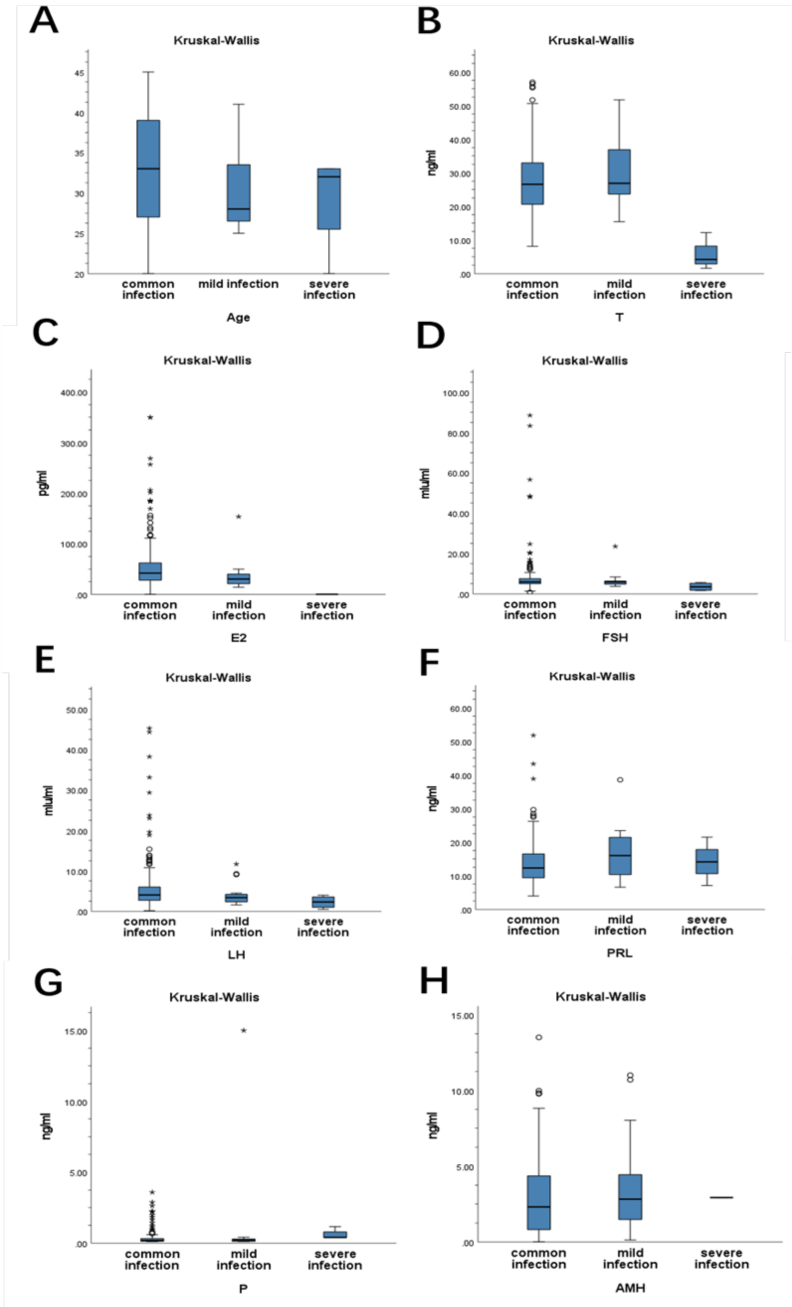

Figure 1. Comparison of female age, sex hormones and AMH between the common infection group, mild group and severe group. Differences of age(A), serum T (B), E2 (C), FSH(D), LH (E), PRL (F) ,P(G) and AMH levels (H) were compared between common infection groups,mild infection

group and severe infection group. The presented data was denoted by mean±SD.

Figure 2 A indicates that there was a relatively even distribution of ages among the patients between the ages of 20 and 45. T was mainly distributed within the frequency range of 27.55 ± 10.49(figure 2 B). The frequency range of E2(figure 2C), FSH(figure 2D), LH(figure 2E) and PRL(figure 2F) were 53.43 ±51.74,7.80 ±9.72,5.57 ±6.24,14.12 ±6.84. The frequency distribution (0.32±0.5) of progesterone(figure 2G) in early follicular stage is consistent with the characteristics of basic ovarian function. AMH(figure 2H) mainly distributed in the range of 2.93±2.53.

Figure 2

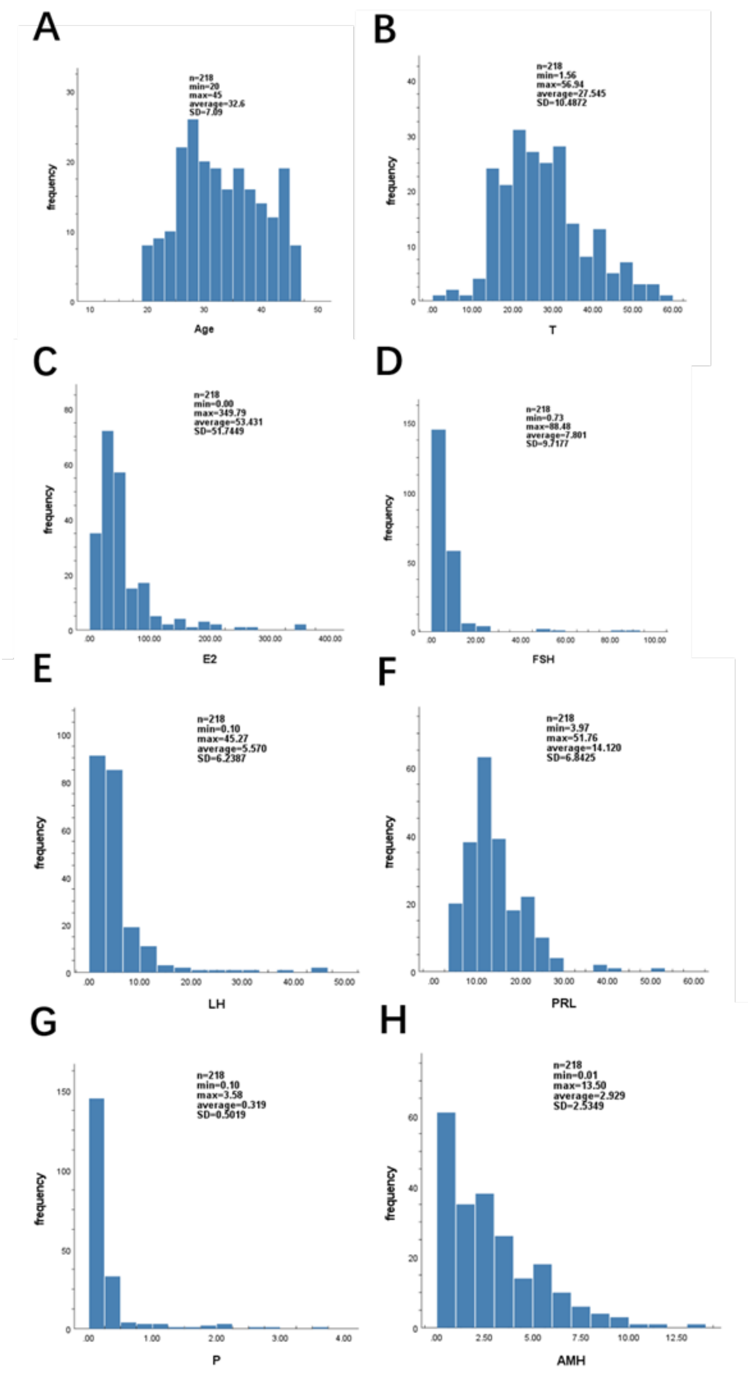

Figure 2. Frequency distribution diagram of age(A), serum T (B), E2 (C), FSH(D), LH (E), PRL (F), P(G)and AMH levels (H) were compared between common infection groups, mild infection group and severe infection group.

DISCUSSION

COVID-19, also known as novel coronavirus pneumonia, is a SARS-CoV-2 infection that can affect multiple systems in the body. It not only causes respiratory tract lesions, but also may cause damage to other systems. In the past reports, injuries were mainly reported in the respiratory system, circulatory system, endocrine system, gastrointestinal system, urinary system and nervous system symptoms (4), but its currently unclear how an infection with SARS-CoV-2 impacts ovarian function and the pituitary gonadal axis. Most existing studies have reflected ovarian damage associated with COVID-19 disease through ovarian reserve biomarkers and sex hormones, such as anti-Mullerin (AMH), follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), prolactin (PRL), progesterone (P), and testosterone (T)(8, 9). The analysis and evaluation of the above sex hormone test results is the most commonly used method for evaluating ovarian function in clinical practice.

After the adjustment of COVID-19 policy and the emergence of waves of infection peaks, the typical long COVID-19 symptoms such as dyspnea, fatigue, and cognition impairment have gradually attracted the public's and researchers' attention. According to several meta-analyses, it has been found that approximately 30-50% of individuals who have recovered from this virus infection have experienced long-lasting COVID-19 symptoms(2, 27), some of them lasting up to one year (28). More importantly, female patients and sufferers with severe onset conditions are more likely to develop long-term sequelae after one year. While individual studies have indicated an association between female sex and long COVID-19 symptoms, the combined evidence from multiple studies has shown that being female is one of the higher risk factors for long COVID-19(29). The development of post-acute COVID-19 syndrome is influenced by biological factors, such as hormone and immune responses, and socio-cultural factors, such as health-related behaviors, psychological pressure, and inactivity. Gender differences related to these factors significantly contribute to the development of post-acute COVID-19 syndrome(30). However, the mechanism is not well understood and the existence of abnormal ovarian function needs to be investigated.

At the initial stage of the COVID-19 outbreak in Wuhan, a study examined the sex hormone levels of 78 COVID-19 infected people of childbearing age showed that COVID-19 was likely to be an independent risk factor respecting ovarian function, which accounted for 3.2% of the decline in AMH, 14.3% of the increase in T, and 20.7% of the increase in PRL. Although anxiety during the pandemic may affect prolactin levels and different studies have different grouping and statistical methods, the research results also suggest that ovarian dysfunction can be observed in women suffering from COVID-19 (8). In the almost same period, a larger sample size (237) study showed that there was no significant difference in average sex hormone levels and AMH concentrations between COVID-19 and normal women of childbearing age (9).After that, from November to December 2020, a study of 60 COVID-19 patients from Ahar regional hospital in Iran showed that,44 individuals (73.33%) exhibited at least one abnormality with a mean item score exceeding 3. Specifically, abnormal test results were recorded in 26 (43.33%) for estradiol, 21 (35%) for follicle-stimulating hormone (FSH), 18 (30%) for luteinizing hormone (LH), 13 (21.67%) for prolactin, 31 (51.67%) for progesterone, 12 (20%) for testosterone, 30 (50%) for cortisol, and 25 (41.67%) for thyroid-stimulating hormone (TSH). The findings indicate that COVID-19 has a discernible impact on hormonal secretion, either through direct or indirect mechanisms(6).

Nearly three years after the outbreak and spread of the SARS-CoV-2, its pathogenicity and transmissibility have evolved. This raises the question of whether there are potential impacts on ovarian function. Based on our findings from 2022 to 2023, the detection values of E2 and T in the severe infection group were significantly lower than those in the common and moderate infection groups. The ovaries serve as the primary organs for estrogen secretion, with estradiol being the predominant form. Within the theca and granulosa cells of ovarian follicles, both estradiol and testosterone are synthesized from cholesterol through a series of conversions. This biosynthetic process is closely linked to the stimulatory influence of LH and its receptor (LH-R) interaction. We also found a similar trend in the detection of FSH and LH as that of E2 and T. FSH and LH exhibited a decreasing trend with disease progression, although the difference was not statistically significant. Commonly known, a sudden physical well-being shift correlates with acute dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis. Another indirect reason for the decrease in estradiol may be that the COVID-19 infection or affected the activity of the HPG. Imaging tests, such as CT and MRI scans, have revealed identification of COVID-19 infection in the central nervous system (31). The expression of ACE-2 in brain tissue (including endothelial cells, neuronal cells, and neurogliocytes) may produce a marked effect in the nerve tissue invasion of SARS-Co-2, with infected women experiencing neurological symptoms such as headache, confusion, taste disturbance, loss of smell, nausea, and vomiting (32). Researches have defined the expression of ACE2 mRNA in cells of the hypothalamus tissue and pituitary gland(33), similar expression of ACE-2 protein was found in the pituitary tissue of patients with COVID-19's death(34). COVID-19 may have a certain connection with pituitary apoplexy(5). Data from studies of stroke, intracranial hemorrhage, and cerebral microhemorrhage events increasingly suggest that COVID-19 targets the nervous

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system including Hypothalamus and pituitary gland(3, 35, 36). Based on the available evidence, the reduction of FSH and LH may be the result of hypothalamus dysfunction and pituitary injuries. This decrement can further exacerbate the decrease in estrogen and testosterone levels that result from female gonadal damage - for example, impaired granulosa and theca cells. Unfortunately, the expression of FSH and LH did not show statistical significance. It cannot be ruled out that the novel coronavirus may affect the ovaries function through cytokine storms, leading to alterations in the expression levels of E2 and T(37-39).

Consistent with the majority of research findings(9, 12, 40), our study indicates that there were no statistically significant differences in AMH values among the three groups. Other studies have reported contrasting results, identifying below-normal serum AMH concentrations in patients with COVID-19(8). Significantly, this variation could be attributed to differences in grouping, limited sample size, and the high prevalence of severe COVID-19 cases within their study cohort (17 out of 78). Furthermore, reduced serum AMH levels were associated with psychological stress and the extent of anxiety(11).

Our research has comprehensively investigated the most common female sex hormones since the COVID-19 regulation policy was released. Based on our findings, the detection values of E2 and T in the severe infection group were significantly lower than those in the common and moderate infection groups. FSH and LH also decreased sequentially in the three groups, but the difference was insignificant. AMH, considered an early and sensitive ovarian reserve biomarker(36), has not changed significantly with the severity of the condition. From the sources and metabolic pathways of estrogen and testosterone, to the position of the ovaries within the entire HPO axis, the decrease in E2 and T may represent a cumulative effect of toxicity or functional impairment on the HPO axis and ovaries. (Figure 3). Whether this effect is short-term or long-term requires further follow-up observation.

Figure 3

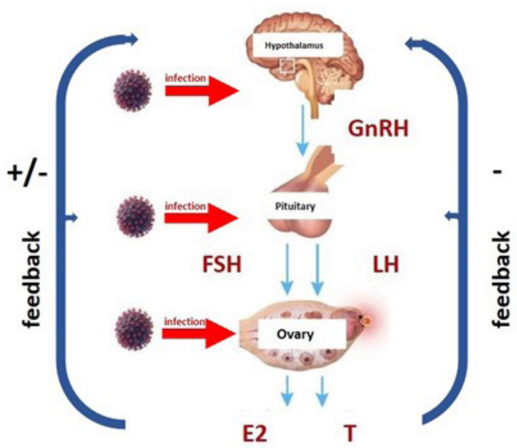

Figure 3. Mechanism of novel coronavirus affecting female sex hormone levels.

Limitations of the study

Our observed data suggest short-term suppression of ovarian function in females with mild or severe SARS-CoV-2 infection. It's worth noting that we only collected one blood sample from each patient to determine hormone levels, and this was done within a brief period after they were infected with SARS-CoV-2. The sample size of critically ill patients was only 5 cases, limited serum sex hormone sample size and short collection time may potentially impact our ability to perform robust statistical analysis. Patients over 40 years old in our study may have occult ovarian dysfunction, whose sex hormone levels can fluctuate, skewering the data. Additional research is required to explore the reproductive implications of COVID-19, specifically in a more extensive group of recovered patients with long-term follow-up. These studies should prioritize evaluating reproductive function and endocrine changes among women of reproductive age who have recuperated from SARS-CoV-2 infection. Some studies suggest that sex hormones such as estrogen may be protective factors of COVID-19. This study did not collect data on sex hormones before infection, so it is impossible to speculate on the relationship between estrogen levels and the progression of COVID-19 symptoms.

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CONCLUSION

This study has revealed a potential clinical phenomenon suggesting that women with COVID-19 may experience ovarian functional damage leading to reproductive endocrine disorder and abnormal sex hormone levels, particularly low levels of E2 and T. The results deduced a latent decreased ovarian endocrine function in the short run due to the attack of COVID-19. The disturbance in reproductive hormones observed in COVID-19 patients could be due to two main factors: direct attack of the virus on the ovaries and the indirect malfunctioning of the HPO axis. These factors can collectively contribute to ovarian functional injury. Nevertheless, additional evidence, which involves both animal studies and clinical hormone intervention research, is needed to confirm the influence of SARS-CoV-2 on ovary function.

Declaration

Ethical Approval and consent to participate

The Ethical Committee of the First Affiliated Hospital of Zhejiang University School of Medicine approved the exemption from informed consent, subject to compliance with ethical regulations.

Consent to Publication

The Ethical Committee of the First Affiliated Hospital of Zhejiang University School of Medicine approved the exemption from informed consent, subject to compliance with ethical regulations.

Data Availability statement

The dataset supporting the conclusions of this article is included with the article.

Conflict of interest

The author declares that they have no competing interests.

Funding

This research was supported by the Joint Funds of the Zhejiang Provincial Natural Science Foundation of China under Grant No. LBY21H180002, Zhejiang Fundamental Public Welfare Research Program (LGF22H200001) and National Natural Science Foundation of China(N0.82101771). The funding bodies had no role in the design of the study, in the collection, analysis, interpretation of data and in drafting the manuscript.

Author contribution

Supervision and Conceptualization: Hui Lu; Methodology and Writing - original draft: Lijun Yin and Ahmad Alhaskawi; Investigation and Data curation: Zhenfeng Liu, Olga Alenikov, Weihua He and Guoliang Xie; Writing - review & editing, Validation and Resources: Sahar Ahmed Abdalbary, Yanzhao Dong, Zewei Wang and Chengjun Yao. The authors have read and approved the final manuscript.

Acknowledgements

Not applicable

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