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Open Access Research Article

The Impact of COVID-19 Infection on Gonadal Hormonal Functions in Iraqi Women

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Abstract:

Background: The COVID-19 pandemic has had effects beyond the respiratory system, impacting health and quality of life. Stress-related to the pandemic has led to temporary menstrual pattern changes in around one-third of women. These changes, likely driven by stress and anxiety, can result in problematic heavy bleeding, causing anemia and negatively affecting women's well-being. This also places a substantial socioeconomic burden on individuals, families, healthcare, and society.

Objectives: This study examined the impact of COVID-19 infection on the hormone levels (estradiol, prolactin, follicle-stimulating hormone, and luteinizing hormone) and heavy menstrual bleeding in Iraqi premenopausal women infected for at least four months.

Methods: This case-control study was conducted from November 2021 to April 2022, involving 100 married women aged 18 to 40. Participants were divided into two groups: 50 women with heavy bleeding post-COVID-19 infection (infection duration of at least four months) and 50 non-infected women.

Results: Comparing the Mean ± SD of the two groups, showed that the LH levels were statistically highly significant in women who suffered heavy bleeding post-COVID-19 infection compared to non-COVID-19 women, with a p-value of 0.000. There was no statistically significant difference in FSH levels between the two groups. The PRL levels were significantly higher for women who suffered substantial bleeding following COVID-19 infection compared to non-COVID-19 women, with a p-value of 0.003. Moreover, The E2 was significantly higher in women who suffered excessive bleeding following COVID-19 infection than non-infected women.

Conclusion: This study suggests that COVID-19 may temporarily disrupt menstrual patterns, possibly due to stress and anxiety affecting the hypothalamus-pituitary-ovary axis. This disruption can manifest as elevated levels of gonad hormones (LH, PRL, and E2) and, in some cases, lead to heavy bleeding after a coronavirus infection.

Keywords: Coronavirus**;** Bleeding; Hormones; Gonads; Premenopausal.

Introduction

Since the announcement of the appearance of the Coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in December 2019, the virus spread quickly and was reported in other countries by the end of January 2020. This virus causes acute respiratory illness. On March 2020, the WHO declared a global pandemic of COVID-19 outbreak (1). Living with COVID-19 is a challenging task, as well as the accumulations produced in the healthcare system as a result of the lockdown due to the coronavirus pandemic, have exacerbated the need for efficient paths to handle women who arrive with excessive monthly bleeding. One of the most prevalent gynecological issues is heavy menstrual bleeding. It can have a significant impact on adolescent girls and women's mental health, welfare, and quality of life, including loss of time in education or employment. It can occur at any time from the start of menarche, through the reproductive phase, and up to the menopause (2). Menstrual flow that lasts longer and is heavier than usual is referred to as heavy bleeding. The bleeding occurs regularly (during periods). It frequently lasts more than 7 days, and women lose a lot of blood, more than 80 ml. Menorrhagia is frequently associated with dysmenorrhea because big clots can produce unpleasant cramping (3). The menstrual cycle is controlled by the interaction of various hormones with the immune system, blood vessels, and coagulation systems, and these interactions can impact menstrual bleeding and the intensity of premenstrual symptoms (4).

The anterior pituitary gland secretes Follicle - Stimulating Hormone (FSH). Its principal function is to induce ovarian follicle development. It causes the ovarian follicle cells to produce estrogen (5). Also, the anterior pituitary gland secretes luteinizing hormone (LH). Its key roles included triggering ovulation, transforming a ruptured dominant ovarian follicle into the corpus luteum, and encouraging the corpus luteum

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to release progesterone (6). Prolactin (PRL) is produced by acidophilic cells called prolactin cells or lactotrophs near the front of the pituitary gland. By increasing the growth of the milk glands, the milk hormone is necessary for initiating and maintaining the process of female milk production (mammary glands) (7). Estrogen (E2) is secreted by the ovary (follicle). Its principal purpose is to enhance endometrial blood vessel formation and increase the amount of endometrium lost. It encourages the maturation of ovarian follicles. It also encourages the production of clear, elastic, and slippery "fertile" cervical mucus to help sperms. High levels promote an increase in LH, which causes ovulation. When levels are extremely low, the anterior pituitary gland produces more FSH and LH, (8). Menstrual disorders are extremely frequent in women. Dymenorrhea, strong menstrual bleeding (menorrhagia), amenorrhea, hypomenorrhea, or irregular and intermenstrual blood loss are some of the symptoms. The causes differ, but there is little doubt that hormonal alterations are the most crucial (9). The primary aim of this study was to investigate the effect of coronavirus infection on women's hormonal levels (estradiol (E2), prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)), as well as the states of heavy bleeding that occur in Iraqi premenopausal women who have been infected with coronavirus for at least 2 to 6 months.

Subjects, Material and Methods:

It is a case-control study that was conducted in Baghdad Medical City (Outpatient Clinic), from November 2021 to April 2022. The research involved 100 married women of childbearing age ranging in age from 18 to 40 years. The study sample was divided into two groups: 50 women of childbearing age who had been infected with coronavirus for at least four months following COVID-19 infection with heavy bleeding, and 50 women who had not been infected with the coronavirus. All of the women involved in this study were informed about the study, and full ethical approval was obtained. All pregnant and breastfeeding women with heavy bleeding periods, women having a history of ovarian malfunction in the 6 months preceding disease onsets, such as a manifestation of delayed menstruation, monthly abnormalities, or premature menopause, and women with ovariectomy were excluded from this study.

Venous blood samples were taken from the women in the morning time on the first three days of the menstrual cycle. For each of the following hormones: estradiol (E2), prolactin (PRL), follicle-stimulating hormone (FSH), and the serum luteinizing hormone (LH) was analyzed using the Roche Elecsys 2010 Rack Immunology Analyze. This device is automated, random access, multichannel immunological test analyzer (Sandwich assay) designed for the quantitative or qualitative assessment of a wide range of analytes in vitro. Because of Electro-chemiluminescence (ECL) technology for heterogeneous immunoassays, the analyzer is uniquely built for high sensitivity, reliability, and reproducibility of results. All the kits used in this device system were by Roche and manufactured in Germany.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 23 was used to analyze the acquired data, and the t-test was performed. The data were presented as mean (M), standard deviation (SD), and correlation coefficient (r). A *P*-value of less than 0.05 was considered statistically significant. The Receiver Operating Characteristic Curve (ROC) curve was used to test the sensitivity and specificity of the Roche Elecsys 2010 device used in this study.

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Results:

The findings of this study are presented in Table (1), which compares the Mean±SD of the two groups investigated. The Luteinizing hormone levels were statistically highly significant in women who experienced heavy bleeding after infection (the mean ± SD was 10.64 ± 7.17 as compared to non-COVID-19 women who had a mean ± SD of 7.59 ± 2.73; P-value was 0.000). The FSH hormone level was statistically insignificant between infected women who experienced heavy bleeding as compared as compared with non-infected women (the mean ± SD was 5.60 ± 2.90 and 5.72 ±2.33, respectively) with p-value of 0.164. The PRL hormone level was statistically highly significant in women who experienced heavy bleeding after infection (the mean ± SD was 19.80 ± 9.08 as compared to non-COVID-19 women who had a mean ± SD of 12.78 ± 5.25) with P-value of 0.003). The E2 hormone level was statistically significant in women who experienced heavy bleeding after infection (the mean ± SD was 135.41 ± 23.47 as compared to non-COVID-19 women who had a mean ± SD of 82.03 ± 49.38) with P-value of 0.024).

Figure (1) depicts the differences in arithmetic averages between women who suffered significant bleeding following COVID-19 infection and women who did not. The ROC Curve results showed that the area under the curve values for LH hormone in the women who had excessive bleeding after contracting COVID-19 was 0.612, and there was statistical significance with a *P*-value of 0.053 with the cut of 7.55, indicating that the Test Quality is Satisfactory. While the E2's test quality was fair, as shown in Table (2).

Figures (2) and (3) depict the relationship between sensitivity and specificity in the ROC curve for LH

and E2 in women with heavy bleeding status in post-COVID-19 infection. The findings revealed a favorable connection between LH and FSH. It is statistically significant (*P*-Value = 0.020), and there is a negative association between LH and PRL that is statistically significant (P-Value = 0.050), as shown in Table (3). While Figure (4)-A represents the correlation between FSH and LH, Figure (4)-B depicts the correlation between E2 and LH.

Table (1): Mean ± SD values of selected study variables in the two groups

Variable	Mean ± SD COVID-19 Patients (N= 50)	Mean ± SD Non COVID-19 Patients (N= 50)	*p*-value
Age (Years)	28.86 ± 5.03	30.08 ± 7.23	0.931
BMI (kg/m2)	26.26 ± 5.73	27.91 ± 6.88	0.265
LH (IU/L)	10.64 ± 7.17	7.59 ± 2.73	0.000**
FSH (IU/L)	5.60 ± 2.90	5.72 ± 2.33	0.668
PRL (µg/L)	19.80 ± 9.08	12.78 ± 5.25	0.001**
E2 (ng/dL)	135.41 ± 23.47	82.03 ± 19.38	0.000**

* Statistically significant
** Statistically highly significant

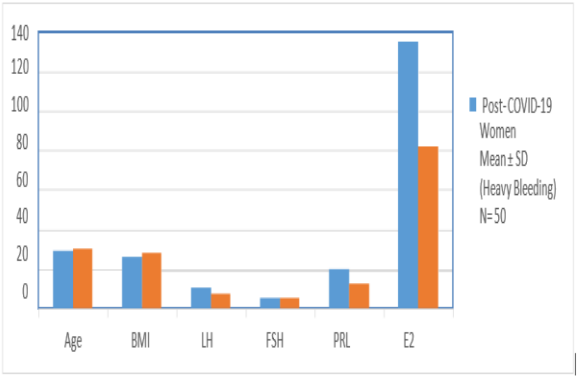

Figure (1): Values of the Mean ± SD of age, BMI, LH, FSH, PRL and E2

Table (2): The ROC Curve of LH and E2 for the Post-COVID-19 women (Heavy Bleeding)

Variable	Area Under Curve Values	*p* – Value	Cut off	95% Confidence Interval		Test Quality
				Lower	Upper	
LH (IU/L)	0.612	0.053	7.55	0.500	0.725	Satisfactory
E2 (ng/dL)	0.552	0.374	57.40	0.430	0.673	Fair

* Statistically significant

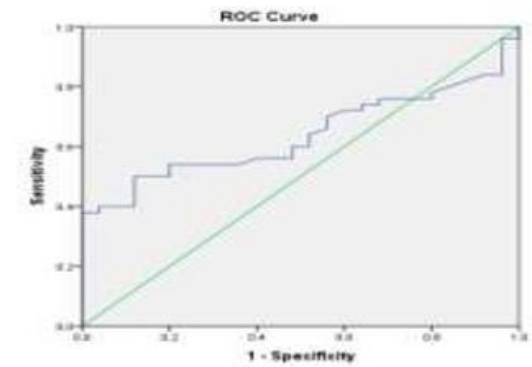

Figure (2): ROC curve sensitivity & specificity ofLH in post-COVID 19 women

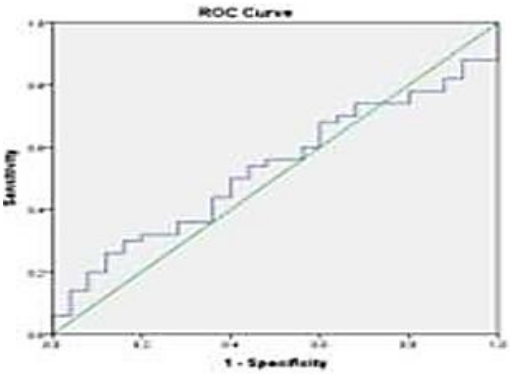

Figure (3): ROC curve with sensitivity & specificityof E2 in post-COVID 19 women

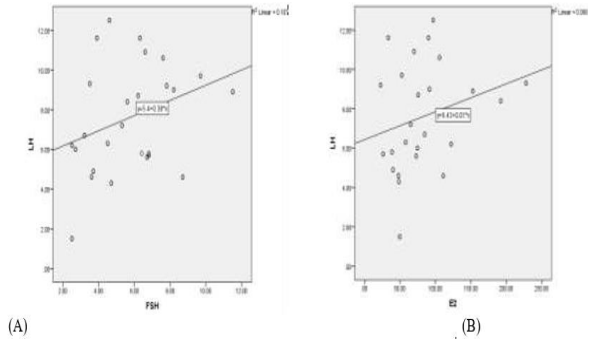

Figure (4): The correlation for post-COVID-19 women (amenorrhea): (A) Between LH and FSH, (B)Between LH and E2.

Discussion:

COVID-19 is a major public health concern with serious morbidity and mortality consequences, and its effects extend far beyond the respiratory system. These have an impact on health and quality of life, as well (10). The current study found that age or BMI did not influence heavy bleeding in the studied groups. However, there was a substantial rise in the level of LH hormone in women who had experienced excessive bleeding following coronavirus infection when compared to non-COVID women. Also, the levels of PRL and E2 were higher in women who had been infected with COVID-19 as compared with those who were not infected with COVID, this in an agreement with some published research stated that; stressful conditions caused by

COVID-19 may trigger PRL release and E2 due to stress (7).

During the COVID-19 pandemic, one-third of people felt the tension, worry, and depression (11). Menstrual periods can be affected by psychological stress. Even if there is no organic cause, stress can activate the hypothalamic-pituitary-ovarian axis, changing gonadotropin-releasing hormone secretion (GnRH). Menstrual alterations were more common in COVID-19 patients who also had systemic COVID problems (11). Following these abnormal findings,female fertility issues arose: changed menstrual duration, frequency, regularity, and volume, increased dysmenorrhea, and worsening premenstrual syndrome (12). Corona virus infection can produce abnormalities in the menstrual cycle, such as heavy bleeding. In general, the menstrual cycle is a complicated interaction of the hypothalamus, pituitary, ovaries, uterus, prostaglandins, and neuroendocrine variables. As a result, menstrual irregularities may occur.

The findings of this study revealed that COVID-19 infection had no effect on the FSH hormone in women who had amenorrhea after COVID-19 infection. It is yet to be determined whether COVID-19 infection affects endometrial physiology and monthly hemorrhage. Data collected during the COVID-19 pandemic demonstrated that COVID-19 infection had a significant impact on endothelial cell function and the immune system (14-15). Furthermore, the COVID-19 receptor, angiotensin-converting enzyme 2, has been discovered in the human ovary and uterus. As a result, COVID-19 may directly impact menstruation parameters in infected people, in addition to the usual effects on hypothalamus function with significant illness and/or stress (16). Aerobic and physical training have been shown to enhance insulin functions, which can help women regulate their menstrual cycles. Insulin receptors are found on the ovary and may modulate steroid hormone synthesis, including progesterone, thereby influencing menstrual cycle management (17). Obese women have reduced levels of sex hormone-binding globulin than normal-weight women, resulting in higher levels of circulating or free testosterone. These hormonal alterations can cause ovulatory dysfunction, which is infrequent ovulation that prolongs the menstrual cycle proliferative phase. This increased exposure to unopposed oestrogen may promote endometrial overgrowth and increase the chance of monthly irregularities (18). Furthermore, vitamins might cause excessive bleeding. Vitamin B6 reduces pro-inflammatory cytokines, improves respiratory function, and controls hypercoagulability by stimulating innate and adaptive immunity, all of which serve to minimize the severity of COVID-19 infection (19). Vitamin C is essential for the reproductive system due to its participation in the manufacture of collagen, steroids, and peptide hormones, as well as its role in avoiding oxidative damage (20). Vitamin C can indirectly influence the menstrual cycle due to its involvement in assisting with the absorption of other fat-soluble vitamins that control the cycle (21). Furthermore, it stimulates the synthesis of oestrogen and progesterone and enhances hormonal levels, which increases the thickness of the endometrium. As a result, its absence may cause heavy menstrual bleeding (22).

Conclusions:

The COVID-19 pandemic may have had an effect on menstruation patterns in women, although this effect was transient and could be attributed to stress and anxiety impacting the sensitivity & specificity of E2 in post COVID 19 women and the women's ovaries. This can disrupt female reproductive system functioning, resulting in high levels of gonad hormones like LH, PRL, and E2 and, in some cases, excessive bleeding after coronavirus infection.

Authors' Declaration

Consent was obtained or waived by all participants in this study. Iraqi Ministry of Health and Environment issued approval 02/2021. Also, we confirm that all the Figures and Tables in the manuscript are ours.

Conflicts of Interest: None.

Authors' contributions

Study conception & design: (Shatha M Kadhim &Nawar S Mohammed). Literature search: (author(s) name). Data acquisition: (Shatha M Kadhim). Data analysis & interpretation: (Shatha M Kadhim &Nawar S Mohammed). Manuscript preparation: (author(s) name). Manuscript editing & review: (Shatha M Kadhim &Nawar S Mohammed).

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تأثير عدوى فيروس كورونا (COVID-19) على وظائف هرمونات الغدد التناسلية لدى النساء العراقيات

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الخلاصة:
خلفية البحث: مع دخول جائحة COVID-19 عامها الثالث ، من الواضح أن آثاره تمتد إلى ما بعد الجهاز التنفسي وهي مهمة سريريًا. قد يكون لهذه العواقب أيضًا تأثير على الصحة ونوعية الحياة. ربما يكون ثلث النساء قد عانين من تغيرات عابرة في أنماط الدورة الشهرية نتيجة للضغوط المرتبطة بوباء COVID-19. وقد يكون هذا التغيير ناتجًا عن التوتر والقلق. يمكن أن يكون عدم انتظام الدورة الشهرية أو غيابها مؤشرًا على انخفاض الخصوبة ، والذي يمكن أن يرتبط بحد ذاته بعدد من الحالات المزمنة ،و قد يتسبب النزيف الحاد في الإصابة بفقر الدم وله تأثير سلبي كبير على نوعية الحياة ويشكل عبئًا اجتماعيًا واقتصاديًا ضخمًا على النساء وأسرهن والخدمات الصحية والمجتمع.
الاهداف : ان الهدف من هذه الدراسة هو النظر في تأثير عدوى فيروس كورونا على مستوى الهرمونات للمرأة (استراديول (E2) ، البرولاكتين (PRL) ، الهرمون المنبه للجريب (FSH) ، والهرمون اللوتيني (LH)) ، وكذلك الحالات النزيف الغزير الذي يحدث عند النساء العراقيات قبل انقطاع الطمث المصابات بفيروس كورونا لمدة شهرين إلى ستة أشهر على الأقل.
المرضى وطرق العمل/ المواد وطرق العمل: اجريت هذه الدراسة البحثية في مدينة بغداد الطبية (العيادة الاستشارية) ، من تشرين الثاني (نوفمبر) 2021 إلى نيسان (أبريل) 2022. وشملت الدراسة 100 امرأة متزوجة في سن الإنجاب تتراوح أعمارهن بين 18 و 40 سنة. تم تقسيم عينة الدراسة إلى مجموعتين ، المجموعة الاولى 50 امرأة في سن الإنجاب مصابات بالنزيف الحاد بعد الإصابة بـ COVID-19 م لمدة أربعة أشهر على الأقل ، و 50 امرأة غير مصابات بالفيروس التاجي.
النتائج: أظهرت نتائج هذه الدراسة ، بمقارنة متوسط ± SD للمجموعتين ، أن مستويات LH كانت ذات دلالة إحصائية عالية لدى النساء اللواتي عانين من نزيف حاد بعد عدوى COVID-19 مقارنة بالنساء غير المصابات بـ COVID-19 ، مع قيمة p 0.000. لم تكن هناك فروق ذات دلالة إحصائية في مستويات FSH بين المجموعتين. كانت مستويات PRL أعلى من الناحية الإحصائية بالنسبة للنساء اللائي عانين من نزيف كبير بعد الإصابة بـ COVID-19 مقارنة بالنساء غير المصابات بـ COVID-19 ، بقيمة p 0.003. كان E2 ذو دلالة إحصائية عالية مقارنة بالنساء اللائي عانين من نزيف مفرط بعد عدوى COVID-19 مقارنة بالنساء غير المصابات.
الاستنتاجات: تشير نتائج هذه الدراسة إلى أن النساء بعد الاصابة بـ COVID-19 قد يكون لهن تأثير على أنماط الدورة الشهرية ، ولكن هذا التأثير كان مؤقتًا ويمكن أن يكون بسبب التوتر والقلق الذي يؤثر على HPA ومبايض النساء. قد يؤدي ذلك إلى اضطراب وظائف الجهاز التناسلي الأنثوي ، حيث تظهر مستويات مرتفعة من هرمونات الغدد التناسلية مثل LH و PRL و E2 وأحيانًا تؤدي إلى حالة نزيف حاد بعد الإصابة بفيروس كورونا.
مفتاح الكلمات: كوفيد -19 ، الغدد التناسلية ، الهرمون اللوتيني ، الهرمون المنبه للجريب ، البرولاكتين ، استراديول ، النساء قبل انقطاع الطمث ، نزيف حاد