The Impact of Covid-19 on Child-Bearing Age Iraqi Women Gonads and Amenorhea Statu

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Abstract
The findings of this study indicate that women the COVID-19 ponsyndemic may have had an impact on menstrual patterns of women, but this effect was temporary and can be due to stress and anxiety affecting the HPA and the women overies.This may lead to disturbance of functions of the female reproductive system, presenting with elevated levels of gonad hormones like LH, PRL, and E2 and resulting in amenorrhea status after coronavirus infection.
Keywords: Health; Iraqi women; COVID-19; Amenorhea status

1. Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Since February 2021 the virus result in over 576 million infections and 6.4
million deaths worldwide, according to the World Health Organization (WHO) COVID-19 dashboard (https://covid19.who.int). The pandemic has significantly impacted the mental health of many people within the population, resulting in loneliness, social isolation, financial strain, as well as the anxiety with fear of contracting the virus, and uncertainty for the future (2).
Psychological distress is not only associated with missed periods but also worsening of symptoms associated with menstruation and psychosexual health. Dysmenorrhoea has been shown to be associated with high stress levels (3), emotional instability and depression (4). Pre-menstrual symptoms and menorrhagia are also associated with high psychological distress (5).
The female menstrual cycle usually comprises of 28-30 days per cycle which contains two phases, the secretory phase and the proliferative phase(6). At the termination of the cycle, the inner uterine layer starts shedding off resulting in menstruation in females(7). However, in some case the absence of menstruation for two months or more in reproductively active female results in amenorrhea(8).
Cessation of menstruation or significant change in menstrual pattern in a hither to menstruating woman triggers anxiety and a sense of "something is wrong with me". Regular menstruation monthly indicates that the hypothalamo–pituitary–ovarian axis is intact. The hypothalamus, pituitary, and ovaries form an endocrine axis that functions through hormonal regulation and feedback loops. This system governs the regulation of menstruation, which is the cyclic, orderly shedding of the uterine lining (3)
The term amenorrhea is defined as a disorder referred to the adolescent girl and women's who are not having normal menstrual cycle(4). Amenorrhea is the absence or abnormal cessation of the menses(5).
The menstrual cycle is regulated by an interaction of several hormones that interact with the immune system, blood vessels, and clotting systems, and these interactions can affect menstrual bleeding and the severity of (pre)menstrual symptoms (6).
Estradiol (E2) is secreted primarily by the ovarian follicles during the female menstrual cycle, and by the placenta during pregnancy(7).
It is secreted to a lesser degree by the adrenal glands, testes and by peripheral conversion of androgens. Estrogen receptors can be found in many tissues (bones, mammary glands, liver, endometrium, etc.).
The synthesis and secretion of estradiol are regulated by the hypothalamic-pituitary axis, through LHRH, LH and FSH(8). Where, prolactin is a hormone secreted from the anterior pituitary. Its principal physiological action is to initiate and sustain lactation. Prolactin secretion is controlled by the hypothalamus through the secretion of dopamine, which inhibits the process (9). The commonest causes of hyperprolactinaemia include stress, pregnancy, drugs, prolactinoma/other pituitary tumours, hypothyroidism and chronic renal failure.(9). The follicle stimulating hormone (FSH) stimulates granulosa cells in the ovarian follicles to synthesize aromatase, which converts androgens produced by the thecal cells to estradiol (10). The FSH is necessary for the selection and growth of ovarian follicles and for the production of estrogens from androgen substrates (11). The gonadotrophic effects of FSH may be subserved by a number of intermediaries, that form part of the cellular and tissue response to FSH stimulation culminating in ovulation. (12) (13)
Luteinizing hormone (LH) is a glycoprotein hormone that is co-secreted along with FSH by the gonadotrophin cells in the adenohypophysis (anterior pituitary), that it is a part of a neurological pathway comprised of the hypothalamus, pituitary gland, and gonads, when the LH release is stimulated by gonadotropin-releasing hormone (GnRH) and inhibited by estrogen in females and

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testosterone in males (14). LH has various functions, it is contributes to triggers the creation of steroid hormones from the ovaries (15), and helps to regulate the length and order of the menstrual cycle in females by playing roles in both ovulation and implantation of an egg in the uterus(14).

Menstrual disorders vary and are very common among women. Symptoms are varied, such as dysmenorrhea, heavy menstrual bleeding (menorrhagia), amenorrhea, hypomenorrhea or irregular and intermenstrual blood loss. Its causes vary, and there is no doubt that the most important causes are hormonal changes(16). The aim of this study was to study the impact of corona virus infection on women hormonals like (estradiol (E2), prolactin (PRL), follicle stimulating hormone (FSH) and luteinizing hormone (LH)), the states of amenorrhea that present in Iraqi pre-menopausal women after they infected with coronavirus for 2 or 6 months at least.

The hypothalamic pituitary gonadal axis plays a crucial role in regulation of the human reproductive system. The anterior portion of pituitary is responsible for the production of LH and FSH, the hypothalamic pituitary gonadal axis regulates female menstrual cycle. The positive loop of feedback between estrogen and LH is responsible to prepare the follicles in the ovary for ovulation and to prepare the uterus for implantation. The hypothalamus and pituitary both have ACE 2 receptors and can be sites of COVID-19 infection (17). The virus may then enter the hypothalamus as the blood–brain barrier is permeable in proximity of this structure. Furthermore, infection of the hypothalamus might result in hypophysitis which would also disturb the hypothalamic pituitary gonadal axis, thereby leading to menstrual abnormalities and infertility (18).

2. Materials and Methods

It is a cross-sectional study that conducted in the Medical City (consulting clinic) in Baghdad, from November 2021 to April 2022. And included (100) married women of child-bearing age between the age of (18-40 years), The study sample was divided into two groups, 50 women of child-bearing age have been infected with corona virus for at least four months post COVID-19 infection with amenorrhea,and 50 women of child-bearing age who did not infected with corona virus.

All the women were informed about the study and the ethical approval was taking from all the women participate in this study

All pregnant or lactating women, women with heavy bleeding period, women with history of a diagnosis ovarian dysfunction in the 6 months before onset of disease such as; a manifestation of delayed menstruation, menstrual irregularities or earlier menopause, and women with ovariectomy have been excluded from this study.

The blood samples were taken from the women vein at the morning time on the first three days of the menstrual cycle. The serum of each of the following hormones : (estradiol (E2), prolactin (PRL), follicle stimulating hormone (FSH) and luteinizing hormone (LH)) was analysed using the Roche Elecsys -2010 device System which is an automated, random access, multichannel analyzer for immunological tests (Sandwich assay), intended for in vitro quantitative or qualitative determination of a wide range of analytes. The analyzer is specially designed for High sensitivity, reliability, and reproducibility of results due to Electro-chemiluminescence (ECL) technology for heterogeneous immunoassays.All the kits used in this device system were provided by Roche company and manifactured in Germany.

3. Statistical Analysis

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) version 23, The Student's T-test was used. The data was presented as mean (M), standard deviation (SD), and correlation coefficient (r), the P-value of less or equal to 0.05 was is considered statistically significant, and the Receiver Operating Characteristic Curve (ROC) curve was performed for testing the sensitivity and specificity of the Roche Elecsys -2010 device that used in this study

4. Results

The results of this study indicate that there was a non -significant differences in Mean ± SD of the age and BMI between the two group (P_ value = 0.954, 0.745) respectively. as shown in Table 1.

Table 1: the comparison in mean ± SD in women hormones between the Post-COVID-19 women with amenorrhea and Non-COVID-19 women variables

Variable	Post- COVID-19 Women Mean ± SD (Amenorrhea) N= 50	Non- COVID-19 Women Mean ± SD (N= 50	P_ value
Age	27.74 ± 7.31	30.08 ± 7.23	0.954
BMI	28.23 ± 7.98	27.91 ± 6.88	0.745
LH	10.70 ± 6.31	7.59 ± 2.73	0.000**
FSH	5.24 ± 1.97	5.72 ± 2.33	0.164
PRL	19.99 ± 9.25	12.78 ± 5.25	0.003**
E2	97.13 ± 20.41	82.03 ± 19.38	0.024*
*statistically significant **statistically highly significant			

There were highly significant differences in mean ± SD of LH hormones between the women who experienced amenorrhea after infection with COVID-19 compared with the Non- COVID-19 women with p value = 0.00 (Table 1)

There were marginal differences in (FSH) levels between the two groups in mean ± SD and there were no statistically significant differences with the p value = 0.164.

The mean ± SD of the (PRL) hormones was statistically highly significant women who experienced amenorrhea after infection with

COVID-19 compared with the Non-COVID-19 women with p value = 0.003

The estradiol (E2) level were deviated in women who experienced amenorrhea after infection with COVID-19 with P value = 0.024.

The differences between with arithmetic averages for both groups are shown in (Figure 1)

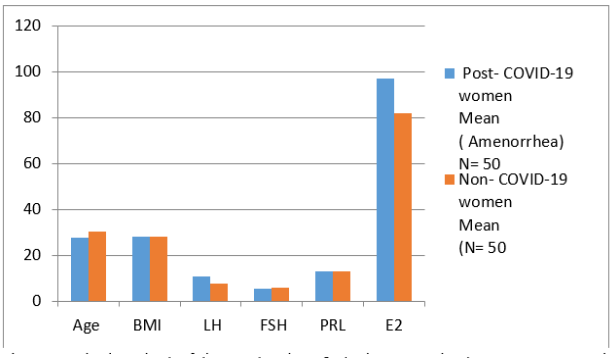

Figure 1: The bar chart of the women hormones between the COVID-19 Amenorrhea and non-COVID-19 presanted in mean

The results of Roc Curve represent the Area Under Curve Values for (LH) hormone for the women who had amenorrhea after contracting COVID-19. It was highly significant for the (LH) hormone with a p value =0.018, but it wasn't significant for the E2 hormone. as shown in table 2

Table 2 : the Roc Curve of LH and E2 for the Post-COVID-19 women (Amenorrhea)

Variable	Area Under Curve Values	P – Value	Cut off	Asymptotic 95% Confidence Interval		Test Quality
				Lower	Upper	
LH	0.638	0.018*	7	0.523	0.752	Satisfactory
E2	0.530	0.600	75.40	0.416	0.645	Fair
*statistically significant						

The following graph shows the correlation between sensitivity and specificity in the ROC curve for LH and E2, respectively. (Figure 3)

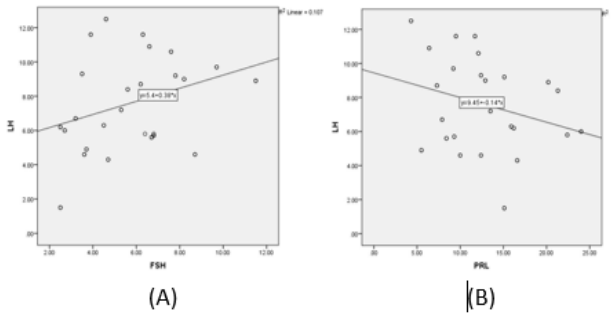

Fig 2: (A) the correlation between (LH) hormone sensitivity and specificity for the post COVID-19 women in the ROC curve. (B) the correlation between (E2) hormone sensitivity and specificity for the post COVID-19 women in the ROC curve.

The results showed that there is a positive relationship between the (LH) with (FSH), there is statistically significant at (P –Value = 0.020), And there is a negative relationship between the (LH) with (PRL), there is statistically significant at (P – Value = 0.050) as shown in (Table3)

Table 3 : the Correlation from LH with Age, BMI, FSH, PRL, E2 for the Post- COVID-19women (Amenorrhea)

Correlation (LH)		
Variable	(Amenorrhea)	P –Value
Age	-0.027	0.852
BMI	-0.050	0.733
FSH	0.327	0.020*
PRL	-0.279	0.050*
E2	0.257	0.072
*statistically significant		

The following graph shows the relationship between the LH with FSH and PRL, respectively. (Figure 1

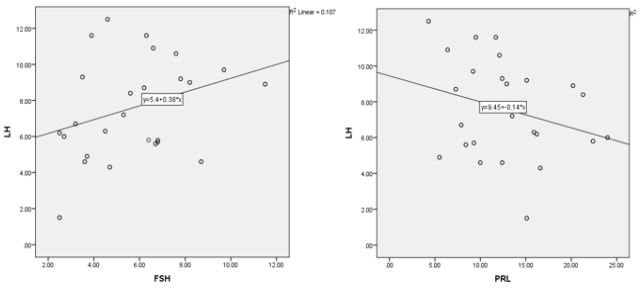

Fig 3: The correlation for post COVID-19 women(amenorrhea) between : (A) LH and FSH, (B) LH and PRL

5. Discussion

As the COVID-19 pandemic enters its third year, it is clear that its effects extend beyond the respiratory system and are clinically significant. These consequences may also have an influence on health and quality of life.

About one-third of the people reported stress, anxiety, and depression during the COVID-19 pandemic (19). Psychological stress can alter the menstrual cycles, Stress, even without any organic cause, can activate the hypothalamic–pituitary–ovarian axis, altering the release of gonadotropin-releasing hormone (GnRH), leading to functional hypothalamic amenorrhea and chronic anovulation.(20)

Psychological stress can lead to secondary amenorrhea and also worsening of symptoms associated with menstruation. Even high stress (21),emotional instability, and depression can lead to disorder in menstruation. (22)

the menstrual changes were observed more commonly in patients of COVID-19 with systemic complications arising out of COVID (23). so female fertility concerns arose after this abnormal findings: altered menstrual duration, frequency, regularity, and volume (heavier bleeding and clotting), increased dysmenorrhea, and worsened premenstrual syndrome (24). Women who earlier had a history of missed periods are more prone to have amenorrhea during the pandemic(25).

In this study, there was no effect of (age, BMI) in

both groups on amenorrhea (P-value = 0.954,0.745) respectively because the subjects were aged within the normal age for childbearing and their weight was within the normal limits.

The results of this study show that women who had experienced amenorrhea after coronavirus infection had a high level of LH hormone when compared with non-COVID women (P-value = 0.000), While the (FSH) hormone is not affected in this study.

This can be caused by their exposure to stress that causes the dysregulation of HPA axis activity which many due to mechanisms like: (i) the inhibition of hypothalamic GnRH release by corticotrophin releasing hormone (CRH), endogen opioids, and glucocorticoids, (ii) decreased pituitary response to GnRH, leading to decreased luteinizing hormone (LH) secretion, (iii) direct inhibitory effect of glucocorticoids on the secretion of estrogen and progesterone, (iv) glucocorticoid-induced resistance to the gonadal steroids in target tissues, and (v) direct catecholaminergic inhibition on follicle stimulating hormone (FSH), LH, and prolactin secretion. (26), In the same line other studies found that some patients with COVID-19 had abnormal levels of sex hormones(27). There was inappropriately high concentrations of luteinizing hormone (LH) seen in patients with COVID-19 (28). This points toward ovarian suppression which might be linked to stress status in COVID-19 self the ovarian function is often suppressed to ensure normal functioning of other organ systems which are essential for life and amenorrhea has also been previously reported in acute diseases. This explains the decrease of menstruation in patients with COVID-19 which may be linked to ovarian suppression due to acute stress of COVID-19 infection and multiple organ dysfunction. (29)

In this study, the PRL level was higher in women that had been infected with the coronavirus as compared with non-COVID women (P value = 0.001). The reason for that could be that the COVID-19 induced stressful status may affect the release of PRL and other stress-mediated hormones(30). The PRL plays an important role in the regulation of immune function during viral infections(31). As a result, increasing the level of PRL in serum to physiological levels with dopamine antagonists may improve immunological function and survival in a variety of critical states (32), Petrulli et al. illustrated that systemic infammation triggers activation of striatal dopamine with a subsequent reduction in the release of PRL (33). Hence, Sen proposed that dopamine antagonists could improve and boost the immune function in COVID-19 through the augmentation release of the immune-stimulant PRL (34). COVID-19 infection can impair the hypothalamic–pituitary–gonadal axis and, by this mechanism, may increase secretion of PRL from the anterior pituitary during COVID-19 infection. (35)

The level of estradiol (E2) was altered in women who experienced amenorrhea after infection with COVID-19 as compared with non-COVID-19 women (p value = 0.024) The reason for this abnormal E2 level is that estradiol (E2) binds to the cytoplasmic estrogenic receptors (ER-and ER-) expressed on T and B cells (36). Momentarily, E2 activates humoral immunity and antibody production against different viral infections (37), leading to a high level of E2 in the blood which is correlated with immune-reactivity around ovulation (38), and the most effective factor is believed to be E2, which may exert a protective effect by regulating cytokines related to immunity and inflammation.(39)

In another context, the COVID-19 infection treatments that have been advised for the patients have been include antipyretics and analgesics drags, such as paracetamol, aspirin and other non-steroidal anti-inflammatories such as dexamethasone which affect the prostaglandin synthesis and endometrial prostaglandin levels (27), which affect menstrual cycle patterns and blood loss through cortisol actions(40). Vitamins and other nutritional factors such as vitamins D and vitamins C) to control these disturbances, and at the same time they have an important role in defending against microbial infectious included COVID-19 (41). Vitamin D facilitates the production of antimicrobial peptides in the respiratory epithelium, reduces the possibility of viral infection and diminishes the severity of symptoms (42). Because COVID-19 is a systemic inflammation, it will lower the circulation of 25 (OH)D resulting in vitamin D deficiency (43). which can cause irregular menstrual cycle including amenorrhea or oligomenorrhea (44) and this condition is mainly due to the direct effect of vitamin D on the circulating androgens (45).

Vitamin C also plays an important role on the reproductive system as it is essential for the synthesis of collagen, steroids and peptides hormones, protection against oxidative damage (46). Vitamin C can affect menstrual cycle indirectly, by playing a role on the absorption of other fat-soluble vitamins which control the cycle (47). Moreover, it acts as promoting factor on the synthesis of estrogen and progesterone and improve hormonal levels, which lead to increase the thickness of endometrium, thus its deficiency may lead to heavy bleeding during the menstruation (48). The menstrual cycle generally is complex interactions of the hypothalamus, pituitary, ovaries, uterus, prostaglandins, and neuroendocrine factors. Therefore, the menstrual disturbances can be resulted from the disruption of any of these interactions.(49)

6. Conclusions

The results of this study provide inconclusive evidence about the effect of COVID-19 infection on the menstrual of childbearing age Iraqi women. More studies are needed to clarify the relationship between COVID-19 and its relationship with female hormones, menstruation, and reproductive capacity.

7. References

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