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The Influence of Obesity and IL-6 on Infertile Iraqi Women with COVID-19 Complications

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Abstract

Infertility is one of the types of diseases that occur in the reproductive system. Obesity is a state that can be occurred due to excessive fats, the progression in obesity stage results in a change in adipose tissue and the development of chronic inflammation, endocrine glands disorders and women's reproductive system, and also increase the infection with covid-19. The study aimed to investigate the effect of the obesity, lipid-profile, and IL-6 on hormones-dysregulation in infertile-women with COVID-19 complications. The current study included 70 samples: 50 infertility-women-with-covid-19-infected, 20 healthy-women/control, the ages of both patients and healthy subjects were selected within the range 18-34 years. Levels of FBS, LH, FSH, and testosterone and lipid profile were measured in addition to calculating BMI. The result showed a significant increase in lipid profile but no HDL that revealed a considerable decline in its level (P=0.001) in patients group relative to control group. Also, the results showed highly increase in LH and LH/FSH-ratio ($p \leq 0.05$(but no FSH that revealed a considerable decline in its level ($p \leq 0.05$). The results also showed that the values of IL-6 (7.46±1.90 ng/ml) and BMI (30.10 ±6.17 kg/m2) in the patients group were significantly higher (P-value=0.001) than their values in the control group (3.13±0.79), (22.09±2.63 kg/m2), respectively. Conclusion: Obesity and Corona-virus-infection negatively affect ovulation in infertile-women due to their effect on the pituitary-gland-hormones, in addition to causing chronic-infections that lead to an increase in the level of interleukin-6, which increases of pituitary gland disorder and the difficulty of treating infertility and increasing of corona complications.

Keywords: Covid-19, FSH, IL-6, Infertility, LH, Obesity, Testosterone.

Introduction

Obesity is one of the most prevalent public health issues in the world today, which has developed like an epidemic across the globe. The world health organization (WHO) predicts that one in five persons globally will be obese by 2025, although the fact that the link between obesity and increased risk of mortality and morbidity has been known for more than 20 years [1-3].

The inability to give birth after one year of frequent sex is called "infertility". The prevalence of infertility is around 13% in women and 10% in men. Overall, it is estimated that 92% of couples become pregnant after 2 years and 84% of couples after 1 year of sexual intercourse [4]. Infertility is not an exclusive problem for women or men; it can be traced back to both. Infertility in many couples manifests a variety of unusual or unexplained problems. For female the cause of Infertility in many couples manifests a variety of injury the fallopian tubes, disablement of ovulation, or develop hormonal disorders [5]. The clinical cases

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that can be occurred and as results of infertility include different types of health problems like inflammation of pelvic, fibrosis of the uterus, early ovarian disorders, ovarian cysts, and damage to the endometrial uterus [6].

From clinical results, it is easily seen that male infertility is caused by poor semen quality giving rise to the implication in more than 40% of couples present for assisted reproduction treatment [7]. Fertility peaks in both men and women at a young and then decrease over time. Also, the age factor affects the possibility of being pregnant or being able to maintain a pregnancy. Towards the end of the month of December 2019, a mysterious illness known as pneumonia of unknown origin broke out in Wuhan, Hubei Province, China. At least 9720 people have been infected in China, 213 of them have died, and 106 people have been diagnosed in 19 other countries as of 31 January 2020. A new coronavirus (nCoV) was found to be the causal agent of unexplained pneumonia a few days later by many different laboratories [8].

Inflammation is a major part of the body's defense against infection and other assaults, but a hallmark of many SARS-CoV-2 infections is the loss of regulation of the inflammatory response. Severe cases of COVID-19 (i.e., those with acute respiratory distress syndrome) are characterized by systemic, or 'cytokine storm.' The hyper expression of pro-inflammatory cytokines and chemokines leads to increased infiltration of immune cells (e.g., macrophages and neutrophils) to the lungs [9]. Interleukin-6 is a tiny glycoprotein (21 KDa). Comprises (212 a.a), 28-amino acids are signal peptide. The gene of IL-6 is located at chromosome 7p21 in humans. IL-6 facilitates clear distinctions between T and B cells, as immunity is acquired. Also, IL-6 may be secreted from non-leukocytes, like epithelial, endothelial as well as malignant cells. Interleukin-6 is known as a pro-inflammatory mediator or anti-inflammatory depending on certain factors and is involved in transferring the information between cells as a signaling molecule. Generally, most the body cells express IL-6 receptors on their membrane [10]. The World Health Organization considered the Coronavirus is a public health issue that has economic and social impacts, and the organization declared that the Coronavirus 19 (Covid-19) epidemic is a global health emergency that has raised international concern and great preparations to confront this epidemic in March 2020 [11]. This study included a number of limitations related to obtaining the required samples, the first limitation is the difficulty in obtaining samples for a woman infected with infertility and Covid-19 together, and the second limitation includes that the sample is drawn only on the 2-3 day of the menstrual cycle due to the occurrence of ovulation during this time. These two factors are considered essential in obtaining samples that provide reliable data to give results with high accuracy. The aim of this study is to investigate the effect of obesity on infertility women and coronavirus infection by assessing the levels of lipid profile and IL-6 with some other relevant parameters (LH, FSH, Testosterone), to find out the extent of the impact and relationship of these factors with the infertility condition that can be occurred under the influence of Covid-19.

Materials and Methods

Blood sample collection: -

The current study conducted on 70 Iraqi women include 50 obese infertility women with covid-19 infected, there aged 18 – 34 years, and 20 healthy women as a control group, during the period between 8/ 2022 to 3/ 2023, participants from Kamal Al- Samarai Hospital at Baghdad city. The practical part was conducted at the laboratories of College of Science for Women / Baghdad University / Iraq.

Vein blood samples 5 ml were drawn from both patients and healthy subjects and collected in plastic syringes, after overnight fasting 2 ml of collected blood was transferred into EDTA tube for an analysis of IL-6 and 3 ml transferred to a gel tube, which is left for 30 minutes for coagulation,

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then it is separated to obtain serum by a centrifuge at a speed of 4000 cycles per minute for 10 minutes, then it is kept at -20 degrees Celsius after it is divided into small parts in small tubes designed for this purpose to measure FBG,LH, FSH, IL-6 and lipid profile levels.

Statistical analysis: -

These analyses were carried out using SPSS version 26. A p-value of 0.05 or less was referred to as it a significant difference.

Inclusion criteria: female patients were selected with infertility and infected with coronaviruses.

Exclusion criteria: Relative subjects are excluded. Also, any patient presented with DM, any type of cancer or tumor, any apparently acute inflammation, Patient treated by insulin, and any immunity diseases.

Results and discussion

Table 1 showed a set of anthropometric measurements for the two groups of patients and healthy women, which included age, body mass index, and menstrual cycle flow. The results revealed that there are no significant differences in each age and menstrual cycle flow for the patients and healthy groups, while the results of the body mass index showed highly significant differences for the patients' group compared to the healthy group.

Table 1. Levels (Mean ± SD) of anthropometric measurements of studied groups

Groups / Parameters	Infertility women with COVID-19 Group (No. 50)	Control women Group (No. 20)	p-value
Age (year)	26.92±5.63	26.15±6.38	NS
BMI (kg/m^2)	30.10 ±6.17	22.09±2.63	**0.001
Menstrual cycle flow (days)	4.12±1.20	4.32±0.83	NS

Results of FBS, Cholesterol, triglyceride, HDL, LDL, and VLDL of both patient and control groups are recorded in Table 2. The outcomes revealed a high important difference ($p<0.05$) between patients and healthy persons. The results displayed that altogether the studied factors increased significantly ($p<0.05$) in patients excluding HDL compared with the healthy group.

Table 2. Levels (Mean ± SD) of FBS and lipid profile of studied groups

Groups / Parameters	Infertility women with COVID-19 Group (No. 50)	Control women Group (No. 20)	p-value
FBS (mmol/L)	5.04±0.53	3.99±0.38	**0.001
Cholesterol (mmol/L)	6.57±1.32	4.85±1.20	**0.001
TGs (mmol/L)	5.20 ±2.09	0.85±0.57	**0.001
HDL (mmol/L)	0.32±0.20	1.57±0.59	**0.001
LDL (mmol/L)	3.91 ±1.45	2.21±1.26	**0.001
VLDL (mmol/L)	2.34±0.97	0.38±0.26	**0.001

The results of the studied hormones (LH, FSH, testosterone and LH/FSH ratio) were recorded in Table 3. They revealed that LH level in patients' group was significantly higher $p<0.05$ than a control group, likewise the mean level of LH/FSH ratio and Testosterone showed a highly significant increase $P<0.05$ in patents group when equated with healthy persons. In contrast, FSH mean level revealed a considerable decrease ($P= 0.001$) in patients than that in healthy subjects.

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Table 3. Levels (Mean ± SD) hormones profile of study groups

Groups / Parameters	Infertility women with COVID-19 Group (No. 50)	Control women Group (No. 20)	p-value
FSH (mIU/ mL)	5.54±2.80	8.25±2.77	**0.001
LH (mlU/ mL)	8.78±4.63	4.83±1.92	**0.001
LH/FSH ratio	1.69±0.55	0.58±0.14	**0.001
Testosterone (Ng/ mL)	0.70±0.25	0.30±0.10	**0.001

Also, the results showed that interlukine-6 (IL-6) levels were significantly increased in the patients group compared to the control group at P= 0.001, as shown in Table 4.

Table 4. Levels (Mean ± SD) of interlukine-6 of study groups

Groups / Parameters	Infertility women with COVID-19 Group (No. 50)	Control women Group (No. 20)	p-value
IL-6 (ng/ mL)	7.46±1.90	3.13±0.79	**0.001

ROC analysis:-

Receiver operator characteristics (ROC) curve used to assess the optimal diagnosis BMI, LH, Testosterone, IL-6 in study participants, as shown in the Fig.1 and Fig. 2.

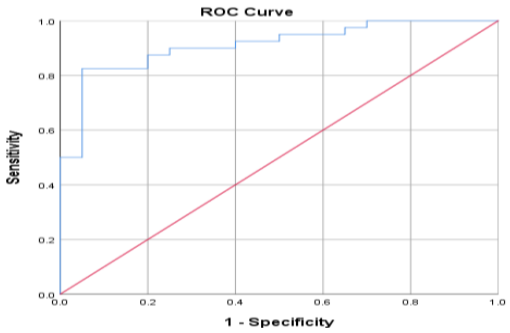

Figure 1. BMI ROC curve

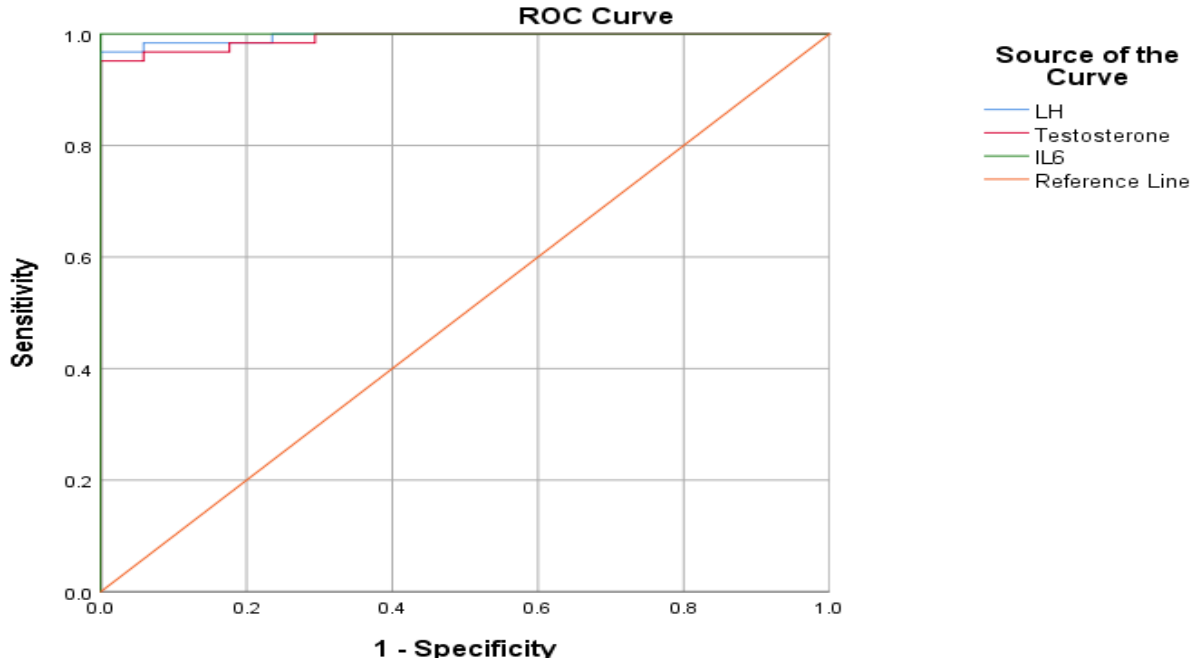

Figure 2. LH, Testosterone, IL-6 ROC curve

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Table 5. Area Under the Curve values of BMI, LH, Testosterone and IL-6

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
BMI	.911	.038	.000	.838	
LH	.995	.005	.000	.986	
Testosterone	.991	.007	.000	.978	
IL6	1.000	.000	.000	1.000	

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Discussion

In the current study, found that BMI significantly increase in patients compared with the control group. this found agreement with Ni, Ying et al. [12], who found that an increase in BMI of women led to infertility, and also agreement with Valerio, Alessandra et al. [13], who found that obesity and overweight in women were associated with increasingly higher risk of developing comorbidities, complications, and symptoms due to covid-19 infection. Furthermore, the results of ROC confirm the importance of BMI, where its value of AUC was found to be equal to 0.911 that means, BMI considers an excellent factor for the diagnosis in this study besides other studied parameters.

Lipid profile abnormalities have been demonstrated to be a significant concern that prepares a diversity of disorders, comprising cardiac diseases, diabetes, obesity, and infertility. The present study findings are consistent with those of Shabana et al.,[14] who studied 250 obese women and 250 controls. They discovered that obese people have higher levels of TGs, TC, VLDL, LDL, and lower levels of HDL when compared to non-obese people as seen in table 2. This is also supported by Amari et al. [15].

It too seems probable that the effects of obesity on lipid metabolism are dependent on adipose tissue spreading, in addition to the feature of inflammation accompany by obesity that can lead to alters lipid metabolism. The results of this study found that FSH, LH, FSH/LH, Testosterone increased in infertility women infected with covid-19 more than in normal women, the current study's findings are consistent with Joon, Tong Li et al.[16], who showed that the women who suffer from excessive weight gain or obesity have a lower level of fertility than women of normal weight, which causes an imbalance in the frequencies of the pituitary gland that regulates the ovarian hormones, which revealed that obesity affects the egg through excess free fatty acids generated as a result of fat metabolism, which may cause toxicity in the female reproductive system, cell dysfunction and damage, and cause a chronic low-grade inflammatory state.

IL-6 is a pro-inflammatory adipokine that also contributes to HPO axis dysregulation. Obesity raises circulating levels of IL-6, which is linked to insulin resistance via adiponectin suppression [17]. Also, the result showed a highly significant increase in IL-6 in patients' infertile women with covid-19, these findings concede with other studies by Demir, Bulent et al. [18], who found that serum IL-6 levels are high enough to decrease estrogen synthesis via suppressing FSH and LH actions, aromatase activities, and directly inhibiting granulosa cells. Moreover, persistent high doses of IL-6 can decrease LH-induced ovulation. These effects are comparable to those of its adipokine equivalents, which also contribute to infertility and the alterations seen in obese women. Statistically, ROC data revealed that each of BMI, LH, testosterone as excellent parameters and IL-6 as a perfect factor for diagnosis of this complicated case (infertility with complications of covid-19) due to the AUC values which were found to be 0.911, 0.995. 991 and 1.00 for each of BMI, LH, Testosterone and IL-6, respectively, as shown in Table 5.

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Conclusion

Obesity and infection with the Coronavirus negatively affect ovulation in infertile women due to its effect on the pituitary gland hormones, in addition to causing chronic infections that lead to an increase in the level of interleukin 6, which increases the development of the difficulty of treating infertility and increases the emergence of complications from Corona. Furthermore, high inflammation and the association between obesity and infertility were confirmed by abnormality of IL-6, LH, BMI and FSH in the studied condition. Subsequently, the data of ROC analysis confirmed also the perfect or excellent of the mentioned parameters to be the best factors for diagnosis of the studied case.

Limitations

This study included a number of limitations related to obtaining the required samples, the first limitation is the difficulty in obtaining samples for a woman infected together with infertility and Covid-19, and the second limitation includes that the sample is drawn only on the 2-3 day of the menstrual cycle due to the occurrence of ovulation during this time. These two factors are considered essential in obtaining samples that provide reliable data to give results with high accuracy.

Acknowledgment

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Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Author's Contribution

F. M. Kh. acquisition of data, do laboratory analytics, interpretation, Conception and design the idea of MS, interpretation, revision and proofreading the MS, K. K. Gh. Conception and design the idea of MS, interpretation, revision and proofreading the MS, F. E. A. Diagnosis of infertility women.

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تأثير السمنة و الانترلوكين-٦ على النساء العراقيات المصابات بالعقم ومضاعفات كوفيد-١٩

فيحاء مقداد خليل[1]، كاظم خضير غضيب[1]، فرح عماد علي[2]

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الخلاصة

العقم هو أحد أنواع الأمراض التي تحدث في الجهاز التناسلي، السمنة هي حالة يمكن أن تحدث بسبب الدهون الزائدة . ينتج عن نشوء السمنة تغير في الأنسجة الدهنية والتهاب مزمن واضطرابات في الغدد الصماء والجهاز التناسلي للمرأة ، وزيادة الإصابة بفيروس كوفيد -19. هدفت الدراسة إلى استقصاء تأثير السمنة والدهون والانترلوكين - 6 على عدم انتظام الهرمونات لدى النساء المصابات بالعقم ومضاعفات الكوفيد – ١٩. تضمنت الدراسة الحالية 70 عينة: 50 امرأة مصابة بالعقم و 20 امرأة صحية كمجموعة سيطرة ، اختيرت أعمار كل من المرضى والأشخاص الأصحاء ضمن المدى 18-34 سنة. وقيست مستويات FBS و LH و FSH وهرمون التستوستيرون والدهون بالإضافة إلى حساب مؤشر كتلة الجسم. أظهرت النتيجة زيادة معنوية في مستوى الدهون لكن ليس HDL الذي اظهرانخفاضًا كبيرًا في مستواه (P = 0.001) في مجموعة المرضى مقارنة بمجموعة التحكم. كما أظهرت النتائج زيادة معنوية عالية($p\leq0.05$) في نسبة LH / FSH باستثناء FSH الذي أظهر انخفاضًا كبيرًا ($p\leq0.05$) ، كما أظهرت النتائج أن قيم IL-6 هي (7.46 ± 1.90 نانوغرام / مل) ومؤشر كتلة الجسم (30.10 ± 6.17 كغم / م ^{2}) في مجموعة المرضى كانت أعلى (قيمة P = 0.001) من قيمهم في المجموعة الضابطة (3.13 ± 0.79) ، (22.09 ± 2.63 كغم / م ^{2}) ، على التوالي. الاستنتاج: إن السمنة وعدوى فيروس كورونا تؤثر سلبًا على الإباضة لدى النساء المصابات بالعقم لما له من تأثير على هرمونات الغدة النخامية ، بالإضافة إلى التسبب في التهابات مزمنة تؤدي إلى زيادة مستوى الإنترلوكين - 6 مما يؤدي إلى زيادة اضطرابات الغدة النخامية وصعوبة علاج العقم وزيادة مضاعفات كورونا.

الكلمات المفتاحية: كوفيد -19 ، هرمون منشط الجريبات ، الانترلوكين -6 ، العقم ، الهرمون اللوتيني ، السمنة ، التستوستيرون.