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Association between sex hormonal and metabolic changes in female with infertility, in Al-Najaf city patients

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection. **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

Background: The anterior pituitary gland secretes two hormones that are important for controlling the reproductive processes of females: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Objective: Studying the relationship between obesity and serum SHBG, LH, and FSH levels as a predictive marker in infertility patients from AL-Najaf governorate/ Iraq.

Patients and methods: We used 120 samples of Iraqi women in the 25–40 age range. Sixty well-diagnosed infertility patients and sixty healthy fertile women made up the control group in an age-matched case-control study. The groups are gathered between May 2024 to October 2024 from Al-Zahraa Hospital in the Najaf governorate. An enzyme-linked immunosorbant assay (ELISA) was used to test each subject's hormonal metabolism and hirsutism scores. The results were analyzed with appropriate statistical methods.

Result: The BMI, LH, LH/FSH ratio, TT, FAI, FIN, FSG, and HOMA-I R values of the infertility patient women were considerably greater than those of the healthy women group.

Conclusion: The current findings indicate that elevated levels of LH and FSH in women with infertility are associated with hyperandrogenism and insulin resistance, which serve as predictors of fibroblast and endothelial cell dysfunction as well as metabolic problems. This research discusses the relationship between SHBG and infertility, as well as associated hormonal levels.

Keywords: SHBG; Female LH; FSH; Sexual hormones; Infertility

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INTRODUCTION

Infertile Women (IW) was well-defined by way of a disorder affecting both (men and women) contraception for despite the occurrence of intercourse and at least six months without regularly using any means of despite the occurrence of pregnancy. Sterility was a public residence disorder that had an emotional influence on the generative structure, described *via* a clinical pregnancy to the absence of aptitude of a couple after one year or more of regular unprotected sexual intercourse. Owing toward conflicts in Iraq, about 2003, Deaths and large numbers of injuries were caused by radioactive materials and destructive chemicals. The Iraqi environment agonized from performances of dissent. The people who endured these overwhelming occurrences either cancer or suffered from infertility [1]. The failure to conceive a healthy child after a year of consistent, unprotected sexual activity is known as infertility. The World Health Organization (WHO) reports that this disorder is estimated to impact 1 in 6 persons worldwide and is acknowledged as a major reproductive health issue [2]. Numerous causes, including medical disorders, environmental variables, and psychological ones, can lead to infertility [3]. Due to the ongoing hostilities that have negatively harmed the ecosystem and public health, infertility rates in Iraq are especially alarming. Healthcare services have been disrupted as a result of the ongoing unrest, which may make it more difficult for people to receive essential fertility treatments and reproductive health information. Additionally, as mental health is a major factor in the results of reproductive health, the psychological stress brought on by conflict might make infertility problems worse [4]. Infertility rates can also be influenced by environmental variables, such as pollution exposure and changes in lifestyle brought on by conflict. Research has indicated that deterioration of the environment can have an impact on reproductive health, resulting in higher rates of infertility in populations exposed to such situations. Consequently, tackling infertility in Iraq necessitates a comprehensive strategy that takes into account the interaction of biological, environmental, and psychological elements, especially in light of the population's ongoing struggles [5]. Insulin resistance and type 2 diabetes are more likely to strike infertile women, particularly if they are overweight or obese. The hormonal abnormalities and metabolic dysfunctions that frequently accompany infertility are primarily to blame for this association. One major risk factor for type 2 diabetes is insulin resistance, a condition in which the body's cells become less receptive to insulin. Research shows that women who are fat have higher rates of insulin resistance than women who are

not obese, which can increase the risk of developing diabetes and other metabolic problems [6]. Furthermore, this elevated risk is further compounded by the hormonal disorders linked to infertility, such as those observed in Polycystic Ovary Syndrome (PCOS).

Insulin resistance, unpredictable menstrual periods, and high testosterone levels make infertility the most common hormonal condition affecting women in their reproductive years. In addition to having a higher risk of type 2 diabetes, women with infertility also have a markedly increased risk of cardiovascular disorders, such as heart attacks and strokes. For women who are experiencing infertility, the combination of obesity, insulin resistance, and hormone abnormalities produces a complex health landscape that requires close monitoring and management of their general health [7]. This is brought on by deficient lipid profiles and heightened vulnerability to atherosclerosis and hypertension [8]. Together with LH, folic-stimulating hormone (FSH) controls the reproductive system. FSH is in charge of promoting the development and maturation of the egg-containing ovarian follicles in females. It also encourages the ovaries to produce more estrogen. FSH is essential for spermatogenesis in males because it stimulates the testicular Sertoli cells, which aid in the production of sperm [9]. Women with infertility, especially those who are obese, usually have low levels of SHBG. Higher amounts of free testosterone are linked to this decrease in SHBG, and these levels may aggravate symptoms including hirsutism, acne, and irregular menstruation. It is believed that insulin resistance, a typical characteristic of infertility, is connected to the decline in SHBG. Raised insulin can inhibit the liver's synthesis of SHBG, resulting in decreased blood levels in those who are impacted [10].

MATERIAL AND METHODS

Using the Rotterdam ESHRE/ASRM 2003 criteria, sixty women, aged 25 to 40, who had been diagnosed female infertility during the previous year were included in this case-control study. Between May 2024 to October 2024, the study was conducted at the AL-Zahra teaching hospital for obstetrics in Al-Najaf city, Iraq. A control group of 60 healthy-appearing volunteer women without infertility was compared to an age-matched group of infertility affected women. Each person endorsed an informed consent form. Participants in this study were excluded if they had any type of chronic illness, including low ovarian reserve, high blood pressure, hypertension, Weight (kg) divided by height (m^2) yields the body mass index (BMI), an anthropometric measurement. After a 12-hour fast, five milliliter samples of venous blood were drawn on cycle day 2 between 8 and 9 a.m. The serum was then split and kept cold until the analysis was finished. Serum glucose (FSG) and lipid profile (Total Cholesterol (TC), Triglyceride (TG), High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C) levels) were measured during the fasting examination using colorimetric techniques and commercial test kits. To measure the amount of free testosterone in the serum, ELISA kits were used (Monobind, USA). ELISA kits (Ela Science/USA) were used to assess fasting insulin (FINS) and sex hormone binding globulin (SHBG) [11]. immune-fluorescence technique (Minividas, Biomerieux, France) was used to detect Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH), and Total Testosterone (TT). The homeostatic model assessment (HOMA-IR), which was developed using a standard computation as follows, was used to calculate insulin resistance. According to Weir and Jan (2019), HOMA-IR can be computed as follows: fasting insulin (IU/L) + fasting glucose (mmol/L)/22.5, with a value cutoff of >2.5. Additionally, the conventional method was used to construct the Free Androgens Index (FAI). Total testosterone (TT)/SHBG × 100 equals FAI.

Statistical analysis

SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Every result's mean and standard deviation were noted. The statistical significance of the study's groups was ascertained using an unpaired student t-test, and t-tests were utilized to compare two independent samples. Pearson's correlation analysis was used to examine the relationship between the variables and compare the parameters across women with infertility. With a P-value of 0.005, the statistical significance was indicated.

RESULTS AND DISCUSSION

The study groups' initial characteristics are shown in **Tab. 1.** The 120 samples consisted of 60 infertility patients; the control group consisted of 60 women who appeared to be in good health. Between the study groups, there is no appreciable difference in the age factors. The patient group's WHR and BMI were significantly higher than those of the healthy groups.

Tab. 2. compares the biochemical parameters of the research groups. The levels of prolactin ($P<0.0001$), free testosterone ($P<0.0001$), LH ($P<0.0001$), and the LH/FSH ratio ($P<0.0001$) were significantly higher in the infertility patient group than in the healthy women. Comparable testing revealed a substantially lower level of FSH ($p=0.01$) in women with infertility compared to healthy women.

While not strictly necessary for diagnosis, elevated Luteinizing Hormone (LH) is a common sign of infertility. Especially in relation to hyperandrogenism, LH is important to the pathophysiology of infertility. It is recognized to augment androgen synthesis in the ovaries, principally by stimulating androgen synthesis in LH-receptor-containing ovarian theca cells. This process is important because it not only causes luteinization and ovulation, but it also raises androgen levels, which are common in infertility patients [12]. Higher LH concentrations have been linked to more severe infertility instances, according to research. For example, research has indicated a positive correlation between follicle count and ovarian volume, indicating that elevated levels of LH may be associated with higher hyperandrogenism and ovarian dysfunction [13]. In addition, women with infertility who have high LH levels typically have more severe irregularities in their menstrual cycles and a higher chance of becoming infertile. The degree of the illness is reflected in this hypersecretion of LH, suggesting that tracking LH levels can reveal information about the general health and ability to procreate of infertility patients [14]. Follicle-stimulating hormone (FSH) plays a key role in follicular growth, and its relative deficit can severely hinder it. An important factor contributing to the hormonal imbalance seen in infertility is an increased frequency of Luteinizing Hormone (LH) pulses. Increased LH pulse amplitude and frequency in infertility affected women restrict the production of follicle-stimulating hormone (FSH). Because

Tab. 1. Biochemical and demographic characteristics of the participating women's groups.

Variables	Groups		P-value
	Infertile Patients group Mean ± SD	Healthy groups Mean ± SD	
No. (120)	60	60	-
Age (Years)	20.21 ± 5.67	20.34 ± 7.16	0.125
BMI (kg/m²)	19.66 ± 1.19	13.62 ± 1.04	0.003
BMI:18.9-24.9	10(12%)	60(100%)	
BMI:25-29.9	25.(38%)	-	
BMI: ≥ 30	25(50%)	-	
WHR	1.08 ± 0.06	0.34± 0.05	0.002
With Hirsutism	34(60%)	-	-
Without Hirsutism	26(40%)	-	-
Primary infertility	21(67%)	-	-
Secondary infertility	15(33%)	-	-
Irregular cycle	18(76%)	-	-
Regular cycle	6(24%)	-	-

Tab. 2. The biochemical traits of both healthy and infertility patient groups.

Parameters	Infertility Patients group Means No.(60)	Healthy group Means No.(60)	P-Value
LH (mIU/L)	12.63 ± 2.99	4.05 ± 2.15	0.0001
FSH (IU/L)	5.28 ± 2.61	5.09 ± 2.40	0.049
LH/FSH	2.18 ± 0.67	0.750 ± 0.23	0.0001
TT (n g/mL)	2.47 ± 0.86	1.03 ± 0.29	0.036
FT (p g /mL)	12.51 ± 2.04	2.98 ± 2.06	0.0001
FAI	9.68 ± 2.67	3.64 ± 2.03	0.0001

increased LH levels have the ability to inhibit FSH release, which is essential for the development and maturation of ovarian follicles, this inhibition takes place. As a result, low FSH causes the ovarian follicles to not receive enough stimulation, which stops them from developing and causes anovulation, an infertility defining feature [6]. Furthermore, the increased LH levels affect the synthesis of estrogen.

The ovarian follicles are the main source of estrogen, and FSH is necessary for the production of estrogen. Estrogen synthesis is also decreased when FSH levels are low as a result of a high LH pulse frequency. This decline causes additional disruptions to the regular ovarian cycle, which in turn leads to the development of polycystic ovaries, which are marked by an abundance of immature follicles that are unable to ovulate [15]. Rivo is recommended to treat type 2 diabetes mellitus; its mechanism of action is to enhance pancreatic insulin production. Its usage has declined precipitously, as studies have shown clear links with an increased risk of heart attack and mortality [16].

The comparison between SHBG level in the study groups revealed in **Tab. 3.** The result demonstrates that serum SHBG level significantly lower in infertility patients' group (P= 0.0001) when compared with healthy control groups.

Tab. 3. The comparison of mean SHBG level in infertility patients and healthy control group.

Variables	Infertility Patients group Means No.(60)	Healthy group Means No.(60)	P-Value
SHBG (pg. m/L)	34.52 ± 7.51	64.33 ± 45.22	0.0001

The current result revealed a significant lower level of SHBG in women with infertility when compared with healthy control women. One important biomarker linked to infertile is sex hormone-binding globulin (SHBG), which is frequently decreased in women with the disorder. The glycoprotein known as SHBG attaches to sex hormones, specifically testosterone and estradiol, to control how bioavailable they are in the blood. Typically, women with infertility have lower concentrations of SHBG because the disease is characterized by high androgen levels. This decrease in SHBG may raise free testosterone levels, which may exacerbate symptoms including acne, irregular menstruation, and hirsutism [17].

Studies reveal that obese adolescents with infertile have low SHBG levels more often than other groups, indicating a substantial correlation between obesity, insulin resistance, and SHBG levels. It has been demonstrated that reduced SHBG levels correspond with greater insulin levels, aggravating the hormonal imbalance. Insulin resistance is a typical metabolic disruption in infertile [18]. Furthermore, compared to healthy controls, women with infertile consistently had lower serum SHBG levels, according to a meta-analysis of several researches. Because SHBG levels can indicate the degree of metabolic abnormalities linked to infertile, this finding highlights the potential of SHBG as an early biomarker for the diagnosis and management of the illness [19].

On the other hand, the correlation analysis between serum SHBG levels with other Anthropometric and Biochemical Parameters in Women with infertility Group as shown in **Tab. 4.** The association between the clinical parameters study and the blood level of SHBG in the infertility women group has been confirmed using data correlation analysis.

The majority of these alterations were validated by correlation analysis, which looked at the strong negative connections between the blood SHBG levels in the infertility patients and their age, BMI, WHR, FT, FIN, and HOMA-IR levels. The current study looked at SHBG levels in people with infertility. Nevertheless, in the infertility patient group, no significant associations were

Tab. 4. The correlation analysis between serum SHBG levels with biochemical parameters in infertility patients' group.

Parameters	r	P-value
Age (year)	-0.290	0.036
BMI (kg/m^2)	-0.490	0.001
WHR	-0.299	0.001
LH (IU/L)	-0.200	0.059
FSH (IU/L)	-0.227	0.058
LH/FSH	-0.149	0.107
TT (ng / mL)	-0.140	0.179
FT (pg./mL)	-0.309	0.001
FAI	-0.197	0.049
FSG (mg/dL)	-0.294	0.001
FIN (mIU/L)	-0.323	0.001
HOMA- IR	-0.192	0.023
HOMA- %B	0.280	0.059
TC (mg/dL)	0.369	0.010
TG (mg/dL)	-0.017	0.910
HDL-C (mg/dL)	0.129	0.399
LDL-C (mg/dL)	-0.061	0.602
VLDL-C (mg/dL)	-0.038	0.783

found between HOMA-%B and serum SHBG and TT, TG, HDL-C, LDL-C, VLDL-C, LH, FSH, FAI, and LH/FSH ratio. Prevalent endocrine disorder infertility is characterized by a variety of symptoms that can result in infertility and multiple metabolic issues. It is recognized as a complex ailment impacted by lifestyle, environmental, and genetic elements. High-fat, low-fiber diets, sedentary lifestyles, smoking, and alcohol use are some of the lifestyle variables that contribute to infertility and increase its risks [20].

The link between infertility and low-grade inflammation is a notable worry as it is thought to have a crucial role in the emergence of metabolic disorders and cardiovascular diseases, such as Type 2 Diabetes (T2D) and specific malignancies. Reduced insulin sensitivity and endothelial dysfunction are two outcomes of this inflammatory state that are important in the pathophysiology of cardiovascular events [21]. The metabolic syndrome is a group of illnesses that raise the risk of diabetes, heart disease, and stroke. It frequently coexists with infertility. Insulin resistance is especially noteworthy in infertility patients since it can result in additional complications [22].

CONCLUSION

Obesity, hyperinsulinemia, hyperlipidemia, and HOMA-IR are risk factors for infertility. Low serum SHBG is linked with the long-term prognosis and consequences of infertility and plays a critical role in its pathogenesis. Hormone levels, the relationship between infertility and SHBG, and related treatment strategies are all included in this study. To find out more about the relationship between SHBG and infertility, how different drugs affect SHBG levels, and whether these therapies can help with infertile.

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