Al-Nahrain Journal of Science
ANJS, Vol. 28 (1), March, 2025, pp. 14 – 19

Level of Sex Hormone Binding Globulin (SHBG) in Sera of Iraqi Women with Polycystic Ovary Syndrome Correlating Infertility

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Article's Information

Received: 19.06.2024
Accepted: 08.09.2024
Published: 15.03.2025

Keywords:
polycystic ovary syndrome,
Primary infertility,
Sex hormone binding,
Insulin resistance,
Fasting blood sugar (FBS)

Abstract

Ovulatory abnormalities are a prevalent cause of infertility in women, and they can result in PCOS, or polycystic ovary syndrome. This study aimed to evaluate and compare fasting blood sugar (FBS), insulin, insulin resistance (IR-OMO), sex hormone binding globulin (SHBG), and follicular, in addition to vitamin D3, stimulating hormone (FSH), testosterone (TT), estrogen (E2), luteinizing hormone (LH), prolactin (PRL), and the incidence of PCOS, associated with primary infertility in sera samples of Iraqi women. A total of 70 primary infertility women, and 30 apparently healthy controls were included in this study, their ages were ranged between 19 - 40 years. Blood samples were collected from patient in addition of healthy controls as (C group). The levels of FSH, LH, prolactin, TT, E2, IR-HOMO, and FBS were higher significantly ($p<0.001$) in patient groups than C group. Results showed that serum levels of SHBG in patient (3.014±0.26 ng/ml) were decreased significantly in comparison with its levels (9.975 ±0.72 ng/ml) in sera sample of C group. On the other hand, vit. D3 levels of patients (11.78 ±1.41ng/ml) were also significantly decreased in comparison with C group (18.13 ±4.07ng/ml). Furthermore, it was found that there was non-significant positive correlation between serum levels of SHBG and LH, TT, E2, insulin, IR-HOMO, VITD3, and negatively associated with FSH, PRL and FSB in patients. Thus, it can be stated that the decreases of level SHBG were associated PCOS with primary infertility.

http://doi.org/10.22401/ANJS.28.1.03
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1. Introduction

Ovulation disorders is a common cause of infertility in women, which leads to polycystic ovary syndrome (PCOS). Infertility is a common issue that has a significant social and economic impact on the population and severely affects one of the most prevalent factors affecting people's quality of life and personal health [1]. Infertility can be caused by various conditions, including issues related to sperms, endometriosis, ovulation disorders, fallopian tubal disease, chromosomal abnormalities, and unexplained infertility, [2-5]. The most prevalent hormonal disorder affecting women is called polycystic ovarian syndrome (PCOS), which is characterized by a variety of signs and symptoms along with different endocrine, metabolic, and reproductive abnormalities that lead to infertility [6]. This syndrome can lead to severe health conditions such as hypertension, type 2 diabetes, infertility, and uterine cancer [7]. Polycystic ovarian syndrome (PCOS) has been associated with several genes, nutritional factors, and environmental factors; still the exact cause of PCOS is still largely unclear [8]. Therefore, the exact causes of polycystic ovarian syndrome remain unknown. Possible causes include genes, inflammatory response, insulin resistance,

environment, and androgen levels [9]. Therefore, approximately 18% of women are estimated to have PCOS according to the Rotterdam criteria. Whereas the American National Institute of Health (NIH, USA) as well as the diagnostic criteria of the National Institute of Child Health and Human Development (NICHD, USA) indicate that 4-8% of women who are reproductively aged have PCOS [10]. Approximately 60–80% of PCOS individuals have an obesity or overweight diagnosis. [11]. A high body mass index is linked to a higher chance of infertility issues, thus, fertility is expected in many obese women [12]. Polycystic ovarian syndrome (PCOS) and obesity are related because obesity intensifies the clinical and hormonal PCOS signs and increases the risk of obesity in women with (PCOS) [13]. A hypothesis has been put up that the pathophysiology of polycystic ovarian syndrome (PCOS) is associated with hormonal imbalance (testosterone combined with FSH, LH, and LH/FSH ratio), which leads to specific physical characteristics [14]. A woman may eventually get tested for PCOS after trying in failed to become pregnant. Polycystic ovarian syndrome (PCOS) is characterized by high level of luteinizing hormone, low level of follicle-stimulating hormone (FSH), and increased insulin as well as androgens in a large percentage of women [15]. Hormonal disorders (rare or no menstruation) can cause both oligo menorrhea and amenorrhea [16]. The ovaries may overproduce androgens (testosterone) or be unable to produce enough estrogen, which can result in additional clinical symptoms such hair and skin complaints [17]. Furthermore, PCOS being the growth of small antral follicles on the ovary's periphery, irregular menstruation, an ovulatory, subfertility, and hyperinsulinemia and hyperandrogenism, can therefore impair the growth of ovarian follicle and cause the hallmarks of polycystic ovary syndrome (PCOS) [18]. A sex hormone binding globulin protein, also known as SHBG, binds to both estradiol and testosterone. Patients differ significantly in how much is present, and the amount of active (bioavailable) testosterone also varies depending on the level of SHBG. Therefore, it is essential to measure SHBG in every patient with polycystic ovarian syndrome [19]. A typical sign of hyperandrogenism in PCOS-affected women is a decrease in the transport carrier plasma sex hormone-binding globulin (SHBG), which binds estrogen and androgens and regulates their biological actions [20–21]. Nonetheless, after a careful review of previous literature, it was observed that there was a lack of knowledge regarding the correlation of the sex hormone binding globulin with some other biomarker in pcos associated primary infertility. Therefore, the study aimed to estimate and correlate (FBS), (IR-OMO), (SHBG), in addition to vit. D3, (FSH), (TT), (E2), (LH), (PRL), and the incidence of PCOS, associated with primary infertility with an emphasis on sera samples of Iraqi women.

2. Materials and Methods

The 70 participants involved in this study included 40 non-infertility controls and 30 PCOS patients with primary infertility. The research ethics committee (REC) at the Training and Human Development Center in Rusafa Health Department, Baghdad, Iraq, has approved this research work. The approval number is (164727). The patients gave their written, informed consent in the native tongue. The patient's age ranged from 19 to 40 years old and primary infertility were the inclusion criteria. The body mass index (BMI) was computed once the medical history was obtained. Every sample was collected starting from Nov. 2023 to March 2024. A case control study was carried out at Kamal Al-samarrai hospital / Baghdad / Iraq. And Exclusion criteria: Patients suffering from hypertension, hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, chronic smoking, and thyroid disorders. The parameters of anatomical measurements: Weight and Height. The same weighing machine was used to record the weight of the patients and controls. Standing with their feet together, head straight forward, heels flat against the upright bar of the height scale, and head erect in the Frankfort horizontal plane, the individual was measured. The apparatus used to measure the examinee's height was a vertical bar with a horizontal wood bar that was pulled down tightly on top of the head [22]. Blood sample collection: During a 10–12 hour overnight fast, each infertile and healthy control woman had approximately 5 ml of whole blood extracted between 7 and 8 a.m. via vena puncture using a disposable syringe. The SHBG was estimated by utilizing an ELISA technique the hormone FSH, LH Prolactin and testosterone were analyzed by the corresponding kit from Cobase Company (Germany) and SHBG ELISA kit from SUNLONG company (CHINA). The mean ±SE was used in the statistical analysis, which yielded the "P" value. A significance threshold of less than 0.05 was applied to a "P" value.

3. Results and Discussion

Table no.1 showed the comparison of the studied parameters between pcos associated with the primary infertile and non-infertility control group. It

was observed that there was a non-significant change in age (p value =0.356) and BMI (P value =0.0001) between the two groups. The obtained results indicated that there was significant increase in the level of hormone SHBG (p value= 0.0001), LH (P value =0.0001), PRL (P value =0.0012), Testosterone (P value =0.0001), Estrogen (P value =0.0349), FBS (P value =0.0001), Insulin resistance (P value =0.0479), while vitamin D3 (0.0089) has significantly decreased in comparison to control group. The level of hormone FSH, as listed in (Table 1) was less in the infertile women group with PCOS as compared to women in fertile group (6.46 ±0.37 vs 6.62 ±0.24 ;p=0.204). Therefore, it was statically not significant.

Table 1. Biomarkers levels in the Study Group

Parameter(unit)	Primary infertile	Control	p-value	sig
Age (years)	26.91 ±1.09	27.56 ±0.81	0.356	NS
BMI (kg/m^2)	28.85 ±1.03	23.74 ±0.30	0.0001**	S
SHBG (ng/ml)	3.014±0.26	9.975 ±0.72	0.0001**	S
FSH (mIU/ml)	6.46 ±0.37	6.62 ±0.24	0.204	NS
LH (mIU/ml)	8.89 ±1.46	5.13 ±0.26	0.0001**	S
LH /FSH %	1.46 ±0.23	0.669± 0.16	0.0001**	S
PRL (ng/ml)	19.42 ±4.44	7.77 ±0.52	0.0012**	S
Testosterone(ng/ml)	0.172 ±0.02	0.131 ±0.01	0.0001**	S
E2 (pg/ml)	129.98 ±64.09	41.97 ±1.66	0.0349*	S
FBS(mg/dl)	103.08 ±3.48	76.88 ±1.80	0.0001**	S
Insulin(mIU/ml)	19.90 ±5.02	12.10 ±1.09	0.307	NS
Insul in resistance%	5.96 ±1.77	2.04 ±0.18	0.0479*	S
VIT D3(ng/ml)	11.78 ±1.41	18.13 ±4.07	0.0089**	S
Values were presented as mean ± SE (BIM) body mass index (FSH) follicular stimulating hormone (PRL) prolactin (LH) lutenizing hormone, (TT) total testosterone (FBS) fasting blood suger (IR) insulin resistance, NS:Non Significant, S:significant.				

In terms of age, of infertile women with PCOS women cases and fertile women, the results showed no significant differences (26.91 ±1.09 vs. 27.56 ±0.81). The results showed that BMI in this study was significantly increased (28.85 ±1.03 vs 23.74 ±0.30) in PCOS with primary infertile when compared with control group. This result is in agreement with Nestler, J. E. et al., [26]. The SHBG illustrates significant decrease in pcos with primary infertile patients compared with control (3.014±0.26 vs 9.975 ±0.72 p =0.0001). This result is in agreement with M.S. Farman et al. who suggested that the suppressive influence of insulin on sex (SHBG). The levels of SHBG are negatively correlated with circulating insulin levels or with the "degree of insulin resistance" in women with or without PCOS [27]. FSH level in Table 1 indicates a decrease in the PCOS infertile women group as compared to women from the fertile group (6.46 ±0.37 vs. 6.62 ±0.24; p=0.204) no significant disagreement previously reported by Ryam et al. (2023). (FSH) levels in women with (PCOS) appear to be low or within the lower follicular range. Their response to gonadotropin-releasing hormone (GnRH) is largely similar to that of ovulatory Control (6.188 ± 2.745 vs 8.406 ± 3.293; P= 0.01) [28]. LH concentration in Table 1 shows a significant statistical increase in the proportion of PCOS-affected infertile women compared to the control group (8.89 ±1.46vs5.13 ±0.26; P=0.001) which agrees with the results reported by Khmil et al. (2020) in infertile women, because of PCOS. One common symptom of (PCOS) is dysfunction in ovulation. Research has shown that GnRH release in PCOS patients is relatively fast. It does not usually slows down in response to progesterone and estrogen. One of the most common signs of PCOS in women is increased LH production [29]. The serum level of PRL was found statistically highly significant the serum PRL in primary infertile group when compared to control group mean & SE (19.42 ±4.44 VS 7.77 ±0.52 ng/ml). The result is in agreement with the result reported by Shikha et al. An elevated level of prolactin in the blood has also been linked to a decreased ability to conceive by inhibiting the hypothalamic-pituitary-gonadal axis and the pulsatility for gonadotropin-releasing hormone (GnRH). Perprolactinemia affects gonadal steroid production, which in turn affects positive feedback on gonadotropins, resulting in follicular immaturity and, ultimately, infertility with anovulation. This is because gonadotropins are secreted and react on at developing follicles in the

ovary [24]. The testosterone concentration increase and statistically significant compare to pcos with primary infertile and control (0.172 ±0.02 vs. 0.131 ±0.01 P = < 0.001) this result agreement with Mariya et al [24]. In this study, the findings showed that there is a significant increase in estrogen hormone in pcos with primary infertile compare with control (129.98 ±64.09 vs. 41.97 ±1.66 P = 0.0349), the finding of my study revealed that women belonging the patient group significantly elevated of FBS compared control group (103.08 ±3.48 vs 76.88 ±1.80 P=0.001) in our finding the result agree with Alev Özer et al. [24]. The insulin increase in patient group compare with control with but no statically significant (19.90 ±5.02 vs 12.10 ±1.09 P=0.307). This result agrees with A. H. Jawad et al., Özer A. et al., Gupta P. et al. [30-32].

Table 2: Correlation of serum SHBG levels in PCOS w ith primary infertile with other biochemical and hormone marker

Parameter	SHBG (ng/ml)	p-value
	r	P
FSH (mIU/ml)	-0.002	0.992
LH(mIU/ml)	0.114	0.605
PRL(ng/ml)	-0.089	0.694
TT(ng/ml)	0.122	0.580
Estrogen(pg/ml)	0.124	0.583
FBS(mg/dl)	-0.016	0.941
Insulin((mIU/ml)	0.000	0.999
IR-HOMO%	0.158	0.663
VitD3 (ng/ml)	0.298	0.323
r: Pearson's correlation coefficient, FSH; follicular stimulating hormone, LH; lutenizing hormone, PRL; prolactin, TT; total testosterone, FBS; fasting blood sugar, IR; insulin resistance		

SHBG in pcos with primary infertile was positively correlated with, LH, TT, estrogens insulin, IR-HOMO, VITD3, and negative correlated with FSH, PRL and FSB as shown in table 2. Meanwhile there were positive correlations highly significant between FSH &E2 (r=0.615, p=0.002), prolactin and insulin (r=0.771, p=0.009), FBS &IR-HOMO (r=0.680, p=0.031). There were no significant negative correlated between insulin and insulin resistance (r=-0.731, p=0.479) and insulin resistance & PRL had no significant positive correlations (r=0.506, p=0.164) were shown in table 2.

Table 3: Correlation of serum SHBG levels in control with other biochemical and hormone marker

Parameter	SHBG(ng/ml)	
	R	P
FSH (mIU/ml)	0.171	0.273
LH(mIU/ml)	-0.066	0.680
PRL (ng/ml)	-0.225	0.146
TT (ng/ml)	-0.18	0.907
Estrogen (pg/ml)	-0.246	0.112
FSB (mg/dl)	-0.081	0.604
Insulin ((mIU/ml)	0.118	0.746
IR-HOMO%	-0.144	0.691
VitD3(ng/ml)	-0.187	0.723
r: Pearson's correlation coefficient, FSH; follicular stimulating hormone, LH; lutenizing hormone, PRL; prolactin, TT; total testosterone, FBS; fasting blood sugar ,IR; insulin resistance .		

Table 3, the SHBG in control was positively correlated with FSH (r= 0.171, p=0.273), insulin (r=0.118,p=0746) and negatively correlated LH, FBS, PRL, TT, estrogen, IR-HOMO,vitD3. Meanwhile, highly significant negative correlation between vit. D3 and insulin resistance (r=-1.000,p=0.000), FSH and LH was weak correlated and positive non-significant. Insulin & IR-HOMO were positive

correlation highly significant (r =0.940,p=0.000). In Iraq there was no previous research that reported this correlation and the present study suggests that SHBG is a good index.

4. Conclusions

The significant variation in the range of these parameters between PCOS patients with primary infertility and control may provide a different perspective on the etiology of infertility. Therefore, it is possible that the current parameters can be used to diagnose PCOS as well as PCOS patients who have complained of syndrome X.

Acknowledgments: Thanks for all the fertile and infertile women (volunteers) who participated in this study.

Conflicts of Interest: The authors declare no conflict of interest.

Funding Statement: This research was self-funded

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