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RESEARCH ARTICLE

ESTIMATION OF SERUM GONADOTROPIN HORMONES AND INSULIN LEVELS AMONG STEIN-LEVENTHAL SYNDROME PATIENTS

^{1,*}Dr. Omer Mohamed Shoaib and ²Ihab Hamed Nourein

¹Department of Clinical Chemistry, Faculty of Medical Sciences, Alzaeim Alazhari University, Sudan

²Department of Histopathology, Collage of Medical Laboratory, University of Sciences and Technology, Sudan

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ABSTRACT

Background: Stein-Leventhal syndrome, also called polycystic ovarian syndrome (PCOS) is the most common endocrinopathy that affects women. Has been one of a major public health problem in Sudan that leads to medical consequences. It causes multifactorial in etiology such as menstrual dysfunction, hyperandrogenism, hirsutism, insulin resistance (IR), dyslipidemia and obesity which increased risk of diabetes mellitus and cardiovascular disease. We know that if patients with PCOS are screened for these diseases, many long-term complications can be prevented.

Objective: The present study was designed to assess serum gonadotropin hormones [luteinizing hormone (LH), Follicle stimulating hormone (FSH)] and insulin in PCOS Sudanese women and to compare them with healthy women as controls.

Materials and Methods: This study was a descriptive, analytic, cross-sectional and hospital-based study, included Sudanese women with PCOS live in Khartoum- State- Sudan, in period from March 2013 to May 2014. A total of two hundred Sudanese women with PCOS were compared with one hundred healthy women as control group, all of them were age matched. Samples were taken from test and control group in morning after overnight fasting, then serum LH, FSH and insulin levels were analyzed using ELISA technique. Data management and analysis were done using Microsoft excel and SPSS software, version 20.00.

Results: The patients with PCOS, having a mean age of 29.61±5.4 years and mean age 31.23±4.93 years of control group. The (mean ± SD) of serum luteinizing hormone, follicle stimulating hormone and insulin in test group were 14.60±9.80 mIU/ml, 6.51±2.04mIU/ml and 11.06±6.21 µIU/ml, respectively while that of control group, the (mean ± SD) of serum luteinizing hormone, follicle stimulating hormone and insulin were 7.00±3.36 mIU/ml, 8.13±3.88 mIU/ml, and 4.52±1.60 µIU/ml respectively. There was statistically significant increased levels of serum luteinizing hormone, insulin and decreased serum level of follicle stimulating hormone in PCOS group when compared to the control group (P<0.05).

Conclusion: It concluded that there was a significant high level of serum fasting LH, insulin and decreased serum FSH, in our study there was no significant correlation could be found between serum LH, FSH and serum insulin. But there was a significant correlation could be found between serum FSH and LH.

INTRODUCTION

Stein-Leventhal syndrome, also called polycystic ovary syndrome (PCOS) is the most common female endocrine (hormonal) disorder, affecting approximately 5-10% of women of reproductive age (Car 1992). It is characterized by chronic anovulation with oligo-menorrhea which occurs in up to 80 per cent of patients, and is one of the leading causes of infertility, metabolic abnormalities, obesity and cardiac disease (Goldenberg *et al.*, 2008; Boomsma *et al.*, 2008; Palacio 2006 15). It is the commonest cause of anovulatory subfertility and recurrent miscarriage. PCOS is seen in around 50-60 per cent of women with more than three early pregnancy losses (Vinker 1997), infertility typical sonographic appearance of the ovaries with multiple small follicles distributed around the

ovarian periphery or throughout the echodense stroma (Jones 1996) and clinical or biochemical hyperandrogenism. Insulin resistance is present in 40-50% of patients, especially in obese women (Aral 1983) although this syndrome was first identified in 1935, physicians still do not know what causes it. Their research today, however, has been focused on the far-reaching effects of this syndrome on a woman's health, as well as its role in infertility. Researchers most recently have achieved a new understanding of the role of insulin-resistance and high levels of insulin in PCOS patients. Insulin resistance can be characterized as impaired action of insulin in the uptake and metabolism of glucose. (Jump up 2013) Impaired insulin action leads to elevated insulin levels, which causes a decrease in the synthesis of 2 important binding proteins: insulin-like growth factor binding protein (IGFBP-I) and sex hormone binding globulin (SHBG). IGFBP-I binds to IGFBP-II and SHBG binds to sex steroids, especially androgens. The triad of hyperandrogenism, insulin resistance, and acanthosis nigricans

*Corresponding author: Dr. Omer Mohamed Shoaib,
Department of Clinical Chemistry, Faculty of Medical Sciences,
Alzaeim Alazhari University, Sudan.

(HAIR-AN) syndrome appears in a subgroup of patients with PCOS. (Jump up 2013; Jump up 2014, Teede *et al.*, 2010) Acanthosis nigricans, a dark and hyperpigmented hyperplasia of the skin typically found at the nape of the neck and axilla, is a marker for insulin resistance. Acanthosis nigricans is usually found in about 30% of hyperandrogenic women.

Increased luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) was the first laboratory abnormality identified in classic PCOS. Elevated LH levels occur in about half of PCOS patients (Teede *et al.*, 2010; Carbutaru *et al.*, 2004). Elevated LH is thought to play a role in the pathogenesis of PCOS by increasing androgen production and secretion by ovarian theca cells (Gambineri *et al.*, 2006; Ehrmann *et al.*, 1995). Patients with PCOS have an increased LH pulse frequency and amplitude (Rosenfield *et al.*, 2010). The increase in LH seems to be the result of abnormal sex steroid feedback rather than the cause of androgen excess (Rosenfield *et al.*, 2010). Although frankly virilizing androgen levels will suppress LH in women, the modest rise in androgen levels in patients with PCOS paradoxically stimulates LH pulsatility.

This is because patients with PCOS are less sensitive to suppression of LH by luteal phase hormones than are controls. Antiandrogen treatment normalizes the elevated LH pulse frequency of PCOS, suggesting that androgen excess interferes with the hypothalamic inhibitory feedback of female hormones, principally progesterone. Other lines of evidence also argue against the hypothesis that PCOS is primarily caused by abnormal pituitary function. About half of patients with PCOS, principally obese patients, do not have elevated LH levels or abnormal gonadotropin responses to gonadotropin-releasing hormone (GnRH) agonist testing (Gambineri *et al.*, 2006; Rosenfield *et al.*, 2011). Furthermore, about half of PCOS subjects with a documented ovarian source of hyperandrogenism were demonstrated to have normal LH levels and LH responses to a GnRH agonist test, also suggesting that their ovarian dysfunction is independent of LH excess.

In women, the gonadotropins act within the hypothalamus-pituitary-ovary regulating circuit to control the menstrual cycle (Johnson *et al.*, 1983; Scott *et al.*, 1989). LH and FSH released in pulses from the gonadotropic cells of the anterior pituitary. The levels of the circulating hormones are controlled by steroid hormones via negative feedback to the hypothalamus. In the ovaries FSH, together with LH, stimulates the growth and maturation of the follicle and hence also the biosynthesis of estrogens in follicle. The FSH level shows a peak mid-cycle, although this is less marked than with LH. Due to changes in ovarian function and reduced estrogen secretion, high FSH concentrations occur during menopause. (Johnson *et al.*, 1983) Determination of FSH concentration is used in the elucidation of dysfunction within the hypothalamus-pituitary-gonads system. The determination of FSH in conjunction with LH is utilized for the following indications: congenital diseases with chromosome aberration (e.g Turners syndrome), polycystic ovaries (PCO), clarifying the amenorrhea (causes) and menopausal syndrome (Scott *et al.*, 1989; Juhl *et al.*,

1994). A high level of LH is found in about 4 in 10 women with PCOS. A high LH level combined with a high insulin level means that the ovaries are likely to produce too much testosterone.

MATERIALS AND METHODS

Reagent

All chemical reagents were purchased from Bio system company (Spine Company for Analytical material and chemical Reagents).

Subjects and Study Population

The present study is descriptive, analytic, cross-sectional and hospital-based study, it was carried out on 200 PCOS subjects in the age group of 17 to 40 years and 100 voluntary age and BMI matched healthy women with normal menstrual cycle as controls. The study was conducted at Khartoum educational teaching Hospital. The diagnosis of PCOS was fulfilled as per Rotterdam criteria. Presence of at least two criteria from clinical, hormonal and abdominal USG category was considered diagnostic of PCOS. Patients with diabetes mellitus, hypertension, dyslipidemia, renal and liver failure and other endocrine disorders and patients receiving hormonal / non-hormonal treatment for PCOS were excluded from the study. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants. A pre-structured and pre-tested proforma was used to collect the data. Baseline data including age, BMI, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology. Serum FSH, LH and insulin were measured in all participants from morning blood samples collected after 12 hours of fasting. Serum FSH, LH and serum insulin were measured by ELSIA technique. Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m²).

Samples Collection and Preparation

The blood samples were drawn in the morning after overnight fasting in the morning (between 0800 and 1100 h). Five ml blood from each individual of study population, were collected from both test and control group, using standard venipuncture techniques. Sample was allowed to clot for 30 minutes and then centrifuged at 3000 rpm for 10 minutes to obtain clear, transparent serum. The separated serum was analysed for serum LH, FSH and insulin estimation or stored at 2-8°C for maximum period of 5 days if not tested immediately. Hormones determined using ELSIA technique.

Statistics analysis

Data were analyzed by computer program (SPSS) version IBM 20. Student T. test was used for the Calculation. $P \leq 0.05$ was considered significant.

RESULTS

On continuous measurements are presented as Mean \pm SD. The basic characteristics of all participants are shown in Table 1,

and mean distribution of biochemical parameters in the cases and controls are depicted in Table 2.

Table 1. Mean ± SD Baseline characteristics of patients with PCOS and control group

Variable	PCOS group	Control group	P. value
Age/years	29.61±5.41	31.23±4.93	0.060
Weight/Kg	72.83±10.88*	68.03±11.31*	0.030
Height/Cm	160.00±6.00	162.60±5.52	0.210
Height/Cm	29.76±4.24*	24.14±3.76*	0.001

P. value <0.05 is statistically significant.

Table 2. Mean ± SD distribution of biochemical parameters in PCOS Cases and controls

Parameters	PCOS group	Control group	P. value
LH mIU/ml	14.60±9.80 *	7.00±5.26*	0.001
FSH mIU/ml	6.51±2.04	8.13±3.88	0.002
Serum insulin (µIU/ml)	11.06±6.21*	4.52±1.60*	0.001

* The means is a significant difference between different values, (P<0.05).

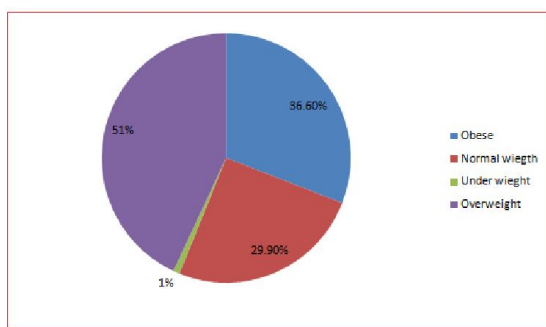


Figure 1. Distribution of percentage of BMI among case study

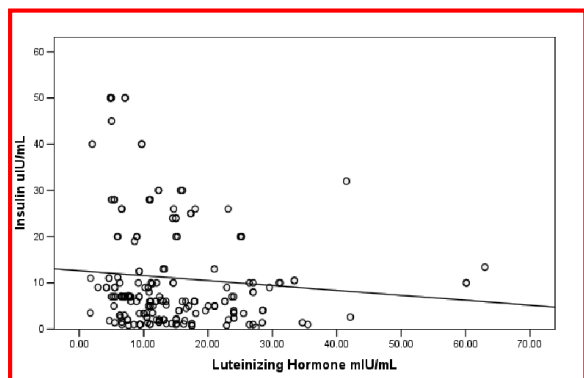


Figure 2. Ascatter polt shows a colration between insulin and Luteinizing hormone (r=-0.08, p=0.025)

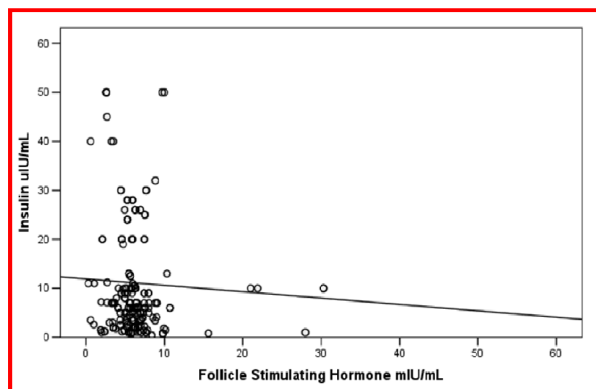


Figure 3. Ascatter polt shows a colration between insulin and Follicle stimalitnig hormone (r=0.05, p= 0.46)

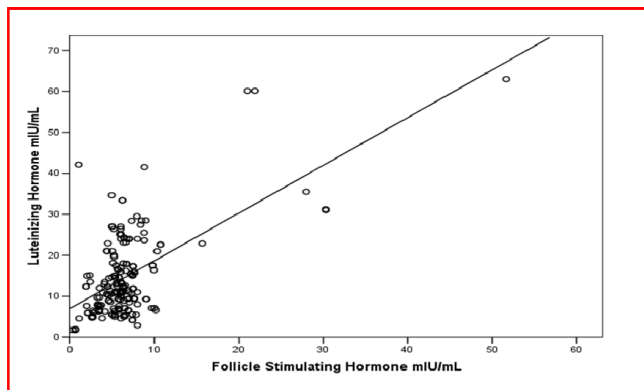


Figure 4. Scatter polt shows a colration between Luteinizing and Follicle stimulating Hormone (r=0.60, p=0.00)

There was no significant difference in age between two groups. Slightly higher mean BMI was recorded in cases than in controls but the difference in mean BMI between the two groups was statistically significant (P<0.05). Higher means of fasting serum Insulin, LH and lower mean of serum FSH were recorded in cases compared to controls and the difference between them were found to be statistically significant (P<0.05). [Figer 1] shows the distribution of percentage of body max index (BMI) among case study. Moreover there was no significant correlations could be found between LH, FSH and serum insulin level in cases study [Figures 2&3], similarly in the persent study, a significant correlation could be found between LH and FSH [Figure 4].

Serum luteinzing hormone

Table (2) shows a highly significant difference between the means of serum LH of the test group (n=200) and the control group (n=100). Mean±SD :(14.60±9.8) versus (7.00±5.26) mIU/ml, P=0.001. Figure [2] shows no a significant correlation could be found between the insulin and the serum levels of LH, (r = -0.08, p = 0.25). In this study 89(44.5%) subjects with PCOS had abnormal high serum levels of LH.

Serum follicle stimulating hormone

Table (2) shows no significant difference between the means of serum FSH of the test group and the control group Mean±SD :(6.51±2.04) versus (8.13±3.88) mIU/ml, P<0.05. However figure [3] shows no a significant correlation between the insulin and the serum levels of FSH. (r=0.05, p= 0.46). In this study 7(3.5%) subjects with PCOS had abnormal high serum levels of FSH.

Serum insulin

Table (2) shows highly significant difference between the means of serum insulin of the test group and the control group. Mean±SD: (11.06±6.21) versus (4.52±1.60) µIU/ml, P=0.001. In this study, 70(35%) subjects with PCOS had abnormal high serum levels of insulin.

DISCUSSION

Polycystic ovary syndrome (PCOS) is a heterogeneous condition that presents in various combinations of a wide variety of physical and biochemical symptoms.

Many of these symptoms arise shortly after menarche, which frequently occurs at a younger age in this population of women. Approaching menopause many of the symptoms of PCOS are ameliorated (Winters 2000). In this study a test group of 200 patients with polycystic ovary syndrome were compared to 100 apparently healthy volunteers, both groups were matched for age and height. Weight and body mass index were significantly raised in patients with polycystic ovary syndrome compared to controls, according to interpretation of BMI, 51% were found to be overweight (BMI between 25 and 29.9 Kg/m²), 36.6% were obese (BMI > 30 Kg/m²), whereas 11.5% were found to have normal reference weight (BMI between 19 and 25 Kg/m²), and only 1% were found to be under weight (BMI < 19 Kg/m²).

In the 1999 National Health and Nutrition Examination Survey in U.S on women with PCOS (Flegal *et al.*, 2002), it was reported that the prevalence of obesity, was found to be (42%) which was higher than in the present study subjects (36.6%) whereas in Spanish patients with PCOS it was (30%) (Asuncion *et al.*, 2002), while the prevalence of obesity in Greek women with PCOS was found to be (38%) (Diamanti *et al.*, 1999). The overweight women with PCOS in the present study constitute about (51%). These data suggest that the majority (more than 83%) of patients with polycystic ovary syndrome in the present study have BMI above the normal reference. In this study, women with polycystic ovary syndrome had significant increased serum levels of Luteinizing hormone and low serum follicle luteinizing hormone when compared with control subjects, our present study demonstrated that only about 44.5% of the PCOS patients had elevated level of circulating LH, this disagrees with finding of (Laven *et al.*, 2002), he reported that, elevated LH concentrations (above the 95th percentile of normal) can be observed in 60% of PCOS women. This means that the (LH) to (FSH) ratios 2:1 is elevated among case in our study, The ratio of LH to FSH, when measured international units is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1 (Banaszewska Wild *et al.*, 2003) or 3:1 (eMedicine, 2011) as tested on Day 3 of the menstrual cycle.

The pattern is not very sensitive; a ratio of 2:1 or higher was present in less than 50% of women with PCOS in one study. (Banaszewska Wild *et al.*, 2003), also our finding in agreement with a study done by (Wild *et al.*, 1985) who reported that patients with polycystic ovary syndrome had higher serum (LH) to (FSH) ratios, also this agrees with a study done by Fauser *et al.*, who reported that, Both the absolute level of circulating LH and its relationship to FSH levels are significantly elevated in PCOS women as compared with controls, this is due to increased amplitude and frequency of LH pulses. Elevated LH concentrations (above the 95th percentile of normal) can be observed in 60% of PCOS women (Laven *et al.*, 2002), whereas the LH/FSH ratio may be elevated in up to 95% of subjects (Yen *et al.*, 1970), if women who have ovulated recently are excluded.

LH levels may be influenced by the temporal relationship to ovulation, which transiently normalizes LH, by the BMI (being higher in lean PCOS women) and by the assay system used. In the current study, there was a very weak negative correlation between the serum levels of luteinizing hormone and the serum levels of insulin, this result agrees with a study done by (Yen *et al.*, 1970) who reported that serum LH concentrations are commonly elevated in women with PCOS.

Conclusion

The current study demonstrated that the, PCOS causes significant increased levels of serum insulin, LH and reduced level of FSH, with increased LH/FSH ratios in women and high body mass index. Weight reduction in obese women with the polycystic ovary syndrome should be encouraged (Dahlgren *et al.*, 1992) in an effort to limit the risk of hyperinsulinemia, type II diabetes and long-term cardiovascular disease. More investigations should be done to demonstrate the relationship between hyperinsulinemia, elevated LH level, and insulin resistance obesity in PCOS patients. In addition to the elevated BMI increases the risk for insulin resistance and Diabetes Mellitus.

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