Effect of Body Mass Index on Abnormal Ovarian Secretion Hormones among Iraqi Women with Polycystic Ovarian Syndrome (PCOS)

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Abstract
Polycystic ovarian syndrome (PCOS) is the most common and complex endocrine disorder affecting women in the reproductive age. The etiology of this syndrome is not completely known, so there is a developing proof that supports genetic basis, PCOS has a strong familial preference. This study was carried out to investigate the effect of body mass index (BMI) on ovarian hormones in women with PCOS and healthy women. Eighty-three women aged (17-40) years were divided into two groups for testing (BMI less than 25 and more than 25). Hormonal study of Luteinizing hormone (LH), Androgen, Estradiol (E2) was done for each patient, the results of these hormones in patients compared with controls in both BMI groups with E2/T ratio showed a significant increase in patients women compared to controls in (p<0.05), While the results of Follicle stimulating hormone (FSH) and Total Testosterone (TT) showed an increase with not statistically significant. It has been concluded that the increase in BMI doesn’t show to have an opposite effect on FSH, Androgen, E2, and TT levels but the result of LH shows a highly significant increase in PCOS groups compared to controls when BMI>25. [DOI: 10.22401/ANJS.22.1.06]

Keywords: Polycystic ovarian syndrome, LH, E2, FSH, TT, BMI, ovarian hormones, Androgen.

Introduction
Polycystic Ovarian syndrome (PCOS) is the most frequent heterogeneous endocrine disorder in reproductive age group [1] according to the study procedure enrollment and the diagnostic criteria [2] PCOS is a lifelong endocrine condition [3] With an estimated worldwide prevalence of 6–21% based on the diagnostic criteria utilized [4], also known as Stein–Leventhal syndrome [5]. The name “polycystic ovarian syndrome” refers to the presence of large cysts in the ovary that appears in the ultrasound due to the ovarian follicle that may be visually similar to ‘cyst’ along the outer periphery of the enlarged ovaries [6].

In 1990 the National Institutes of Health (NIH) proposed the diagnostic criteria for this disorder, based on the presence of hyperandrogenism (clinical or biochemical) and chronic oligoovulation, with the exclusion of other causes of hyperandrogenism [7] such as congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting neoplasms [8]. PCOS is not only a hyperandrogenic disorder associated with young and fertile-aged women but may have some health complications for the women in later life [9]. An agreement conference held in Rotterdam, 2003, reconsidered the 1990 criteria and admitted the chance of including ultrasound morphology of the ovaries to define PCOS as a potential criterion [7]. Overflowing luteinizing hormone (LH) and reduced follicle stimulating hormone (FSH) is more popular in PCOS [10]. High-level of LH is an inextricable characteristic of this syndrome, was observed in approximately half of the patients [11].

Body mass index (BMI) has an opposite relationship with Androgen levels in men whereas it seems to have a synergistic impact in women. The increment in fat tissue and body weight is related to the change in sex steroid equilibrium in premenopausal and postmenopausal women. These changes, for the most part, include androgens and estrogens. The proof for an immediate relationship between BMI and androgens isn't completely clear [12]. Levels of serum androgen both in the circulation and ovaries are increased, that can inhibit ovarian follicular maturation and growth, lead to hirsutism anovulation, acne, and other clinical signs and could produce female infertility and influence women's quality of life. Several factors can cause hyperandrogenisms, such as environment, gene, endocrine, and other
factors [13]. BMI has been measured as weight (in kilograms) divided by height (in meters squared) [14]. Obesity was the factor that predicted the poor quality of life along with hirsutism, nearly 75% of patients are overweight; however, a high Waist-hip ratio (WHR) showing increased abdominal fat even in normal weight with PCOS [3]. Women with PCOS were commonly obese or overweight with cardiovascular disease, impaired glucose tolerance (IGT) and increased risk of type II diabetes [10] while lean patients didn’t have an increased risk of type II diabetes compared to obese women. Treatment with oral contraceptives (OCP) has been accounted for to be related with weight gain [15].

Many investigations propose that adiposity is related to hyperandrogenaemia [16,17]. There are three possible mechanisms have been proposed for androgen hyper-secretion include: an intrinsic functional theca cell defect, hyperinsulinemia following insulin resistance and hypersecretion of pituitary LH resulting in extreme theca stimulation [18]. The Continuous aerobic exercise raises glucose intake, decreases visceral adiposity, functional capacity, and decreases cardiovascular risk factors [14].

Materials and methods

The present study comprised of 83 women (63 patients and 20 controls) the patients suffering from polycystic ovarian syndrome PCOS all the women aged between 17-40 years. The studied group was divided into two group (BMI < 25 Kg/m² contain 13 women in control1 group and 22 women in PCOS1 group and BMI > 25 Kg/m² contain 7 women in control2 group and 41 women in PCOS2 group) some of patients with one child were collected from Kamal AL-Samarai Hospital, center of fertility and in vitro fertilization (IVF) in Baghdad during the period from December 2017 to March 2018 and 20 healthy females with regular periods (26 to 30 days), no history of endocrine diseases, without any drugs intake and devoid of conditions like diabetes mellitus, hypertension, dyslipidemia and heart disease. The diagnosis of disease was made by a physician with exclusion of presence of other diseases known to be associated with PCOS (Late-onset congenital adrenal hyperplasia (CAH), Androgen-secreting tumors, Cushing’s syndrome, Thyroid disorders and Elevated prolactin) [19] any two of the three criteria are sufficient for the diagnosis suggested by the Rotterdam ESHRE/ASRMS sponsored PCOS consensus workshop group [20], Including oligo and/or anovulation, clinical and/or biochemical signs of increased androgen levels; high serum androgen levels and ultrasound criteria of the syndrome; A single ovary contains at least 12 follicle that are 2-9 mm in diameter and/or an enlargement in the ovary’s size to at least 10 cm³ [21].

None of the study sharers had been using hormonal drugs for the previous three months before the hormone measurement. After a woman has been diagnosed with PCOS, they were attributed according to their BMI, the normal weight group was in a range between 18.5 to 24.9 Kg/m² and the overweight group was in a range between 25.0 to 29 Kg/m² [22].

Experimental part

All parameters were estimated by utilizing an ELISA technique, the hormones FSH, LH, E2, and TT were analyzed by corresponding Kits from Monobind Inc. company (USA) and Androgen hormone was analyzed by Human Androgen (ANDROGEN) ELISA kit from Shanghai company (China). Two ml venous blood samples have been collected from each woman of both PCOS and healthy control between 8 AM and 11 AM. The serum collected by putting the blood in a clean dry gel tube and left to clot at 37°C for 20 min then was put in the centrifuge at 6000 rpm for 10 min. Serums are separated in simple plastic tubes and kept in the freezer till used for the hormonal assay.

Statistical analysis

The Data were analyzed using SPSS statistical package for Social Sciences (version 20.0 for Windows, SPSS, Chicago, IL, USA). Shapiro–Wilk normality test was used to determine whether the studied parameters followed a Gaussian distribution. All values were expressed as mean ± standard deviation. Independent samples t-test was used to compare between means of the studied groups.
Results and Discussion

Table (1) and Table (2) show the means and standard deviations (SD) of Androgen, luteinizing hormone (LH), follicle stimulating hormone (FSH), Total Testosterone (TT) and Etradiol (E2) for the PCOS and control groups.

There was a widespread variability in the percentage of women that had a raise in body weight accompanying PCOS across the globe [23]. As represented in the table (1), in PCOS1 group there was an increase in serum TT compared to controls with not statistically significant. This was in agreement with (Holte et al.) [17] who suggested that there were no significant differences in TT levels between the non-obese groups (BMI ≤22 Kg/m²) on the other hand (Koiou et al.) [24] found there was significant increase in TT level (p-value <0.001). PCOS is, heterogeneous and polyfactorial endocrinopathy in women with reproductive age, but, the pathophysiology is still vague [23]. FSH in PCOS1 group shows an increase compared to control1 with not statistically significant. These findings apposed with (Koiou et al.) [24] who found a significant decrease in patients compared to controls. There was a highly significant increase in androgen levels in patients compared to control1. There is evidence that androgen level contributes significantly to the growth of metabolic disorders [25], on the other hand the proof for an immediate relationship between BMI and androgens isn't completely clear [12]. LH shows a significant increase between PCOS1 and control1 this matches with (Koiou et al.) [24] yet; this increase was not statistically significant. In ovarian follicle theca cells, the resistance to FSH and the raised LH/FSH ratio are linked with intensified androgens hyper secretion, which stifles the inhibition of GnRH pulse frequency and decreases follicular growth moreover stimulate the growth of the PCOS phenotype [26].

The present results were in agreement with (Gen et al.) [27] and (Holte et al.) [17] who found that PCOS women with normal weight had higher concentration of serum LH and LH/FSH ratio. In ordinary conditions, final maturation, and also ovulation, happens upon LH incitement. In this syndrome, rapid GnRH pulse frequency may be included by the neuroendocrine abnormality, which supports pulse amplitude over FSH product and LH frequency. The abnormality adds to raised circulating LH/FSH ratio and is usually observed in lean PCOS women not in obese ones [26]. E2 and E2/T show highly significant increase (p=0.000) between PCOS1 and control1 group. By the negative feedback mechanism of a hypothalamic-pituitary system, E2 affects ovarian folliculogenesis, where E2 leads to reductions in the FSH release. It is crucial in the positive feedback mechanism [28]. The sex hormones may play major roles in the metabolism of cholesterol, androgen levels apparently lead to increasing serum levels of estrogens by exerting the opposite influence. The overall influence of these steroids in PCOS women is difficult to predict [26] as not only androgens level but also estrogen effect may be elevated, due to peripheral aromatization; adipose tissue serves as the main site of peripheral aromatization of androgens to estrogens.

The mechanisms between the sex hormones and visceral fat remains not entirely explained. Several studies had documented that the deficiency of estrogen leads to promoted central fat accumulation during the following potential mechanisms: adipose tissue oxidative stress, adipocyte hypertrophy, and inflammation raising the uptake of lipids from the circulation and decreasing energy expenditure [29]. World Health Organization (WHO) made that 25 kg/m² < BMI ≤ 30 kg/m² was considered as overweight and BMI more than 30 kg/m² as obese. Approximately 35%-65% of women with PCOS have overweight or obesity. High BMI can influence both clinical and pathophysiology manifestations of PCOS [30].

Table (1)

Hormonal profile of Control (C1) group and PCOS1 group by BMI<25 (kg/m²).

| Parameters     | (C1) group (n=13) | PCOS1 group (n=22) | P value |
|---------------|-------------------|--------------------|--------|
| Androgen (nmol/L) | 2.81±0.92         | 8.36±3.05          | 0.000  |
| LH (mIU/ml)    | 4.76±1.18         | 5.86±0.89          | 0.04   |
| FSH (mIU/ml)   | 5.13±1.69         | 5.9±1.16           | 0.500  |
| TT (ng/ml)     | 0.42±0.23         | 0.56±0.11          | 0.053  |
| E2 (pg/ml)     | 42.15±13.20       | 97.66±22.36        | 0.000  |
| E2/T ratio     | 0.099±0.04        | 0.171±0.04         | 0.000  |
As summarized in Table (2) the serum Androgen shows a highly significant (p-value 0.000) increase in PCOS2 group compared with the non-PCOS group. PCOS is presumably the consequence of a number of pathophysiological pathways: elevated LH levels, ovarian abnormalities and hyperinsulinemia, all these leading to raised ovarian androgen secretion [31]. LH shows significant increase in patients compared with controls, this matches with (Koiou et al.) [24], the level of LH is an essential parameter in PCOS, but, is not involved in Rotterdam 2003 criteria, due to the level changes with the days of the menstrual period [32]. High level of serum LH is a complicated feature in women with PCOS, which obtained in approximately half of the patients. When LH is minimally suppressed is the best time for determining LH level, and this is between 2 weeks from the beginning of the menstruation cycle and 3 weeks before the following cycle. This stage is named the ‘specific oligomenorrhoic phase’ (SOP) that only present in periods longer than 35 days [11]. FSH shows an increase in patient’s (PCOS2) comparison to control2 with not statistically significant. (Koiou et al.) [24] found decrease in FSH level in patients compared to controls with not statistically significant. usually, the serum LH and LH/FSH ratio measurement is done in the follicular phase of the menstrual period (i.e. day first to third) and hence, the prevalence of raised LH/FSH ratio is underestimated and thus producing a limited role in the diagnosis of the syndrome [32]. TT shows increase with not statically significant in patients compared to controls this matches with (Nur et al.) [33] while (Koiou et al.) [24] found highly significant increase. E2 and E2/T ratio shows a highly significant increase in PCOS group compared to healthy women. In this study, menstrual irregularities were seen in nearly all patients (97%); these results are analogous with the conclusion of (Haider et al.) [32] who similarly showed menstrual period disorders among 99.4% of women with this syndrome.

Table (2)

| Parameters | (C2) group (n=7) | PCOS 2 group (n=41) | P value |
|------------|-----------------|---------------------|---------|
| Androgen (nmol/L) | 2.33±0.66 | 8.60±3.30 | 0.000 |
| LH (mIU/ml)    | 4.10±0.66 | 5.77±1.20 | 0.005 |
| FSH (mIU/ml)   | 5.07±1.52 | 5.66±1.73 | 0.469 |
| TT (ng/ml)    | 0.52±0.19 | 0.62±0.30 | 0.444 |
| E2 (pg/ml)    | 39.25±9.94 | 96.24±28.01 | 0.000 |
| E2/T ratio    | 0.07±0.02 | 0.13±0.033 | 0.000 |

Conclusions

Increase in BMI (18.5-30 Kg/m²) involve lean and overweight women) doesn’t show to have an opposite influence on FSH, Androgen, E₂, and TT levels but the result of LH shows a highly significant increase (p=0.005) in PCOS groups compared to controls in BMI>25.

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