Hormonal Study of the different phenotypes of polycystic ovary syndrome

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Abstract:

This study was done in Kamal al-Samarrai hospital/ Baghdad since the beginning of July2013till December, 2013. Hormonal changes in the serum of polycystic ovary syndrome (PCOS) infertile women and control women were estimated in the second day of the menstrual cycle. Fifty females with PCOS (25 severe, 25 mild) were included in this study in addition to 25 apparently healthy females as a control group. This study aim to evaluate and compare hormonal changes between the different PCOS phenotypes to those in healthy women. LH, LH/FSH ratio and testosterone concentrations was high in severe PCOS than in the mild PCOS and control group ($P<0.05$). Similarly, compared with control group LH, LH/FSH ratio and testosterone level were also elevated in women with mild PCOS ($P<0.05$), while there were no differences in FSH level between the two phenotypes of PCOS and controls ($P>0.05$). In conclusion hormonal imbalance plays an important role in PCOS, as found milder form of hormonal imbalance in mild phenotype of PCOS.

Key words: polycystic ovary syndrome/phenotype/ Hormones.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age [1] and is the most frequent cause of hyperandrogenism and anovulation [2]. In consequence, prevalence is difficult to conclude and depends on the used definition, as well as the ethnicity of the measured population. Most studies report prevalence between 6−15% and sometimes even up to 20%, depending on used criteria [3]. Despite high incidence, the etiology of PCOS remains unknown. Due to the heterogeneity in the representation of clinical and biochemical features, it has been debated whether PCOS actually represents one single disorder or several ones. Symptoms of PCOS often

manifest around puberty, but the origin may be programmed already as early as during fetal development [4]. One of the most common features of PCOS is insulin resistance, represented in 85% of PCOS women [5]. The other common feature of PCOS, elevated androgen levels, affects around 60−80% of PCOS women and can result in the clinical signs: hirsutism, acne, and, to some extent, alopecia [6] and high levels of luteinizing hormone with normal levels of follicle stimulating hormone [7]. The syndrome is also associated with hyperinsulinemia, glucose intolerance, abnormal blood lipid levels, and obesity, which constitute the metabolic syndrome [8],Uncontrolled ovarian steroidogenesis with a thickened thecal layer that secrets excessive androgen is thought to be a primary abnormality of PCOS [9]. In 1990 during an expert conference arranged by the National Institutes of Health (NIH) as chronic anovulation and hyperandrogenism (clinical and/or biochemical) [10]. Both criteria were necessary for the diagnosis. A new expert conference in Rotterdam 2003, arranged by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recognized PCOS as a syndrome that encompasses a broad spectrum of signs and symptoms, including at least two of the following: ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology (PCOM) [11]**.** In 2006, the Androgen Excess and PCOS Society (AES) proposed the AE-PCOS criteria emphasizing that hyperandrogenism should be considered as the key-feature of PCOS [12].

In this study,PCOS is defined according to the Rotterdam criteria[11]. Based on these newer criteria and their clinical manifestations divided phenotype of PCOS into severe PCOS (ANOV+HA +PCO) and mild PCOS (ANOV+PCO).

The 2003 Rotterdam criteria are the subject of ongoing controversy [13]. Some studies suggest mild PCOS, are characterized by less severe endocrine and metabolic abnormalities [14]. However, others reported that these differences are mainly due to the higher prevalence of obesity in women diagnosed with PCOS according to the NIH criteria [14].

FSH is synthesized and secreted by gonadotropins in the anterior pituitary gland; it is a glycoprotein that regulates the development, growth, pubertal maturation and reproductive processes of the human body. In females, FSH stimulation of ovarian function is believed to be important for proliferation of granulosa cells, production of follicular fluid, induction of aromatase enzyme activity starting at mid follicular phase, with the concomitant rise in inhibin B (a complex protein that down regulates FSH

synthesis and inhibits its secretion) and induction of LH receptors in the late follicular phase. FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to ovulation [15].

LH is produced also by the anterior pituitary gland; it is a glycoprotein and essential for reproduction. In females, In the late follicular phase, LH may also play an important role in further growth of the follical, and weakens the wall of the follicle in the ovary and results in the rupture of the ovarian follicles causing the fully developed follicle and development of the corpus luteum [16].

Testosterone is a steroid hormone from the androgen group. It is the principal male sex hormone, produced by testes in men and by thecal cells of the ovaries and placenta in women [17] .Testosterone is also synthesized by zona reticulais of the adrenal cortex in both sexes. In general, Testosterone has both anabolic and virilizing effects [18].

Hormonal profiling forms an important tool to elucidate basic pathogenesis of PCOS and can also be used for differential diagnosis. In addition to clinical prognosis.

This study aim to evaluate and compare hormonal changes of the different PCOS phenotypes and healthy women.

MATERIALAND METHODS

Subjects: - This study was conducted from July, 2013to December, 2013. All women who were diagnosed with PCOS were choosed from Kamal al-Samarrai Hospital while healthy women were choosed from hospital staff and friends. Informed consent was obtained from all patients. Exclusion criteria for all the subjects included hypothyroidism, hyperprolactinemia, Cushing's syndrome, congenital adrenal hyperplasia, current or previous (within the last six months) use of oral contraceptives glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and anti-obesity drugs or other hormonal drugs .The present study included (75) females, 25 healthy women were enrolled as the control group with normal ovulatory cycles, no signs of hyperandrogenism and normal sonographic appearance of the ovaries ,25 patient with phenotype 1 (Severe PCOS) including women with both severe hirsutism and severe menstrual dysfunction either amenorrhea or severe oligomenorrhea and 25 patient with phenotype 2 (mild PCOS) .

The diagnoses of patients with PCOS were evaluated by gynecologist doctor, sonographist and laboratory assessment. Details of the number and age of the three groups are illustrated in Table (1):

Table (1): Details of number, and age of the studied groups.

Groups	Number	Range of age (years)
Control	25	18-42
Severe PCOS	25	18-36
Mild PCOS	25	19-42

Blood Sampling:

Ten milliliters of venous blood was withdrawn from the cubital vein of each participant using disposable syringes during the second day of menstrual cycle.The blood samples were allowed for (15) minutes at room temperature to clot and serum was separated by centrifugation at 3000 rpm for (10) minutes. Serum samples were either analyzed immediately or stored at (-28 □C) until they were analyzed.

Hormonal Assay:

Luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH ,total testosterone, were estimated in the second day of the menstrual cycle using (ELFA) technique using a ready for use kits supplied by (BioMerieux Company, France). The procedure for estimation of each hormone was obeyed precisely as described in the leaflet supplied with the kit.

Statistical analysis:

The means, standard deviations, Kruskal-Wallis Chi square -test and P-value were used to compare the significance of different data. The overall predicted values for the results in both studied groups were performed using SPSS program version 20. When (P-value<0.05), the relation considered to be significant.

RESULTS AND DISCUSSION:-

Data presented in (Table2 and Fig 1, 2) demonsrtreted that, the mean serum levels of LH, LH/FSH ratio, and Testosterone in phenotype 1 (severe PCOS) were significantly higher than phenotype 2(mild PCOS) and control groups (P<0.05). Also results revealed that there is raised LH, LH/FSH ratio, Testosterone in phenotype 2(mild PCOS) compared to control groups (P<0.05). It can be noticed that there was no significant difference in FSH hormone between the different phenotypes of PCOS and controls (P>0.05).

This is in accordance to Legro et al who had reported that the ratio of LH to FSH in PCOS patients was 2.9 compared to a value in the normal group [19]. The gonadotropin releasing hormone (GnRH) pulse frequency designates the preferential production of LH via high frequency pulses versus FSH via low frequency pulses in normal adult women. The pulse frequency is regulated by progesterone in presence of estradiol such that increased progesterone production by corpous luteum slows LH pulse frequency to favor FSH production, which aids in follicular development for the next menstrual cycle. Women with PCOS have abnormally rapid LH pulses with reduced response to progesterone feedback, contributing to elevations in LH: FSH ratios [20]. Hayes et al concluded that the data of their study on the assessment of neuroendocrine and androgen dynamics imply that, the enhanced pituitary sensitivity is responsible for the elevated LH amplitude in PCOS [21].

The present data shows that, the mean LH level is higher in severe PCOS compared in mild and control group. This is in accordance to previous studies. Taylor et al reported that 75% of women with clinical evidence of PCOS have an elevated LH level [22]. An abnormal feedback mechanism by ovarian estrogen is blamed to play role in this discriminated increase in LH release [23].

Our PCOS patients show mean FSH within normal range. Same results has been obtained by Waheed [24] .The negative feedback control of FSH is critical for development of the single mature oocyte that characterizes normal reproductive function in women .The reduction levels of FSH lead to inhibition of aromatase activity thus causing accumulation of androgen, also leads to impaired follicular development and therefore, granulosa cell atresia and not a single follicle is permitted to mature enough for ovulation to occur[25].

Our PCOS patients show mean testosterone were higher in severe PCOS compared in mild and control group compared. These results are in agreement with the study of Fulghesu et al.,[26]. Increasing of testosterone level associated with LH department ovarian over production of androgens[27],This may be because testosterone opposes the inhibitory feedback action of estrogen on the release of gonadotropins ,and at a base line women with PCOS had higher LH pulse response to GnRH, this higher LH lead to hyperplasia of the theca cells and increased androgens production [28]

The high levels of testosterone is responsible of hirsutism s in women lead to presence of the secondary characters of men in women and

this because of high levels of in free androgens which leadto the increase estrogen in esteron form that make a appositive feed back on LH secretion which lead to increase testosterone secretion from the ovary[29].

Table (2) Comparison of serum hormones levels between the different phenotypes of PCOS and the controls .

Parameter	Severe(n=25) Mean ±SD	Mild(n=25) Mean±SD	Control(n=25 Mean±SD	*P- value (overall)	S vsM	S vs C	M vs C
LH(mIU/ml)	9.48±3.60	4.89±2.18	2.50±0.80	0.000	0.000	0.000	0.000
FSH(mIU/ml)	5.37±1.74	4.95±1.72	5.10 ±1.27	NS	NS	NS	NS
LH/FSH	1.78±0.60	0.92±0.21	0.47±0.17	0.000	0.000	0.000	0.000
T(ng/ml)	1.47±0.62	0.94±0.27	0.24±0.17	0.000	0.001	0.000	0.000

SD- standard deviation,*P value less than 0.05 was considered statistically significant. NS=non-significant.

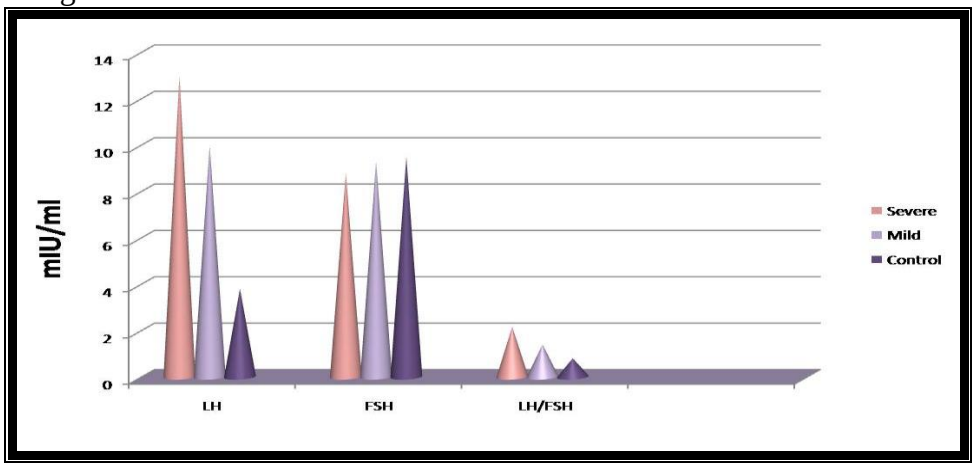

Figure (1): Serum levels of LH, FSH, and LH/FSH ratio between the different phenotypes of PCOS and the controls.

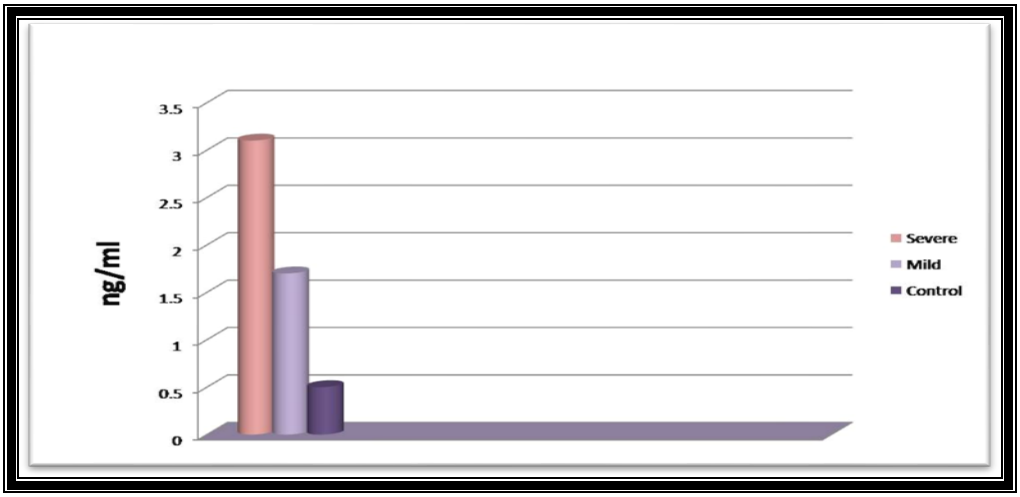

Figure (2): Serum levels of testosterone between the different phenotypes of PCOS and the controls.

CONCLUSIONS:

Women with PCOS, normal gonadotropin-ovarian axis are disturbed. This is reflected by the higher levels of LH and reversal LH: FSH ratio and higher level of testosterone in PCOS, so hormonal imbalance plays an important role in PCOS. We found milder form of (LH, LH/FSH,testosterone) in mild PCOS. Iraqi PCOS women show similar trend in this regards.

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الخلاصة

أجريت هذه الدراسة في مستشفى كمال السامرائي / بغداد منذ بداية تموز 2013وحتى كانون الاول 2013 . تم تقدير التغيرات الهرمونية في مصل النساء العقيمات المصابات بمتلازمه تكيس المبايض والنساء الأصحاء في اليوم الثاني من الدورة الشهرية. اشترك في هذه الدراسه 50 انثى لديهن متلازمه تكيس المبايض (25 شديد، 25 معتدل) بالإضافة إلى 25 من الاناث السليمات كمجموعة سيطره. هذه الدراسة استهدفت تقييم ومقارنه التغيرات الهرمونية بين مختلف الانماط الظاهريه من متلازمه تكيس المبايض لتلك الموجودة في النساء السليمات. تراكيز الهرمونات(LH,LH/FSH ratio and T) كانت عالية في النمط الظاهري الشديد من متلازمة تكيس المبايض مقارنه بالنمط الظاهري المعتدل و مجموعه السيطره ($P<0.05$). وبالمثل مقارنه مع مجموعه السيطره كانت مستويات الهرمونات عاليه في النساء مع النمط الظاهري المعتدل من تكيس المبايض ، في حين لم نجد فروق في مستوى FSH بين اثنين من الانماط الظاهريه لمتلازمة تكيس المبايض ومجموعه السيطره ($P>0.05$). وقد خرجنا بان عدم التوازن الهرموني يلعب دورا مهما في متلازمة تكيس المبايض, كما وجدنا شكل اخف من عدم التوازن الهرموني في النمط الظاهري المعتدل من متلازمه تكيس المبايض .