Journal of Scientific Research in Medical and Biological Sciences
ISSN 2709-0159(print) and ISSN 2709-1511 (online)
Volume 4, Issue 3 Article 4
DOI: https://doi.org/10.47631/jsrmbs.v4i3.646

EVALUATION OF POLYCYSTIC OVARY SYNDROME (PCOS) THROUGH ANDROSTOLONE AND PITUITARY HORMONES LAB TESTING

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ARTICLE INFO

Received: 10 March 2023
Revised: 20 June 2023
Accepted: 26 June 2023

Keywords:
Polycystic Ovary Syndrome (PCOS), Androstolone, Hyperandrogenemia

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ABSTRACT

***Purpose**: Hyperandrogenemia is an essential symptom of PCOS. Androgens are produced in the ovaries and adrenal glands as the final products of a series of enzymatic reactions starting from a common precursor, i.e., cholesterol. The critical intermediate stages of androgen production involve the conversion of cholesterol into dehydroepiandrosterone and androstenedione.*

***Subjects and Methods:** It is estimated that more than 80% of women who exhibit signs or symptoms of hyperandrogenism, including hirsutism, acne, or alopecia, have PCOS.*

***Results:** Abnormalities in the neuroendocrine system like increased pulse frequency of gonadotropin-releasing hormone, stimulating the pituitary for excessive production of luteinizing hormone than that of follicle-stimulating hormone seen in PCOS women. Excess LH stimulates ovarian androgen production, whereas a relative deficit in FSH impairs follicular development.*

***Conclusions:** The imbalance in LH: FSH causes proliferation of ovarian theca cells leading to increased steroid genesis, and ultimately leading to hyperandrogenism in PCOS women.*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, characterized by hyperandrogenism, ovulatory dysfunction, and sonographic evidence of polycystic ovaries (Bernier *et al*., 2022). affecting (5.6-21.3%) of women of reproductive age worldwide (Doretto *et al*., 2020). The Rotterdam criteria are used to diagnose this condition, and at least two of the three criteria are met: 1) hyperandrogenism (HA) clinical or biochemical), 2) menstrual irregularities (oligomenorrhea or amenorrhea), and 3) polycystic ovaries verified by ultrasonography (Kasim & Saadoon, 2022). It is responsible for 40% of infertility cases in women. Moreover, it is a major cause of endometrial cancer, in addition to reproductive abnormalities. PCOS is also associated with a wide range of metabolic disorders, such as hepatic steatosis, glucose intolerance, dyslipidemia, T2DM, and hypertension (Al-Ghanam *et al*., 2022). Dehydroepiandrosterone (DHEA) is an important precursor of androgen

and has been studied and researched extensively for improving the various outcome measures of ovarian stimulation in women with advanced age or poor ovarian response (Noushin et al., 2021). hyperandrogenism is considered as a key element in the pathogenesis of this common endocrinopathy. However, until now, studies about ovarian androgen profile in women are very rare (Bongrani *et al*., 2022).

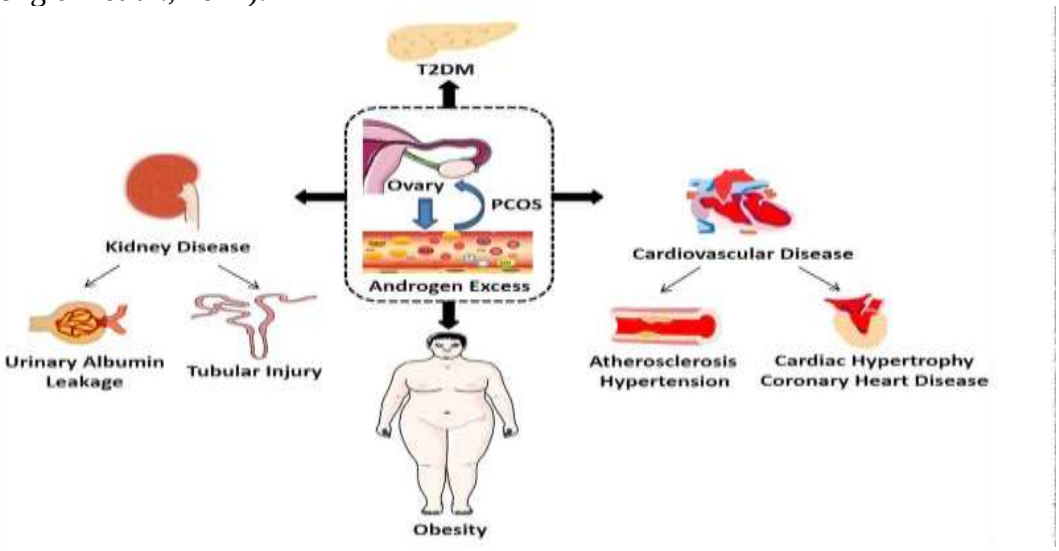

Figure 1: The role of androgen in PCOS and PCOS-related complications (Ye et al., 2021)

Follicle-stimulating hormone (FSH) is a glycoprotein that plays a central role in mammalian reproduction and development. In the ovary, FSH regulates folliculogenesis, oocyte selection, and the synthesis of sex steroid hormones, thus preparing the reproductive tract for fertilization, implantation, and pregnancy (Casarini & Crépieux, 2019). The association between hyperandrogenism and anovulation is complex. Women with PCOS often have an increased pulsatility of gonadotropin-releasing hormone (GnRH), resulting in the increased pituitary release of luteinizing hormone (LH) and an elevated LH/follicle-stimulating hormone (FSH) ratio. LH stimulates androgen synthesis by theca cells, while FSH stimulates the aromatization of androgens to estrogen by granulosa cells, and follicle maturation (Tanbo *et al*., 2018). Follicle-stimulating hormone (FSH) is produced by the pituitary gland in a coordinated hypothalamic pituitary gonadal (HPG) axis event, and plays important roles in reproduction and germ cell development during different phases of reproductive development (fetal, neonatal, puberty, and adult life), and is consequently essential for fertility (Recchia *et al*., 2021).

In females, at the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. With the rise of estrogens, LH receptors are also expressed on the maturing follicle which produces an increasing amount of estradiol. Eventually, at the time of the maturation of the follicle, the estrogen rise leads via the hypothalamic interface to the "positive feedback" effect, a release of LH over a 24–48 hour period (Zhang *et al*., 2019). Luteinizing hormone (LH) is a glycoprotein hormone that is co-secreted along with follicle-stimulating hormone by the gonadotrophin cells in the adenohypophysis (anterior pituitary). Luteinizing hormone is a part of a neurological pathway comprised of the hypothalamus, the pituitary gland, and the gonads. In this pathway, LH release is stimulated by gonadotropin-releasing hormone (GnRH) and inhibited by estrogen in females and testosterone in males. LH has various functions, which differ between women and men (Nedresky & Singh, 2021). LH is responsible for inducing ovulation, preparation for fertilized oocyte uterine implantation, and the ovarian production of progesterone through stimulation of theca cells and luteinized granulosa cells.

Prolactin (PRL), also known as a luteotropic hormone or luteotropin, is a protein known for its role in milk production in mammals, usually females. It affects more than 300 separate processes in different vertebrates, including humans (Mourupoju & Sundaresan, 2018). It is a 23 kDa single-chain protein of 199 amino acids synthesized and released principally by lactotrophs in the anterior pituitary gland. The secretion is mainly under inhibitory control by hypothalamic dopamine and regulated in a negative feedback manner, with prolactin itself providing the afferent signal: short-loop feedback. The main function of prolactin is during pregnancy and lactation in the development of mammary glands, milk synthesis, and maintenance of milk secretion. Serum prolactin levels rise rapidly during pregnancy with an increase in the size and number of lactotrophs (Saleem *et al*., 2018).

METHODOLOGY

The study was divided into two groups: The first group is the patient group, which consists of 45 patients who were identified by a specialized gynecologist of the "Fertility Center in AL-Sadder Medical City in Najaf Province/Iraq, during the period from the 1st of October. 2022 to 1st March. 2023, according to the Rotterdam criteria (2003), which requires the presence of at least two of the following characteristics: polycystic ovaries on ultrasound scan, menstrual irregularities and hyperandrogenism. The age group of the patients ranged from (17-45) years. The inclusion criteria for the patients are all patients with PCOS. The second group is the control group, which consists of 45 women, with a regular menstruation period, and normal ovulation are eligible, with normal ovaries as they were observed by the gynecologists which no take contraceptives, and no past of somewhat malady. The age group ranged from (17-45) years.

Blood collection

The blood samples for this investigation were drawn from females who were in the luteal phase using medical sterile syringes to collect 5 ml of blood from the brachial vein, which was then put in a gel tube. After the blood had been allowed to coagulate for 30 minutes at room temperature, samples were centrifuged for 5 minutes at a speed of 3000 rpm to separate the serum from other blood components. To determine the levels of LH, FSH, Prolactin, Testosterone, and DHEA by ELIZA kits, the serum was micropipette-drawn, divided into two repeaters, and deposited in Eppendorf tubes. These tubes were then maintained in a deep freezer at -20 C.

RESULTS AND DISCUSSION

As shown in Figure (2) and Table (1), the mean level of dehydroepiandrosterone (DHEA**)** in the PCOS patients' group was (168.9) and it was significantly increased than in the control group mean level was (70.4) with high significance (Pvalue<0.001). Also, our study is in agreement with (Khan *et al*.,2021) that found: DHEAS levels were high in lean-PCOS in comparison to obese-PCOS and non-PCOS females. Also, our results are in agreement with (Sutaji *et al*.,2023). Carmina et al., (2022) show that Patients with PCOS presented significantly ($p < 0.01$) higher DHEAS levels than controls.

The results shown in the figure explain the mean level of FSH (2.7mlU/ml) in the patient group was a highly significant (0.001) decrease than in control (6.5mlU/ml). Then, the mean level of LH (16.6 mlU/ml) in the patient group was high significant (<0.001) increase than in the control group (12.3 mlU/ml). Also, the prolactin significantly increased mean level (30.7 ng/ml) p-value (<0.001) in patients more than in control (18.9 ng/ml). Finally, the mean level of Testosterone (1.8 µlU/ml) in the patient group was highly significant (<0.001) a nd more elevated than in the control group (0.75 µlU/ml).

Table 1: Serum DHEA level among polycystic women and control

Parameter	Groups	Mean ± SD*	p.value
DHEA (ng/ml)	**Patients No. (45)**	168.9 ± 40.08	<0.001 H.S
	Healthy control No. (45)	70.4 ± 26.18	

*: Standard deviation; **DHEA**: dehydroepiandrosterone; **H.S**: highly significance; two independent t-test

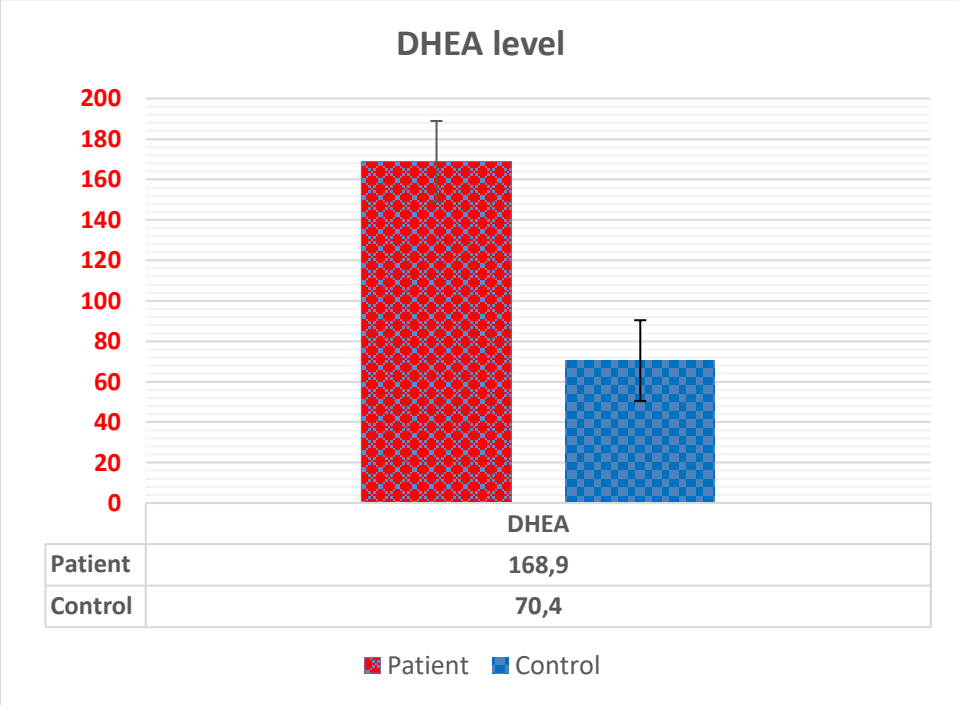

Figure 1: Serum DHEA level among polycystic women and control

Table 2: Hormones level among polycystic women and control

Parameters	Study Group		Statistical test	P-value
	Patients Mean ± SD*	**Control** Mean ± SD		
FSH (mIU/ml)	2.7 ± 1.4	6.5 ± 2.2	**t**=9.5	<0.001**
LH (mIU/ml)	16.6 ± 3.4	12.3 ± 4.06	**t**=5.3	<0.001
Prolactin(ng/ml)	30.7 ± 7.9	18.9 ± 7.1	**t**=7.3	<0.001
Testosterone(ng/ml)	1.8 ± 1.03	0.75 ± 0.2	**t**=6.7	<0.001

***: S**tandard deviation**; FSH:** follicle stimulating hormone**; LH:** luteinizing hormone**; t:** independent t-test**; **:** highly significance.

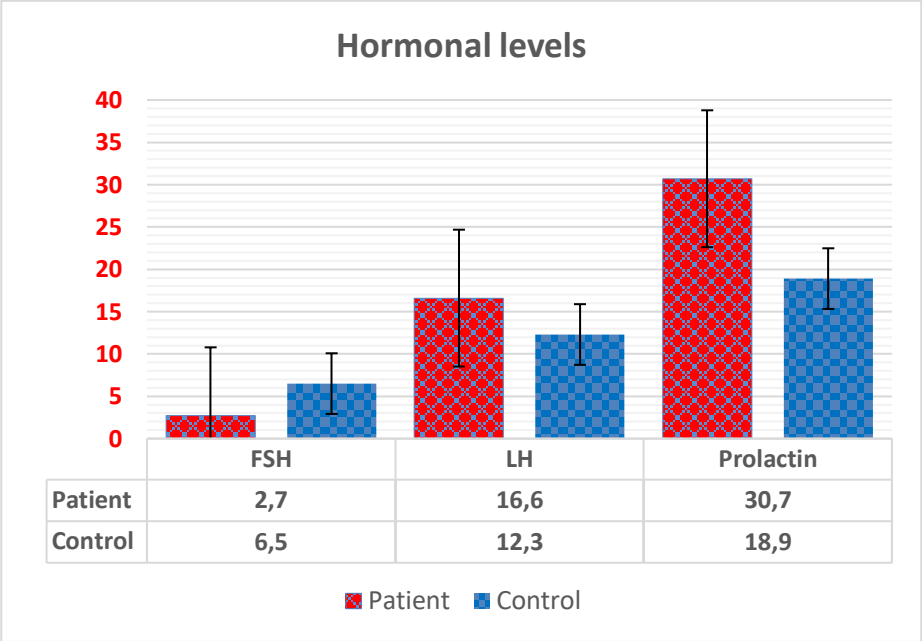

Figure 3: hormones level among polycystic women and control

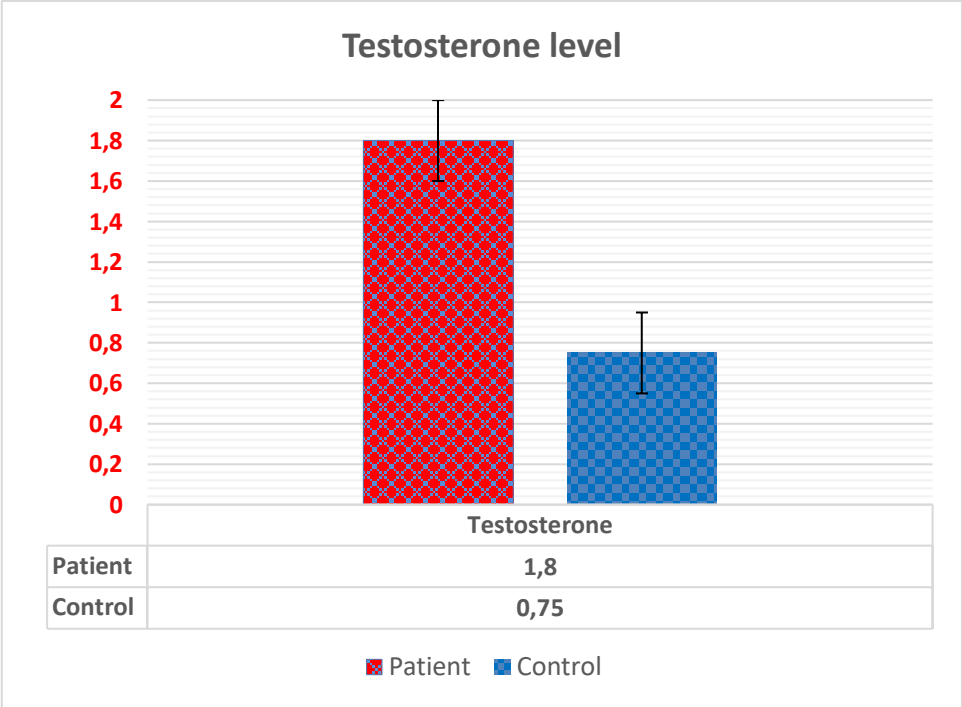

Figure 4: Testosterone level among polycystic women and control

PCOS, the most prevalent illness of endocrine among females in the age of reproduction, is linked with several metabolic syndrome symptoms, including obesity, insulin resistance, hyperlipidemia, hyperpiesia, sleep apnea, and irregular menstruation. These days, the prevalence of PCOS is rising quickly, which could be attributed to dietary and lifestyle changes as well as hormonal imbalances (Zafar *et al*., 2019).

The aberrant ovarian hormonal dynamics associated with PCOS are caused by fast gonadotropin-releasing hormone including recurrence with enhanced pituitary gland sense to gonadotropin-releasing hormone (Okigbo *et al*., 2022a). As a result, there is an increase in the excretion of leutinizing hormone associated with follicle stimulation hormone. Along with

chronic decreasing however continuous estrogen levels. This more strongly limits follicle stimulation hormone than Leutinizing hormone. The sustained rise among gonadotropin-releasing hormones and recurrence is thought as a primary factor among higher production of Leutinizing hormone compared to follicle stimulation hormone from the pituitary. Obesity reduces PCOS-related women's aberrant gonadotropin dynamics. It is thought that higher levels of leptin and/or insulin have a direct inhibitory effect on the release of gonadotropins, mediating this action only at the pituitary (Okigbo *et al*., 2022b).

According to Milnerowicz & Madej (2017), PCOS affects women with hyperandrogenism, which causes Insulin Resistance (IR) amongst muscles of skeletal and tissue of adipose, leading to high levels of circulating insulin. According to Yang et al. (2020a), serum PRL and glucose metabolism interact, with different levels of serum Prolactin having varied effects on how glucose is metabolized. As a result, hyperprolactinemia patients are more prone to experience impaired glucose tolerance and insulin resistance. It is consistent with our study because Jena et al. (2022) found increased prolactin levels in PCOS patients as opposed to the control group. According to Yang et al. (2022b), PRL levels were considerably lower in PCOS patients than controls across all age categories (p 0.05), which is inconsistent with the results of our investigation. The lack of a correlation suggests that abdominal obesity is not the primary cause of LH level abnormalities in PCOS, as could not find any statistically significant changes in LH concentration between PCOS women and the control group. And this is different from our outcomes.

The development of follicles and the production of ovarian steroids both require the gonadotropin FSH. The conversion of androgen to estrogen in polycystic ovary syndrome is abnormal, and FSH and FSH receptors appear to be up-regulated. As with LH, there is a nonstatistic significance difference in this hormone among women suffering from polycystic ovary syndrome and the control group, which is in contrast to the findings of the current investigation. Any increase in hormone release gonadotropin upregulates transcription of the LH -subunit through the FSH -subunit, which produces an increase in the luteinizing hormone / Follicular stimulated hormone percentage amongst polycystic ovarian syndrome patients, according to Khmil et al. (2020), Explanation of the relationship between a significantly higher LH/FSH ratio and PCOS in patients with the condition (Williams *et al*., 2012). Explained that the abnormal levels of DHEA occur in young women, and early adrenarchy was related together with elevated risks of PCOS, in addition Moderately elevated levels of DHEAS in women can cause symptoms of hyperandrogenism, one of the main symptoms of PCOS.

An extreme increase in the hormone may indicate another cause, such as an androgen-producing adrenal tumor (Yoldemir, 2022). In women with PCOS, DHEA prevalence is more than 20 to 30 %. In addition to levels of DHEA decreasing around 45 years of age, the androgens of adrenal gland mechanism increasing amongst females remain non-obvious, because of elevated cortisol metabolisms. This results in low Negative Feedback for adrenocorticotropic hormone excretion (Goodarzi *et al*., 2015). The results of the current study are in agreement with the study by Abd & AL-Azzawie (2021) which described that the women with polycystic ovaries, DHEA hormone secretion is higher in the age group of 31-40 years, and then it begins to decrease with age. However, disagreement with (Cappola *et al*., 2023) mentioned that DHEA levels reach their highest point around the age of 25, after which they steadily fall as you get older.

CONCLUSION

The current study has concluded that the more active fertile age group 20-29 years old are more susceptible to the incidence of PCOS. Increased BMI is associated with an increased incidence of PCOS. Fluctuation of biomarkers in women affected with PCOS. It is observed BMI groups

in PCOS women. The overweight group (25-29.9) is the most group predominant for PCOS women.

ACKNOWLEDGMENTS

This study is supported by the Research Program of the Department of Medical Laboratories, Fertility Center in AL-Sadder Medical City in Najaf Province/Iraq, and Collage of Health and Medical Techniques, Kufa, Al-Furat AL-Awsat University Iraq, My thanks to my teachers and colleagues in the scientific process.

CONFLICT OF INTEREST: No funding sources

FUNDING: None declared

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