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Hormonal disorders changes in women suffering from polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility in reproductive age women around the world and it is identified as hyperandrogenism and chronic anovulation disorder. Because of the great number of women infected by PCOS in Iraq and in Basrah governorate in particular, and due to the increased rates of infertility and miscarriage cases related to PCOS, the current study has been designed to highlight some of the causes of PCOS through the changes in hormonal parameters. This study was done in basrah governorate since May, 2018 until November, 2018, serum samples were collected from (75) PCOS patients and (75) healthy women as control during the luteal phase of the menstrual cycle. Then the consentrations of (estradiol and progesteroneprolactin, testosterone, LH, TSH,T3,insulin ,cortisol, FSH and T4) hormones were measured by using specific ELIZA kits. The results of our study showed that estradiol and progesterone were significantly decreased in PCOS patients than control group ($P<0.05$), while prolactin, testosterone, LH, TSH, T3, insulin and cortisol were significantly increased in PCOS patients than control group ($P<0.05$), but our results showed no differences in the levels of serum FSH and T4 hormones between PCOS patients and controls group ($P>0.05$). In conclusion, the hormonal abnormalities are a characteristic trait in PCOS patients comparing with healthy women with normal hormones and this differences may be play an key role in the origins of PCOS in Basrah women and gives an overview about the causes of the prevalence of this disorder among these women.

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Introduction

Polycystic ovarian syndrome (PCOS),also known as Stein–Leventhal Syndrome, is one of the most common endocrine disorder in a reproductive age women around the world (Azziz *et al*., 2011; Singh *et al*., 2018). A uniform definition of PCOS does not exist because of its diverse and heterogeneous nature, however PCOS is an endocrinopathy and should be referred as a syndrome rather than a disease (Lobo, 1995). PCOS was described at first time in 1935 by American gynaecologist's Stein and Leventhal in seven women suffer from oligoamenorrhea, PCO, obesity hirsutism and acne (Chang *et al*., 2002).

PCOS is characterized by menstrual irregularity, signs of hyperandrogenism like (excess body hairs, acne male-pattern baldness and infertility) also linked to several long term health riskes such as central obesity,dyslipidemia, insulin resistance, type 2 diabetes, hyperinsulinemia, hypertension, cardiovascular diseases and higher rate of early loss of pregnancy (Mccance *et al*., 2010; Chen and Shi, 2010). Whether PCOS is a primary or a secondary ovarian disease remains controversial,the PCOS biological hyperandrogenism can not define PCOS and it has been suggested that the crucial pathophysiological factor of PCOS is dysregulation of the relationship among pituitary, hypothalamus and ovary. However, PCOS also involves in intraovarian functional and morphological abnormalities (Dewailly, 2009).

Recently proposed that PCOS origins in fetal life, it is suggested that exposure to excess androgen, at any stage from fetal development of ovary to puberty leads to several PCOS characteristic features such as LH secretion abnormalities and insulin resistance. The PCOS phenotype development results from a genetic predisposition for the fetal ovary to androgen hypersecretion. It is unclear whether maternal environment influences the PCOS development in offspring and the maternal androgen surplus is improbable to affect the fetus due to the placenta presents an dynamic barrier but the metabolic disturbances during pregnancy could affect development of PCOS in fetus(Franks *et al*., 2006).

A universal agreement among specialty society guidelines that diagnosis of PCOS must be based on the presence of two of the following three criteria at least: clinical or biological hyperandrogenism, chronic anovulation and PCOM also echographic diagnosis have been suggested (Carmina, 2004; Goodman *et al*., 2015). In PCOS patients, the follicle development stops at early stage and ovulation is blocked. The immature follicles turn into cysts and multiple cycles leads to multiple cysts, These cysts are sacs filled with fluid in one or both ovaries and the ovary size enlarged in up to twice the size of normal ovary. In PCOS, eggs are not release due to the follicle development stops so the immature follicle becomes cyst and corpus luteum is either not formed (cyst formation) leading to decrease in progesterone, estrogen hormones and the menstruation delays or stops, or forms when some immature follicle developes normally (Chaudhary and Qamar, 2016).

Different morphological and histological studies of PCOS revealed a thickened in tunica albuginea, hyperplasia in theca interna and cortical stroma with many of subcapsular follicles in several stages of atresia (Ehrman *et al*., 1995). In PCOS, fluid filled sacs grow inside the ovary, these sacs are follicles with immature eggs that never matured to trigger the ovulation which causes hormone imbalances like low levels of estrogen and progesterone with high androgen levels (Pasquali, 2018). Oligomenorrhea in PCOS women found to be associated with epithelial ovarian cancer , while women with irregular menstrual showed a decreased level of many of epithelial ovarian cancer histotypes (Harris *et al*., 2018).

PCOS and endometrial hyperplasia which is a precancerous condition arises in the presence of chronic exposure to estrogen unopposed by progesterone such as in obesity and PCOS are associated with increased risk of endometrial carcinoma (Charalampakis *et al*., 2016). The high levels of LH concentrations in PCOS during the follicular phase have a deleterious effect and may lead to early pregnancy loss so these women do not respond completely to LH treatment (Homburg *et al*., 2016).

It is found that abnormalities in the endometrium of PCOS patients like an increased androgen receptors has a minor effect on fertility and The fertilization rates and normal development of the embryo were lower in PCOS women than in those with regular menstrual cycles (Barnes *et al*., 1996; Apparao *et al*., 2008).

The dysfunctional bleeding in PCOS females and chronic unopposed estrogen associated with anovulation problems leading to endometrial hyperplasia and cancer, while heavy continual bleeding leads to anemia (Carmina and Lobo 1999). Because the increased rates of infertility and miscarriage cases related to PCOS, the current study has been designed to underscore some of the causes of PCOS through the abnormalities in hormonal parameters.

Materialand methods

Subjects

This study was performed in basrah governorate from May, 2018to November, 2018. The diagnoses of women with PCOS were evaluated by gynecologist doctor, sonographist and laboratory assessment froma private gynecological clinic. Required data were collected by using the questionnaire includes (age, marital status ,home, social status, length and weight, number of births, previous abortion, previous ectopic pregnancy, previous,molar pregnancy, oligomenorrhea, other disease, drugs, smoking). Current study included (150) females (75) PCOS patient group and (75) and healthy women (fertile, regular menstrual cycle, no signs of hyperandrogenism and chronic disease) as control group, both groups are age matched (14-45). PCOS paitents and control women did not get any hormonal therapy and medications for last four months of sample collection.

Blood sampling

10 milliliters of venues blood samples from PCOS and control group were collected during the luteal phase in Gel/clot activator tubes and then left for a short time to form blood clot, then serum was separated by using centrifuge (3500 rpm-10 minutes) at room temperature. After that, the serum divided in to 12 eppendorf tubes for PCOS patients and another 12 eppendorf tubes for control group. these tubes were kept frozen at (-20C°) in deep freezer until time of analysis with avoiding multiple freezing.

Hormonal assay

Hormones concentration of PCOS patents and control group were measured by ELIZA kits and the absorbanse was recorded by the ELIZA reader (Mindray (MR-96A)). Sandwich ELIZA method was used for measuring Insulin, Prolactin, Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), (Monobind Inc.) kits, Thyroid-Stimulating Hormone (TSH) (Bioactiva diagnostic) kit,and were measured by using Sandwich ELIZA. Competitive enzyme immunoassay was used for measuring Progesterone, Triiodothyronine (T3), thyroxine (T4) (Monobind Inc) kits, Estradiol (Bioactiva diagnostic), Testosterone (Demeditec Diagnostics) kit and cortisol (Human) kit. The procedure for estimation of each hormone in the serum of PCOS patients and control group was followed exactly as illustrated in the leaflet abounding with the kit and the optical density of these hormones were measured by using ELIZA reader.

Statistical analysis

Statistical Analysis are preformed using SPSS version 20 with $P<0.05$ being considered Statistically significant. Data are expressed as median ± (minimum- maximum) and the difference in the levels of these markers between PCOS cases and control group evaluated by Mann-Whitney Test, Kruskal-Wallis Test and multivariate Anova.

Results and discussion

As shown in the Tables (1,2), the serum levels of estradiol and progesterone are significantly decreased in PCOS patients when compared to control group which are have normal concentrations , while the serum levels of testosterone, prolactin and LH is significantly increased in PCOS patients compared to control group that have normal values, but the level of serum FSH hormone showed no statistical significant difference between PCOS patients and control group. The abnormalities of neuroendocrine in PCOS patients may increase GnRH pulse, which increases the incidence and pulse capacity of LH production

(Banaszewska *et al.*, 2003; Jones, *et al.*, 2015; Dumitrescu *et al.*, 2015) There is several evidences suggests that abnormal ovarian steroidogenesis through over expression of the CYP17 gene being responsible for increased expression of the LH receptor and androgen biosynthesis, which lead the ovarian theca cells to be more sensitive to LH stimulation (Comim *et al.*, 2013).

Table 1. Comparison of serum ovary hormones between control group and PCOS patients.Values was expressed as (median (min- max)).

Ovary hormones	Control(n=75)	PCOS(n=75)
Estradiol(pg/ml)	122.51(37.51-400.01)	48.97(3.707-296.70)**
progesterone(ng/ml)	12.50(0.65-24-21)	1.08 (0.023-18.84)**
testosterone(ng/ml)	0.46(0.02-1.44)	0.91(0.20-8.98)**

*significant at the (P≤0.05)
**significant at the (P≤0.01

Table 2. Comparison of serum pituitary hormones between control group and PCOS patients.

Pituitary hormones	Control(n=75)	PCOS(n=75)
Prolactin(ng/ml)	11.721(1.00-19.92)	25.40(4.64-83.30)**
LH(mIU/ml)	2.23(0.50-10.40)	19.24(4.76-83.50)**
FSH(mIU/ml)	6.40 (1.70-13.50)	4.81(2.39-55.52)

*significant at the (P≤0.05)
**significant at the (P≤0.01)

Ovarian theca cell hyperandrogenism in PCOS patients is a combination of androgen receptor mediated weakness in estradiol and progesterone negative feedback regulation of LH release. The excessive secretion of LH increased the speed of GnRH releasing from median eminence in the hypothalamus, stimulates the steroidogenesis in ovarian theca cell and increase secretion testosterone and androstenedione.

It was assumed that progesterone resistance related with speeding up in LH release. Increased LH levels following acute progesterone receptor blockage diminished the progesterone negative feedback. This dysregulation of LH release in PCOS impaired the feedback mechanism of the hypothalamic GnRH release in evocative of PCOS neuroendocrinopathy. (Abbott *et al.*, 2018).

Elevation of prolactin is caused by reduced dopamine in the tuberoinfundibular tract, Decompensated liver function leads to changing in entering the amino acids in to central nervous system. levels of blood aromatic amino acids increase leading to an increase in the synthesis of false neurotransmitters. These false neurotransmitters may inhibit the releasing of dopamine (Als-Nielsen *et al.*, 2003; Velissaris,2008;Karagiannis and Harsoulis 2005; Jha and Kannan, 2016).

As shown in Table 3, the serum level of insulin, cortisol, TSH and T3 are significantly increased in PCOS patients when compared to control group that have normal concentrations, but there is showed no statistical significant difference in the level of T4 between PCOS patients and control group. Insulin resistance preserves hyperandrogenemia directly, by acting on theca cells stimulating excessive androgen secretion. Insulin also acts as a co-gonadotropin which increasing the effect of LH on ovarian androgen production. In result, Both androgens and insulin inhibit the liver SHBG secretion, increasing free and bioactive androgen levels and making clinical androgen excess more worse. The effect of high LH level and low level SHBG in the liver, induce the increase in androgen secretion in the ovary. then follicle maturation and growth are suppressed (Spritzer, 2014).

The cysts in PCOS are follicles of immature eggs that never matured enough to trigger ovulation so the lack of ovulation causes hormone imbalances such as estrogen, and progesterone levels are low while LH and androgen levels are high, The presence of these cysts are thought to occur because of two abnormalities within the blood hyperandrogenism

and hyperinsulinemia. Hyperandrogenism has been argued to be the defining feature in the disease. Hyperandrogenism causes the egg follicles to be in an arrested state called atresia which inhibits the maturation of the egg. Because the high levels of androgen, the ovary is unable to release an egg for ovulation which causes oligomenorrhea and or amenorrhea (Knisley, 2018).

Table 3. Comparison of serum metabolic hormones between control group and PCOS patients. Values was expressed as (median (min- max)).

Metabolic hormones	Control(n=75)	PCOS(n=75)
TSH (µU/ml)	1.32(0.12-3.70)	1.52(0.34-17.02)**
T3 (µg/dl)	0.93(0.13-1.93)	1.28(0.36-9.34)**
T4 (µg/dl)	7.84 (1.50-11.90)	7.74 (1.57-19.77)
Insulin(µU/ml)	4.53(0.74-109.11)	62.19(1.90-196.07)**
cortisol(ng/ml)	97.71(55.01-250.01)	321.23(17.45-670.140)**

*significant at the (P≤0.05)
**significant at the (P≤0.01)

Increased TSH levels in PCOS patients may be caused by the unopposed esterogen in PCOS patients that excites autoimmune reactions such as formation of thyroid peroxidase antibodies (Padalkar *et al.*, 2017). TSH was found to be positively correlated with testosterone and prolactin in PCOS patients (Chen *et al.,* 2017). The elevated TSH and T3 in PCOS patients may be association with the metabolic changes like insulin resistance, HDL and apolipoprotein A secretion (Yin *et al.,* 2017). The increasing in cortisol level may be occur by the activation of hypothalamic pituitary adrenal axis (Agardh *et al.,* 2003). Cortisol and ACTH levels were found to be higher in PCOS patients than in healthy women. Because overproduction in ACTH in adrenal gland stimulates the increased level of cortisol (Tsilchorozidou *et al.*, 2003).

Increased thyroid hormone increases the secretion of the majority other endocrine glands, it also increases the requirement of these hormones by tissues. Thyroid hormone found to be able to increase the rate of cortisol secretion by the adrenal glands by the inactivation of cortisol in the liver and this leads to feedback increase in adrenocorticotropic hormone production by the anterior pituitary (Guyton and Hall 2006). A shown previously cortisol hormone in the current study was increased in PCOS patients. Which plays an important role to stimulate directly the insulin secretion or indirectly increases gluconeogenesis. This action stimulates β-cells of islets of Langerhans to secret insulin. Increased secretion of cortisol and insulin for a long time leads to attrition of β-cells. Cortisol also decreases the sensitivity of different tissues insulin receptors to the metabolic effects of insulin. Eventually, all these effects can lead to development the diabetes mellitus (Sembulingam and Sembulingam, 2012). High cortisol might contribute to the development of endometrial Insulin resistance by inhibiting the insulin signaling pathway through induction of phosphatase and tensin homolog deleted on chromosome ten expression in endometrial epithelial cells (Qi, *et al.*, 2018).

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