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Abnormalities of Hormones and Inflammatory Cytokines in Women Affected With Polycystic Ovary Syndrome

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Summary
Polycystic ovary syndrome (PCOS) is a common hormone disorder of women. Women with PCOs have difficulty to pregnat and have a high levels of androgens with oligomenorrhea, hirsutism, and obesity.
The present study was designed to investigate of some hormones and inflammatory markers of women with PCOS, Their ages ranged between 23-24 years old. Means of luteal hormone (LH) , testosterone, Insulin, and Homeostasis model assessment (HOMA-IR) were significantly ($p<0.05$) higher in women with PCOs when compared with control women. Concerning means of follicle stimulating hormone (FSH) and estradiol hormone were insignificant different ($p>0.05$) in affected women with PCOs in acomparison with control. Regarding means of inflammatory cytokines including C- Reactive proteins (CRP), interleukin- 6 (IL-6), and leptin have been showed a significant increase ($p<0.05$) in women with PCOS in a comparison with healthy control women. Data obtained from the present study indicate that women with PCOS have hormones disturbances associated with insnlin resistance and elevated levels of inflammatory cytokines may be in turn aggravate infertility of women with PCOS.
Keywords: Polycystic ovary syndrome, insulin resistance, obesity, infertility.

Introduction

Ploycystic ovary syndrome (PCOS) was first recognized in 1935 by two Chicago Gynecologists – Dr. Irving Stein and Michael Leventhal.[1]The consensus conference at Rotterdam would be fulfilled if two out of three features are present: anovulation (usually manifested as oligomenorrhea or amenorrhea), elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestation of androgen excess and presence of polycystic ovaries on ultra sonographi [2,3]. Lines of evidence suggest that PCOS is a heritable disorder. Various approaches have been undertaken to try to define a specific genetic etiology.While a number of candidate genes appear to make modest contributions to the clinical expression of PCOS, no single gene has been confidentaly identified to play predominate role in the pathogenesis of PCOS[4].

The follicles in the ovary are lined by two types of cells , theca cells and granulose cells. Theca cells take cholesterol out of the blood stream and, after a serries of chemical steps, turn it into androstendione, a weak male hormone . Theca cells pass the androstendione on to the adjacent granulosa cells where it is converted in to oestrons a weak oestrogen or female hormone and then converted in to estradiol, a strong female hormone[5].Insulin resistance has been implicated in the pathophysiology of PCOS because of the evidence that insulin stimutates androgen production from the ovary in hyperandrogenic women.Ovarian stroma obtained from hyperandroganic women has been shown to produce high levels of androgens when exposed to insulin [6,7].

PCOS is most of time co-existent with hyperinsulinemia or insulin-resistance which is the key factor for aggravation of ovulation dysfunction and metabolic dearrangements [8]. Also , it has been demonstrated that hyperinsulinemia and insulin resistance are independent of body weight but worsened by obesity[9].

Materials and Methods

- Subject of the study

This study was included 50 diagnosed women with PCOS were recruited in Babylon hospital for maternity and children, and othe outpatient clinics.The dignosis of PCOS is based on the Rotterdam criteria [10], with women satisfy at a least two of the following three criteria:1) oligo menorrhea/ oligovulation ; 2) Clinical hyperandrogenemia, and 3) polycystic ovary on ultrasound examination.

The inclusion criteria of patients involved Body mass index (BMI) $\geq$29, and their ages ranged between 23-40 years. The exclusion criteria were acut illnesses, pregnancy, hypo- hyperthyroidism, hyper prolactinemia, cardiovascular diseases, autoimmune diseases, and smoking. The present study was included 50 aged matched healthy women as a control with normal menstrual cycle.Anthropometric analyses involved ,BMI was calculated by using the formula: weight (in kg / heigh (in meters)[2].The over weight women have BMI $\geq$ 25 kg/m^2. Blood pressure was measured manually with sphygmomanometer.

Fasting blood samples from cases were extracted after diagnosis. Blood was transferred immediately to a non- heparinized tubes for centrifugation . Serum was then transferred to prelabeled plain tubes and stored in-20ºC freezer prior to analysis.

Homeostasis model assessment (HOMA) method for insulin resistance was calcutated by the formula,

fasting serum insulin (milli mole/L)/22.5.Serum luteal hormone , follicle stimulating hormone , estradiol, and testosterone levels were measured according to kits supplied by Biomeariax compamy. Levels of Leptin,. IL-6, and insulin were determined by kits of Biocheck company.

The statistical package for the social sciences (SPSS) version 15.0 was used for statistical analysis.Results was expressed as means ± SD. Differences between means were analyzed by student's unpaired t test. P value <0.05 was considered statistically significant[11].

Results

1- Anthropometric data of women with PCOS and healthy control women are illustrated in table (1). The mean age of women with PCOS was 27. 7 ± 6.31 years and mean age of control women was 26.4± 4.2 years.
2- Hormonal analyses are showed in table 2. The means of LH, testosterone , and insulin showed a significant elevation ($p<0.05$) in women with polycystic ovay syndrom when compared with means of normal women. Level of HOMA-IR pointed out a significant incrase ($p<0.05$) in PCOS. In contrast , the meansof FSH and estradiol showed insignificant differences when compared with control women.
3- Inflammatory cytokines of women with PCOS and healthy women are showed in table 3. The means of CRP, IL-6, and Leptin were significantly higher ($p<0.05$) in women affected with PCOS when compared with healthy normal women:

Table (1): Anthropometric characteristics of women with polycystic ovary syndrome (PCOS) and control women

Parameters	Women with PCOS	Control women
Age (years)	27.7± 6.31	26.4 ± 4.2
BMI (kg/m^2)	29.2* ± 2.5	26.3±1.5
Systolic blood pressnre (mmHg)	126* ± 18	119±14
Diastolic blood Pressnce (mmHg)	85.4± 2.1	80 ±2.3

- Values are means ± SD
- Means with astrik are significantly different ($p<0.05$)

Table (2): Hormonal data of women with poly cystic ovary syndrome (PCOS) and healthy control women

Parameters	PCOS women	Control women
LH (miu/ ml)	12.42* ± 3.15	3.5 ± 1.61
Testosterone (n mole/L)	3.8* ± 104	1.5 ± 0.2
Insulin (mu/ml)	11.1* ± 2.4	7.2 ± 1.2
HOMA-IR	2.6* ±0.3	1.42 ± 0.52
FSH (miu/ml)	8.5 ± 3.2	6.41 ± 2.81
Estradiol (ng/dL)	6.2 ± 3.1	6.8 ±2.1

- Values are means ± SD
- Means with astrik are significantly different ($p<0.05$)

Table (3): Means of inflammatory markers (CRP, IL-6, and Leptin) of women with polycystic ovary syndrome (PCOS) and healthy control women

Parameters	Women with PCOS	Control women
Hs CRP (mg/dL)	8.72* ± 1.4	3.4 ± 2.12
IL-6 (pg/mL)	26.6* ± 4.41	15.72 ± 3.9
Leptin (pg/mL)	30.75* ± 2.5	20.61 ± 4.72

- Values are means ± SD
- Means with astrik are significantly different ($p<0.05$)

Discussion

Women with PCOS have a cluster of metabolic abnormalities . The proposed definition for this is female metabolic syndrome or syndrome XX[12], that begins early in adolescence and lead to prevent pregnancy and may affects other organs such as brain , pancreas , liver, muscles, blood vasculature, and adipose tissues .

The link between OCOS and insulin resistance was first described in 1980 and has later been confirmed in many studies. The exact mechanism of insulin resistance in patients with metabolic syndrome is however still unknown. some patients have increased serine phosphorylation of beta subunit of insulin receptor but also distant parts of the insulin receptor cascade are also affected[13].The cause of PCOS remain unknown. There are several theories focus on the impact of leutinizing hormone (LH) stimulation and the role of insulin in the production of ovarian hyperandrogenism. Increased LH pulse amplitude and frequency have been demonstrated in women and adolescent who have PCOS , suggesting an aberrant pattern of hypothalamic gonadotropin- releasing hormone (GnRH) secretion as a causative factor[14].

Studies have shown that women with PCOS have an exaggerated increase in LH pulse frequency

although whether this is due to an intrinsic abnormality of the GnRH pulse generator or related to the abnormal feedback of low levels of progestin from a ovulation is unclear[15].Previous study showed that the characteristic increase in LH relative to FSH release, have long been appreciated in PCOS[16].

Study of Azziz[17] indicated that frequency of GnRH leads to an increase in alpha and LH beta mRNA expression , there by favoring LH secretion. Some non obese patients who have PCOS have an elevated LH/FSH ratio.This increase in LH leads to increase production of androgens from the theca cells of the ovary preferential LH secretion from GnRH pulsatility may be explained by observations in rats showing that variations of GnRH pulse frequencies result in differential expression of subunit genes[18].

It is well known that GnRH pulse frequency is accelerated in PCOS. However, it is not clear whether this accelerated pulse frequency is primarily or secondarily to the relatively low levels of progesterone resulting in rare ovulatory events . Both situations lead to an increase luteinizing hormone level resulting in increasing ovarian androgens production[19].

There are several theorise to explain how insulin stimulates release of androgens. Insulin stimulate ovarian androgens production by direct and indirect mechanisms. Insulin has been shown to decrease secretion of sex hormone binding globulin (SHBG), which , inturn, increases available and active androgen. Insulin directly increases production of LH and androgens by activating its own receptors on the ovary, adrenal , and pituitary[20].Insulin also binds to the insulin-like growth factor-1 (IGF-1) receptors on the ovary there by directly stimulating androgens production[21].An observational study in five obese women who had PCOS demonstrated that administration of diazoxid, which decreases insulin secretion, resulted in a significant decrease in androgen levels after administration for 10 days[22].

Most women with PCOS have chronically elevated levels of LH and the LH: FSH ratio may be elevated , particularly in women with BMI < 30. LH stimulats the ovarian thecal cells to produce androgens mediated by cytochrome P-450C 17 alpha, a single enzyme with both 17 alpha hydroxylase and 17,20 lyas activity enhances production of androstendione. Androstendione is converted to testosterone by aromatase enzyme of granulose cells to testosterone[23,24].

Insulin and insulin like growth factor -1 act in synergy with LH to stimulate ovarian androgen production via cytochrom. P450C 17 alpha and act to inhibit SHBG production by liver. This allows more testosterone to circulate in the free or active state. Free testosterone stimulates androgen receptors of the pilosebaceous unit which can lead to the clinical findings of hirsutism and acne[25,26].

The present study indicated that women with PCOS have a significant increase ($p<0.05$) in the levels of inflammatory cytokines (CRP, IL-6, and leptin). PCOS consider as pro-inflammatory state as evidenced by elevated plasma concentration of CRP, procalcitonin , and tumor necrosis factor (TNF-alpha)[27].PCOS , as a low- grad chronic inflammatory state, may stimulate the immune response, increasing inflammatory factors such as CRP and IL-6[28]. CRP is secreted in response to cytokines including IL-6. Increased levels of hsCRP in patients with PCOS were reported in some previous studies[4,29].It had been found that hepatic production of CRP primarily is under the control of IL-6 stimulation . Substantial experimental evidence suggests that IL-6 and CRP, two sensitive physiological markers of subclinical systemic inflammation are associated with hyperglycemia, insulin resistance , diabetic melliutus-2 [30,31].Previous studies showed that central adiopcity appear to an important role in the metabolic phenotype through the production of various adipocyte derived cytokines and proteins known as adipokines [32].Enlarging fat cells secret a variety of hormones including TNF-alpha, IL-6, resistin, and Leptin . These hormones act on the muscles to make muscle more resistance to insulin. The pancrease gland therefore has to secrete even larger amount of insulin in order to keep the blood glucose normal and these higher levels of insulin mak fat break down even harder to achieve[33].

The fat cells there fore enlarge further and make even more TNF – alpha, IL-6, Leptin, and resistin, starting the vicious outward spiral of weight gain that commonly affects women with PCOS. Many women with PCOS notice that weight gain occurs easly and that weight loss is difficult , despit diet and exercise[32].Alteration in adepokins production in obese subject has been reported in several studies have shown that increased leptin and decreased adiponectin levels promote carcinogenesis of the breast[34]. In addition, obesity is being increasingly recognized as a form of systemic subclinical inflammation and , accordingly, an increased adipose tissue infiltration by immune cell producing inflammatory substances, including CRP and TNF- alph[35]. CRP was found to be positively correlated with leptin and negatively with adiponectin levels[36].

Data obtained from the present study indicate that women with PCOS have hormones disturbances associated with increase insulin resistance and a high levels of inflammatory cytokines , which inturn aggravate infertility of women with PCOS.

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