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A comparative study of cortisol levels in women with polycystic ovary syndrome and normal women of reproductive age group.

Gynaecology

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ABSTRACT

Background: Among the debatable uncertainties about the etiology of polycystic ovary syndrome (PCOS), the role of altered cortisol levels is significant. Its secretion is dysregulated in PCOS as these women are associated with several psychological disturbances, which leads to chronic stress, resulting in increased activity of HPA axis. **Aim**: To compare the morning plasma cortisol levels in women with PCOS and those not having PCOS. Material and methods: A total of 30 cases and 30 controls were enrolled for this study. Serum cortisol levels were measured early in the morning in both the study and the control groups. **Results:** Serum cortisol levels were significantly higher in PCOS women as compared to controls (16.29 µg/dl v/s 9.82 µg/d; p< 0.01). **Conclusion:** Mean values of cortisol are significantly higher in women with polycystic ovary syndrome.

KEYWORDS:

Cortisol, polycystic ovary syndrome, insulin resistance, hirsutism, hyperandrogenism

INTRODUCTION

Polycystic ovary syndrome (PCOS) is now recognized as the most common endocrinopathy in women of reproductive age group, affecting 5%–10% of women worldwide. It is characterized by oligo-ovulation or anovulation, signs of androgen excess and polycystic ovaries. Metabolic abnormalities particularly obesity and insulin resistance are also prominent features of PCOS1. PCOS receives considerable attention owing to its high prevalence along with reproductive, metabolic and cardiovascular consequences associated with the syndrome.

Among the debatable uncertainties about the etiology of PCOS, the role of altered cortisol levels is significant. Cortisol (hydrocortisone) is the most potent glucocorticoid secreted from the adrenal glands under the control of Hypothalamic –Pituitary-Adrenal (HPA) axis2. It is dysregulated in PCOS, as these women are associated with several psychological disturbances, which leads to chronic stress, resulting in increased activity of HPA axis. Normally, the serum levels of cortisol are highest in early morning hours and decreases throughout the day, with lower cortisol levels during the night. It has been found that PCOS patients have increased Adrenocorticotropic hormone (ACTH) and hence increased cortisol release both in morning and at night. Mean ACTH and cortisol levels are also increased in these patients3.The aim of this study was estimation of cortisol levels in both PCOS women and normal women and to compare the cortisol values in the two groups.

MATERIALS AND METHODS: This cross sectional observational study was carried out in the Department of Obstetrics and Gynecology and Department of Biochemistry, AIMSR, Bathinda over a period of 18 months (March 2015-Oct. 2016). A written informed consent was taken from the patients and the ethical clearance was obtained from the hospital ethical committee before the commencement of the study. Inclusion criteria: Study group; women in reproductive age group with PCOS as per 2003 Rotterdam consensus4, requiring the presence of at least two of the three features: 1) Chronic anovulation, 2) Clinical and biochemical signs of Hyperandrogenism, 3) Polycystic ovaries on USG. Control group; Healthy women matched with study group. Exclusion criteria: Women who have used oral contraceptives, corticosteroid, anti diabetic drugs and antipsychotic drugs in last 3 months, Idiopathic Hirsutism, other known causes of hyperandrogenism like Cushing syndrome, late onset adrenal hyperplasia, androgen secreting tumor and hyperprolactinemia, Diabetes Mellitus, untreated hypothyroidism, Renal, hepatic, cardiac and pulmonary disorders, smokers, alcohol drinkers.

A questionnaire was used to document menstrual, personal, medical and drug history. Signs of androgen excess (hirsutism, alopecia, and acne) were noted in the physical examination. Hirsutism with a Ferriman-Gallwey score of 8 or above was considered as clinical evidence of androgen excess. The body weight (in kilograms), body height (in meters), BMI and waist and hip circumference (in centimeters) were measured. Morning blood sample were sent on day 2 of the cycle for measuring cortisol, LH, FSH, estradiol, testosterone, DHEAS, TSH, Prolactin, fasting blood sugar, fasting insulin and HOMA-IR. All subjects underwent ultrasonography on day 8 of the menstrual cycle for findings of polycystic ovaries.

Laboratory analysis: Five to seven (5-7) ml of Fasting Venous blood sample was taken between 8 to 10 AM on day 2 of the menstrual cycle under aseptic precautions in a vial without any additives. Parameters LH, FSH, Estradiol, testosterone, DHEAS, fasting insulin, TSH, Prolactin and cortisol were measured by TOSOH AIA 360 fully

automatic hormone analyzer and Blood sugar/Glucose tolerance test by fully automatic Biochemistry Analyzer A15-Biosystems. IR (insulin resistance) was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR) by dividing the product of Fasting serum insulin (mU/ml) and Fasting plasma glucose (mg/dl) by 405.

Statistical Analysis: The data thus collected was expressed as mean (SD). Comparison of mean values between controls and PCOS women was performed using unpaired T test. Value < 0.05 was considered significant.

Observations and Results: The base line characteristics and presenting symptoms have been presented in table 1.

Parameter		PCOS women (n=30); Mean ± SD / no. (%age)	Controls (n=30); Mean ± SD / no. (%age)	
Age (years)		24.77 ± 0.83	24.60 ± 0.86	0.89
BMI(kg/m^2)		24.90 ± 4.10	22.90 ± 2.78	0.102
Waist hip ratio		0.87 ± 0.008	0.83 ± 0.009	<0.01
Presenting symptoms	Acne	21 (70%)	0(0%)	
	Hirsuitism	17 (56%)	0(0%)	
	Weight gain	11 (36.7%)	0(0%)	
	Alopecia	1 (3.3%)	0(0%)	
	Acanthosis nigricans	1 (3.3%)	0(0%)	
	Stress due to above symptoms	15 (50%)	0(0%)	

Fasting blood sugar levels and various hormone levels in both study and control group have been depicted in table 2.

Parameter	PCOS women (n=30); Mean ± SD	Control group. (n=30); Mean ± SD	P value
FBS(mg/dl)	85.93 ± 8.6	79.60 ± 7.6	<0.01
Fasting insulin(µg/ml)	11.50 ± 3.44	9.12 ± 2.59	<0.01
LH (mIU /ml)	12.6 ± 5.9	5.93 ± 1.46	<0.01
FSH (mIU /ml)	8.6 ± 2.38	8.54 ± 1.78	0.828
Estradiol (pg/ml)	114.43 ± 64.06	55.63 ± 50.83	<0.01
Prolactin(ng/ml)	13.71± 4.00	12.12 ± 3.3	0.099
TSH(µIU /ml)	2.45 ± 1.04	2.20 ± 0.89	0.316
HOMA-IR levels	2.45 ± 0.81	1.79 ± 0.54	<0.01
Testosterone (ng/dl)	49.2 ± 21.6	38.14 ± 10.33	<0.05
DHEAS (µg/dl)	306.41 ± 127.42	174.0 ± 74.09	<0.01
CORTISOL (µg/dl)	16.29 ± 8.3	9.82 ± 1.65	<0.01

LH: Luteinising Hormone. FSH: Follicle stimulating hormones. FBS: Fasting blood glucose. HOMA-IR: Homeostatic model assessment-Insulin resistance index. DHEAS: Dehydroepiandrosterone sulphate

Discussion: We observed that the mean values of cortisol were significantly higher in PCOS women compared to controls ($p < 0.01$). Other hormonal parameters like LH, Estradiol, FBS, Fasting insulin, GTT, HOMA-IR levels were also found significantly ($p < 0.05$) higher in the cases compared to the controls. However, difference between the mean levels of FSH, prolactin and TSH were statistically non significant between the two groups. As per the observations for the androgen profile, mean Testosterone and DHEAS levels were raised among the PCOS women. On ultrasonography, bilateral ovaries were found bulky with mean ovarian volume and number of follicles significantly higher in the study group.

Various studies about the alteration in adrenal or extra glandular cortisol production and metabolism in PCOS women have been conducted so far, but results are controversial5-12. In our study the mean values of cortisol were significantly higher in PCOS women compared to controls (16.29 µg/dl v/s 9.82 µg/dl, $p < 0.01$). In a study conducted by Tsilchorozidou T, et al, 13 18 lean women with PCOS were compared with 19 lean controls who were closely matched for body mass index (BMI). They demonstrated that there is an increased production rate of cortisol and androgens as measured in vivo in lean PCOS women. Shabir I et al 14 studied 197 cases and 55 controls. Serum cortisol levels were significantly higher in lean PCOS women compared to controls (13.4 ± 5.1 versus 11.3 ± 4.5, $p < 0.01$) and over-weight PCOS women group (13.4 ± 5.1 versus 9.3 ± 3.2, $p < 0.01$). Tock L et al. studied 37 PCOS women (16 non-obese and 21 obese) and 18 non-obese controls. Fasting glucose, insulin, androgens, and gonadotropins levels were determined. Salivary cortisol was measured both before and in the morning after dexamethasone (DEX) 0.25 mg. They observed that non-obese PCOS women had higher basal salivary cortisol and serum dehydroepiandrosterone sulfate and luteinizing hormone (LH) levels than controls and obese PCOS. Kiałka M, et al15 studied 40 PCOS patients and 55 women without features of PCOS. They observed that PCOS women showed the increased evening plasma cortisol level with impacted diurnal secretion rate.

Previous studies have suggested that the cortisol is dysregulated in PCOS, primarily through increased HPA axis activity. The excessive adrenal gland derived androgen secretions suggests that Pituitary Adrenal system in PCOS is up regulated. There is also evidence that suggest that PCOS patients have altered cortisol metabolism because of increase in the 5-alpha reductase activity in women with PCOS, which may be a secondary phenomenon due to hyperinsulinemia 13. In favour of this, our study also demonstrated raised insulin levels in women with PCOS as compared to normal women of same reproductive age group (table 2). Thus there can be increased peripheral metabolism of cortisol because of enhanced inactivation of cortisol by 5 reductase or impaired reactivation of cortisol from cortisone by 11-beta hydroxysteroid dehydrogenase Type 1 which results in decreased negative feedback suppression of ACTH secretion, causing increased ACTH, which leads to increased cortisol and androgens in PCOS.

Conclusion

Mean values of cortisol are significantly higher in women with polycystic ovary syndrome. However small sample size limits the generalisibility of our study.

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