Research Paper: Free Testosterone & Dehydroepiandrosterone Sulfate Serum Levels in Polycystic Ovary Syndrome Women

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ABSTRACT

Objectives: This study designed to detect the prevalence of ovarian and/or adrenal hyperandrogenism in women with Polycystic Ovary Syndrome (PCOS).

Materials: One hundred PCOS women included in this cross sectional study after informed consent and approval of the study by local institute ethical committee. Diagnosis of PCOS based on the Rotterdam ESHRE criteria. Studied women underwent complete physical examination with calculation of body mass index (BMI) and assessment of hirsutism by modified Ferriman Gallway score. Clotted blood sample taken from studied women for measurement of serum total testosterone, sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS) to detect the prevalence of ovarian and/or adrenal hyperandrogenism in PCOS women.

Results: 66% of studied PCOS women presented with hirsutism, 22% of studied PCOS women presented with menstrual irregularities (hypomenorrhea, oligomenorrhea) and dysmenorrhea was the presenting symptom in 12%. Free testosterone was elevated in 50 cases of studied women; DHEAS was elevated in 30 cases of studied women while the remaining 20 cases had elevated both free testosterone and DHEAS. Mean free testosterone was 2.6±1.8 pg/ml and mean DHEAS was 5.5±3.8 mg/l.

Conclusion: The ovary is the main source of excess androgen in PCOS (50% of studied women) and excess adrenal androgen found in 30% of studied PCOS women, further large studies recommended to confirm this finding.

1. Introduction

Adrenocorticotropic hormone and luteinizing hormone stimulate the adrenal glands and ovaries respectively to produce androgens [1]. The secretion of adrenal androgens occurs with adrenarche causing significant increase in the growth of pubic and axillary hairs [2]. The ovaries and adrenal glands equally contribute to testosterone production in women. The contribution of the adrenal

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glands achieved primarily through secretion of androstenedione [2]. Clinical Hyperandrogenism manifested by hirsutism commonly seen in PCOS [3].

Hyperandrogenism manifested by elevated plasma androgen and hirsutism with oligo or anovulation are the diagnostic criteria of PCOS [4,5]. Excess androgen is essential feature of PCOS and arises primarily from the ovaries. Excess Adrenal androgen possibly arising from generalized adrenocortical hyper-response is common feature and present in significant number of PCOS women [6, 7]. In PCOS women, hyperandrogenism manifested by hirsutism, acne, androgenic alopecia and it contributes to chronic anovulation and menstrual dysfunction. Biochemically, hyperandrogenism established by elevated circulating levels of serum total or free testosterone, androstenedione and free androgen index [4]. The use of multiple endocrine parameters showed a high prevalence of biochemical hyperandrogenism in PCOS women. Gil and colleagues reported that two thirds of the PCOS women had adrenal hyperandrogenism and estradiol and insulin did not influence adrenal androgen secretion [8]. This study designed to detect the prevalence of ovarian and/or adrenal hyperandrogenism PCOS women.

2. Materials and Methods

One hundred PCOS women included in this cross sectional study from Ain Shams University Maternity hospital, Cairo, Egypt, after informed consent and approval of the study by local institute ethical committee. Diagnosis of PCOS based on Rotterdam ESHRE criteria by at least 2 out of 3 of the following criteria: oligo-or an-ovulation, clinical or biochemical hyperandrogenism and polycystic ovaries on trans-vaginal ultrasound (TVS) [9].

Women with endocrinal disorders (thyroid dysfunction, Cushing syndrome, hyperprolactinemia and adult-onset congenital adrenal hyperplasia), androgen-secreting tumors (ovarian or adrenal) and women received oral contraceptives pills, corticosteroids, anti-androgens, androgen containing medications or ovulation inducing medications during last 6 months excluded from the study. Studied women underwent complete physical examination with calculation of BMI and assessment of hirsutism by modified Ferriman Gallway score with a score ≥8 diagnosed as hirsutism.

Clotted blood sample taken from studied women for laboratory measurement of serum total testosterone, SHBG and DHEAS. Free testosterone calculated from total testosterone and SHBG. Women with total testosterone levels greater than 200 ng/dl excluded from this study (reliable cutoff for testosterone producing tumors).

Women with only elevated serum DHEAS diagnosed as hyperandrogenism of adrenal origin. In most laboratories, the upper limit of DHEAS level is 350 ug/dl (3.5 mg/l). Normal DHEAS level rules out adrenal disease and moderate elevated DHEAS commonly seen in PCOS women. Threshold values beyond which a neoplasm should considered are 200 ng/dl for testosterone and 7000 ng/dl for DHEA-S [6].

Using data from previous study [8] and G Power software version 3.17 (Heinrich Heine Universität; Düsseldorf; Germany) for sample size calculation, a sample size of 100 women needed to produce significant difference. Data were collected and statistically analyzed using SPSS (Statistical Package for Social Sciences); computer software version 18 (Chicago, IL, U.S.A). Mean and SD (standard deviation) used to represent numerical variables, while, number and percentage used to represent categorical variables. Mann-Whitney's test used for analysis of quantitative data and Spearman's coefficient test to detect relation between different variables. P value <0.05 was considered significant.

3. Result

Mean age of studied PCOS women was 24.2±4.9 years, mean BMI was 28.9±6 kg/m^2 and mean parity was 1±0.3. (Table 1). Sixty six% of studied PCOS women presented with hirsutism, 22% of studied PCOS women presented with menstrual irregularities (hypomenorrhea, oligomenorrhea) and dysmenorrhea was the presenting symptom in 12%.

Free testosterone was elevated in 50 cases of studied women; DHEAS was elevated in 30 cases of studied women while the remaining 20 cases had elevated both free testosterone and DHEAS. Mean free testosterone was 2.6±1.8 pg/ml and mean DHEAS was 5.5±3.8 mg/l. (Table 2). Using Spearman's coefficient test, free testosterone had direct correlation to BMI and parity and indirect correlation to age while DHEAS had direct correlation to age and indirect correlation to BMI and parity (those correlations were statistically insignificant) (Table 3). Studied PCOS women with secondary infertility had significantly high free testosterone and low DHEAS compared to studied women with primary infertility. (Table 4).

4. Discussion

Polycystic ovary syndrome (PCOS) is a complex disorder affects 5%-6% of women during reproductive age group [10]. PCOS is typically associated with menstrual irregularities, obesity, hyperandrogenism, chronic an-

Table 1. Demographic data of the studied women

	Mean±SD	Range
Age (Years)	24.2±4.9	19-36
Body mass index (kg/m^2)	28.9±6	22-35
Parity	1±0.3	0-3

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Table 2. Levels of free testosterone and DHEAS in studied women.

	Mean±SD	Median	Range
Free testosterone (pg/ml)	2.6±1.8	1.96	0.03-7.4
DHEAS (mg/l)	5.5±3.8	6.3	0.5-11.3

DHEAS = dehydroepiandrosterone sulfate

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ovulation and infertility [11, 12]. Androgen overproduction is the key physio-pathologic feature of PCOS [13]. Women presented with clinically evident hyperandrogenism, laboratory evaluation of hormonal profile is an essential step in assessment of PCOS women [8].

Overproduction of androgen best evaluated by measuring serum free and total testosterone and DHEAS to detect the source of hyperandrogenism in PCOS women [4]. In this study, excess ovarian androgen found in 50% of studied PCOS women and excess adrenal androgen (DHEAS) found in 30% of studied PCOS women.

Gil et al. conducted descriptive cross-sectional study including 53 women to reassess the adrenal function of patients with PCOS after the introduction of the Rotterdam's criteria and they found high prevalence of biochemical hyperandrogenism in patients with PCOS. Two thirds of the patients had adrenal hyperandrogenism and estradiol and insulin did not influence adrenal secretion [8]. In addition, Laon at al and Azziz et al. concluded that excess adrenal androgen reported in 20-30% of PCOS women [14, 15]. Also, Chang and colleagues found that excess adrenal androgen in significant number of PCOS women [6].

Table 3. Correlation between free testosterone, DHEAS to studied women age, BMI and Parity

Variables	Free Testosterone		DHEAS	
	r*	P-Value-Significance	r*	P-Value, Significance
Age	-0.09	0.63(>0.05)	0.03	0.8(>0.05)
BMI (Body Mass Index)	0.15	0.99(>0.05)	-0.19	0.6(>0.05)
Parity	0.09	0.8(>0.05)	-0.011	0.1(>0.05)

*Analysis done using Spearman's coefficient test

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Table 4. Comparison between primary and secondary infertile cases as regard free testosterone and DHEAS

Type of Infertility	Primary Infertility (Number=70)	Secondary Infertility (Number=30)	Z*	P-Value, Significance
Free testosterone Mean±SD	3.2±1.6	3.4±2.2	2.9	0.001(<0.05)
DHEAS Mean±SD	7.1±3.3	1.6±0.9	8	0.008(<0.05)

*Analysis done using Mann-Whitney's tests; DHEAS=Dehydroepiandrosterone Sulfate

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The etiology of excess adrenal androgen in PCOS women remains unclear but may be due to generalized adrenocortical hyper-response [6,7]. In spite of this, a systematic review conducted by Aziz et al. to recommend a definition for PCOS based on the available data that PCOS defined as hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) after exclusion of related disorders [7]. Aziz et al. found forms of PCOS without overt evidence of hyperandrogenism [7].

The use of glucocorticoid as adjuvant treatment in clomiphene citrate resistant PCOS women for induction of ovulation by Elnashar and colleagues with significantly higher ovulation and pregnancy rates supports the evidence of excess adrenal androgen in PCOS women [16]. In this study, PCOS women with secondary infertility had significantly high free testosterone (ovarian androgen) and low DHEAS compared to studied women with primary infertility.

Excess androgen is essential feature of PCOS and arises primarily from the ovaries and ovarian hyperandrogenism contributes to chronic anovulation and menstrual dysfunction with subsequent infertility [6, 7]. In addition, Dumesic et al. and Ibáñez et al. concluded that PCOS is typically associated with menstrual irregularities, obesity, hyperandrogenism, chronic anovulation and infertility [11, 12].

5. Conclusion

This study concluded that the ovary is the main source of excess androgen in PCOS (50% of studied women) while excess adrenal androgen found in 30% of studied PCOS women and further studies recommended to confirm this finding.

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Conflict of Interest

The authors declared no conflict of interests.

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