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ORIGINAL ARTICLE

Evaluation of serum PSA after cyproterone compound treatment compared with oral contraceptive pill in hirsute polycystic ovary syndrome patients

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KEYWORDS

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Abstract *Objective:* To evaluate the effect of oral contraceptive on the serum free prostatic specific antigen (PSA) in women with polycystic ovary syndrome (PCOD) compared with cyproterone compound.

Materials and methods: In this randomized clinical trial, 60 hirsute PCOD patients that referred to Imam Hossein hospital were enrolled. Baseline Ferriman–Gallway score (FG), body mass index (BMI), free PSA, 17-hydroxy progesterone (17-OHP), free testosterone, and dehydroepiandrestandione sulfate (DHEAS) were measured. Then patients were divided randomly into two groups. One group received oral contraceptive pill (OCP) and the other one ate cyproterone compound (Diane). Hormonal profile and Ferriman–Gallway scores were evaluated again after 3 months.

Results: Baseline FG score was 10.78 ± 2.4 vs. 11.5 ± 2.3 in OCP and cyproterone compound group, respectively. FG score was reduced after 3 months to 8.06 ± 2.5 vs. 9.2 ± 2.3, respectively (P value = 0.000). There was no significant difference in FG score reduction after the treatment between two groups ($r > 0.05$). Baseline PSA was 0.201 ± 0.3 in OCP group and 0.097 ± 0.12 ng/ml in cyproterone compound group and after the treatment was decreased in both groups

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significantly 0.135 ± 0.24 vs. 0.059 ± 0.05 ng/ml, respectively, but the mean reduction of score was the same for both groups ($r > 0.5$). Free testosterone reduced more in OCP group (2.48 ± 1.3 ng/ml to 2.24 ± 1.0 ng/ml, P value = 0.03) than cyproterone compound (2.00 ± 1.2 to 1.64 ± 0.9 ng/ml, P value = 0.1). There was no statistical differences observed in 17-OHP and DHEAS after the treatment in both groups (P value > 0.5).

Conclusion: Serum free PSA and free testosterone and FG score were decreased after treatment with OCP and cyproterone compound but there was no preference between the two groups of anti-androgen treatment.

1. Introduction

Hirsutism is an excessive growth of hair on inappropriate parts of the body (1). Hair growth depends on excessive androgen which is produced by ovaries and adrenals. Hirsutism is one the most common symptoms in polycystic ovary syndrome and familial history and genetic background have affects on it (1). The incidence of hirsutism is about 5–10% and more than 90% of hirsute women are hyperandrogenic (2). PSA is a 33-kDa serine protease with chymotrypsin-like enzymatic activity (3). Prostatic specific antigen (PSA) is produced by the prostate gland in males and its concentration in serum is a valuable tumor marker in diagnosis to cancer of prostate (4). Initially, it was believed that there should not be any PSA secretion in female tissue and discharges but recently it has been detected in some female organs such as breast, ovary, milk, and amniotic fluid by ultrasensitive assay. Therefore, PSA can be a potential marker for androgen excess in hirsute patients and it can be used to monitor the patients during anti-androgen therapy. Recent papers have shown that PSA might be a useful marker in the treatment and follow up of the hirsute women (5).

PSA production is controlled by steroid hormones of non-prostatic tissues. Androgens increase the expression of the PSA gene through the androgen receptor (6,7). Although androgens, glucocorticoids, and progesterone have promoted the gene expression, estrogen has no effect on PSA regulation and androgen down-regulation, which is induced by PSA production (8). In females it seems that PSA has to be controlled by steroid hormone regulation (8). But, it seems that progestin component of the oral contraceptive pills stimulates the PSA production and cyproterone compound has more effects on PSA reduction and hirsutism score due to more anti-androgenic effect.

Cyproterone acetate combined with ethinyl-estradiol is used as one of the most common treatments of hirsutism because it has potent anti-androgen effects. This study was based on this hypothesis which suggests that the ovarian suppression for 3 months with cyproterone compound compared to oral contraceptive pills can decrease the serum PSA levels in PCOD patients with hirsutism.

2. Materials and methods

This randomized clinical trial included 60 polycystic ovary syndrome patients with hirsutism who were referred to infertility and reproductive health research center and governmental public educational hospital from February 2007 till December 2007. Polycystic ovary syndrome was defined as the diagnostic criteria of 2003 census Rotterdam (9). The age and body mass index were measured in two groups. Hirsutism was defined as the presence of excessive hair in the body and Ferriman–Gallway scores more than 7 (1,10). Women who received hormone therapy during the last 3 months, on a diet or herbal treatment were excluded from the study. The other exclusion criteria consisted of hyperprolactinemia, thyroid disorders, ovarian tumors, and Cushing disease. Hirsutism was determined by the Ferriman–Gallway score and recorded for every patient. Blood samples for serum PSA, and the hormonal profile including free testosterone, dehydroepiandrestandione sulfate (DHEAS), and 17-hydroxyprogesterone (17-OHP) were taken at baseline and at the end of the treatment at the early follicular phase between 3rd and 5th days of menstrual cycle at 8 am.

Patients were divided randomly into two treatment groups according to the computer-based table. One group received oral contraceptive pills and the other one received cyproterone acetate combined ethinyl-estradiol (Diane) for 3 months (1,5,11). Hirsutism score was evaluated after treatment again. The blood samples were taken during the early follicular phase after 3 months of treatment to avoid pharmacological effect of treatment and serum PSA, free testosterone, DHEAS, 17-OHP were measured again. The University ethics committee approved the study and the informed consent was obtained from patients.

2.1. Data analysis

The differences of serum PSA in two groups of oral contraception and cyproterone compound after treatment were compared with Wiloxon signed ranks test. Mann–Whitney U test was used to compare the differences between two groups after treatment. Statistical significance was measured with a value of $P < 0.05$.

2.2. Assays

All the blood samples were frozen in −21 °C and measured in one run after treatment. Serum free PSA was measured by ultrasensitive chemiluminescence enzyme immunoassay with the lowest detection limit of 0.001 ng/ml (Padtanelm, Iran, intra-assay variation 4.5%). Serum free testosterone was measured by ELISA and 17-OHP (DiaMetra, Italy, intra-assay variation 5.6%) and DHEAS (DiaMetra, Italy, intra-assay variation 4.8%) were measured by immunoenzymatic colorimetric.

3. Results

The mean age of the women was 23.97 ± 0.61 years in Diane group and 22/9 ± 0.5 years in OCP group ($P > 0.5$). The

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Table 1 BMI in two groups of patients with OCP and Diane in hirsute PCOD patients.

Variable	OCP (no. 30)	Cyproterone compound (no. 30)	*P* value
Age	22.9 ± 0.5	23.9 ± 0.61	0.428
BMI	21.17 ± 2.06	21.73 ± 2.76	0.375
FG score (before)	10.78 ± 2.4	11.5 ± 2.3	0.45

mean baseline body mass index (BMI) was 21.17 ± 2.76 and 21.73 ± 2.06 in OCP and cyproterone compound group, respectively. According to the *T*-test there was no meaningful difference between these groups in BMI (Table 1).

Baseline FG score was 10.78 ± 2.4 and 11.5 ± 2.3 in OCP and Diane group, respectively. No significant difference was found between the mean baseline FG score in two groups (Table 1). FG score difference in each group was analyzed by nonparametry test of Wilcoxon. Although FG scores were decreased significantly after treatment in both groups according Table 2 (P value <0.000), no meaningful difference was observed between OCP and cyproterone compound group after treatment (2.65 ± 2.18 vs. 2.27 ± 1.63, respectively, P value = 0.5) (Table 3).

Although the serum PSA was not significantly different before treatment between two groups, more statistical reduction occurred in second group. The basal mean level of PSA was 0.201 ± 0.2 ng/ml (range 0.01–1.0) in the OCP group and 0.097 ± 0.1 (0.01–0.6) ng/ml in the cyproterone group. The mean PSA level after treatment decreased to 0.135 ± 0.2 (0.04–1) ng/ml in OCP group (P value = 0.02) and 0.059 ± 0.05 (range 0.1–1) ng/ml in cyproterone group (P value = 0.03).

There was no significant correlation between serum PSA and age in OCP group ($r = 0.007$, $P = 0.97$) and Diane group ($r = 0.211$, $P = 0.263$). No significant correlation was observed between serum PSA and BMI in OCP groups ($r = 0.153$, $P = 0.42$) and Diane group ($r = 0.133$, $P = 0.482$).

Baseline free testosterone was 2.48 ± 1.3 ng/ml and 2.00 ± 1.2 ng/ml in OCP and Diane group vs. 2.24 ± 1.0 ng/ml and 1.64 ± 0.9 ng/ml, respectively, after treatment. Although free testosterone reduced in OCP group more than Diane group none of them was valuable (P value was 0.03 and 0.19, respectively). The baseline serum level of DHEAS and 17-OHP did not change after the treatment in both groups (Table 2).

Data show that the mean reduction of FG score in OCP group was 2 ± 2.1 and for Diane group was 2.2 ± 1.6 after treatment. Mann–Whitney U test showed that there was no significant difference between OCP and Diane in score improvement ($r = 0.505$). Although there was significant reduction in serum PSA level we observed no preference in serum PSA level between OCP and Diane ($r = 0.976$).

Serum free testosterone, DHEAS, and 17 OHP did not have any meaningful differences after treatment and between two kinds of treatment.

4. Discussion

Nowadays there are a lot of evidences which shows that androgens have effects on the serum PSA level and its production (12). Anti-androgens therapy regardless to the kind of drug can reduce the PSA level about 50% and can be a useful marker of androgen action in androgen sensitive tissues (5).

For several years oral contraceptive pills are used as the first line treatment of hirsutism especially with irregular menses. The main effect of OCP is the reduction of androgens and free testosterone but it has other effects such as inhibition of androgen binding to the receptors and prevention of conversion to the active metabolites (13).

It seems that anti-androgen treatments for hirsutism cause to decrease the serum PSA level (10) but there is no significant difference by oral contraceptive pills (11). Therefore, it can be concluded that ovary and adrenal are not the source of PSA and the main cause should be the androgen excess.

It seems that the reduction of androgen after anti-androgen or oral contraceptive therapy is too less where circulating androgen is still sufficient for stimulation and secretion of the PSA from the tissues (11).

The results show that the serum PSA did not decrease by oral contraceptives because the norethindrone containing progestin component of the oral contraceptives with androgenic effects may stimulate the PSA production (14). On the other hand, norethindrone as the progestin component of the OCP has stimulatory effect on the PSA production (14). Moreover, the reduction in hirsutism score and increased SHBG concentrations, suggests that androgenicity of the progestin is not the reason for the lack of reduction in serum PSA levels (11). There is no consistent pattern of decreeing the serum PSA after anti-androgen treatment in hirsute patients. Although baseline PSA concentrations correlated positively with serum free testosterone (15), serum PSA changes are very low by the treatment (16). PSA is independent to BMI, age, and androgen deprivation that was performed by GnRH agonist treatment (1). Whereas, it seems that PSA production is due to the extragonadal sites and through the hyperandrogemic states.

Ultrasensitive assay of PSA showed that the serum PSA in hirsute women is higher than in normal women (16). It is

Table 2 Comparison of parameters after 3 months treatment between OCP and cyproterone compound group in hirsute PCOD patients.

	OCP group			Cyproterone compound group		
	Before	After	*P* value	Before	After	*P* value
FG score	10.78 ± 2.4	8.65 ± 2.47	0.000	11.5 ± 2.3	9.23 ± 2.3	0.000
Free PSA	0.201 ± 0.2	0.135 ± 0.2	0.02	0.097 ± 0.1	0.059 ± 0.05	0.03
Free testosterone	2.48 ± 1.3	2.24 ± 1.0	0.03	2.0 ± 1.2	1.64 ± 0.9	0.19
DHEAS	2.36 ± 1.6	2.05 ± 1.07	0.4	2.41 ± 1.2	2.53 ± 1.4	0.3
17-OHP	1.83 ± 1.9	1.7 ± 0.9	0.1	1.74 ± 1.3	1.6 ± 0.8	0.3

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Table 3 Comparison of reduced FG in OCP and cyproterone group after treatment.

	OCP	Cyproterone compound	*R*
	Mean diff.	Mean diff.	
FG score	2.65 ± 2.18	2.27 ± 1.63	0.505
Serum PSA (ng/ml)	0.066 ± 0.19	0.038 ± 0.12	0.976
Serum free testosterone	0.241 ± 0.6	0.362 ± 1.2	0.19
Serum DHEAS	0.317 ± 0.7	0.119 ± 0.9	0.97
Serum 17-OHP	0.129 ± 0.4	0.141 ± 0.7	0.95

Mann–Whitney test: in all of them $r > 0.05$.

suggested that androgen stimulates the PSA production in non-prostatic tissues (10,11,15). Therefore, anti-androgen therapy might decrease the baseline values of PSA, but the researches showed that the differences were not significant (5). Although, in present study serum PSA was decreased after both treatments and there was no preference in none of them. Data analysis of all patients of two groups showed that the serum PSA decreased significantly (P value = 0.01). It seems that no significant differences are due to limited number of patients or low sensitivity of our equipment to detect the serum PSA.

PSA detection needs the ultrasensitive assay which can detect on 0.002 ng/ml because the clinically useful threshold of serum PSA for decision making is 0.010 ng/ml (17). Conventional PSA assay with a detection limit of 0.1–0.01 ng/ml can detect the PSA only in 10% of females but with ultrasensitive assay it increases (limit 0.001 ng/ml), more than 50% of female. Unfortunately, the available assay in Iran is not sensitive enough to detect small changes in serum PSA that occur after treatment with anti-androgen drugs.

Nowadays the data and evidences about PSA are increasing everyday. Even there are some data which showed that the PSA level in women urine might be more available and more valuable specially in low concentration (18).

Finally, in this study we found that the serum PSA and FG scores were decreased by ovarian suppression and anti-androgen therapy. But the available assay for PSA measurement at present is not useful for monitoring the efficacy of the treatment and it is the reason for non-significant differences. Finally, if there is a possibility to calibrate the equipments for higher sensitive assay we will be able to detect the small changes and better results. In this case also, this marker will be useful as a new valuable marker for androgen activity in peripheral tissues of the body especially in polycystic ovary syndrome, whereas the research population and using of ultrasensitive PSA assays might determine the significant reduction of serum PSA after treatment.

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