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ORIGINAL PAPER

Diagnostic value of prostate-specific antigen (PSA) and free prostate specific antigen (fPSA) in women with ovulatory and anovulatory polycystic ovary syndrome

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Abstract Diagnosis of polycystic ovary syndrome (PCOS) is very difficult in women with ovulatory cycles. We assessed the diagnostic value of prostate-specific antigen (PSA) and free prostate-specific antigen (fPSA) in women with ovulatory or anovulatory PCOS. Study group consisted of 62 women with PCOS and 35 healthy female controls. PCOS group was divided into two subgroups as anovulatory ($n = 42$; 68%, Group A) and ovulatory group ($n = 20$; 32%, Group B). A cut-off level of PSA and fPSA was established for the sensitivity, specificity, positive likelihood ratio, area under curve, diagnostic accuracy, and positive and negative predictive values of diagnosis of PCOS. In group A, a PSA level of greater than 10 pg/ml yielded a sensitivity of 73.2%, a specificity of 80%, and a diagnostic accuracy of 73%, with a positive predictive value of 88.2% and a negative predictive value of 59.3%. An fPSA level of greater than 2.1 pg/ml yielded a sensitivity of 71.2%, a specificity of 80.4%, and a diagnostic accuracy of 87%, with a positive predictive value of 87.2% and a negative predictive value of 58.4%. In group B, a PSA level of greater than 10 pg/ml yielded a sensitivity of 65%, a specificity of 80%, and a diagnostic accuracy of 73%, with a positive predictive value of 76.5% and a negative predictive value of 69.6%. An fPSA level of greater than 2.1 pg/ml yielded a sensitivity of 65.4%, a specificity of 80.4%, and a diagnostic accuracy of 87%, with a positive predictive value of 75.5% and a negative predictive value of 68.4%. Circulating androgens and hirsutism are independently associated with the degrees of PSA and fPSA in PCOS women. Increased plasma levels of PSA (>10 pg/ml) and fPSA (>2.1 pg/ml) could be helpful as a diagnostic tool for women with ovulatory or anovulatory PCOS.

Keywords Hirsutism · Prostate-specific antigen (PSA) · Free prostate specific antigen (fPSA) · Ovulatory PCOS · Anovulatory PCOS

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Introduction

The polycystic ovary syndrome (PCOS), one of the most frequent endocrine disorders in women is a syndrome of ovarian dysfunction. Its cardinal features are hyperandrogenism and polycystic ovary morphology [1]. Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. It is now recognized that women with hyperandrogenism and polycystic ovaries (PCO) may have regular cycles [2–4]. PCOS remains a syndrome and no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. It was clearly denoted that a proportion of patients with PCOS might not demonstrate an overt abnormality in circulating androgens [1, 5–8]. Notwithstanding these limitations, the measurements of free T and the free T (free androgen) index [9] are the most sensitive methods of assessing hyperandrogenaemia [10]. PCOS also remains a diagnosis of exclusion. Known disorders that mimic the PCOS phenotype should be excluded.

Prostate-specific antigen (PSA) is a serine protease with chymotrypsin-like enzymatic activity [11]. In males, PSA

is produced by the prostate gland [12]. PSA has been detected in some female tissues (including breast, ovarian, and endometrial tissues) and body fluids [13]. The presence of PSA in these female tissues seems to be associated closely with steroid hormone regulation, especially androgens, glucocorticoids, and progestins [14]. PSA levels increase in women with androgen excess [15, 16].

A few studies have determined the levels of PSA in women with hirsutism [17–19]. The diagnostic value of PSA and fPSA in women with PCOS has not been studied because the diagnosis of PCOS is very difficult in women with ovulatory and regular menses. PCOS is usually a hyperandrogenaemic state but some cases may not demonstrate an overt abnormality in circulating androgens. However, measurement of only total and free testosterone alone does not appear to be a very sensitive marker of androgen excess [6, 8]. At present, a single and reliable diagnostic marker of PCOS is lacking. If one were available, it would be of great value in clinical practice.

We wanted to (i) assess the levels of PSA and fPSA in PCOS patients and compare them with the healthy control values, (ii) establish if a relationship exists between PSA and/or fPSA and androgenic hormones in patients with PCOS, (iii) determine if there is a correlation between PSA and/or fPSA and hirsutism as assessed the Ferriman–Gallwey scale (FGS), and (iv) determine the diagnostic value of PSA and fPSA levels in PCOS with ovulation or anovulation.

Materials and methods

Patient selection

All patients who were admitted to our endocrinology and metabolism outpatient clinics, with complaints of hirsutism were evaluated. Study protocol was approved by the local Ethics Committee, and all patients gave written informed consent before randomisation. FGS was used for the diagnosis and grading of hirsutism [20]. All women who had a hirsutism score greater than eight were evaluated for the etiology. Patients with adrenal enzyme defects, androgen-secreting adrenal and ovarian tumors, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, and idiopathic hirsutism were excluded from the study. The diagnosis was based according to the consensus on diagnostic criteria of PCOS [21]. The presence of two out of three following criteria was accepted for the diagnosis of PCOS. These are (i) chronic ovulatory dysfunction, (ii) clinical signs of hyperandrogenism (hirsutism) and/or biochemical signs of hyperandrogenism, and (iii) PCO in USG. Chronic ovulatory dysfunction was considered to be present if there was a history of oligomenorrhea (four or less cycles in the past 6 months) or amenorrhea (no cycles in the past 6 months). The primary clinical indicator of androgen excess is the presence of hirsutism, and/or biochemical signs of hyperandrogenism. The criteria for defining PCO in USG are the following: "Presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 ml)" as mentioned at the ESHRE/ASRM PCOS consensus workshop group [21]. Sixty-two young women (mean age: 24.0 ± 7.2 years) with PCOS were enrolled into the study. All subjects in the PCOS group had hirsutism and/or biochemical hyperandrogenaemia. Patients who had been treated for PCOS previously were excluded. Age and body-mass index (BMI) matched thirty-five healthy young women who had a FGS of less than eight, normal androgenic hormone levels, regular menses, and normal ovaries on pelvic USG examination were also included in the study as a control group (mean age: 25.4 ± 5.0 years). Informed consent was also obtained from all control subjects.

Age, body mass index, and FGS were recorded. FGS was determined by two clinicians (KU and AH) independently and the mean of the two determinations was accepted as final value. Blood samples were collected in early follicular phase (3–6 days) in women with regular menses and randomly in patients with oligo/amenorrhea in the morning after an overnight fast and studied in the same day. Testosterone, free testosterone, dehydroepiandrosterone sulphate (DHEAS), LH, FSH, estradiol, 17alpha-hydroxyprogesterone (17OHP), PSA, and fPSA levels were studied. If subjects had regular menstrual cycles, progesterone level was studied at 21st day of the cycle. If not, blood was drawn from subjects with irregular cycles on the same day as their initial exam. Progesterone levels greater than 10 ng/ml, were accepted as indicating that ovulation occurred in these patients.

Patients with PCOS and control subjects were compared. The PCOS group was divided into two subgroups according to the presence or absence of ovulation: the anovulatory group ($n = 42$; 68%) was designated Group A, and the ovulatory group ($n = 20$; 32%) was designated Group B. Subgroup analyses were performed between control subjects, group A and group B. Diagnostic performance of PSA/fPSA parameters were calculated using receiver operating characteristic (ROC) analysis for each PCOS and control group.

Assays

Serum total testosterone, LH, FSH, estradiol, progesterone, cortisol, sTSH, free thyroxine, prolactin, PSA, and free prostate specific antigen fPSA levels were measured with a Modular Analytics E170 auto analyzer by original Roche Diagnostics kits (Roche Diagnostics GmbH, D-68298

Mannheim, Germany) by the electrochemiluminescence immunoassay technique. Intraassay and interassay coefficient of variations were 1.3 and 4.3%, 1.5 and 1.2%, 0.8 and 1.7%, 1.5 and 1.8%, 1.7 and 2.1%, 1.3 and 2.6%, 0.7 and 1.2%, 1.1 and 4.2%, 2.2 and 4.3%, 1.4 and 1.6%, and 1.3 and 1.6%, respectively. Serum-free testosterone levels were measured with a KIPI19000 auto analyzer by original kits (Free testo-RIA-CT Biosource Europe S.A, Nivelles-Belgium) by radioimmunoassay technique. Intraassay and interassay coefficient of variations were 2.3 and 5.7%. 17OHP levels were measured with a KIPI19000 auto analyzer by original kits (17OH-RIA-CT Biosource, Nivelles-Belgium) by radioimmunoassay technique. Intraassay and interassay coefficients of variation were 6.7 and 7.4% respectively. DHEAS level was measured with an Immulite 1000 systems auto analyzer by DPC original kit (DPC, Los Angeles, USA) by the chemiluminescence immunoassay technique. Intraassay and interassay coefficients of variation were 6.8 and 8.1%.

Statistical analysis

Statistical calculations were performed with SPSS 12.0 program. The nonparametric Mann–Whitney *U*-test was used in order to analyze the differences in skewed continuous variables, while differences in normally distributed continuous variables were compared by unpaired Student's *t*-test. Multiple comparisons were assessed by analysis of variance (ANOVA) followed by Bonferroni's test and Kruskall–Wallis test followed by Mann–Whitney *U*-test. Spearman correlation coefficients were used to test the correlation between plasma testosterone, free testosterone, DHEAS, LH, FSH, Estradiol, 17OHP, progesterone, PSA, and fPSA levels. The sensitivities, specificities, positive likelihood ratios, area under curves, diagnostic accuracy, and positive and negative predictive values of two parameters were calculated using ROC analysis for each PCOS and control group. A P value of <0.05 was considered significant. The cut-off values were determined using the MedCalc Demo program, the cut-off value corresponding to the highest accuracy (minimal false-negative and false positive results) is indicated by a sign. A P value of less than 0.05 was accepted as significant. Data are presented as mean ± standard deviation.

Results

Comparison of patients with PCOS and control subjects

In women with PCOS, FGS (13.2 ± 3.1 and 3.1 ± 1.9, $P < 0.0001$, PCOS patients and controls, respectively), testosterone (59.6 ± 19.3 and 38.2 ± 16.1 ng/dl, $P < 0.0001$, PCOS patients and controls, respectively), free testosterone (2.32 ± 1.24 and 1.07 ± 0.45 ng/ml, $P < 0.0001$, PCOS patients and controls, respectively), DHEAS (293.40 ± 125.60 and 160.01 ± 30.80 μg/dl, $P < 0.0001$, PCOS patients and controls, respectively), LH/FSH ratio (1.51 ± 0.82 and 0.68 ± 0.20, $P < 0.0001$, PCOS patients and controls, respectively), and 17OHP (2.31 ± 0.86 and 0.76 ± 0.41 ng/ml, $P < 0.0001$, PCOS patients and controls, respectively) levels were significantly higher than control group. Mean PSA (21.7 ± 19.8 and 8.0 ± 7.6 pg/ml, $P < 0.0001$, PCOS patients and controls, respectively), (fPSA) (4.6 ± 4.2 and 1.7 ± 1.6 pg/ml, $P < 0.0001$, PCOS patients and controls, respectively) levels of PCOS patients were higher than the control subjects.

To define the parameters associated with plasma levels of PSA and fPSA, correlation of PSA and fPSA with FGS, testosterone, free testosterone, and LH/FSH ratio in the whole PCOS group were assessed. There was significant correlation of PSA with FGS ($r = 0.63$; $P < 0.0001$), LH/FSH ratio ($r = 0.39$; $P = 0.002$), testosterone ($r = 0.35$; $P = 0.005$), and free testosterone ($r = 0.44$; $P < 0.0001$) (Fig. 1). There was also significant correlation of fPSA with FGS ($r = 0.70$; $P < 0.0001$), LH/FSH ratio ($r = 0.40$; $P = 0.0015$), testosterone ($r = 0.43$; $P = 0.001$), and free testosterone ($r = 0.48$; $P < 0.0001$) (Fig. 2). The cut-off values were determined as PSA (>10 pg/ml) and fPSA (>2.1 pg/ml) for diagnosis of PCOS (Fig. 3). These cut-off values were evaluated on sensitivity, specificity, positive likelihood ratio, area under curve, diagnostic accuracy, and positive and negative predictive values (Table 1). A PSA level of greater than 10 pg/ml yielded a sensitivity of 70%, a specificity of 80% and a diagnostic accuracy of 73%, with a positive predictive value of 91.5% and a negative predictive value of 47.1% (Table 1).

Comparison of patients with ovulatory and anovulatory PCOS and control subjects

There were significant differences in FGS, testosterone, free testosterone, DHEAS, LH/FSH ratio, estradiol, and 17OHP levels between the group A, group B, and control subjects ($P < 0.0001$, ANOVA test P value for each parameter) (Table 2). Also difference in the levels of PSA and fPSA ($P = 0.002$, Kruskall–Wallis test P value for each parameter) were found among these three groups. Plasma levels of estradiol and progesterone were found to be significantly higher in the group B compared with the group A. While LH/FSH ratio level was found to be significantly lower ($P < 0.0001$, $P = 0.033$, $P < 0.0001$, Bonferroni post hoc test, respectively).

In this study the best diagnostic cut-off levels of PSA and fPSA for diagnosis of PCOS were determined at >10 pg/ml and >2.1 pg/ml, respectively. These cut-off

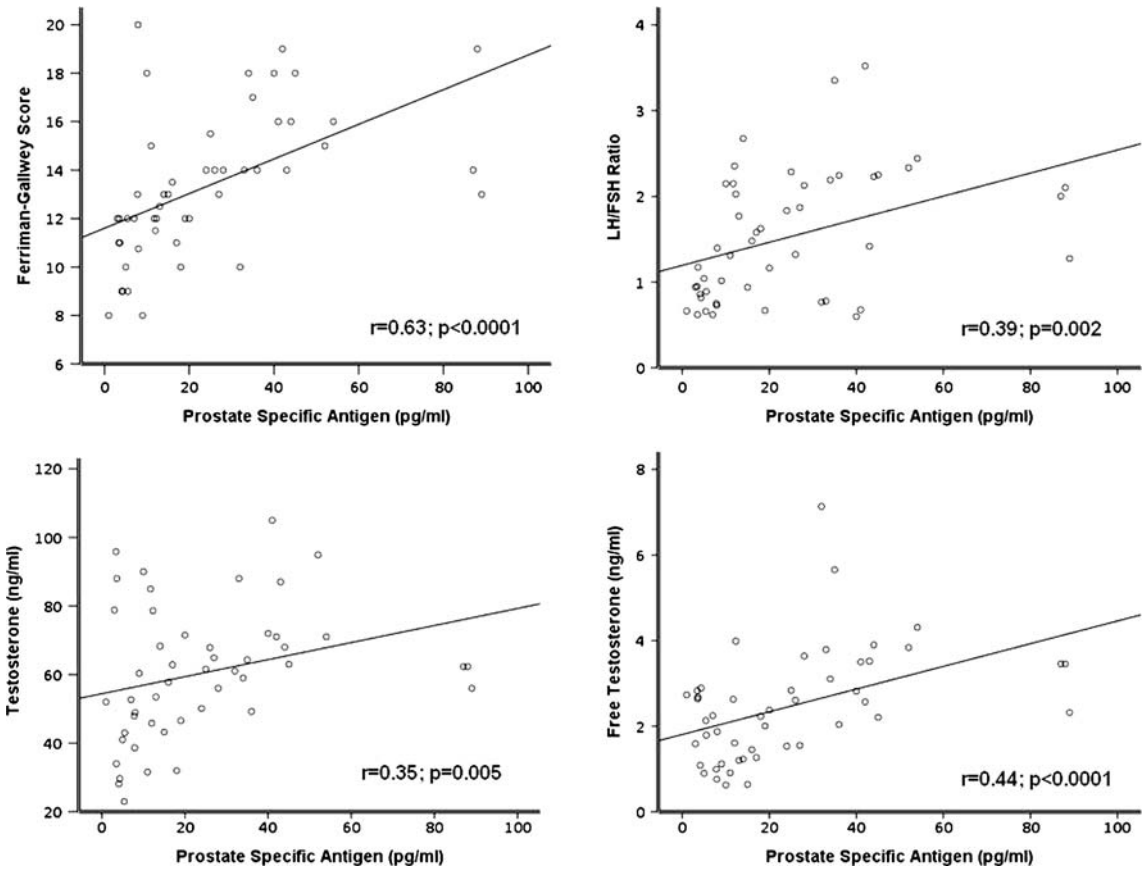

Fig. 1 Correlation of prostate specific antigen with Ferriman–Gallwey score ($r = 0.63$; $P < 0.0001$), LH/FSH ratio ($r = 0.39$; $P = 0.002$), testosterone ($r = 0.35$; $P = 0.005$), and free testosterone ($r = 0.44$; $P < 0.0001$)

levels were also evaluated in group A and group B to establish the sensitivities, specificities, positive likelihood ratios, area under curves, diagnostic accuracy, and positive and negative predictive values (Table 3, 4). An fPSA level of greater than 2.1 pg/ml in anovulatory PCOS group (group A) yielded a sensitivity of 71.2%, a specificity of 80.4% and a diagnostic accuracy of 76%, with a positive predictive value of 87.2% and a negative predictive value of 58.4% (Table 3). And also the same value of fPSA, in the ovulatory PCOS group (group B) yielded a sensitivity of 65.4%, a specificity of 80.4%, and a diagnostic accuracy of 81%, with a positive predictive value of 75.5% and a negative predictive value of 68.4% (Table 4).

Discussion

PSA [17–19] and fPSA [17] levels are significantly elevated in patients with hirsutism and can be used to monitor antiandrogen therapies [22].

In this study, we compared PSA and fPSA levels in women with PCOS and healthy controls. PSA and fPSA were found to be higher in women with PCOS with or without ovulation than control subjects as expected. Also PSA and fPSA levels were positively correlated with LH/FSH ratio, total testosterone, and free testosterone in these PCOS groups. Production of PSA is androgen dependent [23]. Elevated PSA and fPSA levels in PCOS patients and correlation of these parameters with other androgenic hormones support this data. Furthermore in our study, we revealed that FGS was also correlated with PSA and fPSA in PCOS. This was not evident in other studies [17, 18], in which women with idiopathic hirsutism and normal androgen levels were included in the study groups. This seems to be the prominent factor creating a discrepancy between PSA/fPSA levels and FG scores. Correlation of PSA and fPSA with testosterone, free testosterone, and FGS indicate that PSA and fPSA reflect hyperandrogenaemia and are reliable biochemical markers of the biological action of androgens in peripheral tissues. Total and free testosterone levels in our PCOS patients group were mostly in high normal range but PSA and fPSA levels were increased in all patients. We found the best diagnostic results with a PSA level of >10 pg/ml and fPSA level of >2.1 pg/ml. Although we showed increased levels of PSA and fPSA in PCOS group, levels of PSA and fPSA were

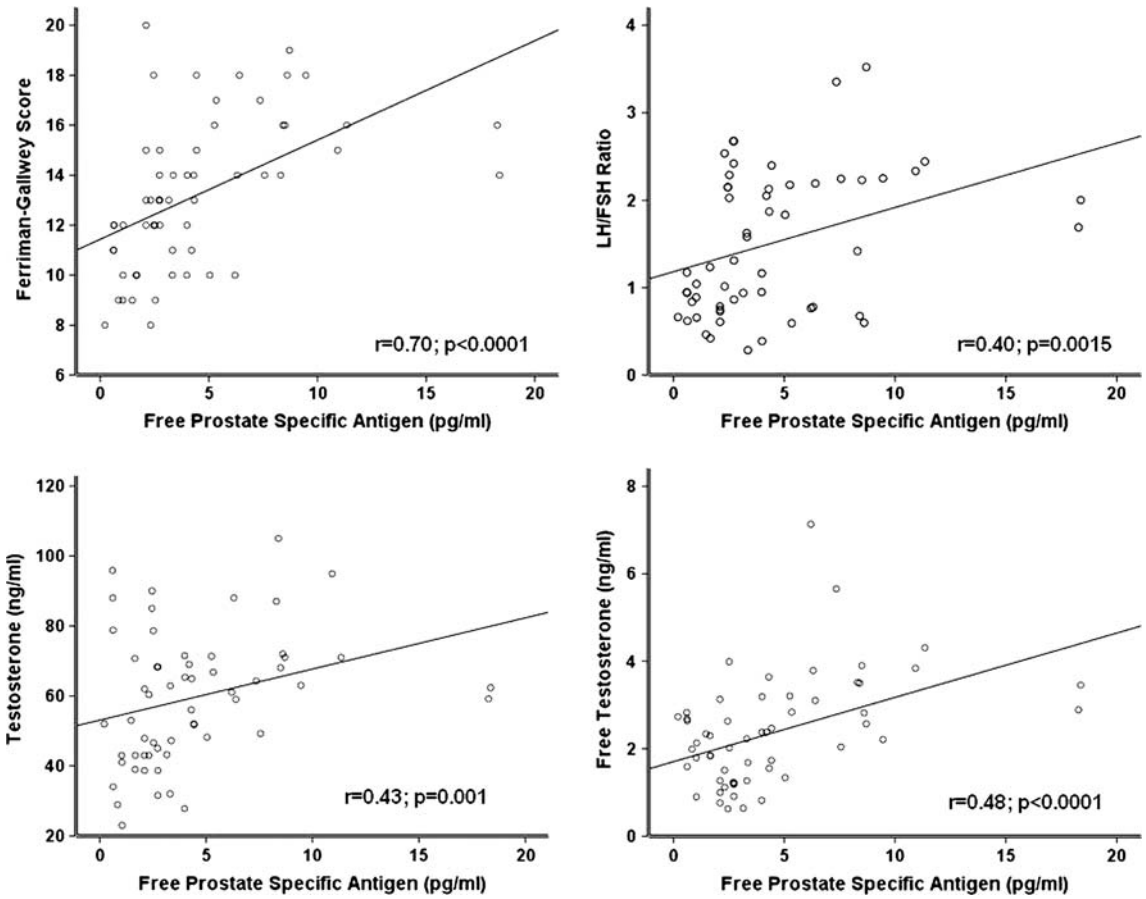

Fig. 2 Correlation of free prostate specific antigen with Ferriman–Gallwey score ($r = 0.70$; $P < 0.0001$), LH/FSH ratio ($r = 0.40$; $P = 0.0015$), testosterone ($r = 0.43$; $P = 0.001$), and free testosterone ($r = 0.48$; $P < 0.0001$)

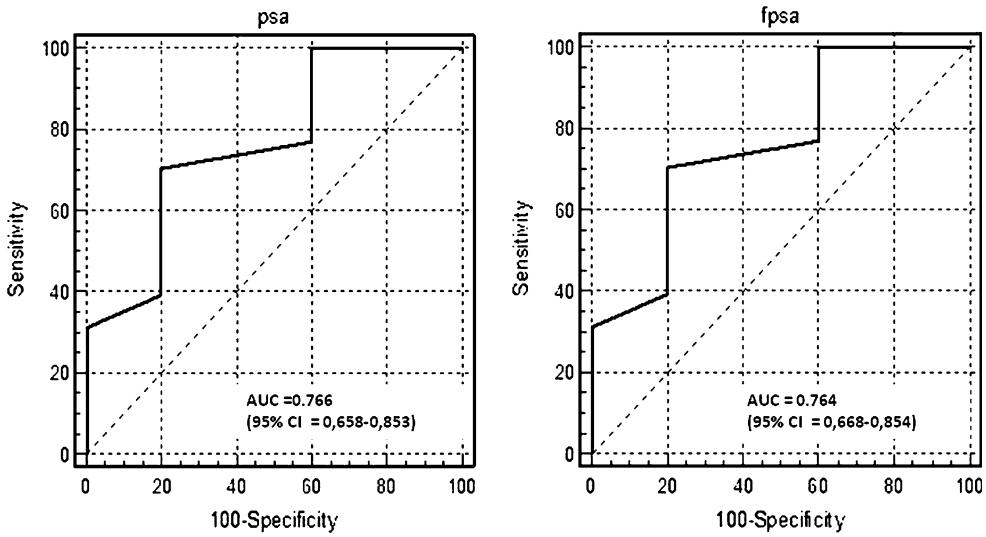

Fig. 3 ROC curves for PSA and fPSA for the diagnosis of PCOS. Best cut-off points for PSA and fPSA are 10 and 2.1 pg/ml, respectively. (CI: Confidence interval)

found to be somewhat lower in a few patients. This false negative finding decreased the sensitivity to 70 and 70.5% for PSA and fPSA, respectively. Healthy subjects had a PSA and fPSA level mostly lower than these cut-off points. So number of false positive patients was quite low and this increased the specificity of PSA and fPSA to 80 and 82%, respectively. The presence of false negative PCOS patients led to a decrease in the sensitivity, the reason of this finding might be the presence of normal testosterone and free testosterone levels in some PCOS patients. In fact, the

Table 1 Diagnostic performance of PSA and fPSA for diagnosis of PCOS

	PSA	fPSA
Cut-off value (pg/ml)	>10	>2.1
Sensitivity (%) (95% CI)	70 (57.4–81.5)	70.5 (57.7–83.5)
Specificity (%) (95% CI)	80 (56.3–94.1)	82 (57.3–93.1)
Positive predictive value (%)	91.5	90.5
Negative predictive value (%)	47.1	46.3
Diagnostic accuracy (%)	73	87
+ Likelihood Ratio	3.52	3.52
Area under curve (95% CI)	0.766	0.754

CI Confidence interval

Table 3 Diagnostic Performance of PSA and fPSA for diagnosis of anovulatory PCOS (Group A)

	PSA	fPSA
Cut-off value (pg/ml)	>10	>2.1
Sensitivity (%) (95% CI)	73.2 (57.1–85.8)	71.2 (56.1–85.6)
Specificity (%) (95% CI)	80 (56.3–94.1)	80.4 (54.3–94.1)
Positive predictive value (%)	88.2	87.2
Negative predictive value (%)	59.3	58.4
Diagnostic accuracy (%)	80	81
+Likelihood ratio	3.66	3.66
Area under curve (95% CI)	0.768	0.764

CI Confidence interval

normal levels of these hormones are a major problem of diagnosis of PCOS. It was shown that measurement of only total and free testosterone levels may not be a very sensitive marker of androgen excess in PCOS [6, 8]. The fPSA is present with equilibrium with PSA in plasma. We also found significant increase of fPSA level in patients with PCOS and diagnostic value of fPSA reached 70.5% sensitivity and 82% specificity for PCOS.

When PCOS patients were evaluated as ovulatory (group A) or anovulatory (group B) groups, we did not find any difference regarding total testosterone, free testosterone, PSA, and fPSA levels. Estradiol was significantly found to be significantly higher in group B than group A. This finding showed us that increased estradiol had no effect on PSA and fPSA levels. Because group A had anovulatory menstrual cycles, hirsutism, increased androgens, and PCO findings on

Table 2 Comparison of subgroups: anovulatory PCOS (Group A), ovulatory PCOS (Group B), and control subjects

	Group A $n = 42$	Group B $n = 20$	Control Group $n = 35$	P
Age (Years)	23.29 ± 5.95	25.45 ± 9.36	25.4 ± 5.0	
Body mass index (kg/m^2)	26.35 ± 7.05	25.55 ± 5.29	26.1 ± 6.9	
Ferriman–Gallwey Score	13.10 ± 3.00	13.30 ± 3.10	3.1 ± 1.9	a
LH/FSH ratio	1.80 ± 0.79	0.93 ± 0.46	0.684 ± 0.202	b
Testosterone (ng/dl)	59.91 ± 19.17	59.00 ± 20.10	38.19 ± 16.13	c
Free testosterone (ng/ml)	2.38 ± 1.12	2.20 ± 1.49	1.069 ± 0.451	d
Estradiol (pg/ml)	57.47 ± 41.16	90.46 ± 31.49	157.97 ± 59.41	e
DHEA-S (μg/dl)	305.10 ± 164.30	287.90 ± 104.90	160.01 ± 30.80	f
Progesterone (ng/ml)	2.07 ± 1.90	14.85 ± 3.18	16.20 ± 2.63	g
17OHP[#](ng/ml)	2.17 ± 0.79	2.61 ± 0.94	0.76 ± 0.41	h
PSA (pg/ml)	20.5 ± 19.2	22.2 ± 20.3	8 ± 7.6	i*
fPSA (pg/ml)	4.7 ± 4.3	4.3 ± 4.0	1.7 ± 1.6	j*
Cortisol (μg/dl)	13.73 ± 4.83	14.43 ± 5.72	14.10 ± 2.62	
TSH (μIU/ml)	1.33 ± 0.98	1.25 ± 0.98	1.38 ± 0.87	
Free T4 (ng/ml)	1.49 ± 0.63	1.32 ± 0.33	1.44 ± 0.21	
Prolactin (ng/ml)	17.49 ± 11.43	15.22 ± 7.19	16.12 ± 5.99	

* Nonparametric Mann–Whitney U-test P value

Other P values are results of parametric Bonferroni Post Hoc test

[#] 17alpha-hydroxyprogesterone

(a) Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.0001$, Group A vs. Group B P: N·S; (b) Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.0001$, Group A vs. Group B $P < 0.0001$; (c) Group A vs. Control $P < 0.0001$, Group B vs. Control $P = 0.00$, Group A vs. Group B P: N.S1; (d)Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.0001$, Group A vs. Group B P: N·S; (e) Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.000$, Group A vs. Group B $P = 0.0331$; (f) Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.0001$, Group A vs. Group B P: N·S; (g) Group A vs. Control $P < 0.0001$, Group B vs. Control P: N·S, Group A vs. Group B $P < 0.0001$; (h) Group A vs. Control $P < 0.0001$, Group B vs. Control $P < 0.0001$, Group A vs. Group B P: N·S; (i) Group A vs. Control $P = 0.013$, Group B vs. Control $P = 0.05$, Group A vs. Group B P: N·S; (j) Group A vs. Control $P = 0.013$, Group B vs. Control $P = 0.05$, Group A vs. Group B P: N·S

Table 4 Diagnostic performance of PSA and fPSA for diagnosis of ovulatory PCOS (Group B)

	PSA	fPSA
Cut-off value, pg/ml	>10	>2.1
Sensitivity (%) (95% CI)	65 (40.8–84.5)	65.4 (41.8–86.5)
Specificity (%) (95% CI)	80 (56.3–94.1)	80.4 (55.3–94.1)
Positive predictive value (%)	76.5	75.5
Negative predictive value (%)	69.6	68.4
Diagnostic accuracy (%)	80	80
+Likelihood ratio	3.25	3.25
Area under curve (95% CI)	0.763	0.764

CI Confidence interval

USG, there was no extra evidence needed for the diagnosis of PCOS in group A. In this group, sensitivity of PSA and fPSA were found to be 73.2 and 71.2%, respectively. And specificity was 80% for both markers. Probably most clinicians do not need a further laboratory marker for the diagnosis of PCOS in group A.

Especially diagnosis of PCOS in patients with ovulatory cycles is a challenge. A new diagnostic tool for this group is needed. Group B had regular and ovulatory cycles accompanied with hyperandrogenism and PCO on USG. PSA and fPSA levels were higher in group B compared to healthy subjects. This result showed us that PSA and fPSA could be used as a complementary marker for the diagnosis of PCOS in ovulatory patients. The same cut-off levels of PSA (>10 pg/ml) and fPSA (>2.1 pg/ml) were calculated also in group B. We determined the 65% sensitivity, 80% specificity, and 80% diagnostic accuracy for the PSA over the 10 pg/ml in group B. On the other hand, the best results with fPSA (>2.1 pg/ml) were determined as 71.2, 80.4, and 80% for the sensitivity, specificity, and diagnostic accuracy, respectively in group B.

In summary, we found that serum PSA and fPSA levels were significantly increased in women with PCOS. And also we showed that PSA and fPSA levels were positively correlated with androgens and hirsutism score that was an evidence of increased androgen levels and peripheral androgen action. These markers could be used in hyperandrogenic conditions, most importantly, for diagnosis of PCOS with high sensitivity, specificity, and diagnostic accuracy.

This study is the first one to report regarding the diagnostic value of PSA and fPSA levels in ovulatory and anovulatory PCOS patients. We recommend that the cut-off levels of PSA and fPSA which were evaluated in our study could be used by clinicians to confirm the diagnosis of PCOS, especially in cycling women infertility problems.

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