Original Article

Diagnostic value of prostate-specific antigen in women with polycystic ovary syndrome *

Farahnaz Mardanian¹, Nasrin Heidari²

Abstract

BACKGROUND: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. Its presentation is that of irregular menstruation associated with ovulation defects. Because of adverse outcomes such as metabolic and cardiovascular disorders, its diagnosis and treatment is very important. Therefore, the diagnostic value of prostate-specific antigen (PSA) in women with polycystic ovary syndrome was evaluated.

METHODS: A total of 32 women with PCOS and 32 aged matched healthy females were recruited in this case-control study. The subjects were compared by means of metabolic measures and serum PSA level. The correlations between these markers were evaluated. Sensitivity and specificity values and cut off levels of PSA were established for diagnosis of PCOS.

RESULTS: Mean PSA, Ferriman Gallwey score (FGS), luteinizing hormone/follicle stimulating hormone ratio (LH/FSH), testosterone, dehydroepiandrosterone sulfate (DHEAS), 17α hydroxyprogesterone (17α HP) levels were significantly higher in PCOS (P<0.001, respectively). PSA levels greater than 0.07 ng/ml yielded a sensitivity of 91% and specificity of 82%, and was helpful as a diagnostic tool for women with PCOS. Circulating androgens and hirsutism were associated with higher levels of PSA in PCOS women.

CONCLUSIONS: Our results showed direct correlation between PSA, hirsutism and hyperandrogenism state. Therefore, it seems logical to use PSA level for detection of hyperandrogenism state in women.

KEYWORDS: Hirsutism, Prostate-Specific Antigen (PSA), Polycystic Ovary Syndrome (PCOS).

Polycystic ovary syndrome (PCOS), one of the most frequent endocrine disorders in reproductive aged women, is a syndrome of ovarian dysfunction. Its frequency in the world is about 6.5-8% and in IRAN is 15.2%.¹ ² PCOS is an important cause of both menstrual irregularity and androgen excess in women. When fully expressed, the manifestations include irregular menstrual cycles together with hirsutism and/or acne; obesity is a frequent concomitant.³ Androgen excess is the main pathology in PCOS. Metabolic abnormalities, insulin resistance, hyperinsulinism, type II diabetes mellitus, endometrial carcinoma, dyslipidemia and psychosocial dysfunction are presented in PCOS.⁴ It was clearly denoted that a proportion of patients with PCOS might not demonstrate overt abnormality in circulating androgens.⁵ ⁸ Insulin growth factor 1 (IGF1) and insulin level, which are able to stimulate androgen synthesis, are suggested to be responsible for hyperandrogenemia.⁹ ¹¹ Hyperandrogenism along with decreased circulating level of sex hormone binding globulin results in higher levels of free androgens.⁴ ¹² Elevated levels of luteinizing hormone (LH) and subsequent influences on the thecal compartment of the ovary may play an additional role in the establishment of clinically apparent hyperandrogenism. Androgen suppression fol-

* This paper derived from a Specialty thesis in Isfahan University of Medical Sciences.
1- Associate Professor, Department of Obstetric and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran.
2- Resident, Department of Obstetric and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran.
Corresponding Author: Farahnaz Mardanian
E-mail: mardanian@med.mui.ac.ir
lowing the diagnosis of hyperandrogenism is the mainstay of treatment in patients with PCOS.13

Prostate-specific antigen (PSA) is a glycoprotein expressed by both normal and neoplastic prostate tissue. PSA is produced as a proenzyme by the secretory cells that line the prostate glands, where the propeptide is removed to generate active PSA. The active PSA can then undergo proteolysis to generate active PSA, of which a small protein then enters the blood stream and circulates in an unbound state (free PSA). Active PSA bounds to protease inhibitors including alpha-1-antichymotrypsin and alpha-2-macroalbumin.14

PSA is produced by prostate gland.15 PSA is used as a highly specific and valuable marker for screening, diagnosis and monitoring of prostatic adenocarcinoma regarding. PSA has been detected in some female tissues such as breast, ovarian and endometrial tissues, amniotic fluid and milk.16 PSA production seems to be associated with steroid hormones such as androgens, progestin and glucocorticoids.15,16

PSA levels increase in women with androgen excess. A single and reliable diagnostic marker of PCOS is lacking. It would be of great value in clinical practice, if one was available.7 In one study, to determine the diagnostic value of PSA and FPSA in women with PCOS, study group consisted of 62 women with PCOS was compared with 35 healthy female controls. PCOS group was divided into A and B groups as anovulatory and ovulatory subjects, respectively. In group A, PSA level greater than 10 pg/ml yielded a sensitivity and specificity of 73.2% and 80%, respectively, positive and negative predictive value of 88.2% and 59.3%, respectively. In group B, PSA level greater than 10 pg/ml yielded a sensitivity and specificity of 85% and 80%, respectively, positive and negative predictive value of 76% and 69%, respectively. Then, it showed to be helpful as a diagnostic tool for women with PCOS.17

In the current study, we aimed to determine levels of PSA in PCOS patients and healthy controls, correlation between PSA and hirsutism and androgen levels and diagnostic value of PSA level in PCOS.

Methods

Patient selection

This study was a case-control study conducted in Isfahan University of Medical Science, Department of Obstetric and Gynecology in a period of two years, 2009-2010. All patients were 20-35 year old and referred for oligomenorrhea and hirsutism to our outpatient clinic. The exclusion criteria were having adrenal enzyme defects, androgen secreting adrenal and ovarian tumors, Cushing’s syndrome, hyperprolactinemia, thyroid dysfunction and idiopathic hirsutism. Patients who had been treated for PCOS previously were excluded too. PCOS diagnosis was made according to the criteria of the Rotterdam ESHRE-ASRM when two out of the following three criteria were present: oligomenorrhea (fewer than six menstrual periods in preceding year) and anovulation; clinical and / or biochemical signs of hyperandrogenism; presence of >= 12 follicles in each ovary measuring 2-9 mm in diameter or ovarian volume > 10 cc; clinical evidence of hyperandrogenism was based on Ferriman Gallwey score (FG). In this scoring, 9 androgen dependent body sites were evaluated. In each site, the growth of hair score is from 0-4. Total score less than 8 was considered normal and 8-15 was considered as mild hirsutism and higher than 15 was considered as severe hirsutism.18 32 women (mean age, 26 ± 4.81 years) with PCOS and 32 healthy women (mean age, 27 ± 4.98 years) in control group were enrolled into the study. Healthy women had a FGS less than 8, normal androgenic hormone level, regular menses and normal pelvic ultrasonography. Age and body mass index (BMI) were matched between the two groups. Age, BMI, FGS and sonography were recorded.

Blood samples (4cc) were collected in early follicular phase (day 2-4) in the morning Total testosterone (TT), dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone (LH),
follicle stimulating hormone (FSH), 17α-hydroxyprogesterone (17α HP), and PSA were measured. Study protocol was approved by the local Ethics Committee and all patients entered the study only after informed consent was obtained.

**Assays**

All blood samples were measured by electrochemiluminescence immunoassay technique Siemens Germany kit. The collected data were processed using SPSS18 (statistical package for social sciences) program. Variables distribution was evaluated by Kolmogrov Smirnov test. Test results showed normal distribution of variables. The continuous variables were expressed as mean ± standard deviation (SD) and the means were compared by using student’s t-test. Pearson correlation was used to test the correlation between plasma TT, DHEAS, LH/FSH and PSA levels. The sensitivity, specificity, positive and negative predictive values were calculated. ROC Curve was used to determine cut off point of PSA in PCOS. Cut off point in ROC curve was determined with the best specificity and sensitivity. Cut off value was determined with highest accuracy and minimal false negative and false positive results; a P value of less than 0.05 was accepted as significant. Data are presented as mean ± SD.

**Results**

The distribution of clinical and biochemical diagnostic criteria of PCOS were compared to those of the control subjects. Mean age of PCOS group and control group was 26 (4.81) and 27.1 (4.98) years, respectively (p>0.05). Mean BMI of PCOS group and control group was 24.78 (2.96) and 23.19 (2.24) kg/m², respectively (p>0.05, Table 1). There were significant differences in FGS, TT, DHEAS, LH/FSH, 17 HP and PSA levels between PCOS and control groups (p<0.001, Figure 1). ROC Curve was used to determine cut off point of PSA in PCOS. The area under ROC curve was 0.92 ± 0.03 (95 CI, 0.85-0.98). Cut off point in ROC curve was determined with the best specificity and sensitivity. The best diagnostic cut off level of PSA for diagnosis of PCOS was determined higher than 0.07 ng/ml based on sensitivity of 91%, specificity of 81.2%, positive predictive value of 81% and negative predictive value of 85%.

**Table 1. Comparison of subgroups: PCOS and control**

| Parameter   | PCOS (n=32) mean ± SD | Control (n=32) mean ± SD | P Value |
|-------------|-----------------------|--------------------------|---------|
| Age         | 26.38 ± 4.8           | 27.1 ± 4.9               | >0.05   |
| BMI         | 24.78 ± 2.96          | 23.19 ± 2.24             | >0.05   |
| FGS         | 11.22 ± 4.43          | 0.06 ± 0.25              | <0.001  |
| LH/FSH      | 1.848 ± 0.589         | 0.82 ± 0.123             | <0.001  |
| DHEAS (µg/ml) | 248.84 ± 101.4     | 109.56 ± 21.45           | <0.001  |
| 17α HP (ng/ml) | 1.6 ± 0.579        | 0.85 ± 0.337             | <0.001  |
| PSA (ng/ml)  | 0.19 ± 0.192          | 0.038 ± 0.046            | <0.001  |
| TT (ng/ml)   | 1.3 ± 0.828           | 0.28 ± 0.410             | <0.001  |

PCOS: polycystic ovarian syndrome; BMI: body mass index; FGS: Ferriman Gallwey score; LH/FSH: luteinizing hormone; LH, follicle stimulating hormone (FSH); DHEAS: dehydroepiandrosterone sulfate; 17α HP: 17α hydroxyprogesterone; PSA: prostate-specific antigen; TT: total testosterone.
Discussion
PCOS appears to be a heterogeneous disorder in which ovarian and adrenal androgen excess is presented by variety of high gonadotropic degrees and metabolic abnormalities. According to the diagnostic criteria accepted by Rotterdam ESHRE/ASRM sponsored by PCOS consensus workshop group, the patients must present either clinical or biochemical findings subsequent to androgen excess to be considered as suffering from PCOS. In spite of additional metabolic criteria involving insulin resistance and hyperinsulinemia, androgen excess is the immediate culprit that determines the endocrine features of PCOS such as hirsutism, acne, androgenic alopecia and irregular menses.

PSA, a 33 KDa serine protease with a chymotrypsin like enzymatic activity has been used as a highly specific marker of normal and cancerous prostatic tissue and highly specific marker for diagnoses and management of prostate carcinoma. Recently, a growing body of information points out the production of PSA from multiple female tissues such as breast, ovary, adrenal tumors and normal endometrium. A few studies were done about PSA in women but information for association between PSA and PCOS is very vague.

In this study, we compared PSA level in PCOS and control groups. This study was the first one to be reported regarding the diagnostic value of PSA in Iran and the second in the world. Because we tested blood sampling in the early follicular phase, higher levels of PSA in our study could not be attributed to the variations through the menstrual cycle. We found that PSA level was higher in women with PCOS and positively correlated with LH/FSH.
ratio and TT, FSG, DHEAS and PSA levels in PCOS. Cut off point of PSA for diagnosis of PCOS was greater than 0.07 ng/ml based on the sensitivity of 91%, specificity of 81.2%, positive predictive value of 81% and negative predictive value of 85%.

In another study, Ukinc et al. achieved cut off point of PSA level for diagnosis greater than 10 pg/ml which yielded sensitivity and specificity of 73.2% and 80%, respectively, whereas cut off point of FPSA level for diagnosis of PCOS greater than 2.1pg/ml yielded sensitivity of 85.4% and specificity of 80.4%. A few studies have determined the level of PSA in women with hirsutism. Some authors noted that there was no correlation between PSA and age. In some studies PSA was not correlated with menstrual disturbances. Obesity is suggested to be related to the increasing serum PSA level when BMI was found to be higher in hirsute women with PCOS. Serum PSA level decreases with antiandrogen treatment (flutamide). Alessandro et al. found that serum level of PSA did not change in healthy pre-menopausal and in menopausal women. In suppression of gonadal axis and ACTH stimulation with glucocorticoid, androgen concentrations did not change PSA level. Diamond et al. achieved a positive correlation between PSA concentrations and 3A-androstenadiol glucuronide in hirsute women and demonstrated higher circulating PSA level in this group. In some studies, direct correlation between PSA, steroid hormone receptors and breast tumor was different. In another study, women with mastopathy regardless of the size of the cysts produced more serum PSA than women without breast pathology. The PSA may be a new marker for the assessment of benign breast disease.

Vural et al. clearly demonstrated elevated serum PSA level in PCOS patients and positive correlations between PSA and FGS, LH/FSH ratio, TT, DHEAS, SHBG, free androgen index and BMI negative correlation of estradiol and PSA level, and no correlation between PSA and age. Because of the correlations between PSA and androgen, PSA can be used as a potential biochemical marker of hyperandrogenism such as PCOS adrenal hyperplasia, adrenal tumor, ovary and breast tumor. Depending on all data, PSA level was elevated secondary to endogenous androgen and whether it might represent a valuable marker for other hyperandrogenism state or not is not clear yet. So, PSA level cannot be used only for diagnosis of PCOS; and other diseases by hyperandrogenism state will be ruled out. Further extensive investigation are needed to evaluate probable role of PSA level for diagnostic value and monitor adrenal hyperplasia, adrenal and ovary, breast tumor and other hyperandrogenism state. Other studies are needed to evaluate correlation between PSA level and prognosis of PCOS in infertility and metabolic disorder. We recommended that the cut off level of PSA could be used by clinicians to confirm the diagnosis and prognosis of PCOS, especially in women with infertility problems. But, a larger prospective controlled study is needed to further determine the sensitivity, specificity and predictability of this marker in other hyperandrogenism states such as hyperplasia, adrenal, ovary and breast tumor.

Conclusion

Our results showed that there were significant differences in FGS, TT, DHEAS, LH/FSH, 17 HP and PSA levels between PCOS and control groups. The best diagnostic cut off level of PSA for diagnosis of PCOS were determined higher than 0.07 ng/ml yielding a sensitivity of 91% and specificity of 81.2%. Because of direct correlation between PSA, hirsutism and hyperandrogenism state, it is advised to use PSA level for detection of hyperandrogenism state in women.

Acknowledgement

This study was supported by the Isfahan University of Medical Sciences (Project no 6821). We thank all the patients who participated in this study and thank the Beheshti Hospital Infertility Center.
Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
F M was the chief supervisor, idea creator and writes the primary protocol and writing manuscript and followup. N H was responsible for writing protocol, data collection and writing manuscript.

References
1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004; 89(6): 2745-9.
2. Mehrabian F, Khani B, Kelishadi R, Ghanbari E. The prevalence of polycystic ovary syndrome in Iranian women based on different diagnostic criteria. Endokrynol Pol 2011; 62(3): 238-42.
3. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005; 352(12): 1223-36.
4. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009; 91(2): 456-88.
5. Escobar-Morreale HF, Roldan B, Barrio R, Alonso M, Sancho J, de la CH, et al. High prevalence of the polycystic ovary syndrome and hirsutism in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 2000; 85(11): 4182-7.
6. Balen AH, Conway GS, Kaltsgas G, Techatasak K, Manning PJ, West C, et al. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod 1995; 10(8): 2107-11.
7. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998; 83(9): 3078-82.
8. Pugeat M, Nicolas MH, Craves JC, Alvarado-Dubost C, Fimbel S, Dechaud H, et al. Androgens in polycystic ovarian syndrome. Ann N Y Acad Sci 1993; 687: 124-35.
9. Cara JF. Insulin-like growth factors, insulin-like growth factor binding proteins and ovarian androgen production. Horm Res 1994; 42(1-2): 49-54.
10. Obiezu CV, Scorilas A, Magklara A, Thornton MH, Wang CY, Stanczyk FZ, et al. Prostate-specific antigen and human glandular kallikrein 2 are markedly elevated in urine of patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2001; 86(4): 1558-61.
11. Thierry van Dessel HJ, Lee PD, Faessen G, Fauser BC, Giudice LC. Elevated serum levels of free insulin-like growth factor I in polycystic ovary syndrome. J Clin Endocrinol Metab 1999; 84(9): 3030-5.
12. Lobo RA. What are the key features of importance in polycystic ovary syndrome? Fertil Steril 2003; 80(2): 259-61.
13. Vural B, Ozkan S, Bodur H. Is prostate-specific antigen a potential new marker of androgen excess in polycystic ovary syndrome? J Obstet Gynaecol Res 2007; 33(2): 166-73.
14. Mikolajczyk SD, Marks LS, Partin AW, Rittenhouse HG. Free prostate-specific antigen in serum is becoming more complex. Urology 2002; 59(6): 797-802.
15. Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. Invest Urol 1979; 17(2): 159-63.
16. Diamandis EP, Yu H. New biological functions of prostate-specific antigen? J Clin Endocrinol Metab 1995; 80(5): 1515-7.
17. Ukine K, Ersoz HO, Erem C, Hacihasanoglu AB. Diagnostic value of prostate-specific antigen (PSA) and free prostate specific antigen (fPSA) in women with ovulatory and anovulatory polycystic ovary syndrome. Endocrine 2009; 35(1): 123-9.
18. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19(1): 41-7.
19. Ferriman D, Galllwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961; 21: 1440-7.
20. Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 1981; 140(7): 815-30.
21. Diamandis EP. Prostate specific antigen--new applications in breast and other cancers. Anticancer Res 1996; 16(6C): 3983-4.
22. Diamandis EP, Yu H. Nonprostatic sources of prostate-specific antigen. Urol Clin North Am 1997; 24(2): 275-82.
23. Gullu S, Emral R, Asik M, Cesar M, Tonyukuk V. Diagnostic value of prostatic specific antigen in hirsute women. J Endocrinol Invest 2003; 26(12): 1198-202.
24. Negri C, Tosi F, Dorizzi R, Fortunato A, Spiazzi GG, Muggeo M, et al. Antiandrogen drugs lower serum prostate-specific antigen (PSA) levels in hirsute subjects: evidence that serum PSA is a marker of androgen action in women. J Clin Endocrinol Metab 2000; 85(1): 81-4.

25. Melegos DN, Yu H, Ashok M, Wang C, Stanczyk F, Diamandis EP. Prostate-specific antigen in female serum, a potential new marker of androgen excess. J Clin Endocrinol Metab 1997; 82(3): 777-80.

26. Bahceci M, Bilge M, Tuzcu A, Tuzcu S, Bahceci S. Serum prostate specific antigen levels in women with polycystic ovary syndrome and the effect of flutamide+desogestrel/ethinyl estradiol combination. J Endocrinol Invest 2004; 27(4): 353-6.

27. Burelli A, Rineladi E, Cionini R, Benelli E, Pinchera A, Pucci E. Serum levels of PSA do not change in healthy premenopausal and in menopausal women, but are increased in subjects with polycystic ovary syndrome (PCOS). Endocrine Abstracts 2006; 11: 685.

28. Escobar-Morreale HF, Serrano-Gotarredona J, Avila S, Villar-Palasi J, Varela C, Sancho J. The increased circulating prostate-specific antigen concentrations in women with hirsutism do not respond to acute changes in adrenal or ovarian function. J Clin Endocrinol Metab 1998; 83(7): 2580-4.

29. Hall RE, Clements JA, Birrell SN, Tilley WD. Prostate-specific antigen and gross cystic disease fluid protein-15 are co-expressed in androgen receptor-positive breast tumours. Br J Cancer 1998; 78(3): 360-5.

30. Narita D, Raica M, Anghel A, Suciu C, Cimpean A. Immunohistochemical localization of prostate-specific antigen in benign and malignant breast conditions. Rom J Morphol Embryol 2005; 46(1): 41-5.

31. Radowicki S, Kunicki M, Bandurska-Stankiewicz E. Prostate-specific antigen in the serum of women with benign breast disease. Eur J Obstet Gynecol Reprod Biol 2008; 138(2): 212-6.