Prostate Specific Antigen in Different Dermatoses Associated with Polycystic Ovary: Review Article

Shymaa Mostafa Rezk [1], Hamasat Abdel Hafeez Abdel Khalik* [3], Wagdy Megahed Amer [2],
Alhassan Mohamed Shahrour*[1] and Eman Mostafa Sanad [1]

[1] Dermatology, Venereology and Andrology, [2] Obstetrics and Gynecology, [3] Clinical and Chemical Pathology
Department, Faculty of Medicine, Benha University, Benha, Egypt
Corresponding author: Hamasat Abdel Hafeez Abdel Khalik,
email: Dr.alhasan_shahror@yahoo.com, mobile: +201110799912

ABSTRACT

Background: Dermatologic signs of hyperandrogenism, such as hirsutism, acne vulgaris, and androgenic alopecia, are common in women with polycystic ovary syndrome (PCOS). Prostatic Specific Antigen (PSA) is a potential new measure of hyperandrogenism in both PCOS and hirsute women.

Objectives: The focus of this research is to examine the potential function of prostate specific antigen in different dermatoses associated with polycystic ovary in females.

Material and methods: We searched Google Scholar, Science Direct, PubMed and other online databases for prostate specific antigen, different dermatoses and polycystic ovary in females. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2006 to February 2021 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: PSA has the potential to be used as a diagnostic marker for PCO and its accompanying hyperandrogenism, particularly in the context of acne. More study is needed, however, to corroborate these findings and develop guidelines for the clinical use of PSA in dermatological practise.

Keywords: Prostatic specific antigen, Polycystic ovary syndrome, Acne vulgaris, Hyperandrogenism.

INTRODUCTION

The most prevalent endocrinopathy in women is hyperandrogenism, which can be caused by ovarian or adrenal androgen overproduction, altered peripheral metabolism, and/or end-organ hypersensitivity. Clinical features of polycystic ovary syndrome (PCOS) include infrequent or absent ovulation, irregular or absent menstrual bleeding, excess androgen production (including hirsutism and acne), elevated insulin levels, and excess body fat [1].

Polycystic ovarian syndrome affects about 5-10% of reproductive-aged women. But when there is an excess of testosterone, along with varying degrees of gonadotropin and metabolic issues, PCOS may be present. It appears that biochemical markers of hyperandrogenemia have widely varying diagnostic performance, and there is yet no single diagnostic tool that is sufficient for clinical diagnosis of PCOS. Women with polycystic ovarian syndrome often exhibit hyperandrogenic skin symptoms such as hirsutism, acne vulgaris, and androgenic alopecia. Hyperandrogenism-related symptoms are present in a subset of patients with PCOS indicating that these people have overt abnormalities in circulating androgens. People with PCOS who don't intend to become pregnant right away, the primary therapeutic option is androgen suppression following a diagnosis of hyperandrogenism. The serine protease known as prostate-specific antigen (PSA) plays a critical role as a diagnostic marker in the study of prostate cancer. In addition to the prostate gland, certain female tissues, including the ovary, endometrium, breast, milk, and amniotic fluid, have been found to contain PSA. PSA synthesis appears to be regulated by glucocorticoids, progestin, and androgens, and steroid hormones [2].

Our objective was to investigate the potential involvement of prostate specific antigen in several dermatoses that are linked to polycystic ovarian syndrome in females (Approval Code: Ms 65-5-2022).

Dermatoses of hyperandrogenism

Hyperandrogenism, which refers to the overproduction of androgens, predominantly affects females. There are a number of diseases in women that have been associated to hyperandrogenism, but PCOS is by far the most common. Common dermatological manifestations of hyperandrogenism include hirsutism, acne, acanthosis nigricans, and androgenic alopecia [3].

✓ Hirsutism

Hirsutism manifests itself in women when they start growing coarse, terminal hairs all over their bodies, just like men. The prevalence of hirsutism in premenopausal women is estimated to be between 5% and 25%. 22,23% PCOS is responsible for between 70% and 80% of cases of hirsutism. 24 Clinicians should approach the issue of hirsutism in women with compassion and understanding [4].

In the past, hirsutism was thought to indicate that a woman had an abnormally high amount of the male hormone androgen (testosterone). This could have been the result of an overactive adrenal gland or an ovarian disorder. Hair on the top lip, chin, upper back, shoulders, sternum, and upper belly tends to grow more

rapidly in hirsute women. In order to clinically quantify hirsutism, Ferriman and Gallwey developed a score [4].

✓ Acne vulgaris

Adolescents frequently suffer from acne vulgaris because of the increase in androgens that occurs during this time. Acne in women that is very severe, persistent, or adult onset is often an indicator of polycystic ovary syndrome or another androgen excess disorder. It is uncertain how often acne appears among PCOS women. Although not all women with acne are PCOS sufferers, one study found that 83% of women with acne had polycystic ovaries, compared to 19% of women in the control group who did not suffer from acne [5].

Eighty percent of women with severe acne, fifty percent of women with moderate acne, and thirteen percent of women with mild acne have higher plasma androgen levels, according to other studies. Increased testosterone levels cause the sebaceous glands to produce more sebum, which in turn causes the follicular epithelial cells to desquamate abnormally and create comedones [6].

Acne vulgaris, characterized by papules and pustules, develops when the comedone is invaded by the bacterium Propionibacterium acnes. It is unclear how exactly androgens influence sebaceous glands. The role of both systemic serum androgens and endogenous androgens has been demonstrated. Blood androgen levels have been linked to acne severity in some studies, however this is not widely acknowledged. Sebaceous gland androgens also have a role in acne development and progression [7].

Acanthosis nigricans

Acanthosis nigricans is a skin ailment characterised by velvety grey, brown, weakly marginated plaques with thicker skin and accentuation of skin patterns, and it typically appears in flexure areas such the neck, axillae, groin, and under the breasts. Insulin resistance manifests itself dermatologically as acanthosis nigricans. On histopathology, skin abnormalities such as papillomatosis and hyperkeratosis are visible [8]. Velvety grey or brown, poorly marginated plaques on the neck, axillae, groin, and under the breasts are the hallmark of acanthosis nigricans. The skin is also thickened, and skin marks are accentuated. Histological examination reveals hyperkeratosis and papillomatosis of the skin. Acne nigricans indicates insulin resistance [9]:

1. Several forms of insulin resistance have been linked to acanthosis nigricans.
2. After getting many insulin injections into the skin, two individuals acquired lesions resembling acanthosis.
3. Classical insulin receptors and insulin-like growth factor (I and II) receptors are both expressed by human fibroblasts and keratinocytes in culture.

4. Insulin has been shown to enter keratinocytes after crossing the dermal-epidermal interface.

✓ Androgenic alopecia

Thinner hair on men androgenic alopecia is characterized by gradual, all-over hair thinning and only affects women. Hair thinning can be divided into two categories [10]:

1. Gradual temple and crown thinning with an unaltered hairline.
2. Alopecia affects both sides of the head. Of 109 women who presented with moderate to severe alopecia, 38.5% were found to have hyperandrogenism. In 43% of cases, hyperandrogenism accompanied a PCOS diagnosis.

✓ Other

It has been suggested that seborrhea is a skin symptom of PCOS. PCOS has a lower prevalence compared to other dermatological disorders than is currently understood. Seborrhea often appears as a dermatitis with periodic flares and the creation of greasy yellow, well-demarcated plaques on areas of the skin with a high concentration of sebaceous glands, such as the face, scalp, eyebrows, nasolabial folds, and ear canals [11].

Polycystic ovary (PCO)

PCO is a complicated endocrino-metabolic condition that is distinguished by polycystic ovarian characteristics, hyperandrogenism, and ovulatory failure. It affects between 5 and 8% of the population and is the most common metabolic and reproductive endocrinopathy in women during their reproductive years. Alterations and revisions to the diagnostic criteria for PCO have occurred during the past decade, resulting in a doubling of the disease's prevalence. PCO is the underlying factor in between 55% and 91% of anovulatory patients [12].

✓ Rotterdam Criteria (2018)

Patients with PCO are diagnosed if they meet two of the following three criteria:
- hyperandrogenism
- ovulatory dysfunction
- ultrasonography evidence of polycystic ovaries [13].

✓ Aetiology and pathophysiology

Genetic and environmental (especially dietary) variables are involved with PCO, although the exact cause of the disorder is unknown.

Primary disordered gonadotropin secretion:

Disrupted gonadotropin production was the first biochemical aberration associated with PCO, namely a higher ratio of LH to FSH. The androgens made by excessive LH did not get converted to estrogen, leading to a chain reaction of issues, because FSH did not stimulate the development of granulosa

cells and the creation of aromatase. This theory clarified the relationships between ovarian morphology, hirsutism, and the inability to ovulate. Ovarian follicular stoppage occurred during the preantral phase due to androgen excess since oestrogen is required for the growth and selection of a dominant follicle [14].

The granulosa cell (GC) layer of the follicle undergoes apoptosis and becomes more atretic as it grows. A thin-walled cyst may develop if GCs disappear from the follicular wall over time. Several small preantral follicles were present in the ovary as a result of this ongoing process and the larger central stroma induced by excessive thecal and stromal hyperplasia due to disordered gonadotropin exposure [15]

Primary ovarian and adrenal hyperandrogenism:
Acne, hirsutism, and alopecia are only some of the symptoms of the syndrome, which is characterized by a rise in circulating androgen levels and an even greater increase in intrafollicular androgen levels in antral follicles [15]. Twenty to thirty percent of women with PCO have evidence of adrenal hyperandrogenism, primarily based on elevated levels of dehydroepiandrosterone sulphate "DHEA-S," an androgen marker of adrenal function. This suggests that the defect in steroidogenesis is primary and affects both androgen secreting glands, i.e., the ovary and the adrenal. Additionally, both female and male relatives tend to have increased DHEA-S levels within PCO families suggesting a heritable component to this feature [16].

Primary disorder of insulin resistance:
There is a two-way connection between insulin resistance and hyperandrogenism as a form of compensatory hyperinsulinemia. Insulin, alone or in combination with luteinizing hormone (LH), promotes the expression and activity of steroidogenic enzymes critical for androgen synthesis in the ovaries and adrenal glands. About half of PCO women experience an alteration in LH pulsatility due to hyperinsulinemia and hyperandrogenism. Obesity is associated with insulin resistance and the accompanying compensatory hyperinsulinemia. Women who are overweight may be ovulatory, although this may be misdiagnosed as oligo ovulatory due to their lengthier menstrual cycles and follicular stages. Similarly, obesity may lower circulating sex hormone-binding globulin "SHBG" levels, resulting in increased levels of free or bioavailable testosterone and, potentially, PCO misdiagnosis [17].

Role of Anti-Mullerian Hormone "AMH" of PCO:
AMH expression abnormalities in PCO may also contribute to increased follicular density. Only GCs in pre-antral and early antral follicles produce this TGF-peptide, which acts negatively on follicle maturation.

Because AMH inhibits aromatase, it has been postulated that increased local synthesis of this protein, along with decreased FSH secretion, could prepare the setting for follicular arrest and decreased ovarian estradiol (E2) production[18]

✓ **Clinical presentation**
Polycystic Ovary Syndrome Signs and Symptoms.
- Enlarged ovaries with numerous small cysts (70%)
- Irregular menstrual cycles
- Pelvic pain
- Hirsutism
- Alopecia
- Acne
- Acanthosis nigricans
- Skin tags

The clinical manifestation of PCO varies greatly. Menstrual disorders (oligomenorrhea, amenorrhea, or prolonged irregular menstrual flow), clinical symptoms of hyperandrogenism, and infertility are common in women with PCO. However, 30% of women with PCO have regular menstruation. PCO affects around 85% to 90% of women with oligomenorrhea and 30% to 40% of women with amenorrhea. PCO affects more than 80% of women who come with testosterone excess symptoms. As many as 70% of PCO-affected women also experience hirsutism, a classic clinical symptom of hyperandrogenism. To evaluate hirsutism, a modified Ferriman-Gallwey scale is utilised [19].

Dermatological manifestations of PCO:
Although acne can be indicative of hyperandrogenism, it is less specific than hirsutism and is more frequent in PCO. Acne affects from 15% to 30% of adult women with PCO. Hair follicles produce more dihydrotestosterone than sebaceous glands do because of variances in 5-reductase expression. This may explain the disparity in the prevalence of Hirsutism and acne. Forty-plus percent of the women who suffered from severe acne were found to have PCO [20]. And so, **Bienenfeld et al.** [21] propose that women with acne must be asked about their menstrual history and checked for additional indicators of hyperandrogenism. Consistent with our findings, previous studies have found that acne is the most common dermatological symptom of PCO, followed by hirsutism, seborrhea, atopic dermatitis, and androgenetic alopecia. Gowri found that 90% of PCO cases had some sort of skin symptom; our study showed that 100% of patients had some sort of skin symptom [22]

The incidence of cutaneous symptoms of PCO is approximately 90%. According to several studies, acne is the most prevalent dermatological symptom, followed by hirsutism, seborrhea, AN, and AG. Hirsutism, which is described as excessive male pattern

terminal hair growth in women, or coarse hair growth, was found to have the greatest influence on the quality of life of women with PCO. Most acne lesions appeared on the forehead, then the cheeks, the chin, and finally the nose. Most acne sufferers also have polycystic ovaries (83%), suggesting a possible causal relationship between the two conditions. Hyperandrogenism manifests itself in hirsutism, acne vulgaris, and androgenetic alopecia (AGA), while hyperinsulinemia manifests itself in atopic dermatitis (AN). It is generally agreed that hirsutism is a more accurate predictor of hyperandrogenism than acne and androgenic alopecia [23]

PCO is diagnosed according to the following parameters:
- Ovarian volume increased by more than 10 cm^3.
- The roundness index (ovarian width/ovarian length) is greater than 0.7, indicating an abnormal roundness index.
- Polycystic appearance, defined as the presence of more than 12 tiny echoless patches ranging in size from 2 to 9 mm.
- Atypical ovarian stroma, defined as an increase in hyperechogenic ovarian stroma.

Outline Treatment of PCO:
Women with PCO are typically treated symptomatically, as there are few medicines that address the wide range of problems that women with PCO come with. Currently, infertility, hirsutism, menstrual irregularities, and obesity are treated with just two therapies: weight loss and hormone replacement treatment (because of lifestyle modification, medical or surgical therapy to reduce weight, or metformin therapy). Anovulatory infertility and hirsutism are particularly challenging because they require separate treatments and can't be administered at the same time. Oral contraceptives, which inhibit ovulation, and anti-androgens, which may be teratogenic in a male foetus, are two examples of the types of drugs that would be counterproductive here. Clinical challenges like these lead to two primary categories for PCO treatment: either treating anovulatory infertility or providing long-term maintenance for PCO-related symptoms (i.e., hirsutism, menstrual disorders, obesity, etc.) [14]

Prostate Specific antigen (PSA):
Both healthy and cancerous prostate tissue express the glycoprotein PSA. PSA is converted from its proenzyme form by secretory cells lining the prostate glands. Proteolysis of active PSA results in free protein that is able to enter the bloodstream and circulate without being bound by any other proteins (free PSA). Active PSA is bound by protease inhibitors such as alpha-1-antichymotrypsin and alpha-2-macroalbumin. PSA is a protein hormone that is made in the prostate. Screening, diagnosing, and keeping tabs on prosthetic adenocarcinoma all use the highly specific and crucial

PSA test. Breast, ovarian, and endometrial tissues, as well as amniotic fluid and milk, all contain PSA. Androgens, progesterone, and glucocorticoids are steroid hormones thought to be involved in PSA production. [24].

Prostate specific antigen and PCO in females
In addition to the prostate gland, PSA has been identified in a variety of female tissues, including the ovary, endometrial, breast, milk, and amniotic fluid. Steroid hormones such as progestin, androgens, and glucocorticoids appear to be connected to PSA production. Androgens increase PSA expression in women. PSA is a potential new measure of hyperandrogenism in both polycystic ovary syndrome (PCOS) and hirsute women. One study, however, concluded that serum PSA levels were not helpful in identifying hirsutism [25]. The role of PSA in PCO patients is unclear, however it has been suggested that it can be used as a clinical marker and potentially as a new diagnostic criterion for hyperandrogenemia in PCO women. There has been an increase in the number of papers attempting to analyse the correlation between PCO and PSA levels, although the results remain controversial. Total PSA (tPSA) and free PSA (fPSA) levels have been shown to be greater in some research including PCO patients, whereas other investigations have found the opposite to be true.[1].

The link between PCO and elevated testosterone levels is well-established. Serum PSA in women may be a good biochemical measure of androgen biological action and, although its origin is uncertain, may represent androgen activity in one or more androgen-sensitive organs. Serum PSA may play a role in the identification of female colorectal and breast cancer, according to the research. In addition, the degree of hyperandrogenism in hirsute patients is correlated with their high blood PSA levels [26]. However, due to a dearth of pertinent pathophysiology investigations, the precise mechanism of serum PSA participation in PCO remains uncertain. DHEAS, hirsutism, and the LH/FSH ratio have all been linked to elevated tPSA and fPSA levels, according to a single study. The fact that is up-regulated by androgens and the idea that serum PSA may be a possible biomarker of hyperandrogenism in females have led to the hypothesis that the PSA enhancer regions and gene promoter include active androgen response elements [1].

Relation between PSA and PCOS patients
In women, an increase in PSA occurs when androgen levels are high. Unfortunately, PCOS lacks a single, definitive diagnostic criterion. In therapeutic settings, such a tool would be invaluable if it existed. The role of serum PSA in PCO pathogenesis is still poorly understood. Serum PSA levels in PCO patients have been shown to be higher than in controls in a number of recent investigations [1]. PSA and PSA in women with PCO have been studied extensively to

prove its diagnostic value. PSA in urine is equivalent to serum PSA, and PSA as a diagnostic tool has a sensitivity of 70.5% and specificity of 82% for prostate cancer diagnosis. As the author points out, PSA has excellent sensitivity, specificity, and diagnostic accuracy, making it a prime candidate for PCO diagnosis. [27]

To determine the diagnostic value of PSA and FPSA in women with PCOS, 62 cases were compared to 35 controls. Individuals with PCOS were classified as either anovulatory (group A) or ovulatory (group B). Group A had a positive predictive value of 88.2%, and a negative predictive value of 59.3% for PSA levels above 10 pg/ml as well as a sensitivity of 73.2%, and a specificity of 80%. Positive and negative predictive values were 76% and 69%, respectively, for PSA levels above 10 pg/ml in group B, while sensitivity and specificity were 85% and 80%, respectively. Then, it was shown to be effective as a PCOS diagnostic tool for female patients [28]. The study indicated that in women with anovulatory PCO, the diagnostic value of PSA and the reported PSA level had a sensitivity and specificity of 85% and 80%, respectively. The study confirmed that PSA and the PSA: PSA ratio are equally useful in diagnosing PCO in female patients. Meta-analysis subgroup analysis showed that PSA and PSA ratio were both elevated in PCO women compared to controls. There is a dearth of research on PSA levels in overweight women.[1]

In this study, PSA levels were evaluated between women with PCOS and a control group. The diagnostic value of PSA was reported for the first time in this study, making it the first in Iran and just the second worldwide. Higher PSA levels in our study could not have resulted from fluctuations in the menstrual cycle because we analysed the blood samples during the early follicular phase. There was a significant correlation between LH/FSH ratio, TT, FSG, DHEAS, and PSA levels. We found that PSA levels were greater in PCOS women. Based on a sensitivity of 91%, specificity of 81.2%, positive predictive value of 81%, and negative predictive value of 85%, the optimal PSA cut off point for diagnosing PCOS was greater than 0.07 ng/ml [29].

Another study by **Ukinc et al.** [30] found that a PSA cutoff of 10 pg/ml had a sensitivity and specificity of 73.2% and 80%, respectively, while an FPSA cutoff of 2.1 pg/ml had a sensitivity of 85.4% and a specificity of 80.6%.

Hanamura et al. [32] found that blood PSA levels did not change between premenopausal and postmenopausal women who were otherwise healthy. When the gonadal axis was inhibited and ACTH was activated with glucocorticoids, PSA levels were unaffected by androgen concentrations. A higher circulating PSA level and a correlation with 3A-androstenadiol glucuronide were found in hirsute women. Other studies found a different direct

connection between PSA, steroid hormone receptors, and breast malignancy. PSA values were elevated due to endogenous androgen, however it is unclear if PSA is a valid indicator of other forms of hyperandrogenism. Therefore, PCOS cannot be diagnosed only by measuring PSA levels, and neither can other illnesses related to hyperandrogenism.[33].

There was a significant correlation between PCOS and PSA, therefore its significance in PCOS patients should not be downplayed in therapeutic trials.

Future direction:
PSA levels may have diagnostic relevance and be used to monitor adrenal hyperplasia, ovarian tumours, breast cancer, and other forms of hyperandrogenism, but more study is needed to confirm this. The prognosis of PCOS in infertility and metabolic problems, as well as its correlation with acne severity, require further study. The therapeutic importance of these findings and the full extent of the link between PSA levels and acne in PCO patients require further study [29].

REFERENCES
1. **Wu Z-H, Tang Y, Niu X et al. (2019):** Prostatic-specific antigen (PSA) levels in patients with polycystic ovary syndrome (PCOS): a meta-analysis. J Ovarian Res., 12: 1-8.
2. **Azziz R, Carmina E, Chen Z et al. (2016):** Polycystic ovary syndrome. Nat Rev Dis Primers, 2: 1-18.
3. **Sharma A, Welt CK (2021):** Practical approach to hyperandrogenism in women. Medical Clinics, 105: 1099-116.
4. **Yilmaz B, Yildiz BO (2019):** Endocrinology of hirsutism: from androgens to androgen excess disorders. Hyperandrogenism in Women, 53: 108-19.
5. **Kameswararao K, Sujani C, Koteswararao N, Rajarao A, Satyanarayanamma P (2019):** A Brief Review on Acne Vulgaris. Research Journal of Pharmacology and Pharmacodynamics, 11: 109-19.
6. **Essah P, Wickham III E, Nunley J, Nestler J (2006):** Dermatology of androgen-related disorders. Clinics in Dermatology, 24: 289-98.
7. **Bernales S (2021):** Acne vulgaris: role of the immune system. International Journal of Dermatology, 60: 1076-81.
8. **Das A, Datta D, Kassir M et al. (2020):** Acanthosis nigricans: a review. Journal of Cosmetic Dermatology, 19: 1857-65.
9. **Prakash N (2019):** Clinical Study of Association of Acanthosis Nigricans with Metabolic Syndrome in a Tertiary Care Hospital: Rajiv Gandhi University of Health Sciences (India), 1: 27-75.
10. **Starace M, Orlando G, Alessandrini A, Piraccini B (2020):** Female androgenetic alopecia: an update on diagnosis and management. American journal of clinical dermatology, 21: 69-84.

11. **Escobar-Morreale H (2018):** Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nature Reviews Endocrinology, 14: 270-84.

12. **Witchel S, Oberfield S, Peña A (2019):** Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. J Endocr Soc., 3: 1545-73.

13. **Smet M, McLennan A (2018):** Rotterdam criteria, the end. Australas J Ultrasound Med., 21: 59-60.

14. **Legro R (2015):** Evaluation and treatment of polycystic ovary syndrome. South Dartmouth., 6: 30-63.

15. **Cluzet V, Devillers M, Petit F** *et al.* **(2020):** Aberrant granulosa cell-fate related to inactivated p53/Rb signaling contributes to granulosa cell tumors and to FOXL2 downregulation in the mouse ovary. Oncogene, 39: 1875-90.

16. **Goodarzi M, Carmina E, Azziz R (2015):** DHEA, DHEAS and PCOS. The Journal of Steroid Biochemistry and Molecular Biology, 145: 213-25.

17. **Unluhizarci K, Karaca Z, Kelestimur F (2021):** Role of insulin and insulin resistance in androgen excess disorders. World J Diabetes, 12: 616.

18. **Dewailly D, Robin G, Peigne M** *et al.* **(2016):** Interactions between androgens, FSH, anti-Müllerian hormone and estradiol during folliculogenesis in the human normal and polycystic ovary. Hum Reprod., 22: 709-24.

19. **Zehravi M, Maqbool M, Ara I (2021):** Polycystic ovary syndrome and reproductive health of women: a curious association. Int J Adolesc Med Health, 33: 333-7.

20. **Uysal G, Sahin Y, Unluhizarci K** *et al.* **(2017):** Is acne a sign of androgen excess disorder or not? Eur J Obstet Gynecol Reprod Biol., 211: 21-5.

21. **Bienenfeld A, Azarchi S, Sicco K** *et al.* **(2019):** Androgens in women: Androgen-mediated skin disease and patient evaluation. J Am Acad Dermatol., 80: 1497-506.

22. **Abusailik M, Muhanna A, Almuhisen A** *et al.* **(2021):** Cutaneous manifestation of polycystic ovary syndrome. Dermatology Reports, 13:65-98

23. **Mihailidis J, Dermesropian R, Taxel P, Luthra P, Grant-Kels J (2017):** Endocrine evaluation of hirsutism. Int J Women's Dermatol., 3: S6-S10.

24. **Kohestani K, Månsson M, Arnsrud Godtman R** *et al.* **(2021):** The GÖTEBORG prostate cancer screening 2 trial: a prospective, randomised, population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate. Scand J Urol., 55: 116-24.

25. **Pérez-Ibave D, Burciaga-Flores C, Elizondo-Riojas M (2018):** Prostate-specific antigen (PSA) as a possible biomarker in non-prostatic cancer: A review. Cancer Epidemiol., 54: 48-55.

26. **Dumitrescu R (2018):** Early epigenetic markers for precision medicine. Cancer Epidemiol., 3: 3-17.

27. **Rudnicka E, Radowicki S, Suchta K (2016):** Prostate specific antigen (PSA) in diagnosis of polycystic ovarian syndrome–a new insight. J Gynaecol Endocrinol., 32: 931-5.

28. **Mardanian F, Heidari N (2011):** Diagnostic value of prostate-specific antigen in women with polycystic ovary syndrome. J Res Med Sci., 16: 999-1005.

29. **Mardanian F, Aboutorabi R, Jefride Y, Amini G (2014):** Study of association between promoter tumor necrosing factor alpha gene polymorphisms in -850T/C, -863 A/C, and endometriosis. Adv Biomed Res., 3: 226.

30. **Ukinc K, Ersoz H, Erem C, Hacihasanoglu A (2009):** Diagnostic value of prostate-specific antigen (PSA) and free prostate specific antigen (fPSA) in women with ovulatory and anovulatory polycystic ovary syndrome. Endocrine, 35: 123-9.

31. **Rifatt M, Rahim S (2017):** Relationship between serum Prostate Specific Antigen (PSA) in women with polycystic ovary syndrome and some reproductive hormones in Kirkuk city. Tikrit j pure sci., 22: 34-9.

32. **Hanamura T, Ohno K, Hokibara S** *et al.* **(2019):** Clinical significance of serum PSA in breast cancer patients. BMC cancer, 19: 1-11.

33. **Musrap N, Diamandis E (2016):** Prostate-specific antigen as a marker of hyperandrogenism in women and its implications for antidoping. Clinical Chemistry, 62: 1066-74.