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WHITE PAPERS

5α-Androstanediol

A Marker of Androgen Status in Women

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INTRODUCTION

SUMMARY

Androgen hormones play a critical role in women's health, influencing multiple organ systems beyond their function as estrogen precursors. When abnormally elevated, androgen activity in women commonly manifests as cutaneous symptoms such as male-pattern hair growth (hirsutism), scalp hair loss (androgenetic alopecia), and acne. These symptoms are thought to stem from the intracellular actions of the most potent testosterone metabolite, dihydrotestosterone (DHT), exerting localized effects inside the cells of peripheral tissues without significantly altering systemic hormone levels. DHT intracellularly converts to its metabolite — 5α-androstanediol — which is released into the bloodstream and excreted in urine. 5α-androstanediol is thought to be the best available marker of intracellular DHT activity in peripheral tissues. While androgen status is commonly assessed using measurement of serum testosterone, circulating testosterone alone does not fully capture localized androgen activity at the tissue level. In this review, we discuss the rationale for taking a broad view of androgens in women's health, evaluating not only testosterone but also its metabolites, to provide a more accurate, comprehensive understanding of androgen activity underlying a woman's symptoms. We review the growing body of research evidence supporting the value of 5α-androstanediol as a marker of androgen excess in women, particularly in cases when circulating testosterone appears normal. Key research findings showed the following:

- 5α-androstanediol levels are abnormally elevated in women with androgen excess symptoms, including male-pattern hair growth, scalp hair loss, acne, menstrual irregularities, and PCOS.
- 5α-androstanediol levels can be elevated even when testosterone levels are within normal range, as in the case of idiopathic hirsutism in women.
- Elevations in 5α-androstanediol levels resolve along with symptom improvement following treatment of androgen excess symptoms in women.
- 5α-androstanediol may be a more sensitive marker of androgenic effects in women than other commonly used androgen markers.

These findings underscore the importance of a more nuanced, metabolite-inclusive approach to androgen assessment in women's health.

INTRODUCTION

Over the last several decades, androgen hormones — traditionally associated with male physiology — have increasingly been recognized as essential for women's health. Androgens exert important physiological effects in women in part through their role as precursors for the production of estrogen. However, beyond their role as estrogen precursors, androgens are now known to have independent effects on multiple organ systems in women, directly affecting mood, cognition, sexual function, skin health, bone mineral density, cardiovascular functioning, and muscle mass. [1]

Circulating levels of androgens are commonly assessed in clinical practice through measurement of serum testosterone. [2] For additional insights about androgen activity

in women, assessing testosterone's downstream metabolites may also be warranted in certain clinical scenarios. In this review, we discuss a growing body of research that points to the value of assessing not only testosterone, but also its metabolites — such as 5α-androstanediol — when more comprehensive information is needed for clinical decision making.

Why pay attention to androgen metabolites?

Most testosterone circulating in blood is bound to proteins such as sex hormone–binding globulin (SHBG) or albumin. The small portion of freely circulating testosterone that is not bound to proteins is the biologically active form of testosterone. Free testosterone can be calculated based on the amount of total testosterone, SHGB, and albumin, and can be important in the diagnosis of many androgen-related diseases. Testing of elevated androgen levels in women experiencing androgen excess symptoms is recommended, especially serum total and free testosterone. [2] However, clinical symptoms of androgenic conditions are not always related solely to testosterone circulating in the bloodstream. [3] The clinical effects of androgens are complex and may arise from an interplay of multiple factors, including interactions with other hormones, variability in androgen receptor sensitivity, tissue-specific effects, and the influence of androgen metabolites. [4,5] As an example of this complexity, certain metabolites of testosterone are more potent than testosterone itself, with DHT being the best illustration of this — DHT is three times more potent than testosterone in both women and men, due to a higher binding affinity for the androgen receptor, a longer duration of action at the receptor, and an inability to convert (or aromatize) into estrogen in the way that testosterone does,[6] all leading to stronger androgenic effects. This underscores the importance of taking a broad view of androgens, comprehensively looking not only at testosterone but also at its metabolites.

Compared to androgens circulating in the bloodstream, the metabolites of androgens better reflect a critical type of localized hormone activity (intracrine activity), where precursor sex hormones are converted into active sex hormones inside the cell without unnecessarily creating fluctuations of systemic blood levels of circulating hormones. [4,7] For example, in peripheral tissues such as skin, free (protein unbound) testosterone enters the cells and converts to DHT by the enzyme 5α-reductase. DHT then activates the intracellular androgen receptor, ultimately leading to gene transcription that regulates hair growth, sebum production, and other physiological effects in the skin. [8] The DHT produced inside this cell remains inside the cell, exerting localized effects without being released into the blood. Essentially, the most biologically meaningful effects of DHT are through its intracellular actions, which cannot be measured in serum. Excess DHT does, however, intracellularly convert to its metabolite — 5α-androstanediol — which is released into the bloodstream and then conjugated to a water-soluble form excreted in urine. [9,10] 5α-androstanediol is thought to be the best marker available of DHT formation and activity inside the cell. [11,12]

In sum, because intracrine actions allow specific tissues to produce and use androgens locally as needed, measuring circulating androgens in the bloodstream does not always offer a full, nuanced picture of androgen activity — their metabolites can serve as better indicators of the production and actions of bioactive androgens, especially of the most potent androgen (DHT) inside the cells of peripheral tissues. [4–8,11,12]

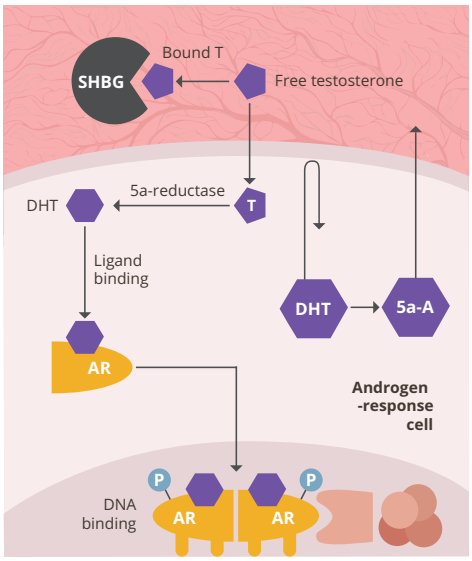
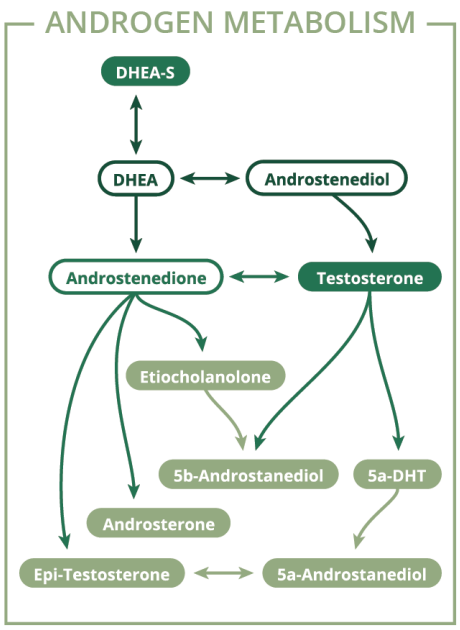
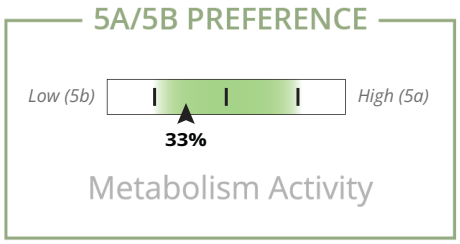


Figure 1: *: DHT acts primarily inside the cell, with only a small fraction exiting the cell into the bloodstream. A larger proportion of its metabolite, 5α-androstanediol, exits the cell into the bloodstream and is subsequently excreted in urine.*





Androgen production and metabolism in women

The ovaries, adrenal glands, and peripheral tissues all play key roles in androgen production and metabolism over a woman's life span, although the relative contribution of each of these sources of androgens shift over time depending on the reproductive stage. [13] In premenopausal women, the ovaries are a major source of androgens, directly producing testosterone and the androgen precursor, androstenedione. Roughly 25% of circulating testosterone in women originates from the ovaries. [14,15] Contributing to another 25% of circulating testosterone are the adrenal glands, which produce androstenedione as well as the upstream androgen precursors dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS). [14,15] Generally, testosterone levels in premenopausal women are considered to be representative of ovarian production, while DHEA and DHEAS levels are reflective primarily of adrenal production. [14] Approximately 50% of testosterone in premenopausal women arises from peripheral conversion, where androgen precursors are converted into bioactive testosterone and DHT in peripheral tissues such as the skin and adipose tissue. [15,16]

In postmenopausal women, due to the significant changes in ovarian function, ovarian production of testosterone declines (but does not disappear). [17–19] The adrenal glands become the main source of androgens in postmenopausal women, with the production of DHEA and DHEAS serving as the dominant precursors for androgen production. [20] Peripheral tissues are essential to convert these adrenal-derived precursors into stronger androgens (testosterone and DHT) that can then exert local androgenic effects.

Significance of 5-alpha versus 5-beta androgen pathways in women

Androgens are metabolized through two distinct routes — 5α and 5β pathways — that lead to the formation of different androgen metabolites, each with varying biological activity and clinical implications. [21] Through the 5α pathway, the enzyme 5α-reductase catalyzes the reduction of testosterone into 5α-DHT, which is further metabolized into 5α-androstanediol. This pathway is associated with higher androgenic activity. In the 5β pathway, the enzyme 5β-reductase (which is concentrated in the liver as opposed to target tissues) catalyzes the reduction of testosterone, eventually leading to formation of 5β-androstanediol and, overall, metabolites with lower androgenic activity. [22] The two contrasting pathways, under normal physiological conditions, play a role in maintaining healthy androgen balance.

Because of its involvement in DHT formation through the 5α pathway, the enzyme 5α-reductase is well known for, essentially, making testosterone more potent. Numerous studies have associated upregulated 5α-reductase activity with symptoms such as facial hair growth, thinning scalp hair, acne, and polycystic ovary syndrome (PCOS) in women. [8,23–27] In contrast, androgen metabolism through the beta pathway is not associated with these clinical symptoms.

ANDROGEN EXCESS SYMPTOMS IN WOMEN: EVIDENCE FOR THE ROLE OF 5A-ANDROSTANEDIOL

A larger amount of research has been devoted to studying androgen excess than androgen deficiency in women, in part because the symptoms of high androgens are more visible and easier to define than the symptoms of low androgens. Although the research findings

so far are mixed, several studies have reported that pre- and postmenopausal women with low androgens (serum total testosterone, free testosterone, and DHEA-S levels) experience low libido and mood. [28–32] Limited published data are available on the symptoms that correlate with low 5α-androstanediol. Studies in postmenopausal women have shown low urinary levels of 5α-androstanediol [33] and a strong inverse relationship between 5α-androstanediol levels and anxiety, in that low plasma levels of 5α-androstanediol correlated with high anxiety. [34] On the other hand, studies in premenopausal women have not found an association between serum 5α-androstanediol levels and mood (anxiety and depressive symptoms). [35,36] As we await more research on the symptoms associated with low 5α-androstanediol levels in women, it is worth considering that 5α-androstanediol's documented role in modulating neuronal excitability and exerting neuroprotective effects in the brain could implicate it in mood and behavior. [37,38] Therefore, low levels of 5α-androstanediol could impact androgen physiology and its related effects on the brain, potentially manifesting as symptoms such as diminished libido, mood, sense of well-being, and increased fatigue. [30,32]

As a marker of intracellular DHT metabolism, 5α-androstanediol has been examined in many studies looking into elevated androgen levels (hyperandrogenemia) and their associated symptoms and conditions. In the following sections, we will review the peer-reviewed research describing the role of 5α-androstanediol in the most common clinical signs of androgen excess in women — male-pattern hair growth (hirsutism), scalp hair loss (androgenetic alopecia), acne, menstrual irregularities, and PCOS. Although the full details surrounding the pathophysiology of these conditions are not yet delineated, it has been proposed that androgen excess symptoms in women result from elevated androgen production, increased enzymatic activity of 5α-reductase, alterations in androgen receptor function, increased sensitivity of hair follicles to androgens, and/or changes in androgen metabolism. [8,16,39] Below, we focus on reviewing the research on changes in androgen metabolism, with an emphasis on 5α-androstanediol. These studies establish a relationship between 5α-androstanediol levels and androgen excess symptoms in women who often display normal testosterone levels, suggesting that 5α-androstanediol may be a more sensitive marker of androgenic effects in the body than other commonly used androgen markers.

Hirsutism

Hirsutism is one of the most common symptoms of excess androgen activity in women, characterized by increased growth of dark, coarse (terminal) hair distributed in a typical male pattern throughout androgen-sensitive skin regions such as the face, chest, back, and abdomen. Hirsutism in women is generally seen with measurably elevated circulating androgens, including elevated serum free testosterone. [40] However, this is not the case in all women with hirsutism. [41–43] Premenopausal women with idiopathic hirsutism (a type of hirsutism without an identifiable medical cause) generally have normal total and free testosterone. [41,44–46] In research on idiopathic hirsutism, there has been an interest in investigating potential missed changes in other androgens, including 5α-androstanediol, to help pinpoint possible androgen-related abnormalities underlying idiopathic cases when testosterone appears normal. [47–49]

Numerous studies show that 5α-androstanediol levels are significantly higher in women with idiopathic hirsutism compared to normal women, whether 5α-androstanediol was

measured in blood [44,50–55] or urine. [45,48,56] In fact, among seven different steroid hormones measured in urine samples, the levels of 5α-androstanediol showed the largest difference between hirsute patients and healthy women, [48] suggesting that its levels may serve as a sensitive discriminatory marker for differentiating between women with and without hirsutism.

In addition to having higher 5α-androstanediol levels in blood and urine, women with idiopathic hirsutism also have skin that is more efficient at converting testosterone into 5α-reduced metabolites — specifically into its more potent form (DHT) and into 5α-androstanediol — compared to healthy women. [23,57] This high conversion of testosterone to 5α-reduced metabolites points to an increased activity of the 5α-reduction pathway in the skin of women with idiopathic hirsutism, which may result in increased androgenic effects on hair follicles.

Overall, the evidence suggests 5α-androstanediol to be a potential laboratory marker of hirsutism in women, especially to help with interpretation of results when testosterone is within normal range. Idiopathic hirsutism has been proposed to be an initial early manifestation of other hyperandrogenic conditions such as PCOS, [58,59] warranting long-term follow up to monitor any progression to more pronounced hyperandrogenic symptoms or conditions over time.

Androgenetic alopecia

Paradoxically, while androgen excess can contribute to increased hair growth in some areas (e.g., face), it can contribute to increased hair loss in other areas (scalp) due to differences in follicle sensitivity, androgen receptor activity, and enzyme levels, and in how hair follicles respond to androgens in different areas of the body. [60] In the scalp, excess DHT shortens the active growth (antigen) phase of the hair growth cycle and promotes structural miniaturization of androgen-sensitive hair follicles, leading to hair follicles becoming thinner and shorter, as seen in androgenetic alopecia (also known as androgenic alopecia). [39] Along with enhanced DHT formation locally in the scalp skin, women with androgenetic alopecia also have higher levels of 5α-reductase and an increase in androgen receptor density in the affected areas of the scalp. [39]

Several studies have demonstrated that women with androgenetic alopecia have significantly elevated blood levels of 5α-androstanediol compared to healthy women. [8,61–64] Further, when the degree of women's scalp hair loss is considered more closely, the level of 5α-androstanediol is found to correlate with the severity of alopecia (grade I, II, or III), where circulating 5α-androstanediol levels increase as the grade of alopecia increases. [62] These findings suggest that women with androgenetic alopecia have alterations in their androgen metabolism that could influence thinning of scalp hair. When considered collectively alongside the studies on hirsutism, [44,45,48,50–56] the overall evidence points to 5α-androstanediol serving as a meaningful marker for DHT activity in the hair follicles of women displaying androgen excess symptoms.

Acne

Female acne vulgaris, a multifactorial skin disorder occurring at the level of the pilosebaceous unit, is considered to be a condition of androgen excess. [65] The correlation between androgen excess and the development of acne in women is well documented.

Briefly, androgens are involved in the pathogenesis of acne by increasing sebum production and stimulating sebaceous gland growth (creating an environment conducive for anaerobic bacteria to flourish), as well as contributing to inflammation in the sebaceous gland. [65,66]

Numerous studies have reported increased circulating levels of androgens in female acne, including higher free testosterone and DHEAS levels, compared to women without acne. [67] Androgen metabolites, especially androsterone, have also been found to be preferentially increased in women with acne. [68,69] With respect to 5α-androstanediol, research on its role in female acne is still emerging. [8,54] Interestingly, when a group of female acne patients previously determined to have normal androgen hormone levels were further evaluated, half of the women in fact had elevated serum 5α-androstanediol levels. [70] Similarly, another study found threefold higher levels of plasma 5α-androstanediol in a subset of female acne patients compared to a control group, even though levels of other androgens (DHEAS, androstenedione, and total and free testosterone) were within normal ranges in these patients. [12]

More research is needed on the specific contributions of androgen metabolites to acne in women. However, these initial findings in female acne add to the broader body of work supporting the role of 5α-androstanediol as a marker of intracrine androgen activity in target tissues, [7] in this case in the skin of women with acne. [12,70] The findings also suggest the potential usefulness of a comprehensive androgen evaluation of each female acne patient in order to detect hyperandrogenic states and to be able to follow with an appropriately tailored choice of therapeutic management, especially considering new treatment options targeting the androgen receptor in female acne. [71]

Menstrual cycle irregularities

In addition to the cutaneous signs of androgen excess discussed above (hirsutism, androgenetic alopecia, and acne), systemic signs of androgen excess have similarly been explored in research, including menstrual cycle irregularities. Androgen receptors are widely expressed in women's reproductive tissues including in the endometrium, [72] allowing androgens to regulate various functions of the uterus, such as tissue repair during menstruation. [73,74] While many factors contribute to menstrual cycle changes, higher levels of circulating androgens (testosterone and free androgen indices) have been associated with menstrual irregularities in a variety of female populations, including in adolescents with menstrual disorders, [75] premenopausal women without any other chronic health conditions, [76,77] and women with uterine diseases. [78]

Some studies have hinted toward an association between menstrual cycle disturbances and changes specifically in 5α-androstanediol. For example, elevations in 5α-androstanediol are seen in a higher proportion of women with an androgenic condition (hirsutism or androgenetic alopecia) that co-occurs with oligomenorrhea, compared to women with an androgenic condition and normal ovulatory cycles. [62,79] The same has been shown for elevations in other androgens (DHEAS and testosterone) in hirsute women with oligomenorrhea or amenorrhea, compared to hirsute women with regular menstrual cycles. [80,81] These early findings on a potential link between 5α-androstanediol and cycle abnormalities align with the broader literature on hyperandrogenemia being associated with irregular menstrual cycles. [75–78]

Polycystic ovary syndrome

The underlying etiology of androgen excess symptoms in many women often turns out to be PCOS, a complex multifactorial condition arising from the interplay of genetic predisposition, [82] metabolic risk factors (e.g., insulin resistance), [83] and hypothalamic-pituitary-ovarian dysregulation, [84] all leading to excess androgen production from the ovaries. Women with PCOS exhibit androgen excess in two ways: either as clinical symptoms (hirsutism, androgenetic alopecia, acne, menstrual cycle disturbances) or as biochemical changes (hyperandrogenemia as reflected by high circulating androgens), or both. [85,86] Of note, androgen excess has been proposed to not only be a feature of PCOS but to possibly be a key driver of the condition, [84,85,87,88] reinforcing the importance of understanding the full picture of the androgen profile (e.g., production, metabolism) in PCOS.

Currently, there is no reliable diagnostic laboratory test available to detect PCOS. Measurement of serum free testosterone has been studied as a useful diagnostic tool for differentiating between women with PCOS from healthy women [89–92] (provided that attention is paid to the accuracy and sensitivity of the method used to measure testosterone in women [93]). While most women with PCOS do have serum testosterone levels higher than normal reference values, some do not, [94–97] which adds a layer of complexity to the diagnosis of PCOS. This discrepancy has spurred initial research on the untapped value of other lesser-studied androgens and metabolites for possible diagnostic use in PCOS.

For example, in one study, 40 different steroids were analyzed from 24-hour urine in women with or without PCOS. [98] The results showed that 14 of these steroid metabolites were significantly higher in women with PCOS compared to healthy women, including nine androgens and four glucocorticoids. Interestingly, the study's analysis of the diagnostic performance parameters of the 40 steroids yielded one androgen metabolite in particular — 5α-androstanediol — as being the best single discriminative marker for distinguishing between women with PCOS and healthy women without PCOS. These results are consistent with other reports of a significant elevation in 5α-androstanediol in women with PCOS compared to controls at baseline [99,100] and after an oral challenge with the androgen precursor DHEA (to evaluate downstream conversion to androgens), [25] as well as altered enzymatic activity of 5α-reductase in PCOS. [23,26,27] Collectively, the research to date suggests the possibility that women with PCOS may be differentiated by their levels of 5α androgen metabolites including 5α-androstanediol.

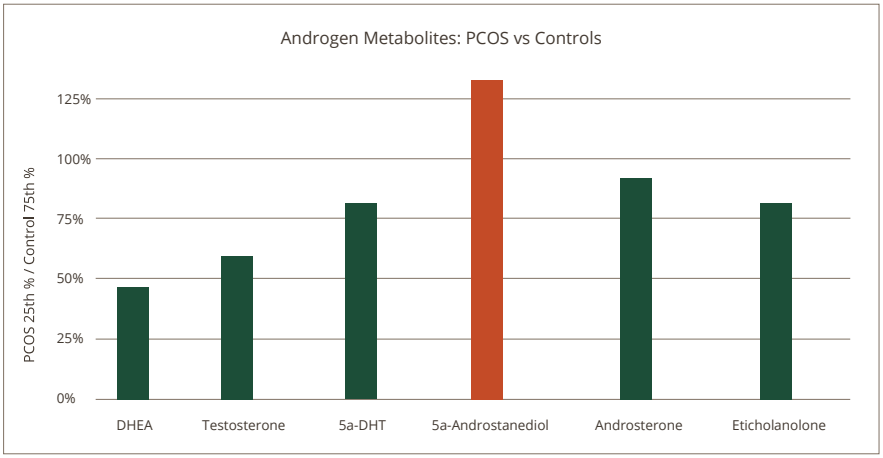


Figure 2: *An analysis of androgen metabolites in 24-hour urine (nmol/24h) in women with or without PCOS shows that, for 5α-androstanediol, the 25th percentile value for PCOS patients is more than 125% of the 75th percentile value for normal controls. Essentially, even the lower end of the PCOS range (25th percentile) exceeds the upper end of the normal range (75th percentile) for healthy controls, suggesting no overlap between the normal range and the PCOS range for 5α-androstanediol. [98]*

Correlation of 5α-androstanediol with treatment response

In addition to lifestyle interventions, [101] androgen excess symptoms in women are often treated with various hormone-modulating therapies. [102] While clinical symptom improvements (such as facial hair growth reduction in hirsutism) are more meaningful than changes in hormone levels when evaluating the efficacy of a treatment, some practice guidelines recommend that androgen levels can be measured 3-6 months after initiating hormone-modulating therapy to gauge the adequacy of androgen suppression. [103] In this vein, studies have explored whether measurement of androgen levels could serve as a biochemical parameter correlating with the clinical response to treatment of hyperandrogenic symptoms in women.

In several studies, [104–106] women with hirsutism who experienced symptom improvement after 3-6 months of treatment with a 5α-reductase inhibitor (oral finasteride) also displayed concomitant decreases in serum DHT and 5α-androstanediol. Similar correlations of 5α-androstanediol with the clinical response to therapy have been observed with other hormone-modulating treatments such as spironolactone, oral contraceptives, or gonadotropin-releasing hormone agonists for hirsutism in women, [51,107] or retinoids (isotretinoin) for female acne. [108] These findings suggest that changes in 5α-androstanediol levels during treatment of female androgen excess symptoms might reflect clinical efficacy and could offer a potential biochemical measure (complementary to clinical measures) of a treatment's effectiveness in reducing hyperandrogenic symptoms in women.

CONCLUDING REMARKS

Summary of key research findings

Based on the research reviewed here on 5α-androstanediol in women's health, the evidence suggests that:

1. 5α-androstanediol levels reflect intracellular DHT activity and androgen metabolism in peripheral tissues.
2. 5α-androstanediol levels are abnormally elevated in women with androgen excess symptoms, including male-pattern hair growth, scalp hair loss, acne, menstrual irregularities, and PCOS.
3. 5α-androstanediol levels can be elevated even when testosterone levels are within normal range, as in the case of idiopathic hirsutism in women.
4. Elevations in 5α-androstanediol levels resolve along with symptom improvement following treatment of androgen excess symptoms in women.

Clinical relevance

Overall, the studies in women with androgen excess symptoms demonstrate the importance of comprehensively assessing the androgen profile, evaluating not only parent androgens but also androgen metabolites including 5α-androstanediol, to provide a fuller understanding of the androgen changes underlying associated symptoms. Androgen metabolites such as 5α-androstanediol are key indicators of intracrine androgen metabolism, reflecting localized hormone activity at the tissue level that may not be captured through a single test of circulating testosterone alone. Further,

the research supports the relevance of 5α-androstanediol as a biochemical marker of androgen status in women experiencing androgen-related symptoms, especially in otherwise normoandrogenic cases where there may be diagnostic uncertainty. Potentially, 5α-androstanediol may also have some use in monitoring treatment response in women being treated for androgen excess symptoms.

In a research setting, 5α-androstanediol levels in women with excess androgen symptoms are measured using either blood or urinary sampling. However, in a clinical setting, there are important distinctions to consider in selecting urine or blood collection for hormone assessment. Firstly, urine collection is more feasible, convenient, and noninvasive than blood collection for patients. [109] Also, when a broader picture of longer-term hormone exposure is needed, urine provides a better representation of hormone metabolism and excretion over a span of time, whereas serum testing is informative about circulating hormone status only at the moment of collection. Therefore, validated urinary methods of testing 5α-androstanediol may be considered as a more appropriate or feasible option for some patients.

Given the complexity of androgen metabolism and its role in female physiology, a more comprehensive assessment of androgens can enhance clinical decision making. Consideration of 5α-androstanediol within androgen testing panels holds the promise of complementing existing routine laboratory tests to assess androgen status in women and to ultimately support personalized treatment strategies for women experiencing androgen excess symptoms.

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