

Endocrinology ROUNDS™

February 2006
Volume 6, Issue 2

AS PRESENTED IN THE ROUNDS
OF THE DIVISION OF
ENDOCRINOLOGY AND METABOLISM,
ST. MICHAEL'S HOSPITAL

www.endocrinologyrounds.ca

Diagnosing Hyperandrogenism in Women

BY MARIA KRAW, M.D.

All women produce androgens in their adrenal glands and ovaries. Androgens have important physiological effects in women through their direct effects on androgen receptors and as precursors for estrogen biosynthesis. Hyperandrogenism in women can present with varying severity and primarily affects the pilosebaceous unit (hirsutism, acne, and alopecia) and ovulatory function (amenorrhea, ovulatory dysfunction, and infertility). It can also be a forerunner of other metabolic disorders, such as hyperinsulinemia and dyslipidemia. Although polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenism in women, other conditions must be ruled out. The appropriate clinical and biochemical diagnosis of hyperandrogenism in a woman can direct optimal management of her signs and symptoms. This issue of *Endocrinology Rounds* reviews androgen production in pre-menopausal women, the clinical manifestations of hyperandrogenism, laboratory testing of androgens, and the common disorders of excess androgens in women of reproductive age. Management of these disorders is beyond the scope of this review.

Sources of androgens in women

Androgen biosynthesis occurs in both the adrenal gland and the ovaries and is modulated by several important cytochrome P450 enzymes (Figure 1). Androgen secretion occurs in the adrenal gland and the ovary due to stimulation of adrenocorticotropin hormone (ACTH) and luteinizing hormone (LH), respectively. Other stimuli include intraglandular, paracrine, and autocrine mechanisms. No physiological negative feedback loop has been demonstrated to regulate androgen production in women.¹ The major androgens in pre-menopausal women listed in descending order of serum concentration are:

- dehydroepiandrosterone sulphate (DHEAS)
- dehydroepiandrosterone (DHEA)
- androstenedione (A)
- testosterone (T)
- dihydrotestosterone (DHT).²

Although most abundant in the circulation, the first 3 are better considered as "pro-hormones" that require conversion to "T" to express their androgenic effects (Table 1). This conversion occurs in the adrenal glands, the ovary, and in peripheral tissues such as hair follicles, external genitalia, and adipose tissue.

Dehydroepiandrosterone sulphate: DHEAS is the second most abundant steroid in the human circulation after cholesterol. It is secreted solely by the adrenal zona reticularis under the regulation of ACTH with some influence by prolactin, insulin-like growth factor (IGF-1), and estrogen. Serum concentrations increase at adrenarche (age 7 to 8 years), peak between age 20 to 30, and decline slowly with age.³ There are no significant changes in circulating levels diurnally or during the menstrual cycle.

Dehydroepiandrosterone: DHEA is produced in the zona reticularis of the adrenals and the ovarian theca cells with the remainder converted from circulating DHEAS by steroid sulphatase.⁴ The decline in levels with age parallels that of DHEAS. DHEA concentrations are higher in the morning and during the luteal phase of the menstrual cycle.

Androstenedione: A is produced in equal amounts by the adrenal zona fasciculata and the ovarian stroma under regulation of ACTH and LH, respectively. Serum concentrations show circadian variation and mid-cycle elevation in parallel with the mid-cycle estradiol peak.⁵ It can be produced intracellularly from DHEAS via DHEA.

Testosterone: T is the most significant biologically-active androgen in women. It is secreted by the adrenal zona fasciculata, the ovarian theca cells, and via peripheral conversion, primarily from A. Serum T concentration is at its lowest in the early follicular phase of the cycle, rising to



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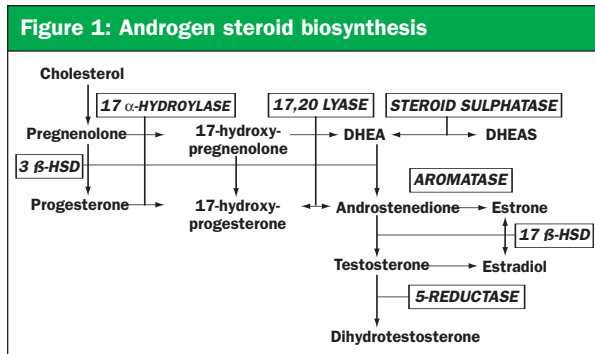
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St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

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3β-HSD = 3β-hydroxysteroid dehydrogenase
 17β-HSD = 17β-hydroxysteroid dehydrogenase

a mid-cycle peak with luteal phase concentrations higher than those in the early follicular phase.³ T shows circadian variation with peak levels in the early morning hours. As with the other androgens, T can be produced intracellularly from DHEAS.

Testosterone circulates in the peripheral blood of women bound to sex hormone binding globulin (SHBG) (60%-91%), loosely bound to albumin (7%-38%) or unbound (free) (1%-2%).⁶ The percentage of binding varies considerably between individuals. Biologically active T (bioavailable T) consists of both the unbound (free) and loosely albumin-bound (half-dissociation time <1 second) fractions, although recent evidence suggests that SHBG-bound (half-dissociation time >20 seconds)⁷ T may bind to cell surface receptors, resulting in non-genomic effects.⁸

Dihydrotestosterone: DHT is primarily a peripheral product of T conversion in androgen-sensitive tissues and circulates in low concentrations in serum. A small quantity is secreted directly by the adrenal zona fasciculata. DHT is a non-aromatizable androgen and metabolism is via intracellular glucuronide conjugates.

Clinical manifestations of hyperandrogenism

Hirsutism: Hirsutism in women is defined as male-type terminal hair growth and distribution, often presenting on the face, neck, chest, and lower abdomen. This disorder is a result of increased androgen action of hair follicles due to increased circulating androgen levels or increased sensitivity of hair follicles to normal levels of circulating androgens. DHT, which is synthesized in the skin and directly stimulates dermal papillary androgen receptors to affect hair growth, is thought to be the predominant androgen responsible for the development of hirsutism.

In 1961, an effort to objectively quantify the degree of hirsutism was introduced by Ferriman and Gallwey.⁹ The original scoring system involved quantifying the degree of hair growth from "0" (absence of terminal hair) to "4" (extensive terminal hair) in 11 regions of the body, whereas the more commonly used modified version (mF-G) is based on only 9 regions.¹⁰ The assessment of hirsutism is problematic as few clinicians use the standardized scoring system and many women will have undergone treatment for hirsutism prior to assessment. In an unselected population of American women where hirsutism was defined as a mF-G score of 6 or 8, the prevalence of hirsutism was 8.0% and 2.8% in white women and 7.1 and 6.1% in black women, respectively.⁷

Although 60%-80% of women with hirsutism have elevated serum androgen levels, the degree of hirsutism cor-

Table 1: Circulating androgens in pre-menopausal women

Androgen	Adrenal	Ovary	Peripheral conversion	Daily production	Serum concentration
DHEAS	100%	-	-	3.5 - 20 mg	3 - 12 µmol/L
DHEA	50%	20%	30%	6 - 8 mg	3 - 35 µmol/L
Androstenedione	50%	50%	-	1.4 - 6.2 mg	2 - 8 µmol/L
Testosterone	25%	25%	50%	0.1 - 0.4 mg	0.6 - 2.5 µmol/L
Dihydrotestosterone	-	-	100%	4.3 - 12.5 mg	0.17 - 1 µmol/L

relates poorly with absolute levels.¹² Ovulatory dysfunction is present in 71% of hirsute women.¹³ Hirsutism is uncommon in Asian women, present in only 30% of those with elevated serum androgen levels and/or ovulatory dysfunction.¹⁴ Therefore, the absence of hirsutism cannot be used to exclude hyperandrogenism in Asian women.

Acne: Acne vulgaris is a common skin disorder that usually develops on the face, although up to 50% of women with hyperandrogenism will have acne lesions on the neck, chest, and upper back.¹⁵ Increased androgen levels stimulate enlargement of the sebaceous glands, which then convert circulating androgens into active metabolites (especially DHT), resulting in further sebaceous gland enlargement. The enlarged glands promote bacterial growth (*Priopionibacterium acnes*) that alters the sebum and stimulates inflammation, resulting in comedone, pustule, and cyst formation. There is conflicting evidence on the relationship between serum androgen levels and acne severity.¹⁶

Scalp alopecia: Androgenic alopecia is defined as progressive, non-scarring, patterned loss of scalp terminal hairs. The loss is usually diffuse over the crown with preservation of the frontal hairline. An early sign of androgenic alopecia is widening of the hair part. Although the sole presence of androgenic alopecia has not been well studied as an indicator of hyperandrogenism, it appears to be a relatively poor marker of androgen excess, unless present in the setting of oligo-anovulation.¹⁷

Virilization: An early report of androgen excess disorders (surgically-proven PCOS, but possibly including patients with undiagnosed ovarian or adrenal tumours) described a 21% incidence of mild virilization, mostly mild degrees of cliteromegaly.¹⁸ Although clinical experience suggests a much lower incidence of cliteromegaly, it is rarely looked for. If present, other virilizing signs (voice deepening, broadening of the shoulders due to increased muscle mass, decreased breast size, loss of vaginal rugae), and the possibility of adrenal or ovarian androgen-secreting tumours should be ruled out.

Ovulatory dysfunction: Women with hyperandrogenism have varying degrees of ovulatory dysfunction that may lead to infertility. These women may have normal or delayed menarche, followed by irregular menses. Even in women reporting normal menstrual cycles (27-32 days), a considerable proportion have poor ovulatory activity, prolonged follicular phases, shortened luteal phase or anovulation^{19,20} (see the *Polycystic-ovary syndrome* section).

Psychological distress: The clinical manifestations of hyperandrogenism can have devastating psychological effects on women of reproductive age.²¹ Associated obesity can have

a further negative effect on self-image and self-esteem. Ovulatory dysfunction is often associated with premenstrual symptoms such as dysphoria and is often made worse by the fear and stigma of infertility. Appropriate diagnosis and correction of the underlying cause of their hyperandrogenism is often accompanied with considerable relief in these women.

Laboratory diagnosis of hyperandrogenism

DHEA and DHEAS: These major adrenal steroids are measured by radioimmunoassay (RIA) or enzyme chemiluminescence immunoassay (ECLIA). Although DHEA is the major product of the adrenal cortex, 99% is sulphated before secretion; therefore, it is rarely measured. DHEAS is often measured to exclude the presence of an androgen-secreting adrenal neoplasm,²² although the clinical presentation is likely the best predictor of virilizing neoplasms.

Androstenedione: Androstenedione is the immediate precursor of T and its serum concentrations tend to mirror those of T. Androstenedione has been suggested as a good measure of adrenal and ovarian androgen production,²³ but the paucity of normative and clinical data about A in women with hyperandrogenism limit its routine use.

Challenges in measuring testosterone: In order to diagnose hyperandrogenism with laboratory testing, it would be ideal to have accurate and well-validated measurements of androgen activity. Attempts to evaluate the biologically active androgens (namely T) in women are limited on several fronts. There is no method of serum testing that takes into account the full extent of *in vivo* factors that possibly influence androgen activity, ie, an androgen binding protein on vessel walls. As well, adequate accuracy and sensitivity of androgen assays is particularly problematic in women who have 10-fold lower plasma concentrations of T and 20-fold lower concentrations of free T than men.²⁴

Due to the wide inter-individual variability in binding distributions, an accurate measure of biologically-active T is entirely dependent on an accurate assay for total T and SHBG. These are affected by protein and hormone concentrations and protein association and dissociation rates which, in turn, are influenced by temperature and pH.

Cross-reactivity can occur in competitive T immunoassays since the antibodies used are generated from modified forms of T (T by itself is too small to be very antigenic).⁶ Because T and DHT are structurally similar, these antibodies can cross-react with DHT (<5%).⁶ This is usually not a problem since DHT concentrations are quite low but, in certain settings, this cross-reactivity may be problematic.

Total testosterone: Total T measurements refer to the serum measurement of unbound (free) T, weakly albumin-bound T, and SHBG-bound T. Total T values are currently measured by immunoassay performed either directly on unextracted serum or following extraction (chemically releasing the T from its binding proteins using organic solvents, followed by quantitation by column chromatography). The direct method is performed in most automated clinical labs, but a study of 10 commonly-used direct immunoassays revealed that none were sufficiently reliable in women.²⁵ The method following extraction is considered to be more reliable among women. Better analytical choices include high-performance liquid chromatography (HPLC) or gas chromatography with mass spectrometry (GC-MS), neither of which is currently done in clinical settings. However, current GC-MS methods

have poor sensitivity at low concentrations, and so, even the so-called “gold standard methods” are unreliable in low ranges.

Sex hormone binding globulin: SHBG measurements are plagued by several problems. There are several circulating forms of SHBG due to differences in glycosylation. SHBG assay antibodies vary in their specificity and recognition of these varying forms. Large differences in commercially-available SHBG kits have been reported²⁶ and, currently, no gold standard method exists for measuring SHBG. SHBG levels increase with oral estrogens, androgen deficiency, hyperthyroidism, aging, anticonvulsant use, or hepatic cirrhosis. Reduced SHBG levels are seen in moderate obesity, hypothyroidism, androgen, glucocorticoid, or progestin use, or in the nephrotic syndrome.²⁷

Free testosterone: Of the methods currently available, equilibrium dialysis is considered the best approximation of free T, although it is technically difficult and generally unavailable outside of the research setting. Ultra-filtration is another method that, while faster than dialysis, may be adversely affected by factors involving binding constants (force applied to membrane) or other variables (eg, temperature, pH, and ionic strength). Currently available direct RIAs are the most widely available and easy to perform, but fare poorly when compared to equilibrium dialysis.²⁴ The free androgen index (FAI), $100 \times T/SHBG$ appears to correlate well with free T by equilibrium dialysis in some ($r=0.93$),²⁴ but not in all studies.²⁷ The FAI is not generally recommended because it can be altered by changes in either T or SHBG and it is a unit-less number, without reference to the physical reality of free T.²⁴

Bioavailable testosterone: The measurement of bioavailable T is based on the principle of differentially precipitating the SHBG-bound (and, therefore, not bioavailable) T, using varying amounts of ammonium sulfate prior to centrifugation. The percentage of T in the supernatant is then quantitated using a tritium tracer, direct measurement, or mathematical formulas based on affinity constants and concentration of protein binders. A study using mass action mathematical formulas revealed a high correlation ($r=0.99$) compared with free testosterone by equilibrium dialysis.²⁴ Bioavailable T values are about 11-fold higher than free testosterone concentrations.⁶

Dynamic testing: A two-day adrenal suppression test has been suggested as a diagnostic tool for evaluating the source of hyperandrogenemia.²⁸ In this test, T, DHEAS, and cortisol levels are measured before and after a 2-day course of 0.5 mg dexamethasone q6h. An adrenal source is suspected if high levels of T and DHEAS are suppressed by more than 40% and 60%, respectively. If T levels fail to suppress, but DHEAS and cortisol respond, the source of increased androgens is likely ovarian. Both glands are responsible for the excessive secretion if T levels suppress <40%. If cortisol levels do not suppress, the patient either has adrenal hyperfunction (Cushing's syndrome or an adrenal neoplasm) or did not take, or overly metabolized, the dexamethasone. An ACTH-stimulation test is conducted to detect steroidogenic enzyme deficiencies of the adrenal gland, predominantly 21-hydroxylase deficiency seen in congenital adrenal hyperplasia (see the *Non-classical congenital adrenal hyperplasia* section below).

Recommended initial testing: The following plasma hormone concentrations may be useful in evaluating patients with suspected hyperandrogenism: total and bioavailable

testosterone, DHEAS, LH and FSH, and prolactin. Specimens should be drawn in the morning after fasting during the first 3-7 days of a spontaneous or progesterone-induced menstrual cycle. Depending on clinical suspicion of the hyperandrogenic disorders listed below, the following tests may be of particular interest: androstenedione, TSH, glucose, and lipid profile, and/or 17-hydroxy progesterone (17-OHP).

Disorders of androgen excess in women

With the increased accuracy of serum testing and genetic screening, the criteria for the diagnosis of hyperandrogenic disorders have become more precise over the last few decades. The most common hyperandrogenic disorders in reproductive-aged women are described below in order of prevalence (Table 2).^{29,30}

Polycystic-ovary syndrome: PCOS is diagnosed in the presence of at least 2 of the following 3 abnormalities:

- oligo- or anovulation
- hyperandrogenism (clinical and/or biochemical)
- polycystic ovaries and the exclusion of other etiologies.³¹

Since the majority of women do not track the signs of ovulation (cervical mucous changes and/or basal body temperature [BBT]), menstrual periods are often taken as a surrogate marker of ovulatory function. But menses do not equal ovulation: 15% of oligo-ovulatory patients have apparent eumenorrhea (ie, bleeding interval of 27-34 days) and 40% of hirsute eumenorrheic women were found to have ovulatory dysfunction when evaluated using luteal phase progesterone levels and/or BBT monitoring.³⁰ Additionally, menstrual regularity increases with age, even though the proportion of anovulatory cycles also increases.³²

Hyperandrogenism is the second characteristic feature of PCOS, presenting in about 70% of women with the syndrome.³³ It is estimated that one-third of women with PCOS have acne,³⁴ and conversely, that the majority of women with severe acne have PCOS.³⁵ The frequency of hirsutism in PCOS depends on racial background: in Caucasian woman with PCOS the incidence is 60%-70% versus only 30% in Japanese women with PCOS.³⁶ Androgenic alopecia is present in 3%-6% of women with PCOS.³³

Polycystic ovaries (PCO) are defined by ultrasound evidence of ≥ 12 follicles measuring 2-9 mm in diameter and/or increased ovarian volume >10 mL performed on day 3-5 of the menstrual cycle.²⁹ These represent relatively normal immature arrested and atrophic follicles, rather than true cysts (as the name suggests). PCO would seem the most obvious feature of the syndrome that bears their name, but unfortunately, they are neither sensitive nor specific for PCOS. PCOS is present in about 20% of the general population and these women have more irregular periods, more hirsutism, higher LH than those without PCO; however, PCO have not been consistently linked to clinical or biochemical abnormalities.³⁷

Conversely, although common in the general population, PCO are not always present in women with other features of PCOS (hyperandrogenism and oligo-anovulation).³⁸ To further dilute their specificity, they are common in other causes of menstrual irregularities

Table 2: Prevalence of androgen excess disorders in women referred for hyperandrogenism and/or ovulatory dysfunction

	Azziz et al ³⁰ (n=950)*	Carmina et al ²⁹ (n=873) [†]
PCOS		
– classic anovulatory [‡]	82%	56.6%
– ovulatory [§]	–	15.5%
Idiopathic hyperandrogenism	6.8%	15.8%
Idiopathic hirsutism	4.7%	7.6%
HAIRAN syndrome	3.1%	–
NCAH	1.6%	4.3%
CAH	0.7%	–
Androgen-secreting tumours	0.2%	0.2%

PCOS = polycystic ovary syndrome

HAIRAN = hyperandrogenic insulin-resistant acanthosis nigricans

NCAH = 21-hydroxylase-deficient non-classical congenital adrenal hyperplasia

CAH = 21-hydroxylase-deficient congenital adrenal hyperplasia

* Women referred to an Obs/Gyn Clinic for hyperandrogenism and/or ovulatory dys

† Women referred to an Endocrine Clinic for hyperandrogenism

‡ 1990 National Institute of Health-sponsored conference consensus criteria for PCOS (oligo-anovulation and hyperandrogenism)

§ 2004 Rotterdam ESHRE/ASRM sponsored PCOS Consensus Working Group Criteria

(eg, hyperprolactinemia, hypothyroidism, hypothalamic amenorrhea, and congenital adrenal hyperplasia with 21-OH deficiency).³⁹ Because of the lack of sensitivity and specificity, one must exclude the other disorders that may overlap with these diagnostic criteria.

PCOS has been strongly linked with insulin resistance in both lean and obese women.⁴⁰ Compensatory hyperinsulinemia contributes to hyperandrogenism, both directly (through stimulation of androgen biosynthesis in the ovarian theca cell and the adrenal zona fasciculata), and indirectly, through its suppressive effects on SHBG and insulin-like growth factor binding protein-1 (IGFBP-1) production by the liver.⁴¹ Insulin resistance is associated with an increased risk for several metabolic disorders, including impaired glucose tolerance and type 2 diabetes,⁴² hypertension,⁴³ dyslipidemias⁴⁴ (low high-density lipoprotein cholesterol and high triglycerides), and atherosclerosis.⁴⁵ It is, therefore, recommended that women with PCOS be screened for the above metabolic conditions.³¹

Idiopathic hyperandrogenism: Idiopathic hyperandrogenism is a diagnosis of exclusion in patients who have clinical hyperandrogenism and increased serum androgen levels above the 95th percentile (serum T levels ≥ 2.94 nmol/L, free T ≥ 0.026 nmol/L, and/or serum DHEAS 6.64 μ mol/L),¹¹ in the presence of normal ovulatory cycles (luteal phase serum progesterone levels ≥ 12.7 nmol/L or BBT rise of $>0.5^\circ$ F) and normal ovaries on ultrasound.²⁹

Idiopathic hirsutism: Idiopathic hirsutism is a diagnosis of exclusion in patients who have clinical hirsutism and normal serum androgen levels in the presence of normal ovulatory cycles and normal ovaries on ultrasound.

Non-classical congenital adrenal hyperplasia: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (CYP21) deficiency is one of the most common autosomal recessive metabolic disorders. Due to enzyme dysfunction, affected individuals are unable to synthesize cortisol and aldosterone efficiently, resulting in excessive stimulation of the adrenal cortex by cortico-

tropin, leading to overproduction of cortisol precursors (progesterone and 17-OHP). These precursors are diverted to the biosynthesis of sex hormones and result in signs of androgen excess (Figure 1). The non-classical form of the disease (NCAH) is characterized by late-onset symptoms, including premature adrenarche, hirsutism, menstrual disturbances, and infertility. Several mutations of the CYP21 gene have been characterized in NCAH (V281L being the most common);⁴⁶ these mutations are associated with about 30%-40% residual enzymatic activity in vitro.^{47,48} NCAH occurs in 0.2%-1% of the general population, although it is more frequent in certain populations (Ashkenazi Jewish 1:27, Hispanic 1:53, Slavic 1:63, Italian 1:333).⁴⁹

Biochemical criteria for the diagnosis of NCAH remain controversial due to inter- and intra-individual variations in 17-OHP levels due to circadian rhythms, menstrual phase, stress, and other influences on the corticotropin-releasing hormone (CRH)-ACTH-adrenal axis.⁴⁷ Women with untreated NCAH usually have morning follicular phase basal 17-OHP levels that are above normal. Basal levels of 17-OHP of <6 nmol/L effectively rule out NCAH, with a negative predictive value approaching 100%.⁵⁰ In women with NCAH, values >6 nmol/L reveal a sensitivity of 100%, but a poor positive predictive value (PPV) of 7.3% to 18.8%.⁵¹ Higher cut-off values improve PPVs at the cost of decreased sensitivity. Therefore, until access to genetic screening for CYP21 mutations becomes more readily available, it appears reasonable to perform ACTH (250 µg) stimulation in women with morning follicular phase 17-OHP levels that are >6 nmol/L. ACTH-stimulated 17-OHP levels >30 nmol/L suggest NCAH,⁵² although some authors suggest a higher cut-off of 60 nmol/L.⁴⁷

HAIRAN syndrome: The syndrome of hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) is diagnosed by a fasting insulin >80 µg/L or an insulin level during a 3-hour oral glucose tolerance test of >300 µg/L, in the setting of hyperandrogenism and acanthosis nigricans.⁵³ Recent reports have questioned the diagnostic criteria for this syndrome, based on lack of validation in large studies and suggestions that this syndrome may be part of the PCOS diagnostic spectrum.²⁹

Androgen secreting tumours: Individuals with rapid onset of virilization, or markedly elevated serum androgens (total T >8.67 nmol/L or DHEAS >21.7 µmol/L) should undergo transvaginal sonography and computerized tomography of the adrenals at 5-mm intervals to exclude ovarian and adrenal neoplasms, respectively.⁵⁴

Other hyperandrogenic disorders: Cushing's syndrome can lead to virilization. Clinical features suggestive of this diagnosis include violaceous striae, proximal muscle weakness, atypical visceral fat distribution (abdominal, dorsal, "moon" facies), and an elevated 24-hour urine free cortisol or a failure to suppress cortisol levels with dexamethasone. Hyperandrogenism can result from use of exogenous pharmacological agents (eg, danazol, anabolic steroids, or testosterone). Oral contraceptives containing levonorgestrel, norethindrone, or norgestrel tend to be more androgenic than those containing ethynodiol diacetate, norgestimate, and desogestrel.

Hirsutism can develop on medications that cause hyperprolactinemia (eg, metoclopramide, methyl dopa, phenothiazines, or reserpine).⁵⁵

Conclusion

All women produce androgens, although excessive production or sensitivity to these hormones can lead to distressing signs and symptoms. Hyperandrogenism can affect the pilosebaceous unit leading to hirsutism, acne, and alopecia. Ovulatory function can also be affected, manifesting as amenorrhea, ovulatory dysfunction, and infertility. Because of the physiological and psychological consequences of excess androgens, it is essential that the appropriate evaluation be performed in such women. This may include serum androgen levels (mindful of assay limitations) and imaging, as directed by the clinical presentation.

References

1. Serafini P, Silva PD, Paulson RJ, Elkind-Hirsch K, Hernandez M, Lobo RA. Acute modulation of the hypothalamic-pituitary axis by intravenous testosterone in normal women. *Am J Obstet Gynecol* 1986;155:1288-1292.
2. Burger HG. Androgen production in women. *Fertil Steril* 2002; 77(suppl 4):S3-5.
3. Orentreich N, Brind JL, Rizer RL, Vogelmann JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 1996;81: 1173-1178.
4. Longcope C. Adrenal and gonadal androgen secretion in normal females. *J Clin Endocrinol Metab* 1986;15:213-227.
5. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. *J Clin Endocrinol Metab* 1974;39:340.
6. Klee GG, Hesser DW. Techniques to measure testosterone in the elderly. *Mayo Clin Proceed* 2000;75:S19-25.
7. Vermeulen A. Reflections concerning biochemical parameters of androgenicity. *Aging Male* 2004;7:280-289.
8. Rosner W, Hyrb DJ, Kahn MS, Nakhla AM, Romas NA. Androgen and estrogen signalling at the cell membrane via G-protein and cyclic adenosine monophosphate. *Steroids* 1999;64:100-106.
9. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961;21:1440-1447.
10. Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, Etiology and management. *Am J Obstet Gynecol* 1981;140: 815-830.
11. Knochenhauer ES, Key TH, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovarian syndrome in unselected black and white women of the Southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998;85:840-849.
12. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 1991; 79:845-9.
13. Azziz R, Waggoner WT, Ochoa T, Knochenhauser ES, Boots LR. Idiopathic hirsutism; an uncommon cause of hirsutism in Alabama. *Fertil Steril* 1998;70:274-278.
14. Ewing JA, Rouse BA. Hirsutism, race and testosterone levels: comparison of East Asians and Euramericans. *Hum Biol* 1978;50: 209-215.
15. Archer J, Chang RJ. Hirsutism and acne in polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynecol* 2004;18:737-754.
16. Green J, Sinclair R. Skin manifestations of polycystic ovary syndrome. In: Kovacs GT (ed.). *Polycystic Ovary Syndrome*. Cambridge University Press. 2000:79-97.
17. Futterweit W, Dunaif A, Yeh C, Kingsley P. The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. *J Med Acad Derm* 1988;19:831-836.
18. Goldzieher JW, Axelrod LR. Clinical and biochemical features of polycystic ovarian disease. *Fertil Steril* 1963;14:631-653.
19. Steinberger E, Rodriguez-Rigau LJ, Smith KD, Held B. The menstrual cycle and plasma testosterone levels in women with acne. *J Am Acad Dermatol* 1981;4:54-58.
20. Smith KD, Rodriguez-Rigau LJ, Tcholakian RK, Steinberger E. The relationship between plasma testosterone levels and the lengths of phases of the menstrual cycle. *Fertil Steril* 1979;32:403-407.
21. Kitzinger C, Willmot J. 'The thief of womanhood': women's experience of polycystic ovarian syndrome. *Soc Sci Med* 2002;54:349-361.

22. Derksen J, Nagesser SK, Meinders AE, Haak HR, van de Velde CJ. Identification of virilizing adrenal tumours in hirsute women. *N Engl J Med* 1994;331:968-973.
23. Laven JS, Imani B, Eijkemans MJ, Fauser BC. New approaches to PCOS and other forms of anovulation. *Obstet Gynecol Surv* 2003;57:755-767.
24. Miller KK, Rosner W, Lee H, et al. Measurement of free testosterone in normal women and women with androgen deficiency: Comparison of methods. *J Clin Endocrinol Metab* 2004;89:525-533.
25. Taieb J, Mathian B, Millot F, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women and children. *Clin Chem* 2003;49:1381-1395.
26. Bukowski C, Grigg MA, Logncope C. Sex-hormone-binding globulin concentrations: difference among commercially available methods. *Clin Chem* 2000;46:1415-1416.
27. Matsumoto AM, Bremner WJ. Editorial: Serum testosterone assays – accuracy matters. *J Clin Endocrinol Metab* 2004;89:520-524.
28. Steinberger E, Todriguez-Rigau LJ, Smith KD. The prognostic value of acute adrenal suppression and stimulation tests in hyperandrogenic women. *Fertil Steril* 1982;37:187-192.
29. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience; relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. *J Clin Endocrinol Metab* 2006;91:2-6.
30. Azziz R, Sanchez LA, Knochenhauer ES, et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 2004; 89:453-462.
31. Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group. 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19-25.
32. Elting MW, Korsen TJM, Rekers-Mombarg LTM, Schoemaker J. Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. *Hum Reprod* 2000;15:24-28.
33. Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynecol* 2004; 18:671-683.
34. Balen A, Conway G, Klatas G. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum Reprod* 1995;10:2107-2111.
35. Eden J. The polycystic ovary syndrome presenting as resistant acne successfully treated with cyproterone acetate. *Med J Austral* 1991;155:677-680.
36. Lobo R. Hirsutism in polycystic ovary syndrome: current concepts. *Clin Obstet Gynecol* 1991;34:817-826.
37. Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. *Clin Endocrinol* 1999;51:779-786.
38. O'Driscoll JB, Mamtora H, Higginson J, Pollock A, Kane J, Anderson DC. A prospective study of the prevalence of clear-cut endocrine disorders and polycystic ovaries in 350 patients presenting with hirsutism or androgenic alopecia. *Clin Endocrinol* 1994;41:231-6.
39. Abdel Gadir A, Khatim MS, Mowafi RS, et al. Implications of ultrasonically diagnosed polycystic ovaries. I. Correlations with basal hormonal profiles. *Hum Reprod* 1992;7:453-457.
40. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989;38:1165-74.
41. De Leo V, La Marca A, Petraglia F. Insulin-lowering agent in the management of polycystic ovary syndrome. *Endocrine Reviews* 2003;24:633-667.
42. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;22:141-6.
43. Dokras A, Bochner M, Hollinrake E, Markham S, Vanvoorhis B, Jagasia DH. Screening women with polycystic ovary syndrome for metabolic syndrome. *Obstet Gynecol* 2005;106:131-7.
44. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 2001;111:607-13.
45. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. *Ann Intern Med* 1997;126:32-5.
46. Glinborg D, Hermann AP, Brusgaard K, Hangaard J, Hagen C, Andersen M. Significantly higher adrenocorticotropin-stimulated cortisol and 17-hydroxyprogesterone levels in 337 consecutive, premenopausal, Caucasian, hirsute patients compared with healthy controls. *J Clin Endocrinol Metab* 2005;90:1347-1353.
47. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Hum Repro Update* 2004; 10:469-485.
48. Deneuve C, Tardy V, Dib A, et al. Phenotype-Genotype correlation in 56 women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2001;86:207-213.
49. Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A, New MI. High frequency of nonclassical steroid 21-hydroxylase deficiency. *Am J Hum Genet* 1985;37:650-657.
50. Azziz R, Zacur HA. 21-Hydroxylase deficiency in female hyperandrogenism: screening and diagnosis. *J Clin Endocrinol Metab* 1989;69:577-84.
51. Azziz R, Hincapie LA, Knochenjauer ES, Dewailly D, Fox L, Boots LR. Screening for 21-hydroxylase deficient non-classic adrenal hyperplasia among hyperandrogenic women: a prospective study. *Fertil Steril* 1999;72:915-925.
52. Escobar-Morreale HF, San Millan JL, Smith RR, Sancho J, Witchel SF. The presence of the 21-hydroxylase deficiency carrier status in hirsute women: phenotype-genotype correlations. *Fertil Steril* 1999;72:629-638.
53. Barbieri RL, Ryan KJ. Hyperandrogenism, insulin resistance and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiological features. *Am J Obstet Gynecol* 1083;147:90-101.
54. Waggoner W, Boots LR, Azziz R. Total testosterone and DHEAS levels as predictors of androgen-secreting neoplasms: a population study. *Gynecol Endocrinol* 1999;13:394-400.
55. Leung AK, Robinson WL. Hirsutism. *Int J Dermatol* 1993;32:773-7.

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CONTACT: Email: karen.maris@eshre.com

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Boston, Massachusetts

CONTACT: www.endo-society.org

18-21 October 2006

10th Annual CDA/SCEM Professional Conference and Annual Meetings

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Disclosure Statement: Dr. Kraw has stated that she has no disclosures to announce in association with the contents of this issue.

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This publication is made possible by an educational grant from
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