Effects of Sex Steroids on Women’s Health: Implications for Practitioners

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Androgen excess in women is manifested typically by clinical features that may include hirsutism, acne, central obesity, male-pattern baldness, upper torso widening, increased waist-to-hip ratio, clitoral hypertrophy, and deepening of the voice. The differential diagnosis includes androgen-producing ovarian and adrenal neoplasms, Cushing’s syndrome, polycystic ovary syndrome, and the intake of exogenous androgens. Physicians treating patients for one symptom of androgen excess must be alert for other symptoms and signs. The cosmetic manifestations of androgen excess belie the serious health risks associated with this condition, including cardiovascular disease, intravascular thrombosis, and insulin resistance. Prompt clinical recognition of androgen excess, understanding of the androgen-related biochemical abnormalities underlying the risks associated with this condition, and implementation of risk modification can reduce the incidence of associated morbidity and mortality. An interdisciplinary approach to management is strongly recommended.

CLINICAL EVALUATION OF HYPERANDROGENISM

Clinical Features

Androgen excess, the final common metabolic pathway of a disparate group of disorders, is typically manifested by remarkably similar clinical features in hyperandrogenic women. Physicians responsible for the care of women should be alert to the physical manifestations of hyperandrogenism, signs of which indicate androgen excess at some time in the woman’s life. Those diagnosing and treating one symptom of androgen excess should be alert for other symptoms and signs. However, the presence of overt virilization should be interpreted cautiously. Such signs do not necessarily mean that active disease is present at the time of evaluation.

Hyperandrogenic women typically present with increased hair that may be apparent in the upper pubic triangle (male escutcheon), inner thighs, periareolar area, anterior chest, chin, upper lip, outer cheeks, arms, and/or legs. Luxuriant growth of facial hair may require depilation or shaving. Other observable manifestations may include acne, with
androgen excess may be confirmed by measuring plasma androgen levels and performing other simple laboratory studies (Table I). An interdisciplinary approach to management is strongly recommended. Such an approach will ensure greater clinical recognition of androgen excess syndromes and permit cost-effective diagnostic and management strategies.

### History and Physical Examination

Obvious signs of androgen excess should prompt a screening history and physical examination. Attention should be directed toward determining the age at onset, the duration, and the rate of progress of hirsutism and/or virilization. The occurrence of oligomenorrhea in a hirsute woman increases the probability that androgen excess is the underlying cause. A family history (for idiopathic hirsutism, polycystic ovary syndrome [PCOS], congenital adrenal hyperplasia [CAH], myocardial infarction, diabetes, and gestational diabetes) and a drug history should be obtained. Increased aggressiveness is a common finding in female bodybuilders using anabolic steroids.

The physician must also evaluate the type, pattern, and extent of hair growth; signs of virilization (including assessment of clitoral size) or defeminization; evidence of Cushing's syndrome (plethora, purple striae, and dorsocervical and supraclavicular fat pads); and the presence of hypertension, galactorrhea, or an abdominal or pelvic mass.

### Differential Diagnosis

Clinicians evaluating women for androgen excess should know the differential diagnosis of hyperandrogenism (Table II). The recent onset and rapid progression of severe hirsutism associated with other signs of virilization suggest an androgen-producing ovarian or adrenal neoplasm. These findings warrant appropriate additional diagnostic evaluation [3]. The gradual onset and slow progression of hirsutism with minimal virilization suggest other causes of endogenous androgen excess or the possible intake of exogenous androgens. The use of OCs with high androgen potency should always be considered.

Women with Cushing's syndrome can present with signs of hyperandrogenism, usually with associated evidence of glucocorticoid excess. In younger women, one common condition causing signs of increased androgen activity is PCOS. Suggestive findings include late menarche, childhood obesity, infertility, and menstrual abnormalities. Idiopathic hirsutism may be a part of the spectrum of PCOS. The presence of normal menses, normal-sized ovaries, no evidence of ovarian or adrenal tumors, nor-
mal adrenal function, normal or elevated estrogen levels, and estrogen suppressibility of the hyperandrogenic state support the diagnosis of idiopathic hirsutism. In ovarian hyperthecosis, a more severe variant of PCOS, islands of luteinized cells develop in the stroma. Insulin resistance (IR) and acanthosis nigricans (ACN) frequently occur in association with hyperthecosis, and the ovaries are usually markedly enlarged.

**HEALTH RISKS OF ANDROGEN EXCESS**

Hirsutism, acne, alopecia, and central obesity are psychologically distressing, but most clinicians assume these to be harmless cosmetic manifestations of hyperandrogenism. However, these external signs belie the serious health risks associated with androgen excess that include cardiovascular disease (CVD), intravascular thrombosis, and diabetes. Therefore, prompt recognition and clinical intervention are crucial for risk prevention.

**Cardiovascular Disease**

Coronary artery disease (CAD) is the leading cause of mortality among women in the United States. Almost 2.5 million women are hospitalized and 500,000 die annually from CAD [4]. CAD in women is more likely to present as angina than as myocardial infarction (MI) or sudden death [5]. Although women present with MI less often than do men, initial infarction is more likely to be fatal and the postinfarction prognosis poor [6]. While premenopausal women enjoy relative protection from CAD compared with men, by age 65 the incidence of the disease is the same for both sexes [7]. Premature menopause (natural or surgical) increases the risk of CAD [8]. Although risk of CAD does not abruptly rise at the onset of natural menopause, rates of heart disease increase sharply during this period.

Is the increased incidence of postmenopausal CAD due to reduced levels of endogenous estrogen? Extensive evidence suggests that estrogen protects women against CAD [9]. Both endogenous and exogenous estrogens increase protective plasma high-density lipoprotein cholesterol (HDL-C) concentrations, especially HDL2-C, and reduce deleterious low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels [10].

Godsland and coworkers [11] provided evidence that testosterone and androgen have the opposite effect? Kirkland and coworkers [12] provided evidence that testosterone is a significant determinant (although not necessarily directly causal) of reduced plasma HDL-C levels, at least during pubertal development. In each phase of a three-phase study, they showed that increasing plasma testosterone levels at spontaneous or induced puberty were accompanied by decreasing HDL-C levels.

Simons [13] reviewed the mortality data from 19 industrialized countries and analyzed the relationship between plasma lipids and lipoproteins and CAD death. His findings highlight the contributions of elevated total cholesterol and the total cholesterol/HDL-C ratio to CAD mortality in men. However, similar analyses in women were not particularly informative. Weyrich and associates [14] demonstrated that testosterone increased total cholesterol and LDL-C levels and decreased HDL-C levels in monkeys.

Many studies have reported significant reductions in coronary disease risk among women who have taken postmenopausal estrogen replacement [15,16]. The usefulness of estrogen replacement therapy depends, in part, on its influence on plasma lipids. Miller and associates [17] recently reported that two different doses of conjugated equine estrogen (0.625 mg and 1.25 mg daily) significantly lowered LDL-C and raised HDL-C and sex hormone binding globulin (SHBG, testosterone-binding globulin) plasma concentrations. The addition of a progestin (medroxyprogesterone acetate) reduced HDL-C but not LDL-C. A previous study by the investigators showed that any putative improvement in cardioprotection by favorable changes in HDL-C levels with conjugated equine estrogen was reversed by pharmacologic doses of the progestins norgestrel (NG) and norethandrolone (NET).

Estrogen may also provide cardioprotection independent of its effects on plasma lipids. Even when HDL-C levels fall with use of combined HRT preparations, investigators have shown no progression
of atherosclerosis (e.g., no increase in prevalence or extent of plaque formation) compared with controls [18,191. Its vasodilatory effect has been reported to lead to a decrease in arterial peripheral resistance and an increase in cardiac output [20,21].

Early case-control and cohort studies linked the estrogen component of OCs to increased cardiovascular (CV) risk (primarily due to venous thromboembolism) in premenopausal women, which led to reductions in the estrogen dose from pills containing 150 μg to those with <50 μg while maintaining contraceptive efficacy. Later, a link between high-dose-progestin OC use and an increased rate of arterial disease was reported, showing a twofold to fivefold increase in the risk of myocardial infarction with OC use. The events were most frequent among older users who smoked cigarettes, but there was a statistically significant increase in risk even among nonsmokers [22]. This is now thought to result from thrombotic events superimposed on preexisting plaque formation [23]. Currently used multiphasic OCs containing low-dose progestins with low androgenicity cause minimal adverse changes in plasma HDL-C and are unlikely to increase plaque formation. Formulations that do not lower HDL-C may actually have a beneficial effect on CV risk [24].

Intravascular Thrombosis

When a thrombus occludes the lumen of a coronary artery, usually at the site of a disrupted atherosclerotic plaque, blood flow distal to the obstruction ceases and myocardial ischemia occurs, leading to an acute coronary event. Reversible ischemia due to partial thrombotic obstruction of blood flow causes unstable angina with or without non-Q-wave MI or sudden death. Persistent ischemia (≥4–6 hours) due to complete obstruction of the lumen results in acute MI with or without sudden death.

Platelet aggregation, the first step in the formation of a thrombus, is prevented by prostaglandin I2 (PGI2, prostacyclin), a vasodilatory and antiaggregatory eicosanoid, and is mediated by thromboxane B2 (TXB2), a vasoconstricting and proaggregatory eicosanoid. Nakao and coworkers [25] showed that testosterone inhibited PGI2 production in aortic smooth muscle cell cultures. Weyrich and associates [14] demonstrated that testosterone significantly increased TXB2 in monkeys. Thus, in contrast to estrogens, androgens may contribute to the platelet aggregation that precedes acute partial or complete coronary occlusion and other vaso-occlusive states. In addition, platelet aggregation is associated with increased LDL-C levels and decreased HDL-C levels. Of note, OC users who smoke manifest alterations in the PGI2/TXB2 ratio, which may account for the increased incidence of acute thrombotic events.

Insulin Resistance

Hyperinsulinemia is associated with excessive ovarian androgen production, and IR is an important risk factor for atherosclerotic CVD. Androgen excess occurs in the presence of IR due to insulin receptor abnormalities (decreased receptor number or diminished binding of insulin) [26]. The type A (hereditary) IR syndrome, associated with ACN, predominantly affects young women who are hyperinsulinemic and markedly glucose intolerant. Ovarian dysfunction with primary or secondary amenorrhea is very common in these women, and the syndrome is often accompanied by varying degrees of virilization, moderately elevated plasma testosterone levels, and polycystic hyperandrogenic ovaries. A common type A variant is found in a subset of patients with PCOS and hyperandrogenism who commonly present with infertility, hirsutism, and mild virilization. These patients, who have ACN, are more hyperinsulinemic and insulin resistant than is a matched cohort of hyperandrogenized women with simple obesity. The significant IR seen in women with PCOS is independent of obesity, glucose tolerance, and body composition. Whether IR precedes or follows androgen excess remains unresolved. Hyperinsulinemia may contribute to ovarian hyperstimulation via its effect on theca cells and may also lead to androgen excess, ACN, and the other features of the syndrome.

Some women taking OCs develop IR, associated with reduced levels of HDL-C, hypertriglyceridemia, and hypertension as well as hyperinsulinemia and impaired glucose tolerance [27]. Reduction in estrogen dose and modification of progestin content have resulted in formulations with no adverse effect on HDL-C and blood pressure, but IR and hypertriglyceridemia remain. Historically, IR in OC users has been attributed to the progestin component, and hypertriglyceridemia to estrogen; however, Godsland et al [27,28] have shown that both can be caused by estrogen. Progestin can modulate insulin sensitivity [29], an effect that appears to depend on progestin type.

Decreased Sex Hormone Binding Globulin

Testosterone is transported in plasma bound to protein, largely albumin and a specific transport protein, SHBG. Only 1–3% of plasma testosterone is unbound (free testosterone). The free and albumin-bound fractions are available for entry into tissues and represent 40–50% of the total plasma testosterone. Testosterone bound to SHBG is unavailable to target tissues. Hyperandrogenemia is
associated with decreased levels of SHBG, resulting in an increased availability of testosterone for entry into target tissues and the potential for further increased androgenic effects, such as weight gain or acne. Increases in SHBG can be associated with decreases in plasma levels of free testosterone, and this decrease may be clinically beneficial in some women.

With the use of combination OCs, plasma levels of SHBG rise under estrogenic stimulation unless this elevation is prevented by an androgenic progestin. SHBG was shown to increase markedly, while total and free testosterone and DHEAS fell after administration of two newer progestin OCs with minimal androgenic impact: gestodene (GSD) and desogestrel (DSG) [30]. A third progestin with minimal androgenic activity, norgestimate (NGM), significantly increased plasma SHBG and decreased free testosterone [31].

**EFFECTS OF ORAL CONTRACEPTIVES**

**Plasma Lipids and Lipoproteins**

Endogenous estrogen and progesterone have not been associated with increased CV risk. However, exogenous sex steroids, such as those found in OCs, have measurable and reproducible effects on lipid metabolism, and CVD increases in some subsets of women who use OCs, especially smokers and older women. Estrogens and progestins generally produce opposite effects on plasma lipid concentrations. Ethinyl estradiol (EE), the estrogen component of essentially all OCs, beneficially elevates HDL-C levels and reduces LDL-C levels, while most progestins adversely reduce HDL-C levels and increase LDL-C levels. HDL-C concentrations fall in relation to the androgenicity of the progestin and its effect on increasing hepatic lipase activity [32–34].

Levonorgestrel (LNG) and NG are the most potent progestins based on their impact on lipids. Interestingly, these progestins also have the greatest androgenic activity when measured by ventral prostate growth and receptor studies [35]. In the doses used currently, OCs containing a progestin with high androgenic potency appear to have greater adverse lipid effects than those containing a progestin with lower androgenic potency. HDL-C levels significantly decrease by 11–21% following use of OCs containing high doses (150–250 μg) of LNG compared with controls [36]. Even low doses of LNG have adverse lipid effects. HDL-C levels significantly decrease by 17–21% with the use of monophasic low-dose LNG-containing OCs compared to OCs containing low doses of the relatively nonandrogenic progestin NET [37].

Compared with older progestins, the newer progestins NGM, DSG, and GSD have relatively greater affinity for progesterone receptors than for androgen receptors [38]. These selective progestins have desired progestational activity at relatively low concentrations or doses and undesired androgenic effects only at relatively high concentrations or doses. Their higher ratios of progestational to androgenic activity provide the basis for the reduction in androgenic adverse effects observed with their clinical use.

Janaud and associates [31] compared the effects on lipid metabolism of triphasic OC formulations containing EE and LNG or NGM in a study of 66 healthy women treated through six menstrual cycles. There was a statistically significant between-regimen difference in levels of HDL-C, which were favorably increased with EE/NGM but reduced with EE/LNG. Burkman and coworkers [39] reported the combined results of two studies of a triphasic preparation of EE and NGM over a 2-year period in 1,783 healthy women. Mean values for plasma HDL-C levels were increased significantly, with a percent change of 13.2. Values for the ratio of LDL-C to HDL-C were reduced throughout the study period (mean change of −6.4%).

**Virilization**

Cullberg and associates [40] studied the effects of a low-dose EE/DSG combination on hirsutism, androgens, and SHBG in women with PCOS. Compared with 22 normal controls, plasma levels of free and total testosterone and androstenedione were significantly elevated in 20 women with PCOS, as were body weight, blood pressure, hair diameter, and depilation frequency. SHBG binding capacity was lower. Following treatment of the PCOS patients for 8 months, total and free testosterone levels were depressed but androstenedione levels did not change significantly. SHBG binding capacity was increased fivefold. Body weight decreased in the obese women, hair growth was significantly suppressed and the hair itself was less coarse, depilation intervals were longer, and acne, present before treatment began, disappeared. Blood pressure did not change (Table III).

Anderson [41] reviewed the data generated in clinical OC trials of EE/NGM [41]. Of the women with acne at the beginning of the study, 38% (1,940 of 5,086) reported improvement, while only 1% reported either the first appearance of acne or worsening of existing acne. In comparative OC trials of EE/NGM versus EE/NG, plasma SHBG levels increased significantly in the EE/NGM group, by 161.1% by cycle 4; increases were not statistically significant in the EE/NG group (p = 0.0007).
TABLE III
PCOS Women on EE/DSG for 8 Months

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<td><strong>Free testosterone ↓</strong></td>
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<td><strong>Androstenedione -</strong></td>
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<td><strong>Body weight ↓</strong></td>
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<td><strong>Hair growth ↓</strong></td>
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<td><strong>Hair coarseness ↓</strong></td>
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<td><strong>Depilation interval ↑</strong></td>
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<td><strong>Acne ↑</strong></td>
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BP = blood pressure; DSG = desogestrel; EE = ethinyl estradiol; PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin.

Adapted from 1401.

Risk Reduction Strategies in Androgen Excess Syndromes

Cardiovascular disease is the most important long-term sequela of hyperandrogenism. Specific risk factors for CVD include a family history of premature heart disease, cigarette smoking, hypertension, diabetes, obesity, a diet high in saturated fat, increasing age, sedentary lifestyle, and low HDL-C.

Compared to men, women are especially sensitive to HDL-C in terms of primary heart disease and CV risk. In projecting risk, particular attention should be paid to elevated total cholesterol and LDL-C levels, potential for thrombosis, and alterations in carbohydrate metabolism. With respect to carbohydrate metabolism, diabetic women are at greater risk of CAD and CVD than are diabetic men. Next to smoking, diabetes has the most adverse effect on CAD mortality in women.

Because ischemic heart disease remains the leading cause of death among postmenopausal women, the effect of the combined use of estrogen and progestin on the risk of heart disease is a critical issue. As noted, estrogen and progestins generally have opposite effects on plasma lipid and lipoprotein concentrations. HDL-C and triglyceride levels are increased by estrogen, while most progestins reduce these levels. The importance of lowering moderately elevated triglyceride levels remains uncertain. Estrogens reduce LDL-C, while progestins have an opposite effect. Nabulsi and associates showed that the use of estrogen combined with progestin in postmenopausal women was associated with a better physiologic profile than was the use of estrogen replacement alone. This cross-sectional population-based study of 4,958 women showed that current users of estrogen alone had higher triglyceride, factor VII, and protein C levels than either nonusers or current users of combination estrogen plus progestin therapy, which probably mediates the effects of estrogen monotherapy.

Oral Contraceptives

The adverse effects of each OC formulation must be assessed as a unit, since estrogen and progestins have dichotomous effects on CV risk. Most OCs, especially those containing LNG, increase LDL-C and decrease HDL-C levels. The adverse effects of progestin are mediated primarily by dose and androgenic potency. That is, the greater the progestin dose and the greater its potency and androgenicity relative to estrogen, the greater the reduction in HDL-C and, possibly, the greater the increase in LDL-C. Particular care should be taken when OCs are prescribed for older women, since these patients are at greater risk for CVD. Women >35 years old should be evaluated for a history of smoking, central fat distribution, elevated blood pressure, an abnormal plasma lipid profile, and elevated blood glucose.

Combination OCs containing low androgenic progestins may be used to treat the clinical manifestations of androgen excess due to PCOS, idiopathic hirsutism, ovarian stromal hyperthecosis, and late-onset CAH. These agents may also be effective in retarding the progression of potential long-term sequelae of hyperandrogenism, such as CVD.

Other Interventions

National Cholesterol Education Program recommendations for lowering total and LDL-C levels are equally applicable to women and men. Like men, women benefit from aspirin therapy for primary prevention of MI. Ideal weight should be achieved and maintained without fluctuations. Cessation of smoking is the most important single factor that will decrease CAD morbidity and mortality among women, and the benefit extends to older age groups. Exercise in older women may not have as much impact on risk reduction as it does in men because of the attendant decrease in estrogen level. However, exercise may modify other factors favorably and improve IR, especially in obese women. Patients taking OCs for birth control may be switched to newer combinations containing progestins with no androgenic activity. Finally, overwhelming evidence documents the benefit of postmenopausal estrogen replacement therapy in decreasing the risk of CAD.

CONCLUSION

Androgen excess in women is associated with a recognizable pattern of clinical features that make the diagnosis relatively simple. A number of underlying endocrinologic causes or the use of exogenous
androgenic agents may be responsible for the characteristic findings. Regardless of the underlying cause, androgen excess is related to and increases the risk of CVD. The androgen/estrogen ratio may be the key factor in predicting risk.

REFERENCES
17. Miller VT, Muesing RA, LaRosa JC, et al. Quantitative and qualitative changes in lipids, lipoproteins, apolipoprotein 