

Estrogen replacement therapy: effects on the endogenous androgen milieu

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Objective: To review the impact of exogenous estrogen replacement therapy (ERT) on the production, binding, and metabolism of ovarian and adrenal androgens.

Design: Review of the scientific literature from January 1966 through June 2001 using MEDLINE.

Conclusion(s): Although no precipitous drop in androgen production is apparent at the time of the menopause, androgens decrease slowly and progressively from early adulthood until old age. The impact of aging and of estrogen replacement therapy, particularly oral ERT, significantly reduces androgen bioavailability after menopause. The combined effects of reduced production with aging and the pharmacologic effects of oral ERT dramatically reduce the endogenous bioavailable androgen milieu. These changes may have adverse clinical implications for susceptible individuals. (Fertil Steril® 2002;77(Suppl 4):S77-82. ©2002 by American Society for Reproductive Medicine.)

Key Words: Estrogens, androgens, steroid bioavailability

It is commonly assumed that estrogen replacement therapy (ERT) has a neutral role in androgen bioavailability, although it is now well documented that ERT, particularly at higher doses and when administered orally, reduces the bioavailability of both ovarian and adrenal androgens (1, 2). Estrogen replacement therapy reduces androgen bioavailability by several mechanisms including decreased production from both the ovary and adrenal glands and increased binding to serum proteins.

Although there appears to be no direct estrogen regulated feedback loop controlling postmenopausal ovarian or adrenal androgen secretion, ERT does decrease trophic LH (3). Adrenocorticotrophic hormone (ACTH) does not appear to control the adrenal androgen reductions associated with aging or during ERT (4), but ERT, particularly at higher doses *does* reduce adrenal androgen production. The administration of oral estrogens dramatically increases hepatic production of sex hormone-binding globulin (SHBG) and to a lesser degree cortisol-binding globulin (CBG) (5). These binding globulin changes further reduce free and bioavailable testosterone.

Orally administered androgens (i.e., methyltestosterone) significantly reduce SHBG con-

centrations (2). This action liberates endogenous estradiol and testosterone accentuating its own androgenic action. Parenterally delivered testosterone (i.e., testosterone patches) has little impact on SHBG suggesting that the route of androgen administration may impact different mechanisms of action (6). Androgen production, metabolism, and bioavailability are reviewed in this article, with an eye toward these bioavailability phenomena in hopes of bringing greater clarity to these very complicated but often over simplified clinical phenomena.

BACKGROUND

Oral contraceptives (OCs) and ERT, or hormone replacement therapy (HRT), have dramatic effects on androgen bioavailability. Oral contraceptives, available since the 1960s, provide menstrual regulation, contraception, reduction in acne, and relief from dysmenorrhea. Estrogen replacement therapy and HRT, available for more than 50 years, ameliorate short-term menopausal symptoms such as hot flashes, night sweats, and vaginal dryness, while reducing the long-term health risks associated with hypoestrogenism (i.e., osteoporosis). The impact of these therapies on androgen bioavailability and action are seldom consid-

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ered. Androgen actions on the cellular level are mediated by direct binding of the androgenic hormone to the androgen receptor, by conversion to other active androgens such as dihydrotestosterone, and/or by conversion to estradiol, among other actions.

The importance of androgens in health and disease is only now emerging, underscored by the results from steroid hemodynamic studies, which show that the primary source of estrogen in postmenopausal women comes from the aromatization of circulating adrenal androgen in the peripheral fat tissue (7).

A growing body of evidence demonstrates the positive effects estrogen-androgen therapy exerts after menopause. These investigations have focused on sexual desire, mood, cognitive functioning, and overall well-being (2, 6, 8). In addition, androgens have been shown to have direct bone-stimulating effects in postmenopausal women (9), although this effect remains controversial. It must be understood that these beneficial effects are preliminary and must be viewed against a backdrop of the complexities of the androgen's production, metabolism, and interaction with estrogen and estrogen-induced binding globulins. Our current knowledge of the biological effects of androgens in women is extraordinarily superficial, particularly those effects on the central nervous system. This void in our knowledge offers an extraordinary opportunity for further investigation.

MENOPAUSAL ANDROGEN PRODUCTION AND METABOLISM

For more than 50 years, clinical research has clarified the relationships between androgens, estrogens, and menopause with regard to plasma concentrations, blood production rates, and metabolism (as outlined in the following paragraphs), yet many questions remain. The serum concentrations of most endogenous androgens reach peak concentrations in early adulthood and decrease slowly with aging. This stands in contrast to the rather abrupt fall in estradiol concentrations following both a natural or surgical menopause. It is often misunderstood that androgens (i.e., testosterone) do not follow the same pattern of change as estradiol at menopause. However, the alterations in the endogenous androgen milieu during ERT and HRT, particularly when administered by the oral route, cause profound effects on the production, metabolism and bioavailability of both ovarian and adrenal androgens.

Serum Androgen Concentrations

The concentrations of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to decline between the ages of 30 and 40 and continue to do so gradually throughout life (10, 11). In 37 healthy women ranging in age from 21 to 75, Zumoff and colleagues (10) reported that 24-hour mean plasma concentrations of DHEA and DHEAS showed a clear linear inverse correlation between concentration and age in

both sexes. Menopause, whether natural or surgical, caused no additional significant alterations in these adrenal steroids in the women studied.

In contrast, the concentrations of androstenedione and testosterone decline just before or at menopause (11, 12). In a separate study, Zumoff and coworkers (11) measured 24-hour concentrations of total testosterone in 33 healthy, regularly cycling, nonobese women between the ages of 20 and 50. In these women, 24-hour mean plasma total testosterone concentrations declined progressively with aging.

Longcope and colleagues (12) added to these observations by measuring estrogen and androgen concentrations from the time of last menses in 88 women. At baseline, the age range of the women was 45 to 58 years, all of whom had cyclic menses every 1 to 2 months or were amenorrheic for greater than 3 months. Serum samples were obtained at intervals of 3 to 4 months. As expected, there was a *gradual* decline in the concentrations of estradiol, estrone, and estrone sulfate as the time from the last menses increased. In addition, the concentrations of testosterone, dihydrotestosterone, androstenedione, DHEA, and DHEAS remained relatively constant as the time from the last menses increased. These authors noted that plasma testosterone levels were generally lower following the last menses when compared with plasma testosterone levels from young women, but not dramatically different from women just prior to menopause.

Androgen Binding In Vivo

Steroids circulate in the blood in essentially three forms: free, loosely bound to albumin, and tightly bound to specific binding globulins, in the case of testosterone, SHBG and CBG (Table 1). The bioavailable form of a steroid can pass from the blood into a tissue and exert its biological activity and/or be metabolized in that tissue (13). The nonprotein-bound steroid is the biologically active fraction. For most steroids, however, the dissociation from albumin is so rapid that the albumin-bound steroid is considered part of the bioavailable steroid pool (13–15). The SHBG-bound and CBG-bound steroids are not considered bioavailable.

The percentage of bound to unbound steroid differs among the four androgens (testosterone, androstenedione, DHEA, DHEAS) (16–22). Testosterone is strongly bound to SHBG (15, 20, 21), with less than 50% of the total circulating testosterone concentration being bioavailable to tissues. In contrast, androstenedione, DHEA, and DHEAS are not strongly bound to SHBG. Approximately 95% of circulating androstenedione is available to tissues (22). The binding affinities of each androgen to SHBG do not change with age or menopause. Thus, factors that affect SHBG concentration can potentially have an important impact on the unbound or bioavailable levels of androgens in the blood. The following discussion focuses on testosterone because of its significant binding to SHBG, and the very small proportion of this compound that circulates free of binding (approximately 1%) (19–21).

TABLE 1

Steroid distribution in women.

Follicular phase	Total (nM)	Unbound (%)	SHBG (%)	CBG (%)	Albumin (%)
Testosterone	1.3	1.4	66.0	2.3	30.4
DHT	0.7	0.5	78.0	0.1	21.0
Estradiol	0.3	1.8	37.0	0.0	61.0
SHBG	37.0	85.0	—	—	—

Note: DHT = dihydrotestosterone; SHBG = sex hormone-binding hormone.

^a From Dunn J.F., et al. (25). Reprinted by permission of the publisher.

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Production Rates of Androgens

Blood production rates of androgens provide an accurate indication of the amount of steroid entering the blood from all sources. With regard to androgens, the primary sources of production in women are the ovary, adrenal glands, and peripheral tissues, particularly adipose and muscle tissue (Table 2).

In young premenopausal women, approximately 90% of DHEAS in the circulation is secreted by the adrenal glands (12, 23, 24). The remaining 10% is formed through the sulfation from DHEA in peripheral tissues. The primary source of DHEA production in the premenopausal woman is the adrenal gland (60%) and from the peripheral conversion of DHEAS (30%). The ovaries produce small amounts of DHEA (10%). Androstenedione is produced in much lower amounts overall (3–5 mg/day) than DHEA, with approximately equal proportions being secreted by the adrenal glands (50%) and the ovaries (40%). In premenopausal

women, approximately 200–250 mcg/day of testosterone is secreted by the adrenal glands (25% of the total), another 200–250 mcg/day is secreted by the ovaries (25% of the total), and the remainder is produced by the peripheral tissues (50% of the total). Androstenedione accounts for approximately half (50%) of the testosterone produced in the peripheral tissues of premenopausal women (12, 23, 24).

Following menopause, the contribution of the adrenal glands, ovaries, and peripheral conversion to the total circulating DHEAS and DHEA concentrations remains essentially the same (12, 23, 24), but the amount of DHEAS and DHEA produced by the adrenal glands decreases by 50%. Although a small proportion of circulating DHEA is produced in the ovary of younger women, very little is produced by the ovary in postmenopausal women.

The reduction in postmenopausal ovarian androgen production is not precipitous, similar to the fall in estradiol at menopause. Instead, ovarian testosterone production decreases slowly over the 5 to 10 years following the last menstrual period. Ovarian androstenedione production decreases substantially more at the time of menopause than does testosterone production, changing the relative contribution of the ovary to systemic androgen levels (Table 2). Prior to menopause, the ovary contributes approximately 50% and 25% of circulating androstenedione and testosterone, respectively. After menopause, the ovarian androstenedione contribution decreases to 20%, while ovarian testosterone accounts for 50% of total testosterone (12, 23, 24).

The overall impact is that there is a marked decline of all androgens at the time of and after the menopause. Although ovarian production of testosterone does not change at menopause, circulating testosterone concentrations do continue to decline. The most important reason for this decline is that the concentrations of the testosterone precursors (mostly of adrenal origin), androstenedione, DHEAS, and DHEA are significantly reduced.

Metabolic Clearance

The metabolic clearance of androgens is not influenced by menopause. Dehydroepiandrosterone and DHEAS circulate in

TABLE 2

Distribution of androgen production in women.

	Contribution of each source (%)		Peripheral conversion
	Ovarian secretion	Adrenal secretion	
DHEAS			
Premenopause	0	90	10
Postmenopause	0	90	10
DHEA			
Premenopause	10	60	60
Postmenopause	10	60	30
Androstenedione			
Premenopause	40	50	10
Postmenopause	20	70	10
Testosterone			
Premenopause	25	25	50
Postmenopause	50	10	40

Note: Adapted from Longcope C. et al. (12); Judd H.L. et al. (23); and Adashi E. (24).

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the blood mostly bound to albumin with a small amount not bound to protein. Dehydroepiandrosterone is cleared rapidly from the blood with a metabolic clearance rate (MCR) in the range of 2,000 L/day. The clearance of DHEAS is much slower. Its MCR is in the range of 13L/day. DHEA and DHEAS can interconvert, with about 6% of DHEA reentering the circulation as DHEAS, and 60%–70% of the DHEAS reentering as DHEA. Both DHEA and DHEAS can be converted in peripheral tissues to androstenedione, testosterone, and dihydrotestosterone. Both DHEA and DHEAS can also be aromatized to estrogens (16, 17). Androstenedione is bound weakly to albumin and its metabolic clearance rate is 1,800 to 2,000 L/day (20, 22). Testosterone is bound strongly to SHBG, and to a lesser extent CBG, and has a MCR of approximately 500 L/day (22) (Table 1).

The pathways of metabolism, measured in either blood or urine, are not altered at menopause, with one exception (19), the process of aromatization. The aromatization of DHEA, androstenedione, and testosterone to estrone and estradiol all increase with age (7, 26, 27). This increase appears to be due to an increase in tissue levels of aromatase enzyme (28). The increased aromatase activity following menopause results in the peripheral tissues taking on a greater role in the production of estrogen compared with this process in younger women. The major precursor for this peripheral conversion is androstenedione. The increase in aromatase activity after menopause is likely due to two synergistic phenomena; the progressive increase in body fat with aging, and an increase in aromatase activity per unit of fat with decreased endogenous estrogen (28). Increased total body fat has other effects as well. One of the most important of these is that body mass index (BMI) has an inverse effect on SHBG, the greater the body mass the lower the SHBG concentration (22). This has very significant implications for the bioavailability of androgens as well (as outlined in the following paragraphs).

Taken together, the ovarian and adrenal changes associated with menopause and aging, respectively, lead to decreased production rates for all androgens. One of the results is a reduced serum testosterone concentration. Although the overall androgen metabolic pathways remain unchanged, as previously mentioned, there is a marked increase in aromatization of androgens (i.e., androstenedione) to estrogens in the peripheral tissues. The presence of androgen receptors throughout the body, but particularly in the central nervous system (CNS) and the slow and progressive decline in serum androgen concentrations associated with menopause and aging suggests the potential for significant clinical impact for these “physiologic” changes (see below).

IMPACT OF ERT ON THE ENDOGENOUS ANDROGEN MILIEU

Although the changes of menopause and aging are important with regard to the bioavailability of androgens (as discussed earlier), these changes are minor in comparison to

those induced by standard doses of ERT, particularly when it is administered by the oral route. Oral estrogens dominate the U.S. market with more than 85% of U.S. women choosing this form of ERT. Because the pituitary–ovarian axis appears to remain intact after a natural menopause (29), ERT at standard “physiologic” or higher doses has a significant suppressive effect on gonadotropins (negative feedback), particularly LH (3) and, thereby, reduces the production of androgens (i.e., testosterone) from the early postmenopausal ovary. The changes in gonadotropin secretion occur about equally for both oral and nonoral estrogens when administered at equipotent doses (3). Although these gonadotropin changes are well documented using immunoassays, they have not been extensively evaluated and confirmed with bioassays of gonadotropin potency.

Estrogen replacement therapy and HRT also dramatically alter the levels of SHBG and CBG present in serum (5). Testosterone and dihydrotestosterone are primarily bound to SHBG (66% and 78%, respectively) (25). In addition, testosterone is bound to CBG and albumin (25). Although small oral doses of ERT have a dramatic impact on SHBG concentrations, it requires larger ERT doses to significantly increase CBG. Judd et al. (5) demonstrated that doses of conjugated equine estrogens (CEE) as low as 0.15 mg daily significantly increased SHBG, while standard doses (0.625 mg daily) increased SHBG by approximately 300% above baseline. Similarly, they showed that 0.625 mg of CEE could significantly increase CBG, although only to a small degree, while 1.25 mg of CEE was capable of increasing CBG concentrations by approximately 25% over baseline levels (5).

Several studies demonstrate the clinical importance of these binding globulin changes. Tazuke et al. (1) studied the plasma steroid hormone and sex hormone binding globulin levels in frozen plasma obtained from 977 women age 50 to 79 from 1972 to 1974. Almost all the 301 ERT users were taking oral CEE; none reported use of any progestogen. The women taking estrogen were significantly younger, thinner and more likely to smoke cigarettes than the women not taking estrogen. Sex hormone-binding globulin and all endogenous hormones except testosterone were negatively correlated with age; estradiol was positively and cortisol and SHBG were negatively associated with obesity. After adjusting statistically for both age and obesity, DHEAS, androstenedione, and free testosterone were all significantly lower in the women currently taking estrogen than in the women not using estrogen. These differences were independent of cigarette smoking (Table 3). Simon and colleagues (2) have shown these same phenomena in a prospective randomized clinical trial. They demonstrated that while total testosterone did not change, standard doses of esterified estrogens (0.625 mg, 1.25 mg) increased SHBG in a dose-dependent fashion, and thereby reduced bioavailable testosterone significantly.

TABLE 3

Age- and body mass index (BMI)-adjusted variables by current exogenous estrogen use in postmenopausal women.^a

Hormone ^b	Estrogen use (mean)		P value
	Nonusers (n = 676)	Current users (n = 301)	
Dehydroepiandrosterone sulfate (umol/L)	2.20	1.55	<.001
Androstenedione (nmol/L)	2.16	1.81	<.001
Testosterone (nmol/L)	0.86	0.83	.91
Free testosterone (nmol/L)	0.40	0.30	<.001
Estradiol (pmol/L)	54	89	<.001
Sex hormone-binding globulin (× 10 ⁻⁵ M)	4.48	6.60	<.001

Note: Adapted from Tazuke S., et al. (1).

^a Rancho Bernardo 1972–1974, ages 50–79.

^b Age = and BMI-adjusted.

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Dehydroepiandrosterone sulfate and androstenedione were also reduced at the higher estrogen doses (Table 4).

The mechanism(s) by which these higher estrogen doses reduce adrenal androgen concentrations, remains a matter of speculation. Several competing hypotheses have been suggested. These hypotheses are: that estrogen, through dopaminergic neurons in the brain, actually decreases bioactive ACTH production and/or releases that estrogen may mediate its effect on adrenal androgens through the release of inhib-

TABLE 4

Changes in endogenous androgens and SHBG with estrogen or estrogen/androgen treatment.

	Esterified estrogens (0.625 mg)	Esterified estrogens (1.25 mg)	Estrogen/ androgen half- strength ^a	Estrogen/ androgen ^b
Testosterone (total)	↔	↔	↓	↓
SHBG	↑	↑↑	↓↓	↓↓
Bioavailable testosterone (T/SHBG ratio)	↔	↓↓	↑↑	↑↑
DHEAS	↔	↓↓	↔	↔
Androstenedione	↔	↓	↔	↔

Note: All ↑ or ↓ represent statistically significant changes (P<.05).

SHBG = sex hormone-binding globulin; T/SHBG = testosterone/sex hormone-binding globulin ratio; DHEAS = dehydroepiandrosterone sulfate.

^a Estrogen/androgen half-strength, esterified estrogens 0.625 mg/methyltestosterone 1.25 mg.

^b Estrogen/androgen, esterified estrogens 1.25 mg/methyltestosterone 2.5 mg.

Adapted from Simon J., et al. (2).

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itory molecules reducing prolactin's bioactivity; or that estrogen reduces the, as yet, unidentified putative adrenal androgen-stimulating hormone (AASH) also known as cortical adrenal-stimulating hormone (CASH). Finally, several studies demonstrate estradiol's inhibitory impact on adrenal androgen biosynthesis. Estradiol's effects on biosynthesis appear to be mediated by either the inhibition of the 17-hydroxylase/17-20 lyase enzyme system, or alternatively, by a reduced sensitivity of the zona reticularis cell to ACTH stimulation (30). The effect of this inhibition would be to decrease adrenal androgen production. Regardless of the exact mechanism, the phenomena of decreased adrenal androgen concentrations have been demonstrated with both oral ERT and oral contraceptives (31).

The clinical importance of ERT reduced androgen bioavailability has been demonstrated. Sherwin and Gelfand (32) demonstrated that high dose injectable estradiol actually reduced the percentage of coital acts ending in orgasm in otherwise sexually functional, surgically menopausal females. This phenomenon was in sharp contrast to the insignificant effect of placebo injections in this same population. Similarly, estrogen/androgen injections had little effect on orgasmic function, despite improving sexual motivation as evidenced by self-reported sexual desire, fantasies and arousal. Simon and colleagues (2) demonstrated progressive improvement in somatic symptom relief (hot flashes, night sweats, and vaginal dryness) with increasing levels of oral estrogen/androgen. This combination of esterified estrogens and methyltestosterone reduced SHBG levels, which correlated inversely with increasing both free estradiol and bioavailable testosterone concentrations. In this setting, a lower dose of estrogen when administered with this nonaromatizable androgen (methyltestosterone) provided similar somatic symptom reduction to the higher dose of estrogen alone. Testosterone administered by the nonoral route (i.e., transdermal patch) did not significantly reduce SHBG concentrations but was capable of improving sexual function and mood in surgically menopausal women rendered hypoandrogenic by treatment with oral CEE (6).

SUMMARY

Both endogenous and exogenous estrogens have a dramatic impact on androgen production, metabolism and SHBG/CBG binding. Together these effects alter androgen bioavailability. Despite the simplistic approach presented here, it should be remembered that androgens and estrogens have reciprocal functions with regard to estrogen receptors, namely, that estrogens down-regulate androgen receptors and androgens down-regulate estrogen receptors. Biological responses to estrogens and androgens reflect the relative balance between these separate and unequal steroid mechanisms. In addition, androgens and progestins interact with each other as well. Because ERT is seldom given without progestin, this effect takes on even more importance. For

example, androgen and progesterone receptors, while structurally related, are different; however, pharmacological levels of androgens and progestins can influence each other's receptor activities. In addition, progestins can act as antiandrogens, because they compete with androgens as substrate for the 5 α reductase enzyme. Finally, there are a number of *receptor independent* actions of androgens. Androgens like DHEAS and DHEA are agonistic for the GABA-A receptor (such as progesterone and its metabolites). Yet, these steroids are antagonists for the NMDA receptor. Overall, the agonist and antagonistic effects of DHEA in the brain likely represent the combination of both the genomic, receptor-mediated actions of these hormones, their receptor-independent actions, and the actions of their breakdown products [see Plouffe and Simon (33) for review].

CONCLUSION

Both ovarian and adrenal androgens decrease with aging, due to reduced production rather than altered metabolism. Ovarian androgens are reduced to a greater degree after surgical menopause. Aromatization, an important reversible function whereby androgens are commonly converted to estrogens (or vice versa), increases with age and body mass index, leading to increased conversion of androgens to estrogens (i.e., androstenedione to estrone and testosterone to estradiol). Oral and high-dose parenteral estrogen administration, in the form of ERT or HRT, reduces endogenous androgen bioavailability by several mechanisms, including reduced production of androgens and increased binding of androgens. These changes can result in initiation or exacerbation of symptoms like decreased libido, reduced energy and sense of well-being, or decreased muscle and bone mass, etc. Whether these symptoms are directly related to androgen bioavailability, estrogen bioavailability, or both remains the subject of ongoing investigation. Other factors, including estrogen's effect on adrenal androgen production, reciprocal regulation of androgen receptors, alterations of transcription factors, coactivators or repressors, nonclassical effects of androgens, etc., all remain to be determined.

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