FERTILITY AND STERILITY®
VOL. 77, NO. 4, SUPPL 4, APRIL 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Androgen production in women

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Objective: To describe the sources, production rates, circulating concentrations, and regulatory mechanisms of the major androgen precursors and androgens in women.

Design: Review of the major published literature.

Result(s): Quantitatively, women secrete greater amounts of androgen than of estrogen. The major circulating steroids generally classified as androgens include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T), and dihydrotestosterone in descending order of serum concentration, though only the latter two bind the androgen receptor. The other three steroids are better considered as pro-androgens. Dehydroepiandrosterone is primarily an adrenal product, regulated by adrenocorticotropic hormone (ACTH) and acting as a precursor for the peripheral synthesis of more potent androgens. Dehydroepiandrosterone is produced by both the ovary and adrenal, as well as being derived from circulating DHEAS. Androstenedione and testosterone are products of the ovary and the adrenal. Testosterone circulates both in its free form, and bound to protein including albumin and sex steroid hormone-binding globulin (SHBG), the levels of which are an important determinant of free testosterone concentration.

Conclusion(s): The postmenopausal ovary is an androgen-secreting organ and the levels of testosterone are not directly influenced by the menopausal transition or the occurrence of menopause. Dihydrotestosterone (DHT) is primarily a peripheral product of testosterone metabolism. Severe androgen deficiency occurs in hypopituitarism, but other causes may lead to androgen deficiency, including Addison's disease, corticosteroid therapy, chronic illness, estrogen replacement (leads to elevated SHBG and, therefore, low free testosterone), premenopausal ovarian failure, or oophorectomy. (Fertil Steril® 2002;77(Suppl 4):S3–5. ©2002 by American Society for Reproductive Medicine.)

Key Words: Dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone, dihydrotestosterone, sex steroid hormone binding globulin

The major androgens in women, listed in descending order of serum concentration, include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T), and dihydrotestosterone (DHT). However, the first three are more correctly considered as pro-androgens, which require conversion to T to express their androgenic effects. Androgen biosynthesis occurs both in the adrenal and in the ovary and is modulated by two critical cytochrome P450 enzymes: P450 SCC, which catalyzes cholesterol side-chain cleavage, and P450 c17 which catalyzes 17-hydroxylation and 17-20 bond cleavage (17-20 lyase) required for DHEA and A production from pregnenolone and progesterone respectively (Fig 1). The side-chain cleavage enzyme, together with steroidogenic acute regulatory protein (StAR) is rate limiting for all steroid synthesis.

Other important enzymes include 3β-hydroxy steroid dehydrogenase (3β-HSD), which catalyzes conversion of pregnenolone to progesterone and DHEA to A, and 17β-hydroxy steroid dehydrogenase (17β-HSD), which catalyzes conversion of A to T (Fig. 1). The regulation of androgen secretion involves stimulation by ACTH (adrenal) and LH (ovary) together with intraglandular paracrine and autocrine mechanisms. Liver, adipose tissue, and skin have 3β-HSD and 17-β-HSD, as well as aromatase, catalysing androgen conversion to estrogen. Substantial androgen production originates from circulating DHEAS in target tissues.

Production rates and circulating concentrations of the androgens discussed in the next section are based on ranges provided in a variety of publications.

SOURCES OF FEMALE ANDROGENS

Dehydroepiandrosterone Sulphate

Dehydroepiandrosterone sulphate is a unique secretory product of the adrenal zona

Received October 16, 2001; revised and accepted January 11, 2002.

Presented at an International Consensus Conference: "Female Androgen Deficiency Syndrome: Definition, Diagnosis and Classification," June 29–30, 2001, Princeton, New Jersey.

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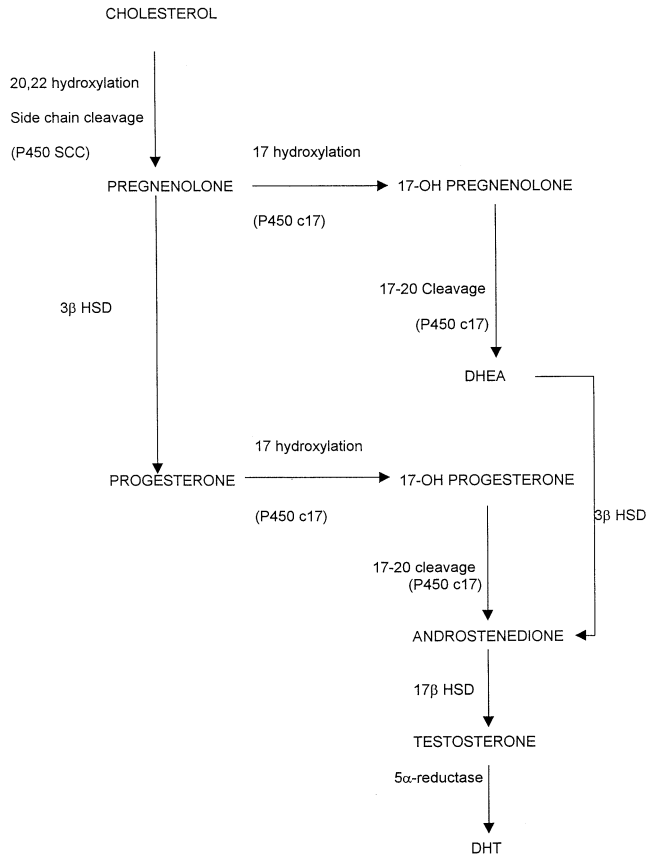
0015-0282/02/$22.00
PII S0015-0282(02)02985-0

FIGURE 1

Schema of androgen biosynthesis.



Burger. Androgen production in women. Fertil Steril 2002.

reticularis (1) and is produced at a rate of 3.5 to 20 mg daily during reproductive life. Circulating concentrations are in the range of 1–4 μg/mL (3–12 μmol/L). Serum concentrations increase from age 7 to 8 (adrenarche) (2) and peak in the 20s and 30s followed by a steady decline with age, the rate of decline slowing over the age of 50 to age 60 (3). Dehydroepiandrosterone sulfate secretion is modulated by ACTH and may also be influenced by prolactin, IGF1, and estrogen. Circulating concentrations do not change significantly during the menstrual cycle and changes in concentration are not related to the menopausal transition or the menopause (4). Clinical deficiency of DHEAS can be seen in Addison's disease, hypopituitarism with adrenal involvement, corticosteroid therapy, chronic illness, and estrogen replacement. Dehydroepiandrosterone sulfate is an important source of peripheral androgen production, for example, in the ovary (5).

Dehydroepiandrosterone

Dehydroepiandrosterone is a secretory product of the adrenal zona reticularis (50%) and the ovarian theca (20%) and 30% is derived from circulating DHEAS, catalyzed by steroid sulphatase (6). The production rate is 6–8 mg/day and circulating concentrations are of the order of 1–10 ng/mL (3–35 nmol/L). Dehydroepiandrosterone can also be produced intracellularly from DHEAS in the course of peripheral androgen synthesis and its levels decrease with age.

Androstenedione

Androstenedione is secreted by the adrenal zona fasciculata (50%) and the ovarian stroma (50%, but varying through the menstrual cycle). Daily production rate is 1.4–6.2 mg/day and circulating concentrations are in the range 0.5–2 ng/mL (2–8nmol/L). Oophorectomy in postmenopausal women results in an approximately 30% fall in circulating levels (7).

Androstenedione shows circadian variation and a mid cycle elevation in concentration parallel with the mid cycle estradiol peak (8). As noted earlier, it can be produced intracellularly from DHEAS via DHEA. Circulating concentrations are substantially reduced in hypopituitarism (9). During the menstrual cycle administration of exogenous corticosteroid leads to a suppression of circulating levels (8).

Testosterone

The most potent androgen, T is secreted by the adrenal zona fasciculata (25%) and the ovarian stroma (25%), each approximately 50 μg per day, with the remaining 50% being produced from circulating A (6). Daily production rate is in the order of 0.1–0.4 mg and circulating levels are in the range 0.2–0.7 ng/mL (0.6–2.5nmol/L). Testosterone is at its lowest concentrations in the early follicular phase of the cycle, rises to a mid-cycle peak and the luteal phase concentrations are higher than those in the early follicular phase (8). Sensitive assays have indicated that T shows circadian variation, peak levels being seen in the early morning hours. Both premenopausally and postmenopausally oophorectomy leads to an approximately 50% fall in circulating levels (7). As with the other androgens, T can be produced intracellularly from DHEAS.

As expected from its dual origins, T is suppressed following the administration of circulating corticosteroids (8). Concentrations in the ovarian vein of postmenopausal women are considerably higher than those in peripheral blood (10), providing evidence that the postmenopausal ovary is primarily an androgen-secreting organ.

Testosterone is carried in peripheral blood substantially bound to sex steroid hormone-binding globulin (SHBG) and the levels of both total and free T have been shown to be markedly reduced in women with hypopituitarism, both premenopausally and postmenopausally, and whether or not they are on estrogen therapy (9).

Testosterone does not change significantly in relation to the menopausal transition, but T levels fall slowly with age (4). It should be noted that across the menopausal transition there is a significant fall in circulating levels of SHBG and,

as a result, free androgen levels rise across the menopausal transition, as indicated for example by an increase in free androgen index (T ÷ SHBG × 100) (4). It is important to note that oral estrogen therapy substantially increases circulating SHBG levels with a consequent fall in free T concentrations (11). This is not observed with transdermal estrogen administration, except at very high doses.

Dihydrotestosterone

Dihydrotestosterone is primarily a peripheral product of T conversion and circulates in low concentrations in serum (8). A small quantity is secreted directly by the adrenal zona fasciculata. Daily production rates have been calculated at between 4.3 and 12.5 mg/day, almost entirely derived by peripheral conversion and circulating concentrations are about 0.02 ng/mL. Metabolism is via glucuronide conjugates. Although T is aromatisable to estradiol, DHT is a non-aromatisable androgen.

SUMMARY AND CONCLUSIONS

Androgens in the female are secreted by the adrenal and the ovary and are formed peripherally, particularly from DHEAS. No direct evidence is available for an endocrine regulatory feedback loop, although intravenously administered testosterone, leading to elevated concentrations in serum does alter LH pulsatility and gonadotropin-releasing hormone (GnRH) responsiveness (12). No evidence is available to indicate whether lowered serum androgen levels would result in an elevation in circulating gonadotropins. The postmenopausal ovary is an androgen-secreting organ. Decreased androgen production is seen in hypopituitarism, Addison's disease, exogenous corticosteroid administration, chronic illness and with estrogen replacement, as well as in premature ovarian failure and following oophorectomy.

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