REVIEWS

Management of Female Sexual Dysfunction in Postmenopausal Women by Testosterone Administration: Safety Issues and Controversies

Glenn D. Braunstein, MD

Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

DOI: 10.1111/j.1743-6109.2007.00516.x

ABSTRACT

Introduction. A Food and Drug Administration advisory group has questioned the long-term safety of testosterone administration to postmenopausal women. Although only short-term data exist on safety from the double-blind, placebo-controlled trials, testosterone has been used for more than 50 years. Therefore, some data concerning the long-term safety issues must exist in the literature.

Aim. To review the published data concerning the safety of administration of testosterone to women.

Methods. Review of published articles identified by a search of the Ovid databases and bibliographies from articles identified as dealing with the topics of testosterone or androgen treatment of women.

Results. The major adverse reactions to exogenous androgens are the expected androgenic side effects of hirsutism and acne. High-density lipoprotein levels may be decreased with oral androgens. There are insufficient long-term safety data regarding breast, endometrium, or heart safety to draw strong conclusions, although the data available to date are reassuring.

Conclusions. Testosterone administration to postmenopausal women that result in physiological to slightly supra-physiological serum-free testosterone levels is safe for at least 2 years. **Braunstein GD. Management of female sexual dysfunction in postmenopausal women by testosterone administration: Safety issues and controversies. J Sex Med 2007;4:859–866.**

Key Words. Breast Cancer; Cardiovascular Disease; Endometrial Cancer; Hirsutism; Menopause; Testosterone

A number of well-designed, randomized controlled studies have demonstrated that testosterone administration to postmenopausal women improves libido and sexual function [1,2]. However, anecdotal reports of adverse effects in women receiving pharmacological doses of androgens, or extrapolation from studies in men (whose serum testosterone levels are 10–20 times higher than women), along with the concerns about sex steroid hormone administration raised by the Woman's Health Initiative and the Heart and Estrogen/Progestin Replacement Study, have led the U.S. Food and Drug Administration (FDA) to request long-term safety studies of testosterone before considering approval of such therapy for postmenopausal women with hypoactive sexual desire disorder [3]. Although testosterone and other androgens have been used for this purpose for more than half a century, very limited long-term safety data are available. What information is available about androgenic effects, and the effects of testosterone on the cardiovascular system, endometrium, breast, and the liver will be reviewed here. An in-depth analysis of the relationship between androgens and behavior is beyond the scope of this review, and only passing reference to the effects of exogenous testosterone on behavior will be made. The sources used to identify studies included Ovid database and

bibliographic citations in articles dealing with androgens and testosterone therapy in women.

Androgenic Effects

The effects of hirsutism—the growth of terminal hairs in the androgen-sensitive areas of the body—and acne are the predominant ones noted in women receiving physiological to slightly supraphysiological doses of androgens.

Hirsutism incidence depends in part upon the dose and duration, but not the route, of testosterone administration. Often 4–6 months of exposure are necessary to detect the increase in hair growth. Although the frequency of hirsutism in various studies of testosterone administration alone or with estrogen varies from 1% to 36% [4], most studies that have used testosterone to increase libido or treat vasomotor symptoms suggest that hirsutism is reported in 3–8% of those receiving doses that result in serum testosterone levels in the normal or slightly above normal range for reproductive-aged women [5–8]. In fact, in many of the randomized, double-blind studies of testosterone therapy in women receiving concomitant estrogens, no significant differences in reported or observed hirsutism rates were noted between the women on testosterone plus estrogen and those on estrogen alone [9–12]. However, the lengths of those studies were 1 year or less, so it is unknown whether a difference would have emerged with a longer duration of exposure.

Acne has been reported in up to 45% of women receiving 10 mg of oral methyltestosterone daily, although most of the well-controlled studies demonstrate that less than 10% of women receiving physiological doses of testosterone note acne [5,6,8,13–18]. Also, in the short-term randomized, controlled trials, there was no significant difference in the occurrence of acne in those receiving testosterone plus estrogen over those receiving estrogen alone [10–12].

Virilization, which includes temporal hair recession, the development of clitoromegaly, increase in muscle mass, and deepening of the voice, is rare and is generally only seen when the serum testosterone levels are elevated several times above the upper limit of normal for women [19,20]. Thus, women with androgen-secreting tumors of the ovary or adrenal, women with the 21-hydroxylase form of congenital adrenal hyperplasia, and women who receive large amounts of testosterone as part of the female-to-male transsexual conversion do become virilized [21]. Virilization is usually not seen in women receiving more physiological doses of testosterone, and there have been no significant differences in reports of voice deepening, clitoromegaly, or alopecia in the double-blind, controlled, short-term studies of testosterone administration to postmenopausal women with low libido [11,12].

Cardiovascular System

Endogenous Androgens and Cardiovascular Disease

Women with polycystic ovarian syndrome have been found to have an increased risk of the metabolic syndrome and cardiovascular disease [22]. Because hyperandrogenism is part of the syndrome, it has been speculated that the elevated testosterone concentrations may be a primary risk factor for these complications. However, the polycystic ovary model is complicated by the insulin resistance and hyperinsulinemia that many of these women exhibit.

Case–control studies of women with established coronary artery disease have shown either no difference in testosterone levels between cases and controls or a significant relationship to free testosterone levels. In cross-sectional or longitudinal community-based studies that examined the relationship between androgen levels and coronary artery disease or markers of atherosclerosis, either no relationship, a decreased risk, or an increased risk has been reported [23]. Unfortunately, many of these studies did not adjust for the independent effect of estrogens and other factors. Because there is a positive correlation between testosterone and estrogen levels in many studies, failure to adjust for an estrogen effect is a major confounder. Barrett-Connor and Goodman-Gruen prospectively followed residents in Rancho Bernardo, CA, over 19 years, and examined the relationship between a variety of hormones measured from blood obtained at the time of enrollment and the risk of death from cardiovascular disease [24]. There were no differences in the age-adjusted hormone concentrations in women with or without cardiovascular disease at baseline, and none predicted which women would develop or succumb to heart disease.

Exogenous Androgens and Cardiovascular Disease

There exist no long-term prospective studies that have been sufficiently powered to examine the cardiovascular risk of the exogenous administration of testosterone to women. No increased risk was

identified in an examination of postmarketing data on a product containing esterified estrogens and 1.25 or 2.5 mg of methyltestosterone (Estratest®, Solvoy Pharmaceuticals, Marietta, GA, USA) [4]. Similarly, there was no increase in the frequency of myocardial infarction, hypertension, or cardiovascular deaths in 293 female-to-male transsexuals who received male testosterone replacement doses for 2 months to 41 years in comparison with the expected incidence in the population [25]. No increased risk of cardiovascular disease has been noted in the randomized, double-blind, placebo-controlled trials of testosterone given to women for low libido, but the short duration of treatment and relatively small numbers of women involved in the studies severely limit the ability of those studies to detect an increase in events in the testosterone-treated groups.

Blood Pressure

No relationship between blood pressure and endogenous androgen levels has been found in most of the epidemiological studies, with the exception of the Study of Women Across the Nation, in which a relationship between diastolic, but not systolic, blood pressure and total testosterone and free androgen index was noted [26].

The various treatment trials with oral methyltestosterone or testosterone undeconate, transdermal patches, or subcutaneous testosterone pellets have not shown an increase in either systolic or diastolic blood pressure. Similarly, no increase in blood pressure has been noted in female-to-male transsexuals receiving large amounts of testosterone [21].

Lipids

The lipid alterations noted with exogenous testosterone depend upon the route of administration, the dose, and whether testosterone is given alone or in combination with estrogens or estrogens and progestins. An increase in total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglycerides and a decrease in high-density lipoprotein (HDL)-cholesterol occur in female-to-male transsexuals receiving testosterone in sufficient concentrations to raise the serum testosterone into the upper part of the normal male range [21]. In contrast, when lower doses are given to postmenopausal women via injections or subcutaneous implants along with estrogen, the total cholesterol, LDL-cholesterol, and triglycerides decrease, and the HDL-cholesterol increases [27]. Testosterone delivered transdermally in physiological doses along with estrogens is neutral in regards to lipids in comparison with the estrogen-only group.

Because of the first pass effect on the liver, oral testosterone given concomitantly with estrogens generally results in a mild decrease in total testosterone and triglycerides, variable changes in LDL-cholesterol, and a decrease in HDL-cholesterol [27]. It is not known whether the net effect of these changers in regards to cardiovascular risk is positive, negative, or neutral.

Vascular Reactivity

High-dose testosterone administration to female-to-male transsexuals did not alter the flow-mediated vasodilatation measured following release of occlusion of the brachial artery in comparison with age-matched normal women, while there was a decrease in brachial artery dilatation following nitroglycerine in the transsexuals [28]. However, the transsexuals had a larger vascular diameter than did the controls, which may have confounded the interpretation. Both flow-mediated vasodilatation and nitroglycerine-induced vasodilatation were enhanced in women on stable estrogen treatment who were studied 6 weeks after receiving subcutaneous implants of 50 mg of testosterone [29]. Thus, physiological doses of androgens appear to have beneficial effects on vascular reactivity in women.

Viscosity

An increase in blood viscosity, which is mostly determined by the concentrations of triglycerides and fibrinogen, raises the risk of cardiovascular disease. In one study of 20 women receiving 2.5 mg of oral methyltestosterone along with 1.25 mg of esterified estrogens, the viscosity decreased significantly, which appeared to be primarily related to a decrease in the triglycerides, because fibrinogen levels increased [30]. No significant changes in viscosity have been noted in the trials using transdermal testosterone [3].

Coagulation Factors

A hypercoagulable state from either an excess of coagulation factors or a decrease in fibrinolytic activity may lead to cardiovascular disease. In a study that examined the effect following 2 years of use of subcutaneous testosterone implants of 100 mg replaced every 6 months in comparison with age-matched women, there were no significant differences in the levels of fibrinogen, or other thrombotic or fibrinolytic proteins, nor was

there a difference in prothrombin time [31]. A slight antithrombotic effect was noted following large doses of testosterone given to female-to-male transsexuals [32].

Polycythemia

Polycythemia, which is a risk factor for cardiovascular disease, has been noted in some hypogonadal men receiving large doses of testosterone. However, this has not been found in women receiving physiological doses of testosterone given either by injection, subcutaneous implants, transdermally, or by the oral route. The large doses of testosterone used to treat female-to-male transsexuals only increase the hemoglobulin to the level seen in normal men [33].

Insulin Resistance

Insulin resistance is present in many women with endogenous hyperandrogenism associated with polycystic ovary syndrome, and such resistance is associated with the metabolic syndrome and is a major cardiovascular risk factor. Insulin is a stimulus for androgen secretion from the ovarian theca cells. Whether hyperandrogenemia causes insulin resistance has been the subject of several studies. Using the hyperinsulinemic, hyperglycemic, and/or euglycemic clamp methods in normal women receiving 15 mg of methyltestosterone daily or female-to-male transsexuals receiving high doses of intramuscular testosterone, a decrement in whole-body glucose uptake has been noted with supraphysiological, but not with physiological, insulin levels [28,34,35]. In transdermal testosterone trials in bilaterally oophorectomized women receiving estrogen, and in HIV-infected women with weight loss, basal insulin and glucose levels remained unchanged, and in the latter group there were no alterations in insulin sensitivity during an intravenous glucose tolerance test [9–12,36,37]. On the whole, these studies offer reassurance that testosterone administration in near physiological doses will not lead to insulin resistance and its adverse consequences.

Endometrium

Numerous studies have documented that prolonged exposure of endogenous or exogenous estrogens on the endometrium without the protective effects that endogenous progesterone or exogenous progestogens confer, increases the risk of endometrial proliferation and neoplasia [38]. Although in vitro data indicate that androgens antagonize the effects of estrogens on endometrial cells, there is a concern that the high aromatization ability of the endometrium may convert exogenous testosterone to estrogen locally and adversely affect the uterus [39]. Endogenous testosterone levels have not been shown to be associated with the risk of endometrial carcinoma, when the data are appropriately adjusted for the independent effect of estrogen levels, which track with the androgen concentrations [40]. No increase in endometrial proliferation was found in women taking 1.25 mg of methyltestosterone daily along with esterified estrogens vs. women taking esterified estrogens alone [6]. In women with natural menopause taking concurrent estrogens and progestins, there were no adverse effects of transdermal testosterone on the uterus in comparison with women receiving placebo [41]. However, a cautionary note is raised by the finding that almost two-thirds of female-to-male transsexuals receiving testosterone enanthate developed a proliferative endometrium, including a few with cystic hyperplasia [42]. Thus, there are insufficient data concerning endometrial safety of aromatizable androgens at this time.

Breast

As with the uterus, there is a concern that the aromatase enzyme complex present in the breast fat and stromal tissue may utilize exogenous testosterone to produce high local concentrations of estradiol that will stimulate breast glandular proliferation through a paracrine mechanism. However, androgens may inhibit growth of breast cancer cells in vitro as well as in breast cancer animal models [43]. Oophorectomized rhesus monkeys who receive estrogen add-back therapy have an increase in proliferation of breast epithelium, which is antagonized by physiological concentrations of testosterone [44].

Epidemiological studies that have attempted to correlate quartiles of endogenous testosterone concentrations with breast cancer risk are difficult to interpret. Some have shown an association, while others have not. Most studies that have adequately controlled for the confounding effects of estradiol levels and other variables have not shown a significant increase in risk [43]. Methodological problems also make it difficult to interpret the one prospective cohort study, or the three retrospective studies that have attempted to examine the risk [45–49]. Of importance, women with

polycystic ovarian disease do not have an increase risk of breast cancer despite their chronically elevated testosterone levels.

Examination of mastectomy specimens from female-to-male transsexuals showed no important differences from breast tissue of normal women, adding further reassurance that androgen administration may not increase the risk of breast cancer [50].

Liver

High doses of oral halogenated androgens have been associated with abnormalities in liver function and the development of peliosis hepatis and liver adenomas [25,51]. However, such abnormalities have not been found when more physiological doses of methyltestosterone are given. Transdermal testosterone also has not been associated with liver abnormalities [9–12].

Sleep Apnea

Although there is a theoretical risk based on the occurrence in some men with risk factors for sleep apnea following the institution of androgen replacement therapy, this problem has not been found in women.

Behavioral Changes

High doses of androgens given to men have been associated with aggressive behavior; however, clinical trials in women with more physiological testosterone treatment have not shown an association with adverse behavior. In a double-blind trial of injectable androgens, an increase in hostility scores was noted on a psychometric test [52]. Isolated reports of reversible aggressive behavior have been reported to the FDA, although neither the numerator nor denominator is known to estimate the true incidence of these findings [15].

Summary and Conclusions

The main adverse reactions to exogenous androgens given in physiological to slightly superphysiological concentrations are androgenic side effects, primarily hirsutism and acne (Table 1). Virilization is generally not seen. Androgen treatment does not appear to have adverse cardiovascular effects, with the possible exception of a lowering of HDL-cholesterol with oral, but not parental or transdermal, androgens. The effects on the endometrium are unknown at this time because of a paucity of data. Although long-term safety in regards to the breast is unknown, the short-term studies, as well as the animal and in vitro data, provide some degree of reassurance. Studies in women who are not receiving concomitant estrogens or estrogens and androgens are also needed in order to dissect out the safety issues of testosterone alone.

In conclusion, testosterone administered by the nonoral route, which results in serum levels of free testosterone that fall within the physiological range for women during the reproductive years, is safe for up to 2 years when given concomitantly with exogenous estrogens to postmenopausal women. Long-term prospective or postmarketing studies are required before firm conclusions about safety beyond this period can be made based upon adequate data. Also, because there are no androgen preparations approved by the FDA for the treatment of low libido in women, careful monitoring of serum testosterone levels is essential to avoid overtreatment with compounding pharmacy preparations or products prepared for androgen replacement in men. Finally, a trial of androgen administration should only be carried out in menopausal women after other causes of low libido have been eliminated or treated.

Table 1 Summary of effects of exogenous testosterone treatment of postmenopausal women for low libido

System or organ	Effect
Skin	Mild hirsutism and acne; dose and time related
Cardiovascular	
Blood pressure	NS
Lipids	↓ HDL with oral route; NS with other routes
Vascular reactivity	Enhanced vasodilatation
Viscosity	NS
Coagulation factors	NS
Hemoglobin	No polycythemia
Insulin resistance	NS
Uterus	Endometrial proliferation with high doses; no Ca
Breast	Probably no ↑ risk
Liver	NS
Central nervous system	
Sleep	No sleep apnea
Behavior	Possible ↑ aggressiveness

Ca = carcinoma; HDL = high-density lipoproteins; NS = nonsignificant.

Corresponding Author: Glenn D. Braunstein, MD, Room 2119, Plaza Level, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA. Tel: (+1) 310 423 5140; Fax: (+1) 310 423 0437; E-mail: braunstein@cshs.org

Conflict of Interest: Dr. Braunstein has been a consultant and principal investigator on trials evaluating transdermal testosterone therapy for postmenopausal women sponsored by Proctor and Gamble Pharmaceuticals. He is a consultant for M&P Pharmaceuticals.

Statement of Authorship

Category 1

(a) Conception and Design:
Glenn D. Braunstein
(b) Acquisition of Data:
Glenn D. Braunstein
(c) Analysis and Interpretation of Data:
Glenn D. Braunstein

Category 2

(a) Drafting the Article:
Glenn D. Braunstein
(b) Revising It for Intellectual Content:
Glenn D. Braunstein

Category 3

(a) Final Approval of the Completed Article:
Glenn D. Braunstein

References

1 Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. J Sex Med 2007;4(suppl. 3):227–34.
2 Schwenkhagen A. Hormonal changes in menopause and implications on sexual health. J Sex Med 2007;4(suppl. 3):220–6.
3 Advisory Committee for Reproductive Health Drugs. Available at: http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4082T1.htm (accessed December 2, 2004).
4 Gelfand MM, Wiita B. Androgen and estrogen-androgen hormone replacement therapy: A review of the safety literature, 1941–1996. Clin Ther 1997;19:383–404; discussion 367–8.
5 Barrett-Connor E, Timmons C, Young R, Wiita B. Interim safety analysis of a two-year study comparing oral estrogen-androgen and conjugated estrogens in surgically menopausal women. J Womens Health 1996;5:593–602.
6 Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79:1341–52.
7 Sherwin BB. Use of combined estrogen-androgen preparations in the postmenopause: Evidence from clinical studies. Int J Fertil Womens Med 1998;43:98–103.
8 Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N. The management of persistent menopausal symptoms with oestradiol-testosterone implants: Clinical, lipid and hormonal results. Maturitas 1984;6:351–8.
9 Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med 2000;343:682–8.
10 Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C, Buch A, Watts NB. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: A randomized, placebo-controlled trial. Arch Intern Med 2005;165:1582–9.
11 Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P. Testosterone patch for low sexual desire in surgically menopausal women: A randomized trial. Obstet Gynecol 2005;105(5 part 1):944–52.
12 Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A, Rodenberg C, Lucas J, Davis S. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab 2005;90:5226–33.
13 Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, Shoukri K, Smith J. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. J Clin Endocrinol Metab 1996;81:37–43.
14 Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, Nolan J. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. J Reprod Med 1999;44:1012–20.
15 Phillips E, Bauman C. Safety surveillance of esterified estrogens-methyltestosterone (Estratest and Estratest HS) replacement therapy in the United States. Clin Ther 1997;19:1070–84.
16 Cardozo L, Gibb DM, Tuck SM, Thom MH, Studd JW, Cooper DJ. The effects of subcutaneous hormone implants during climacteric. Maturitas 1984;5:177–84.
17 Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–36.
18 Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. Menopause 2003;10:390–8.

19 Urman B, Pride SM, Yuen BH. Elevated serum testosterone, hirsutism, and virilism associated with combined androgen-estrogen hormone replacement therapy. Obstet Gynecol 1991;77:595–8.
20 Gelfand M. Elevated serum testosterone, hirsuitsm, and virilism associated with combined androgen-estrogen hormone replacement therapy [letter]. Obstet Gynecol 1991;78(part 1):474.
21 Meyer WJ 3rd, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: A longitudinal study. Arch Sex Behav 1986;15:121–38.
22 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
23 Wu FC, von Eckardstein A. Androgens and coronary artery disease. Endocr Rev 2003;24:183–217.
24 Barrett-Connor E, Goodman-Gruen D. Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. BMJ 1995;311:1193–6.
25 van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47:337–42.
26 Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell S, Pasternak RC, Lloyd-Jones D, Sowers MF, Torrens JI. Sex-hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). Circulation 2005;111:1242–9.
27 Cameron DR, Braunstein GD. Androgen replacement therapy in women. Fertil Steril 2004;82:273–89.
28 Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 2003;58:562–71.
29 Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR. Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. J Clin Endocrinol Metab 2001;86:158–61.
30 Basaria S, Dobs AS. Safety and adverse effects of androgens: How to counsel patients. Mayo Clin Proc 2004;79(4 suppl.):S25–32.
31 Buckler HM, McElhone K, Durrington PN, Mackness MI, Ludlam CA, Wu FC. The effects of low-dose testosterone treatment on lipid metabolism, clotting factors and ultrasonographic ovarian morphology in women. Clin Endocrinol (Oxf) 1998;49:173–8.
32 Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 2003;88:5723–9.
33 Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. Arch Sex Behav 1998;27:475–92.
34 Diamond MP, Grainger D, Diamond MC, Sherwin RS, Defronzo RA. Effects of methyltestosterone on insulin secretion and sensitivity in women. J Clin Endocrinol Metab 1998;83:4420–5.
35 Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 1994;79:265–71.
36 Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: A randomized, placebo-controlled trial. Menopause 2006;13:387–96.
37 Herbst KL, Calof OM, Hsia SH, Sinha-Hikim I, Woodhouse LJ, Buchanan TA, Bhasin S. Effects of transdermal testosterone administration on insulin sensitivity, fat mass and distribution, and markers of inflammation and thrombolysis in human immunodeficiency virus-infected women with mild to moderate weight loss. Fertil Steril 2006;85:1794–802.
38 Pike MC, Ross RK. Progestins and menopause: Epidemiological studies of risks of endometrial and breast cancer. Steroids 2000;65:659–64.
39 Tuckerman EM, Okon MA, Li T, Laird SM. Do androgens have a direct effect on endometrial function? An in vitro study. Fertil Steril 2000;74:771–9.
40 Boman K, Strang P, Backstrom T, Stendahl U. The influence of progesterone and androgens on the growth of endometrial carcinoma. Cancer 1993;71:3565–9.
41 Shifren JL, Davis SR, Moreau M, Waldbaum A, Bouchard C, DeRogatis L, Derzko C, Bearnson P, Kakos N, O'Neill S, Levine S, Wekselman K, Buch A, Rodenberg C, Kroll R. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: Results from the INTIMATE NM1 study. Menopause 2006;13:770–9.
42 Futterweit W, Deligdisch L. Histopathological effects of exogenously administered testosterone in 19 female to male transsexuals. J Clin Endocrinol Metab 1986;62:16–21.
43 Somboonporn W, Davis SR. Testosterone effects on the breast: Implications for testosterone therapy for women. Endocr Rev 2004;25:374–88.

44 Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D, Bondy C. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. Menopause 2003;10:292–8.
45 Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med 2006;166:1483–9.
46 Brinton LA, Hoover R, Fraumeni JF Jr. Menopausal oestrogens and breast cancer risk: An expanded case-control study. Br J Cancer 1986;54: 825–32.
47 Ewertz M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. Int J Cancer 1988;42: 832–8.
48 Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause 2004;11:531–5.
49 Braunstein GD. Comment on "Combined estrogen and androgen therapies increase risk of breast cancer." First to Know (http://www.menopause.org/news.html). September 12, 2006, pp. 4–6.
50 Burgess HE, Shousha S. An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: A comparison with normal female breast and male breast showing gynaecomastia. J Pathol 1993;170: 37–43.
51 Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. Lancet 1977;2:262–3.
52 Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: A double-blind, cross-over study. Psychoneuroendocrinology 1985;10:325–35.