Long-Term Treatment of Transsexuals with Cross-Sex Hormones: Extensive Personal Experience

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Context: Transsexuals receive cross-sex hormone treatment. Its short-term use appears reasonably safe. Little is known about its long-term use. This report offers some perspectives.

Setting: The setting was a university hospital serving as the national referral center for The Netherlands (16 million people).

Patients: From the start of the gender clinic in 1975 up to 2006, 2236 male-to-female and 876 female-to-male transsexuals have received cross-sex hormone treatment. In principle, subjects are followed up lifelong.

Interventions: Male-to-female transsexuals receive treatment with the antiandrogen cyproterone acetate 100 mg/d plus estrogens (previously 100 μg ethinyl estradiol, now 2–4 mg oral estradiol valerate/d or 100 μg transdermal estradiol/d). Female-to-male transsexuals receive parenteral testosterone esters 250 mg/2 wk. After 18–36 months, surgical sex reassignment including gonadectomy follows, inducing a profound hypogonadal state.

Main Outcome Measures: Outcome measures included morbidity and mortality data and data assessing risks of osteoporosis and cardiovascular disease.

Results: Mortality was not higher than in a comparison group. Regarding morbidity, with ethinyl estradiol, there was a 6–8% incidence of venous thrombosis, which is no longer the case with use of other types of estrogens. Continuous use of cross-sex hormones is required to prevent osteoporosis. Androgen deprivation plus an estrogen milieu in male-to-female transsexuals has a larger deleterious effect on cardiovascular risk factors than inducing an androgenic milieu in female-to-male transsexuals, but there is so far no elevated cardiovascular morbidity/mortality. Low numbers of endocrine-related cancers have been observed in male-to-female transsexuals.

Conclusions: Cross-sex hormone treatment of transsexuals seems acceptably safe over the short and medium term, but solid clinical data are lacking. **(*J Clin Endocrinol Metab* 93: 19–25, 2008)**

Transsexualism is the condition in which a person with apparently normal somatic sexual differentiation is convinced that she or he is actually a member of the other sex. This conviction is accompanied by an irresistible urge to live in the other gender, which requires hormonal, anatomical, legal, and psychosocial adaptations. Since its initiation in 1975, 876 female-to-male (F2M) and 2236 male-to-female transsexuals (M2F) have received hormonal treatment. Eligibility criteria for hormone treatment will not be addressed here, but guidelines provided by the World Professional Association for Transgender Health (http://www.wpath.org) were followed.

The acquisition of the secondary sex characteristics of the other gender is fundamental to sex reassignment. Acquisition of these secondary sex characteristics is contingent on sex steroids. There is no known essential difference in sensitivity to the biological action of sex steroids on the basis of genetic configura-

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Abbreviations: F2M, Female-to-male; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M2F, male-to-female.

tions or gonadal status. The typical transsexual requesting treatment is a young to middle-aged and healthy person, and therefore, there are usually no or few absolute or relative contraindications against cross-sex hormone administration. For suppression of androgen secretion or action, several agents are available. In Europe, the most widely used drug is cyproterone acetate (usually 50 mg twice daily), a progestational compound with antiandrogenic properties. If not available, medroxyprogesterone acetate, 5–10 mg/d, is a less effective alternative. Spironolactone (up to100 mg twice daily, if tolerated), a diuretic with antiandrogenic properties, has similar effects. Long-acting GnRH inhibit gonadotropin secretion. Finasteride (5 mg/d), a 5α-reductase inhibitor, might also be considered. Hormone treatment of transsexuals has been reviewed in recent years (1, 2).

M2F Transsexual Treatment

There is a wide range of estrogens from which to choose. Oral ethinyl estradiol (50–100 μg/d) is a potent and inexpensive estrogen but may cause venous thrombosis, particularly in those over age 40 (1, 3). It should therefore not be used in the dosage required by M2F (50–100 μg/d). Oral 17β-estradiol valerate, 2–4 mg/d, or transdermal 17β-estradiol, 100 μg twice a week, are the treatments of choice and are much less thrombogenic than ethinyl estradiol (3). Many transsexuals favor injectable estrogens, because they generate high levels of circulating estrogens. However, they have the potential risk of overdose.

There is no evidence that progestagens add to the feminization process of M2F. In female reproductive endocrinology, progesterone prepares the uterus for conception and the breasts for lactation. Some patients strongly believe that progestagens are a necessary addition to estrogens in their feminization process. But this is not the case, and progestagens may have side effects, such as salt/water retention leading to elevated blood pressure or venous varicosis. In the large-scale study of postmenopausal hormone use in women, the combination of estrogens and progestagens appeared to be associated with a higher incidence of breast cancer (4) and cardiovascular disease.

F2M Transsexual Treatment

The goal of treatment in the F2M is to induce virilization (including a deepening of the voice), production of male-pattern body hair growth and physical contours, and cessation of menses. The principal hormonal treatment used to accomplish these goals is a testosterone preparation. The most commonly used preparations are injectable testosterone esters administered im in doses of 200–250 mg every 2 wk. In some countries, testosterone undecanoate (1000 mg) is available, and injections may be spaced at 10–12 wk. Use of androgen gel or transdermal patches can also provide good, steady-state testosterone levels. Occasionally, menstrual bleeding does not cease, and the addition of a progestational agent is necessary, almost always needed when transdermal or oral testosterone is used.

After ovariectomy, androgen therapy must be continued, but progestational drugs can be stopped. When F2M receive treatment with testosterone, part of it is aromatized to estradiol (5). When hysterectomy is delayed, there is some concern about endometrial cancer (6).

Long-Term Treatment and Its Effect on Health

After reassignment surgery, which includes gonadectomy, hormone therapy must be continued. It is reasonable to assume that the principles of treatment are very similar to those of other subjects without their own gonadal hormonal secretion. An unresolved question is whether in the long term all functions of sex steroids of a subject are adequately covered by cross-sex hormones and whether the administration of cross-sex hormones is appropriately safe, or at least as safe as administration of sex steroids in a subject receiving long-term sex-appropriate sex steroids. There are presently no indications that there are fundamental sex differences in sensitivity to hormone action of sex steroids. Nearly all hormone-related biochemical processes can be sex reversed by the administration of cross-sex hormones.

It is likely that that there is an underreporting of (serious) complications of cross-sex hormone therapy. Although the initial treatment with cross-sex hormones is mainly concentrated in specialized centers, complications occurring in the long term are seen in general practice, and these complications are only occasionally reported in the scientific literature. The authors have been contacted by other physicians on medical occurrences in transsexuals, but these cases are often lost for follow-up and for registration of (potential) complications of cross-sex hormonal treatment. The latter situation prevents a fair comparison with epidemiological data in the general population. Recently, a web site has been opened for reporting side effects of cross-sex hormone treatment: http://www.wpath.org/resources_transgender.cfm (click under transgender information: resource links).

In 1997, we published a report on mortality/morbidity in transsexual subjects (7). This was a retrospective, descriptive study of 816 M2F and 293 F2M who had been treated with cross-sex hormones for a total of 10,152 patient-years. Standardized mortality and incidence ratios were calculated from the general Dutch population (age- and gender-adjusted) and they were also compared with side effects of cross-sex hormones in transsexuals reported in the literature. Mortality was not higher than in the general population. Venous thrombosis occurred frequently but could be related to the use of oral ethinyl estradiol (3), and the incidence decreased to the incidence in the general population when its use was relinquished. The conclusion of the report was that in the short and midterm, cross-sex hormone treatment was acceptably safe.

Cross-sex hormone administration took off in the 1970s, so several transsexual subjects are now in their 60s, 70s, and even 80s. Another important but unresolved question is until what age cross-sex hormone treatment must be continued. This question must be set against the information that has become available on hormone replacement therapy in perimenopausal and postmenopausal women (National Institutes of Health State-of-the-Science Conference Statement on management of menopause-

related symptoms). Should estrogen administration to M2F be discontinued for the reasons applicable to postmenopausal women? Not needing progestagens to prevent estrogen stimulation of uterine hyperplasia and malignancy, would M2F benefit from continued estrogen-only administration in view of the reportedly favorable effects of estrogens on bone, the cardiovascular system, and the brain? The issue seems less pressing in F2M receiving treatment with testosterone because in this group there is no high risk of androgen-related malignancies. Transsexuals themselves are usually inclined to continue cross-sex hormone administration for fear that they would lose physical characteristics of the reassigned sex.

The following will address some areas where sex hormones are known to play a role and continuation/discontinuation and dose of hormone administration may be relevant.

Cross-Sex Hormones and Osteoporosis

Sex steroids play a pivotal role in the maintenance of the integrity of the skeleton in both men and women. Postmenopausal women and hypogonadal men have an increased risk of fractures. The risk of bone loss in subjects undergoing sex reassignment has been well recognized in the literature (8–11). In the longer term, bone mineral density is preserved during cross-sex hormone administration (10). Apparently, estrogens alone are capable of maintaining bone mass in M2F. Conversely, testosterone administration maintains bone mineral density in F2M. Part of testosterone is converted to estradiol, resulting in circulating estradiol levels well above the plasma level of estradiol critical for preserving bone mineral density in men (*i.e.* 40–50 pmol/liter) (5). In our study, there was an inverse relationship between serum LH concentrations and bone mineral density, so serum LH may serve as an indicator of the adequacy of sex steroid administration (10). It is not known whether cross-sex hormone administration can be responsibly discontinued at a certain age without inducing an unacceptable risk of osteoporosis and bone fractures.

Cross-Sex Hormones and Cardiovascular Disease

Men have a higher incidence of cardiovascular events than women of similar ages (12). There is, however, no evidence supporting a causal relation between higher testosterone levels and heart disease (12). There is as yet no true insight into the effects of cross-sex hormone treatment on cardiovascular health. As can be expected, cases of cardiovascular complications of transsexuals have been reported in the literature, but it is not warranted to generalize them to the whole population of transsexuals. There is as yet no true insight into the effects of cross-sex hormone treatment on cardiovascular health. As can be expected, cases of cardiovascular complications of transsexuals have been reported in the literature, but it is not warranted to generalize them to the whole population of transsexuals. Over the past 15 yr, we have extensively investigated the effects of cross-sex hormone administration to transsexuals on (biochemical) risk factors of cardiovascular disease.

Cardiovascular risk in M2F transsexuals

Men with prostate cancer, treated with androgen deprivation, develop an increase of fat mass with an altered lipid profile (13). These patients also appear to develop insulin resistance, hyperinsulinemia, and hyperglycemia (13). The risks of diabetes mellitus increase by 44% and mortality of cardiovascular diseases by 16% during a follow-up of up to 10 yr. Is there a parallel in M2F upon androgen deprivation?

Several studies have been done in M2F transsexuals who received estrogens and antiandrogens (either 100 μg ethinyl estradiol per day or transdermal 17β-estradiol 100 μg twice a week, with or without 100 mg cyproterone acetate). Many changes in cardiovascular risk factors were found, and the results of these studies in M2F are summarized in Table 1.

Weight, body mass index, total body fat, and visceral fat increased during treatment in M2F (Table 1), resembling features of the metabolic syndrome. The observed changes in cardiovascular risk factors observed in transsexual patients may be primarily caused by the increase of the amount of visceral fat in M2F (14, 15). The increase in fat tissue may lead to an increased hepatic triglyceride influx and a rise of plasma leptin (14).

High-density lipoprotein (HDL) cholesterol, its subfractions, and triglyceride levels increased (Table 1), to a similar extent as seen in men treated for prostate cancer (13). Total cholesterol was unaffected, and low-density lipoprotein (LDL) cholesterol levels decreased by 12% in M2F (14), whereas total and LDL cholesterol levels were found to increase by 9% in men treated for prostate cancer (13). The low estrogen state observed in these men is responsible for the increases in total and LDL cholesterol. The latter was not observed in our transsexual patients who receive, in addition to the androgen deprivation, treatment with estrogens. The slight decrease in LDL cholesterol seen in transsexuals was, however, accompanied by a decrease in LDL particle size (14), another known cardiovascular risk factor. A study by another group found that administering GnRH agonists plus oral 17β-estradiol valerate to M2F induced endocrine changes similar to our studies but without an impairment of the lipid profile. The use of cyproterone acetate might explain the differences. Indeed, a study using cyproterone acetate in prostate cancer patients found a serious deterioration of the lipid profile.

The effects on insulin sensitivity encountered in our studies were largely in the same detrimental direction (14) as in men with prostate cancer treated with GnRH agonists (13). The deleterious effects on insulin sensitivity are, therefore, likely due to androgen deprivation. We found that insulin sensitivity (assessed by hyperinsulinemic euglycemic clamp) decreased, and this was accompanied by a compensatory increase in fasting plasma insulin concentration preventing hyperglycemia (Table 1) (14). Endogenous glucose production (measured by isotope dilution with titrated glucose) was, however, not affected by cross-sex hormone administration, indicating that the observed changes in glucose requirement during a hyperinsulinemic euglycemic clamp procedure were due to the diminished peripheral glucose uptake (16), a finding that was later confirmed by Elbers *et al.*

TABLE 1. Changes over 4–12 months in risk factors for cardiovascular disease in M2F transsexuals

	Refs.	Absolute change	Relative change	Effect on CVD morbidity/ mortality
Body composition				
Weight		+4 kg	+6%	↑
Body mass index	14, 17, 34	NS, +1 kg/m^2	NS, +5%, +6%	↑
Total body fat	34	+2 kg	+17%, +21%	↑
Visceral fat	14	+7 cm^2 on MRI	+18%,	↑
Lipid spectrum				
Total cholesterol	14, 35	NS	NS	−
LDL cholesterol	14, 35	NS, −0.3 mmol/liter	NS, −12%	− ↓
HDL cholesterol	14, 34	+0.1, +0.2, +0.3 mmol/liter	+10%, +15%, +24%	↓
VLDL cholesterol	14	NS	NS	−
Triglycerides	17, 34	NS, +0.4, +0.7 mmol/liter	NS, +34%, +70%	− ↑
Fish fatty acid (DHA)	36	+0.2% by weight	+35%	↓
Insulin sensitivity				
Fasting glucose level	14, 17	NS	NS	−
Fasting insulin level	14, 15, 17	+13, +21 pmol/liter	+30%, +50%	↑
Insulin sensitivity	14, 16	−150 mg glucose/min, −0.7 mmol glucose/kg LBM·h	−18%, −25%, −33%	↑
Vascular functioning				
Heart rate	17	+4 bpm	+6%	↑
Diastolic blood pressure	14, 17	NS, +6 mm Hg	NS, +8%	− ↑
Systolic blood pressure	14, 17	NS, +7 mm Hg	NS, +6%	− ↑
Distensibility coefficient	17	NS	NS	−
Compliance coefficient	17	NS, −0.2 mm^2/kPa	NS, −20%	− ↓
Hemostasis/fibrinolysis				
Activated protein C resistance	3	+0.7, +2.9	+54%, +241%	↑
Prothrombin	3	NS, +9%	NS, +9%	− ↑
Fibrinogen	34	NS, +8.0%	NS, +7%	− ↑
Tissue-type plasminogen activator antigen	37, 38	NS, −4, −5 ng/ml	NS, −52%	− ↓
Plasminogen activator inhibitor-1 antigen	37, 38	NS, −12,−17 ng/ml	NS, −62%, −65%	− ↓
Other CVD risk factors				
Total homocysteine	34	−3 μmol/liter	−26%, −29%	↓
C-reactive protein	34	NS, +0.2 mg/liter	NS, +20%	− ↑

−, No change in CVD risk; ↑, increased CVD risk; ↓, decreased CVD risk; CVD, cardiovascular disease; DHA, docosahexaenoic acid; LBM, lean body mass; MRI, magnetic resonance imaging; NS, no statistically significant change.

(14). We further found that blood pressure slightly increased during estrogen and antiandrogen treatment, and there was a small detrimental effect on arterial stiffness (17).

Cardiovascular risk in F2M transsexuals

Hyperandrogenism in women, usually resulting from the polycystic ovarian syndrome, is associated with an unfavorable cardiovascular risk profile. However, hyperandrogenism in polycystic ovarian syndrome is usually clustered with features of the metabolic syndrome (hyperinsulinemia, visceral obesity, hypertension, and dyslipidemia). It is difficult to disentangle the contributions that the various components of the metabolic syndrome make to this unfavorable cardiovascular risk profile, more precisely, what the role of hyperandrogenism *per se* is.

The results from studies in F2M transsexuals are summarized in Table 2. The observed changes in cardiovascular risk factors seen in F2M may again be secondary to the increase in weight and the amount of visceral fat (14). Our group has shown that testosterone administration to F2M decreases plasma leptin (14); furthermore, a decrease in serum adiponectin concentration has been reported. We found a slight decrease of insulin sensitivity in one of our studies (14, 16). Furthermore, increases were found in HDL cholesterol, fasting triglycerides, total homocysteine, and C-reactive protein (Table 2). Blood pressure and arterial stiffness, unlike in other reports, were unaffected by cross-sex hormone treatment (17).

Concluding remarks on cardiovascular risk

Cross-sex hormone administration in M2F and F2M both improves and impairs profiles of cardiovascular risk factors. It remains difficult to determine how much weight must be attributed to these alterations in risk factors and whether these changes are of clinical significance. With these reservations in mind, the overall impression is that inducing androgen deprivation and an estrogen milieu in M2F has a larger deleterious effect on the risk factors, than inducing an androgenic milieu in F2M (Tables 1 and 2).

So far the only data available on hard clinical endpoints is from our study on cardiovascular morbidity and mortality in both M2F and F2M (7). This study reports no elevated (cardiovascular) morbidity and/or mortality in the cohort of transsexuals treated at the Amsterdam clinic. Yet, to reduce the risk of the metabolic syndrome and cardiovascular disease and to increase

TABLE 2. Changes over 4–12 months in risk factors for cardiovascular disease in F2M transsexuals

	Refs.	Absolute change	Relative change	Effect on CVD morbidity/ mortality
Body composition				
Weight	14, 15	+3 kg	+4%	↑
Body mass index	14, 17, 35	+1 kg/m^2	+3%, +4%, +6%	↑
Visceral fat	14, 15, 39	NS, +5 cm^2 on MRI	NS, +13%	−↑
Lipid spectrum				
Total cholesterol	14, 35	NS	NS	−
LDL cholesterol	14, 35	NS	NS	−
HDL cholesterol	14, 17	−0.2, −0.3 mmol/liter	−20%, −23%	↑
VLDL cholesterol	14	NS	NS	
Triglycerides	17	+0.2 mmol/liter	+26%	↑
Fish fatty acid (DHA)	36	−0.1% by weight	−24%	↑
Insulin sensitivity				
Fasting glucose level	14, 17	−0.1, −0.4 mmol/liter	−2%, −8%	↓
Fasting insulin level	14, 15, 17	NS	NS	−
Insulin sensitivity	14, 16	NS, −0.5, −0.8 mmol glucose/ kg LBM·h	NS, −10−20%	−↑
Vascular functioning				
Heart rate	17	NS	NS	−
Diastolic blood pressure	14, 17	NS	NS	−
Systolic blood pressure	14, 17	NS	NS	−
Distensibility coefficient	17	NS	NS	−
Compliance coefficient	17	NS	NS	−
Hemostasis/fibrinolysis				
Activated protein C resistance	3	−0.7	−35%	↓
Prothrombin	3	NS	NS	−
Tissue-type plasminogen activator antigen	38	NS	NS	−
Plasminogen activator inhibitor-1 antigen	38	NS	NS	−
Other CVD risk factors				
Total homocysteine	38	+1.3 μmol/liter	+17%	↑
C-reactive protein	40	+0.5 mg/liter	+141%	↑

−, No change in CVD risk; ↑, increased CVD risk; ↓, decreased CVD risk; CVD, cardiovascular disease; DHA, docosahexaenoic acid; LBM, lean body mass; MRI, magnetic resonance imaging; NS, no statistically significant change.

life expectancy, it is important to advise transsexuals to adopt healthy lifestyle and dietary behaviors.

Cross-Sex Hormones and Hormone-Dependent Tumors

Some cancers (of reproductive organs) are hormone related. Hormone-dependent tumors are practically not occurring in hormonally treated F2M and seem a rare occurrence in M2F. But transsexualism is a rare phenomenon (the highest estimates are one in 12,000 males and one in 30,000 females) (18); if, in addition, the prevalence of hormone-dependent tumors is low, this may lead to an underestimation of tumors.

M2F, as a rule, use higher doses of estrogens than women lacking production of gonadal hormones. In transsexuals, exposure to estrogens is usually over a shorter period of lifetime, because transsexuals mostly start cross-sex hormone treatment well after puberty, although this is changing. Presently, adolescent transsexuals may be eligible for cross-sex hormone treatment. Furthermore, transsexuals beyond the ages of 50 or 60 yr have a strong inclination to continue cross-sex hormones, increasing their period of time of exposure to sex steroids. The following is a summary of reports in the literature on tumors in transsexuals.

The first documented hormone treatments of transsexuals started in the 1970s, and the length of time of exposure to hormones may have been too short for tumors to manifest themselves. Therefore, the conclusion that hormone-related tumors are not highly prevalent among the transsexual population must be drawn with great caution.

Lactotroph adenoma

Several cases of lactotroph adenoma (prolactinoma) after high-dose estrogen administration have been reported in patients with normal serum prolactin concentrations before therapy (7, 19–21). We have recently encountered a case of development of a pituitary microprolactinoma in a M2F, only occurring after 14 yr of normal-dose estrogen treatment. Although causality has not been established, we recommend that serum prolactin levels continue to be monitored in estrogen-treated M2F in the long term.

Breast cancer

There are two reports of M2F who developed breast carcinomas while receiving estrogen treatment (22, 23). Breast fibro-

adenomas in M2F receiving hormonal treatment have been observed. In our series of approximately 2200 M2F, cumulative over 30 yr, until recently, no single case of breast cancer had been observed, but there is now one case. On the basis of the above information, one would be inclined to think that breast carcinomas in M2F are rare, but it has to be kept in mind that 1800 subjects, with a strong variation in estrogen exposure (from 1–25 yr), do not allow firm conclusions in assessing risk. Aging is a factor in the development of cancer, and prolonged exposure to estrogens may also prove to be a factor. Therefore, the discussion as to the age at which estrogen treatment in M2F should be terminated is pertinent. In any case, in addition to regular medical examination, breast self-examination must be part of the monitoring of estrogen administration, following the same guidelines that exist for other women.

Amazingly, breast cancer has been reported in a F2M after bilateral sc mastectomy while receiving treatment with testosterone. This occurred in residual mammary tissue after 10 yr of treatment with testosterone, which is partially aromatized to estradiol (24).

Benign prostate hyperplasia and prostate cancer

The prostate is not removed with sex reassignment surgery. Prostatectomy is a surgically cumbersome operation, with possible complications, such as urinary incontinence. As expected, the prostate volume shrinks after androgen deprivation. Estrogen exposure does not induce signs of hyperplasia or (pre)malignancy (25). Two cases of benign prostate hyperplasia, requiring transurethral prostate resection, have been described in subjects who had been orchidectomized and had been treated with only estrogens for more than 20 yr. Another case of squamous metaplasia of the verumontanum has been reported, leading to obstruction due to hypertrophy (26).

Three cases of prostate cancer in M2F taking estrogen have been reported (27–29). It is not clear whether these cancers were estrogen sensitive or whether they were present before beginning estrogen administration and then subsequently dedifferentiated to become androgen independent. These patients were each over 50 yr of age when they started cross-sex hormone treatment (with total androgen ablation). Epidemiological studies have shown that orchidectomy before age 40 prevents the development of prostate cancer and benign prostate hyperplasia, and the above cases do not contradict this notion. In most clinics, screening for the development of levels of prostate-specific antigen is not routinely done.

Ovarian cancer

Ovariectomy is recommended in F2M when they are eligible for surgical sex reassignment, in our clinic, usually 18–24 months after the start of testosterone administration. We have observed two cases of ovarian carcinoma in testosterone-treated F2M, diagnosed before they underwent surgery (30). Another case has been reported recently (31).

The ovaries of F2M transsexuals taking androgens resemble polycystic ovaries (5). The earlier notion that polycystic degenerated ovaries are more prone to develop cancer appears not tenable, but there is an up-regulation of androgen receptors in ovarian and uterine tissue in long-term treated F2M (32).

Conclusions

It is now clear that sex reassignment of transsexuals benefits their well-being, (33) although suicide rates remain high (7). Regrets are rare (0.5–3.0%). Cross-sex hormone administration to transsexuals is acceptably safe in the short and medium term. However, potentially adverse effects in the longer term are presently unknown. The data, although limited, of surrogate markers of cardiovascular disease and the reports of cancer in transsexuals leave room for a cautious optimism. But true insight can only come from close monitoring and thorough reporting of adverse effects in the literature.

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