17 Hormonal Therapy of Gender Dysphoria

The Male-to-Female Transsexual

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Fascination with cross-gender states appears to be intrinsic to being human. The "evidence" for the existence of a pope who appeared to be a man but was a fertile woman was recently the subject of the presidential address for the Endocrine Society (New & Ketzinger, 1993). Current medical understanding says that gender dysphoria or true transsexualism is a neuroendocrine condition of unknown cause, unknown inheritance, and has a prevalence of about 1:18,000 in the male population (Asscheman, 1989). Transsexualism has been shown to be poorly responsive to intense psychotherapy to change the identity disturbance. Therefore, treatment of a biological male with female hormones becomes the primary therapy followed by anatomical reassignment after a period of living as a woman.

The purpose of this chapter is to outline and review the more than 10-year experience of the clinical program at Vancouver Hospital (University of British Columbia) in treating men who are true transsexuals.

Overview of Hormonal Therapy

A review of the literature and communication with other centers reveals that the current standard therapy for male-to-female transsexuals (MTF) is 2.5 to 10 mg/d continuously of conjugated equine estrogen (Premarin®, CEE) or 0.1 to 1.0 mg/d of ethinyl estradiol (EE) (Meyer, Webb, Stuart, Finkelstein, et al., 1986; Asscheman, Gooren, & Eklund, 1989; Asscheman & Gooren, 1992). Similar doses of estrogen were in use when our clinic began (average dose of CEE was 3.9 ± 2.3 mg/d and of EE was 7.1 ± 7.2 mg/d) (Prior, Vigna, Watson, & Diewold, 1986; Prior, Vigna, & Watson, 1989). In addition, these men were commonly asking their family physicians for and receiving additional injected estrogen in their intense desire to become female (Prior, Vigna, Watson, & Diewold, 1986).

The differences in our approach to therapy are that we have added to estrogen therapy a nonandrogenic progesterone, medroxyprogesterone acetate (MPA). A progesterone is needed for two main reasons: feminization involves the action of both the estrogen and progesterone (secreted cyclically in the biological woman), and testosterone suppression is accompanied with lower estrogen doses. We also consistently prescribe a drug that competes with testosterone at its receptor. We began using spironolactone, a hypertension medication with which one of us (Prior) had experience during its initial clinical development to exploit its antiandrogenic properties (Prior, Vigna, & Watson, 1989). The concerns in this center, which has now had experience with over 238 male-to-female transsexuals, were to avoid the potential or documented complications of treatment with high doses of estrogens (thromboembolism, prolactinoma, myocardial infarction, breast cancer) (Asscheman, Gooren, & Eklund, 1989).

Men with gender-related concerns are not referred for endocrine treatment in the Centre for Sexuality, Gender Identity and Reproductive Health (formerly the Gender Dysphoria Programme) until they have been carefully screened and determined to have true transsexualism. They are initially interviewed by a psychiatric social worker, psychologist, or nurse clinician, and referred for two independent psychiatric assessments. Spironolactone may be given during the assessment and appears to help with the intense anxiety during the several-month process. Any men already on oral contraceptives or estrogen are told that they must discontinue current therapies and adopt those prescribed by this clinic at the time of endocrine assessment. Written information concerning this center's hormonal therapy program is provided ahead of the consultation. In this material and verbally, they are warned that estrogen therapy mandates discontinuation of cigarette smoking. Therefore the period of initial evaluation allows them to prepare for a new set of therapies.

Objectives for Hormonal Management

Hormonal therapy for the man who feels he is, and wants to become more externally like, a woman, has several goals. These are summarized and then explained in detail below:

1. To reduce androgen activity through:
   a. decreased production of testosterone (T) and dihydrotestosterone (DHT)
   b. decreased effects of T and DHT
2. To promote estrogen and progesterone effects on secondary female sexual characteristics.

3. To prevent any negative effects of testosterone deprivation (such as accelerated bone loss or inadequate bone formation).
4. To provide adequate hormonal support prior to, during, and following recovery from sexual-reassignment surgery (SRS).
5. To minimize potential complications of exogenous hormone therapy (worsening of hypertension, diabetes, hyperlipidemia, or production of hyperprolactinemia, thromboembolic disease, or breast cancer).

Reduction of Androgen Activity

The first objective, decreasing androgen production and effects (Table 17.1), is met by combined therapy with an estrogen (CEE or transdermal estrogen [TDE]), a nonandrogenic progestin, MPA, and spironolactone as an antiandrogen. Figure 17.1 shows the actions of these different drugs to suppress the hormone levels and receptors. Estrogen and MPA feed back to the

TABLE 17.1. Actions of Testosterone and/or DHT

1. Sexual Function
- Erection
- Ejaculation
- Time to Orgasm
- Sexual Dominance

2. Cerebrum
- Sexual Desire
- Energy
- Well-being

3. Metabolism
- RBC Production
- Anabolic to Muscle and Bone
- Lipids—HDL Reduction
- HbA1C ↑

4. Physical/Sexual Characteristics
- Development of Male Genitalia and Prostate
- Beard and Male-Pattern Body Hair
- Skin Texture
- Fat Distribution
- Scalp-Hair Loss
- Deepening of Voice
- Skeletal Structure

pituitary and the hypothalamus to reduce luteinizing hormone (LH) production, decreasing the stimulation of testicular production of testosterone. This therapy has been shown, in a prospective but nonrandomized one-year study, to decrease testosterone levels into the female range in all of 50 MTF transsexuals (Prior, Vigna, & Watson, 1989).

The usual daily regime is:

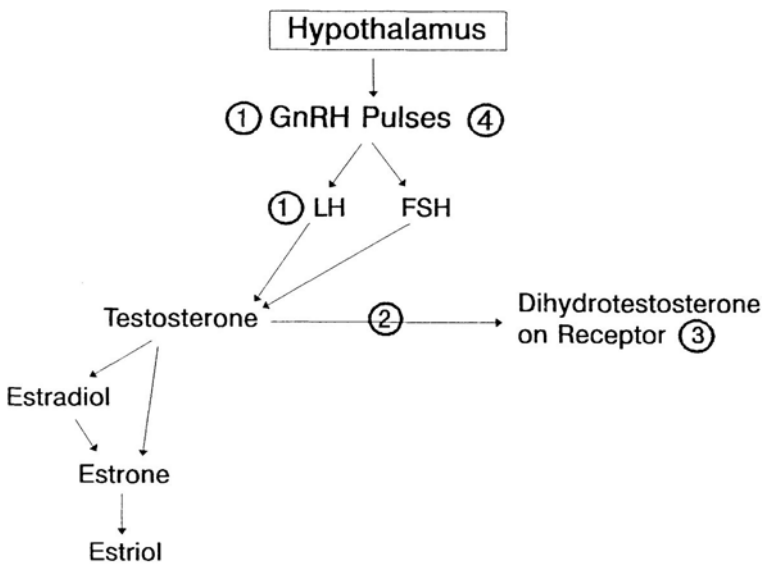
1. CEE 0.625 to 1.25 mg/d days 1–25 of the month or TDE 50–100 μg twice/week, with 7 patches/month
2. MPA 20–50 mg/d

Medroxyprogesterone is given in low pharmacological doses. The latter medication is felt to be far safer (objective #5) than estrogen because it does not increase the risk for thrombosis or cancer (Clarke & Sutherland, 1990), lowers triglycerides and total cholesterol (Gallagher, Kable, & Goldgar, 1991) (although it may slightly decrease the HDL increase that occurs on oral estrogen [Writing Group for PEPI Trial, 1995], and has positive effects on bone formation (Prior, 1990; Prior, Vigna, Barr, Rexworthy, et al., 1994). Despite clinical reports, a double-blind, placebo-controlled trial showed no adverse effects to MPA therapy (Prior, Alojado, McKay, & Vigna, 1994). MPA in doses of 20–40 mg/d is needed to adequately suppress LH. MPA is a weak antiandrogen because it competes for the 5-alpha reductase enzyme that transforms testosterone into DHT, and thus is preferable to other available progestins, (e.g. norethindrone or norgestrol with androgenic effects), or the new progestins derived from norgestrol (desogestrel and norgestimate, which, although not androgenic, lack any antiandrogenic effect). However, because MPA may become androgenic at higher doses, oral micronized progesterone therapy has begun to be used, as it just became available in Canada. Progesterone activity also allows the full maturity of breast and nipple development (maturation to Tanner stage 5 requires progesterone [unpublished Prior, 1989]).

Spironolactone, which is commonly begun in a dose of 100 or 200 mg/day by the referring family physician or psychiatrist prior to our assessment, is increased to 300 or 400 mg/d in combination with the hormones listed above (Prior, Vigna, & Watson, 1989). It acts by at least three mechanisms to decrease the production and the effect of endogenous androgens (Corrol, Michaud, Menard, Freifeld, et al., 1975). First, it works through cytochrome P450 to decrease testosterone production by the gonad and adrenal glands. Secondly, it antagonizes testosterone or DHT effects at the intracellular nuclear receptor; and finally, spironolactone is a 5-alpha reduc-

tase inhibitor and interferes with the conversion of testosterone to DHT, its active intracellular form. It also may slightly reduce LH production (Prior, Vigna, & Watson, 1989).

Spironolactone, with which we have extensive experience (Prior, Vigna, & Watson, 1989), is an easy medication to administer, is not expensive in generic formulation, and has few and nonserious side effects. In our population, only two transsexuals have experienced a drug-related rash. Because spironolactone is an aldosterone antagonist and a mild diuretic, patients are always cautioned to drink plenty of fluids in the first several



Inhibition at the following steps:

1. Progesterone—Provera
   Estrogen—Estradiol, Conjugated Estrogens
   Cyproterone Acetate
   Spironolactone
2. Progesterone—Provera
   Cyproterone Acetate
   Spironolactone
   Finasteride
3. Cyproterone Acetate
   Flutamide
   Spironolactone
4. GNRH Agonists

Figure 17.1. This diagram outlines the areas of the hypothalamic, pituitary gonadal axis at which the various gonadal steroid hormones, anti-androgens and other pharmacological agents act.

weeks of use and whenever they are exercising strenuously or in hot environments. The initial diuretic effect decreases in 1–4 months. Potassium levels do rise (usually to 4.8–5.2 mmol/L), but not significantly above normal if renal function is unimpaired and a potassium supplement or high fruit diet are not taken. We do not routinely measure serum potassium levels.

Alternative antiandrogenic drugs include cyproterone acetate, also a powerful antiandrogen and a progestagen, an antigonadotrophic agent which also competes with DHT binding to the receptor. Its use is limited by serious risks of interference with corticosteroid production, its high cost, and the common side effects of depression, fatigue, weight gain, and headaches (de Vries, Gooren, & van der Veen, 1986). Similarly, ketoconazole, which interferes with testosterone synthesis, is avoided because of possible hepatotoxicity and the same risk of interference with other steroid production rates. We have no experience using "pure antiandrogen" drugs such as flutamide; however, the secondary increase in LH and testosterone, the expense, and the short half-life would not be desirable. It may prove useful after SRS for persistent beard growth. Finasteride, as a 5-alpha reductase, is also a potential therapy, but it is expensive and would only oppose the formation of the DHT, and not of testosterone itself.

Spironolactone is often discontinued after SRS. However, for some, the sensitivity of the beard hair-cell receptors for testosterone is such that even normal adrenal androgen production appears sufficient to maintain beard growth. In these patients, spironolactone is continued, perhaps at a lower dose, until all male pattern hair is gone.

Promotion of Estrogen and Progesterone Effects

The second objective is to provide effective estrogen and progesterone actions. Estrogens, either CEE or TDE, are given in physiological doses (0.625–1.25 mg/d or 50–100 µg/d, respectively). In addition, we provide them cyclically days 1–25 or 26 of the month to mimic the time of low estrogen during the menstrual flow phase of the normal menstrual cycle. It is of note that the estrogen doses are in the physiological ranges for "hormonal replacement." Others (Asscheman, Gooren, & Eklund, 1989) have used ethinyl estradiol 100 µg (it is of note that this was the dosage used in the birth-control pills in the 1960s when they were documented to cause adverse cardiovascular effects), a dose that is approximately 15 times higher than physiological female levels. Doses ten times higher than this are also prescribed (Meyer, Finkelstein, Stuart, Webb, et al., 1981). The oral route of these high-dose estrogens leads to very altered liver metabolism with increased production of coagulation factors, triglycerides, and renin. High-dose estrogen is also a potent direct stimulant of pitu-

itary prolactin production (Asscheman, Gooren, & Eklund, 1989; Goh & Ratnam, 1990; Goh, Li, & Ratnam, 1992; Kovacs, Stetaneanu, Ezzat, & Smyth, 1994). Pituitary prolactin-producing adenoma growth has been recorded in male-to-female transsexuals being treated with conventional high-dose estrogen therapy (Asscheman, Gooren, & Eklund, 1989; Kovacs, Stetaneanu, Ezzat, & Smyth, 1994). For this reason we routinely monitor prolactin levels, which serve as an indicator of high estrogen self-medication.

Prevention of Potential Adverse Bone Effects

The third objective is to prevent the negative effects of hypogonadism on bone metabolism (Orwoll & Klein, 1995). Men with anorexia, hyperprolactinemia, and congenital causes for low testosterone levels are known to have lower-than-normal bone-density levels and show increased rates of bone loss (Orwoll & Klein, 1995). Bone density has not been well studied in MTF transsexuals. A bone histomorphometry investigation studying specimens obtained during SRS at a time when these men had been off estrogen therapy for one month showed no consistent state of bone remodelling (Lips, Asscheman, Uitewall, Netelenbos, et al., 1989). At the Centre for Sexuality, Gender Identity and Reproductive Health, a prospective pilot study is in progress in which dual energy X-ray absorptiometry (DXA) of the spine and hip are measured at the time of enrollment in the program. Preliminary results show osteopenia in a higher-than-expected number of transsexual men prior to any hormonal or antiandrogen therapy (Personal communication, Prior, 1996). Negative life-styles (cigarette abuse and alcohol excess) and stress-induced delayed puberty may contribute to this observation. In addition, it is not currently known whether the combination of hormones and antiandrogen therapies can prevent the bone loss that would be expected following castration in SR surgery. Medroxyprogesterone therapy is used in addition to estrogen to stimulate bone formation (Prior, 1990).

To Provide Hormonal Support during and after Surgery

The fourth objective is to provide appropriate hormonal support through the presurgical, surgical, and post-reassignment periods if surgery is an option. Concern that estrogen therapy, especially in the high doses used in some centers, may increase the risk for thromboembolic events during and following surgery has led to the decision, both in Amsterdam (Lips, Asscheman, Uitewall, Netelenbos, et al., 1989) and in our center, to discontinue estrogen one month prior to hospital admission for surgery. In our experience, however, discontinuation of all medications, as sometimes recommended by the surgeon, is associated with a regrowth of beard hair that effectively obliterates months of progress toward feminization. Our recommendation is that both MPA and

spironolactone be continued until the day of surgery and be restarted as soon as any oral therapy is possible postoperatively. Neither of these medications poses a risk for thrombosis, and this strategy appears to prevent rebound beard growth and may also help prevent increased bone turnover and potential bone loss that can occur with abrupt discontinuation of estrogen therapy (Lips, Asscheman, Uitewall, Netelenbos, et al., 1989). Estrogen is restarted when the person is fully ambulatory. Because surgeries for our patients are performed at other centers, and they experience, therefore, immobilization during long return flights, we do not resume estrogen therapy until the individual is home.

Sometimes vasomotor symptoms typical of menopause develop following surgery. Estrogen would not be appropriate initially, but medroxyprogesterone doses can be increased to treat these symptoms (Schiff, Tulchinsky, Cramer, & Ryan, 1980) until estrogen therapy is reinstituted.

There are no traditional guidelines for hormonal therapy following gender-reassignment surgery. Obviously there is decreased need for an antiandrogen once the primary source of androgens is removed. Our approach has been to gradually lower any previously pharmacologic doses of hormones into the physiological range and to discontinue spironolactone when beard growth is adequately eliminated. The plan is to continue the cyclic estrogen and continuous progestin therapy at least until the age of natural menopause in women (about 50 years). Bone density screening is appropriate prior to discontinuing hormonal therapy—if spinal bone density is low, hormonal or nonhormonal bone therapies would be needed. The long-term health risks of having neither ovarian nor testicular sex steroid production are not known.

To Prevent Complications of Estrogen Therapy

The final objective of the endocrine therapy of male-to-female transsexuals is to do no harm (Prior, Vigna, Watson, & Diewold, 1986; Prior, Vigna, & Watson, 1989). Prior to any hormonal prescription, therefore, the following health-related factors are considered:

Cardiovascular Effects From Smoking

Our guideline has been that smoking cigarettes precludes estrogen administration because both nicotine use and high-dose estrogen therapy in men increase risks for vascular disease (Coronary Drug Project Research Group, 1973). (It is simply not known whether "low-dose" estrogen increases the risk of heart disease in men.) This approach has provided the necessary motivation for smoking cessation for many of the transsexuals. In the occasional patient whose psychological problems are such that the nicotine addiction cannot be dealt with until the gender dysphoria is addressed, we

would start transdermal estrogen in low doses (usually 25 μg).

Glucose Intolerance

Glycosylated hemoglobin (HbA1C) is monitored before therapy and every 6–12 months. We have only rarely seen a significant increase, and this has been associated with weight gain related to the stress of coping with the gender dysphoria itself, usually in association with a family diabetes mellitus history.

Hypertension

Nine of 27 men assessed in the clinic, having previously been on pharmacological doses of estrogen, had elevated blood-pressure levels (Prior, Vigna, & Watson, 1989). However, because spironolactone is an antihypertensive and because we prescribe physiological doses of estrogen, we rarely create an increase in blood pressure. Those with initially elevated pressures usually become normal.

Lack of Exercise

Encouragement of a more active lifestyle is a key part of our health education. Exercise is not only known to decrease risks for cardiovascular disease (Powell, Thompson, Caspersen, & Kendrick, 1987) and osteoporosis (Pate, Pratt, Blair, Haskell, et al., 1995), but may improve sleep and sense of well-being, and prevent depression. While male-to-female transsexuals are anatomically ambivalent, however, swimming and aerobics classes can be embarrassing and are not practical forms of activity.

Hyperlipidemia

Mild to moderate elevation of cholesterol will decrease during hormonal therapy. Unfortunately, reduced high-density lipoprotein cholesterol (HDL) levels tend to remain low. Those with abnormally low HDL levels will benefit from oral micronized progesterone therapy (300–400 mg at bedtime) rather than MPA because it has no negative HDL effect (Hargrove, Maxon, Wentz, & Burnett, 1989). To pharmacologically increase HDL, oral rather than transdermal estrogen would be most effective. Hypertriglyceridemia, by contrast, requires the use of transdermal rather than oral estrogen.

Breast-Cancer Family History

Although there are epidemiological data showing an increased risk for breast cancer in menopausal women treated with estrogen (Grady, Rubin, Petitti, Fox, et al., 1992), most of these women would have been exposed to 20 to 30 years of high endogenous estrogen. In contrast, the male-to-female transsexual will have an increased breast-cancer risk only with prolonged dura-

tion of therapy (Pritchard, Pankowsky, Crowe, & Abdul-Karim, 1988). Estrogen doses are kept in the low portion of the physiological range for the MTF transsexual who has a close relative with breast cancer. A pause in estrogen administration the last five or six days in each month is prescribed to mimic the low estrogen levels during normal menstrual flow. It may decrease breast tenderness symptoms. All MTF transsexuals are taught breast self-examination to learn their individual breast nodularity so that a change could be appreciated. After 10 years of exogenous estrogen use an initial and possibly yearly mammogram is recommended.

History of Thrombotic Complications

A previous deep vein thrombosis (DVT) is not considered an absolute con-

Table 17.2. Comparison of Two Programs for Therapy of Male-to-Female Transsexuals

	Vancouver	*Amsterdam**
Years studied	1985–1995	1980–1989
Number of male-to-females in active follow-up	196	303
Mean duration (in years) of hormone follow-up	5.5	4.4
Therapy		
Mean estrogen	CEE 0.9 mg cyclically	EE 100 μg daily
Antiandrogen	Spironolactone 300 mg daily	Cyproterone a. 100 mg daily
Progestin	Medroxyprogesterone 20 mg daily	—
Percentage of Complications		
Thrombotic	1.5%	6.3%
Prolactinomas**	0	1.7%
Hyperprolactinoma (>3 times upper female nl range)	<1%	21.4%
Clinical Depression	<1%	8.3%

*as reported in Asscheman, H., Gooren, L.J., & Eklund, P.L. (1989).
**All with higher-than-normal prolactin levels were followed. None have had persistent high levels or have been screened with pituitary imaging.

traindication to estrogen therapy unless it occurred during estrogen therapy. We would prescribe transdermal estradiol cautiously, in low doses, for a transsexual person with a history of thrombosis.

Outcome in Terms of Feminization Achieved

Observed Effects of Testosterone Antagonism

The degree to which the various actions of testosterone and DHT (Table 17.1) can be eliminated or antagonized is extremely variable. Bodily *bony structure* such as stature and the shoulder and chest widths cannot be al-

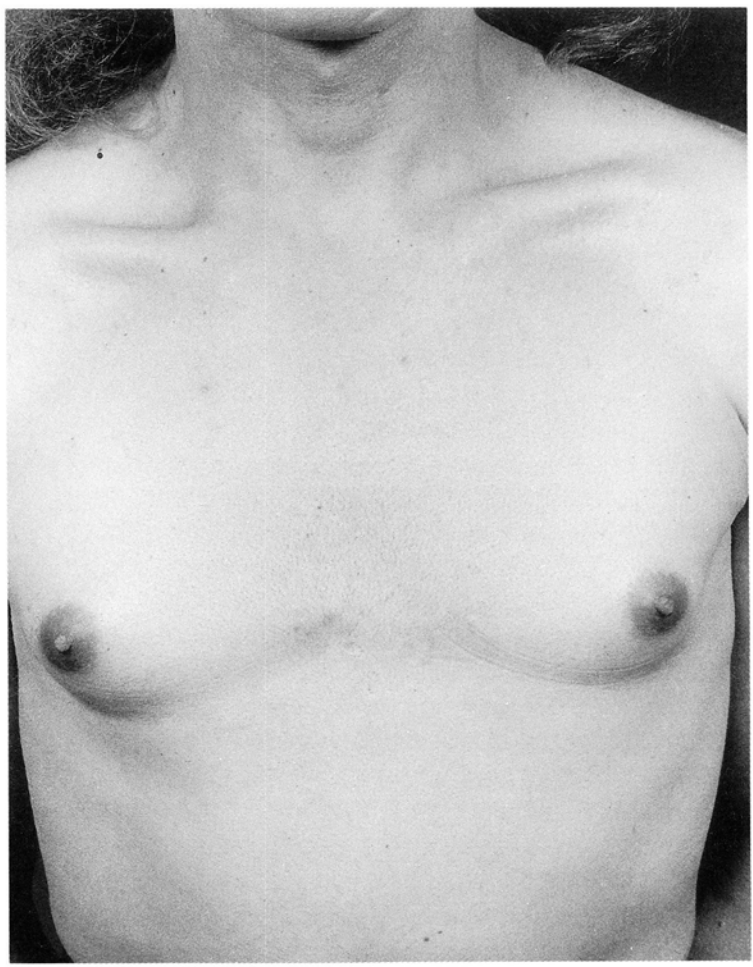


Figure 17.2. The broad chest, shoulders, and muscular neck of a biological male create a setting in which normal female breast enlargement and development may appear inadequate.

tered (Figure 17.2). Major clues to male biology may include the large sizes of hands and feet, prominence of the "Adam's apple" or laryngeal cartilage, and the angularity of nose and chin. Similarly, testosterone causes vocal-cord thickening, which leads to a *deeper voice*. This voice change is irreversible despite production of low levels of testosterone and increase in estrogen levels into the female range. Voice therapy is used in our clinic to train MTF individuals to speak with upper registers and to use female-like vocal patterns.

Fertility will be lost as sperm production ceases. The reversibility of azospermia has not been systematically assessed. Some patients may request that their semen be frozen and stored prior to beginning feminizing therapy. *Sexual function* will progressively change as the testosterone levels drop. Often desire or libido is reduced first, followed by an increased time to ejaculation, and a reduced ejaculate volume; eventually, ejaculate becomes absent. If orgasm can still be reached, it will be of reduced intensity. There is also progressive difficulty achieving and maintaining an erection. Sleep-induced erections are lost quickly, followed by the loss of sexual erections, even with self-stimulation or with partner stimulation. Some erectile capacity (usually insufficient for vaginal penetration) may persist despite low testosterone levels, especially with adequate visual stimulation, since visually induced erections are testosterone independent.

The positive early changes noticed with decreased production and ac-

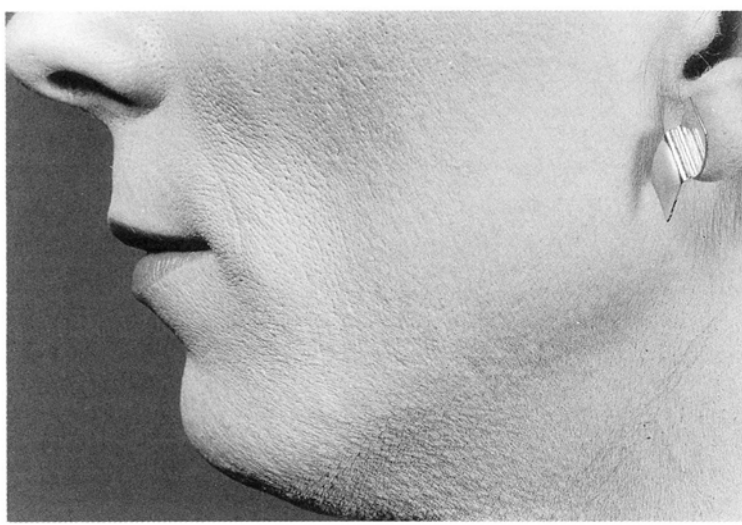


Figure 17.3. This male-to-female transsexual, who is now successfully living as a woman, had extensive electrolysis prior to the onset of anti-androgen and physiological hormonal therapy. Although beard growth is well controlled, she is left with scarring and skin changes that are difficult to cover up, even with makeup.

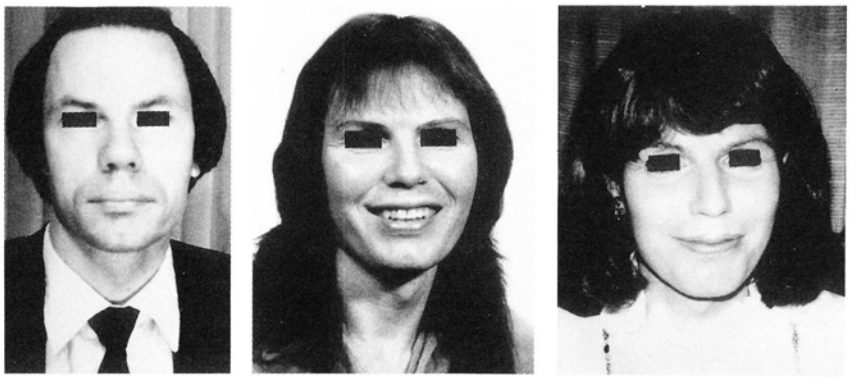


Figure 17.4. These three facial views are of the same individual in the process of gender reassignment. The high forehead with receding hairline is effectively covered by hair styling. Whether hormonal changes contribute to the subtle facial changes is unclear.

tion of testosterone are that hair softens, becomes pale, and disappears in male-pattern areas of trunk and pubic regions; and skin becomes smoother and less oily. The beard and head hair are more resistant to change. Beard hair was traditionally assumed to be nonresponsive to hormonal therapy; electrolysis alone was believed to be effective (Asscheman, 1989). When we first began the endocrine therapy of MTF transsexuals, most had undergone years of electrolysis with resulting facial scarring (Figure 17.3). However, with the combined estrogen, progestin, and antiandrogen therapy, gradually the hair is less coarse and less apparent high on the cheeks. The pattern of hair loss appears to reverse the pattern of acquisition of hair in puberty, with the last region of development being high on the cheeks. The hair on the upper lip and at the tip of the chin, which are the first hair seen during male puberty, may never disappear, even after castration. The high sensitivity of hair-cell receptors in certain regions to the little (adrenal) androgen that still circulates appears to explain the beard persistence.

Loss of hair on the temples and vertex of the scalp is only very partially reversible, perhaps because hair follicles in these regions become sclerosed or obliterated. Some soft, almost villous hair does grow back, but often the hair loss remains resistant to medical management (Figure 17.4). Styling of hair to cover a large forehead, or the use of light-weight, well-crafted hair pieces or wigs is usually effective.

Observed Effects of Estrogen & Progestin Therapy

Predicting the effects of the exogenous estrogen on sexual characteristics remains challenging. Estrogen and progesterone effect depends on appropri-

ate suppression of androgen production and action. In addition, it is unclear which typical feminine characteristics are progesterone and which are estrogen effects, since both hormones work in the same tissues, often interact at receptor levels, and are synergistic.

Redistribution of *fat onto lower abdomen and thighs and buttocks* increases continually through the years. A degree of *breast development* may begin early, even with spironolactone alone, but often 4–6 years are needed for full maturation. Being underweight or smoking seems to often prevent full breast development. Progesterone appears to be necessary for maturation of the areolae and nipples to Tanner stage 5.

Sexual function changes appear to be predominantly related to the loss of testosterone rather than to the activity of estrogen and progesterone. However, some patients report experiencing a *need for intimacy,* as opposed to sexual activity per se, associated with female hormone therapies. Changes in mood with an apparent calmness and improved sleep are also reported. Some say they experience increased sensitivity of emotions, and feel more intuitive or tolerant.

Principles of Therapy Put into Practice

To illustrate the principles outlined above, we will now illustrate with a typical story and hormonal profile, sexual function, and secondary sexual characteristics of one of our 238 evaluated persons with male-to-female gender dysphoria. "C.C." presented to the clinic in 1990 at age 40, and was diagnosed to be a high-intensity male-to-female transsexual by two psychiatrists. He had never previously received hormonal or antiandrogen therapy. He reported a life-long low sexual desire, with very few sexual thoughts or sexual fantasies, and minimal self-stimulation. He had never sought erotica (videos, magazines, etc.). His wife had been his sole sexual partner for the previous 17 years. Nocturnal erections were completely firm and lasted for several minutes. Self-stimulated erections, although rarely attempted, were also firm—ejaculation occurred after a few minutes, with a reasonable fluid volume. During intercourse with his wife, he experienced chronic and variable situational erectile dysfunction, often without orgasm or ejaculation.

Past history was normal. There was no family history of heart disease, diabetes, or osteoporosis. He lived with his wife, worked as a landscape gardener, used neither cigarettes nor alcohol, and had no regular recreational physical activity. On physical examination, he was a normal man who weighed 67 kg (148 lb.) and was 168 cm (5ft. 4 in.) tall, had minimal temporal balding, normal male-pattern body hair, and normal male genitalia.

There were no abnormalities of the respiratory, neurological, abdominal, or cardiovascular system. Blood pressure was 130/80.

At presentation, his hormonal profile was as follows:

Total testosterone	23.0	(10.4–34.7 nmol/L—male range)
FSH	8.4	(1.0–15.0 IU/L)
HDL	1.43	(0.9–1.94 mmol/L)
Total Cholesterol	7.4	(2.92–4.59 mmol/L)
Triglyceride	1.08	(0.5–2.4 mmol/L)
HbA1C	0.055	(0.043–0.062)
Prolactin	12.0	(3.0–18.0 µg/L)

Bone density of the spine was performed before hormones were given, and showed a value of 1.01 gram/cm^2, which was within one standard deviation of the young normal value. Therapy was begun with spironolactone in a dose of 300 mg/day, and later increased to 400 mg daily, CEE 0.625 mg days 1–25 of each month, and MPA 10 mg twice a day and later twice a day. During the therapy and before sex-reassignment surgery (SRS), typical values for her hormonal profile were:

Total testosterone	6.0	(0.5–3.1 nmol/L—female range)
Free testosterone	20.0	(2.5–12.0 pmol/L—female range)
HDL	1.3	(0.9–1.94 mmol/L)
Total cholesterol	5.05	(2.92–4.59 mmol/L)
Triglyceride	1.00	(0.5–2.4 mmol/L
HbA1C	0.052	(0.043–0.062)

Sexual function showed further reduction in the low sexual desire. However, she reported experiencing increased yearning to be physically intimate with a partner (but without genital stimulation or orgasm). Sexual thoughts included visualization of taking a female role in intercourse. Self-stimulation was rarely occurring. If she tried, she had difficulty reaching orgasm and the ejaculation volume was markedly diminished. In time, orgasms no longer occurred even in sleep, and the last few that occurred before self-stimulation stopped were reported as being of very low intensity. Sleep-induced erections stopped. Erections during sexual activity became soft.

Breast development gradually increased over the two and a half years of hormonal and antiandrogen therapy before surgery to Tanner stages III and IV, and bra with a B-cup. Body hair softened and was quite minimal within 1 year. Beard growth lessened significantly on the cheeks. Hair growth

on chin and upper lip had never been particularly heavy, and after 1 year, with the help of weekly electrolysis for approximately six months, she could shave carefully once a day, apply makeup skillfully, and feel and look feminine. There was some redistribution of fat to the lower abdomen, thighs, and cheeks, as well as to the breasts. Her weight remained at 68–71 kg (150–156 lb.).

After SRS, spironolactone was reduced to 200 mg daily. She rarely uses electrolysis. CEE doses are still 0.625 mg cyclically and MPA is now prescribed at 10 mg b.i.d.. A repeat bone density study one year after surgery was unchanged and normal. Her hormonal profile post SRS revealed:

Total testosterone	<0.7	(0.5–3.1 nmol/L—female range)
Free testosterone	<2.2	(2.5–12.05 pmol/L—female range)
Prolactin	10.0	(3.0–18.0 μg/L)
Total cholesterol	4.9	(2.92–4.59 mmol/L)
HDL	1.21	(0.9–1.94 mmol/L)
HbA1C	0.057	(0.043–0.062)

Sexual function following SRS was characterized by an increasing sexual desire with more sexual thoughts and fantasies (in which she is exclusively the woman with a male partner). There has not yet been any sexual activity with a partner—nor has she had any relationship during the two postoperative years. There is still minimal sexual need for self-stimulation, but this has occurred as a process of discovery related to exploring her reactions after the surgery. There is pleasant sexual arousal from both stimulation within the new vagina and stimulation to the nipples and to the amputated portion of the dorsal nerve of the penis, which is covered by a crease of skin designed to resemble a clitoral hood. There has been no orgasmic experience, even in sleep. She reports a definite progressive return of sensation to the genital area—some areas, particularly around the posterior margin of the new introitus, had seemed totally anesthetic for the first six months. She was initially concerned that the spongy tissue left around the urethra became erect when she stimulated herself. This was distressing, as it reminded her of penile swelling. This seems to have lessened, and is no longer of concern.

Program Experience and Complications

The Gender Dysphoria Program, which officially began in 1986 within the Department of Psychiatry, has always been interdisciplinary, with co-leadership from endocrinology. Over the 10 years between 1986 and 1995, 238 male-to-female transsexuals have been evaluated and treated within the endocrine program of the center. There are 196 who continue to be in active

therapy, of whom 55 have undergone sexual-reassignment surgery. (There are 42 who are inactive because they have moved away, have decided not to pursue transsexualism, were predominantly transvestitic, or had substance abuse preventing compliance with the program.) We have over 1,000 person-years of follow-up on these patients. Although this program is somewhat smaller than that reported from Amsterdam (Asscheman, Gooren, & Eklund, 1989), comparison of therapies and complications provides some assessment of the different approaches to feminization. Table 17.2 shows the characteristics of both programs. Notice that the incidence of thrombotic complications is significantly less in the Vancouver Centre. Both prolactin adenomas and hyperprolactinemia also appear to be less prevalent on the lower doses of estrogen. The apparently lower experience of depression may relate to the use of spironolactone rather than cyproterone acetate, which has depression as a potential side effect.

Thrombosis, a life-threatening complication of estrogen therapy in men (Coronary Drug Project Research Group, 1970, 1973), by inference, appears to be dose-related. Whether the incidence of thromboembolism can be lowered further by more universal use of transdermal rather than oral estrogen is worth study. None of the patients on the therapy we have outlined has experienced myocardial infarction (MI) during therapy. Over the 10 years, two patients have experienced MIs, but one was 67 years old, an alcoholic smoker with a positive family history of ischemic heart disease, and had previously received "standard" (i.e., high-dose) estrogen therapy. All estrogen was discontinued when he was first seen in the clinic in 1986. He remained on MPA and spironolactone alone, but had a fatal MI one year later. A second patient had a myocardial infarction some months after being started on spironolactone as the only medication because he was perceived to be at high risk of myocardial infarction.

The therapy we have used is effective in achieving feminization, decreasing male hormone effects, and appears to meet our goals of safety and improved quality of life. However, this report and those in the literature that have examined hormonal therapy in gender dysphoria are retrospective (except for our 1989 publication). Perhaps it is now appropriate to design and perform a multicenter, randomized, double-blind clinical trial in which feminization, hormonal levels, lipids, complications, and quality of life are prospectively and objectively documented.

Summary

Men who are true transsexuals are intensely driven to become hormonally and physically female. Supraphysiological doses of estrogen have been tra-

ditionally given in an attempt to speed the external transformation of a man into a woman.

In contrast to the usual high-estrogen hormonal treatment, this center has used an antiandrogen and nonandrogenic progestin along with physiological levels of estrogen to meet the therapy goals for men with true transsexualism. Our retrospective 10-year review of 196 active male-to-female transsexuals shows a significantly lower incidence of thrombosis, hyperprolactinemia, and depression than reported from Amsterdam's large program (Asscheman, Gooren, & Eklund, 1989). Prior to any estrogen therapy, it is important to screen for any risk factors that are relative or absolute contraindications to estrogen therapy (such as cigarette use, hypertriglyceridemia, uncontrolled hypertension, active liver disease, or a history of thromboembolic disease).

The development of a female body habitus and breasts is similar in timing and progression to changes during normal puberty—the transition needs from 4 to 5 years. Beard and male-pattern body hair also respond (slowly) to hormonal therapy—the distribution of hair loss is in reverse to its acquisition during puberty.

At present, the therapy of male-to-female transsexualism is largely empirical. This chapter has presented a review of the current scientific literature, the clinical experience in our center, and a case history to provide the rationale for our center's modified, more physiological hormonal approach to the therapy of male-to-female transsexuals.

Acknowledgments

This chapter is possible only through the support of all members of the clinic, especially Drs. Diane Watson and Oliver Robinow for psychiatric expertise, Dr. B. Anne Prestman for endocrinology, and Drs. Stacy Elliott and Marjorie Zapf-Gilje as family physician/sexual-medicine members of the endocrinology team. Special thanks to Teresa Janz for bibliographic work, to Teresa and also to Karen Smith for help with the database, to Alice Chan, RN, for dedication, conscientiousness, and support, and to Maureen Piper for her help in manuscript preparation.

References

Asscheman, H. (1989). *Cross-gender hormone treatment, side effects and some metabolic aspects.* Ph.D. Thesis, Centrale Hussdrukkerij Vrije Lemierscteit, (Amsterdam), pp. 1–113.

Asscheman, H., & Gooren, L.J. (1992). Hormone treatment in transsexuals. *Journal of Psychology & Human Sexuality, 5,* 39–54.

Asscheman, H., Gooren, L.J., & Eklund, P.L. (1989). Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism, 38,* 869–873.

Clarke, C.L., & Sutherland, R.L. (1990). Progestin regulation of cellular proliferation. *Endocrine Review, 11,* 266–301.

Coronary Drug Project Research Group. (1970). Coronary drug project: Initial findings leading to modifications of its research protocol. *Journal of the American Medical Association,* 214, 1303–1313.

Coronary Drug Project Research Group. (1973). Coronary drug project: Findings leading to the discontinuation of the 2.5 mg/day estrogen group. *Journal of the American Medical Association, 226,* 652–657.

Corrol, P., Michaud, A., Menard, J., Freifeld, M., et al. (1975). Anti-androgenic effect of spironolactone: Mechanism of action. *Endocrinology, 97,* 52–58.

de Vries, C.P., Gooren, L.J., & van der Veen, E.A. (1986). The effect of cyproterone acetate alone and in combination with ethinylestradiol on the hypothalamic pituitary adrenal axis, prolactin and GH release in male-to-female transsexuals. *Hormones, Metabolism, and Research, 18,* 203–205.

Gallagher, J.C., Kable, W.T., & Goldgar, D. (1991). The effect of progestin therapy on cortical and trabecular bone: Comparison with estrogen. *American Journal of Medicine, 90,* 171–178.

Goh, H.H., Li, X.F., & Ratnam, S.S. (1992). Effects of cross-gender steroid hormone treatment on prolactin concentrations in humans. *Gynecology and Endocrinology, 6,* 113–117.

Goh, H.H., & Ratnam, S.S. (1990). Effect of estrogens on prolactin in secretion in transexual subjects. *Sex and Behavior, 19,* 507–516.

Grady, D., Rubin, S.M., Petitti, D.B., Fox, C.S., et al. (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. *Annals of Internal Medicine, 117,* 1016–1037.

Hargrove, J.T., Maxon, W.S., Wentz, A.C., & Burnett, A.L. (1989). Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstetrics & Gynecology, 73,* 606–612.

Kovacs, K., Stetaneanu, L., Ezzat, S.D., & Smyth, H.S. (1994). Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration: A morphological study. *Archives of Pathology and Laboratory Medicine, 118,* 562–565.

Lips, P., Asscheman, H., Uitewall, P., Netelenbos, J.C., et al. (1989). The effects of cross-gender hormonal treatment on bone metabolism in male-to-female transsexuals. *Journal of Bone Mineral Metabolism, 4,* 657–662.

Meyer, W.J., Finkelstein, J.W., Stuart, L.A., Webb, A., et al. (1981). Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Archives of Sexual Behavior, 10,* 347.

Meyer, W.J., Webb, A., Stuart, C.A., Finkelstein, J.W., et al. (1986). Physical and hormonal evaluation of transsexual patients: A longitudinal study. *Archives of Sexual Behavior, 15,* 121–138.

New, M.I., & Ketzinger, E.S. (1993). Pope Joan: A recognizable syndrome. *Journal of Clinical Endocrinology and Metabolism, 76,* 3–13.

Orwoll, E.S., & Klein, R.F. (1995). Osteoporosis in men. *Endocrine Review, 16,* 87–116.

Pate, R.R., Pratt, M., Blair, S.N., Haskell, W.L., et al. 1995. Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association, 273,* 402–407.

Powell, K.E., Thompson, P.D., Caspersen, C.J., & Kendrick, J.S. (1987). Physical activity and the incidence of coronary heart disease. *Annual Review of Public Health, 8,* 253–287.

Prior, J.C. (1990). Progesterone as a bone-trophic hormone. *Endocrine Review, 11,* 386–398.

Prior, J.C., Alojado, N., McKay, D.W., & Vigna, Y.M. (1994). No adverse effects of medroxyprogesterone treatment without estrogen in postmenopausal women: Double-blind, placebo-controlled, cross-over trial. *Obstetrics & Gynecology, 83,* 24–28.

Prior, J.C., Vigna, Y.M., Barr, S.I., Rexworthy, C., et al. (1994). Cyclic medroxyprogesterone treatment increases bone density: A controlled trial in active women with menstrual cycle disturbances. *American Journal of Medicine, 96,* 521–530.

Prior, J.C., Vigna, Y.M., & Watson, D. (1989). Spironolactone with physiological female gonadal steroids in the presurgical therapy of male to female transsexuals: A new observation. *Archives of Sexual Behavior, 18,* 49–57.

Prior, J.C., Vigna, Y.M., Watson, D., & Diewold, P. (1986). Spironolactone in the presurgical therapy of male to female transsexuals: Philosophy and experience of the Vancouver Gender Dysphoria Clinic. *Journal of the Sex Information and Education Council of Canada, 1,* 1–7.

Pritchard, J.J., Pankowsky, D.A., Crowe, J.P., & Abdul-Karim, F.W. (1988). Breast cancer in a male-to-female transsexual. *Journal of the American Medical Association, 259,* 2278–2280.

Schiff, I., Tulchinsky, D., Cramer, D., & Ryan, K.J. (1980). Oral medroxyprogesterone in the treatment of postmenopausal symptoms. *Journal of the American Medical Association, 244,* 1443–1445.

Writing group for PEPI trial. (1995). Effects of estrogen and estrogen/progestin regimens on heart disease risk factors in postmenopausal women: The postmenopausal estrogen/progestin interventions (PEPI) trial. *Journal of the American Medical Association, 273,* 199–208.