CLINICAL PRACTICE

Care of Transsexual Persons

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy and successful 40-year-old man finds it increasingly difficult to live as a male. In childhood he preferred playing with girls and recalls feeling that he should have been one. Over time he has come to regard himself more and more as a female personality inhabiting a male body. After much agonizing, he has concluded that only sex reassignment can offer the peace of mind he craves. What would you advise?

THE CLINICAL PROBLEM

Gender identity is the sense one has of being male or female.[1,2] A significant incongruence between gender identity and physical phenotype is known as gender identity disorder; the experience of this state, termed gender dysphoria,[1] is a source of chronic suffering. Manifestations of gender identity disorder range from simply living as a member of the opposite sex to partial or maximal physical adaptation through hormonal and surgical treatment. For most transsexuals (about 66%), the disorder has an early onset, in childhood; for the remainder, it develops much later in life.[3] For this older group of patients, usually men, the transition to a new sex from one they have lived in for many years is particularly difficult.[4]

Traditionally, gender identity disorder has been viewed as a psychiatric condition, and it will probably retain its classification as such in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (Table 1).[3,4] However, a substantial proportion of the transgender population does not have a clinically significant coexisting psychiatric condition,[2] and sex reassignment benefits this group.[5,6]

The cause of gender identity disorder is unknown. Postmortem studies of small numbers of male-to-female transsexuals have shown a typically female pattern of sexual differentiation in two areas of the brain — the bed nucleus of the stria terminalis and the hypothalamic uncinate nucleus[7] — suggesting that gender identity disorder may be a sexual differentiation disorder affecting the brain.[8,9] Gender identity disorder cannot be explained by variations in chromosomal patterns or identifiable hormonal abnormalities.[8] Nor is there convincing evidence that psychological factors (being exposed to certain family dynamics or being raised as a member of the opposite sex) cause this condition.[10] The diagnosis relies on assessment by a mental health professional according to the criteria specified in the fourth edition (text revision) of the DSM (DSM-IV-TR)[4] (Table 1) and elaborated in clinical practice guidelines from the Endocrine Society.[11]

The estimated prevalence of adult transsexualism in the Netherlands has been stable over time, at a rate of 1 case per 11,900 men and 1 per 30,400 women[12]; similar or lower rates have been reported elsewhere. Estimates of the prevalence in North America are less precise, but the number of persons seeking help for gender identity disorder in North America has recently increased.[13] Among trans-

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Table 1. Diagnostic Criteria for Gender Identity Disorder.*

Strong and persistent cross-sex identification (not merely a desire for any perceived cultural advantages of being the other sex)
Children (at least four criteria must be met)
Repeatedly stated desire to be a member of the other sex or insistence on actually being a member of the other sex
In boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypically masculine clothing
Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being a member of the other sex
Intense desire to participate in the stereotypical games and pastimes of the other sex
Strong preference for playmates of the other sex
Adolescents and adults (at least one criterion must be met)
Stated desire to be of the other sex
Frequent attempts to pass as the other sex
Desire to live or be treated as the other sex lives or is treated
Conviction of having the typical feelings and reactions of the other sex
Discomfort with original sex or sense of inappropriateness in the role of that sex
Children (at least one criterion must be met)
In boys, assertion that penis or testes are disgusting or will disappear, assertion that it would be better not to have a penis, or aversion to rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will have a penis, assertion that she does not want to have breasts or menstruate, or marked aversion to normative feminine clothing
Adolescents and adults (at least one criterion must be met)
Preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics and simulate the other sex) or belief in having been born with the wrong sex
No concurrent physical intersex condition
Clinically significant distress or impairment in social, occupational, or other important areas of functioning

* These criteria were adapted from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (fourth edition, text revision).[4]

sexual adults, a male:female ratio (according to original sex) of 3:1 is common throughout the Western world[12] but not elsewhere (e.g., Japan and Serbia).[14,15] A male preponderance is also noted before puberty, but gender identity disorder in children often resolves, and in adolescents the ratio is closer to 1:1.[16,17] The subsequent increase in the male:female ratio is explained by the higher frequency of men with late-onset gender identity disorder.[12] Transsexualism after early puberty is generally an unalterable condition.[5,16]

STRATEGIES AND EVIDENCE

GENERAL PRINCIPLES OF TREATMENT

Professional acceptance of transsexualism and its hormonal and surgical treatment has grown. Interventions are indicated only after comprehensive psychological assessment has confirmed not only that the DSM diagnostic criteria have been fulfilled but also that the patient meets the criteria for readiness to make the transition to the other sex (as detailed below).[11]

Persons with gender identity disorder may have unrealistic expectations about what being a member of the opposite sex entails.[1,11] Hormonal treatment should therefore be preceded and accompanied by an extended period (at least 1 year) during which the patient lives full time as a person of the desired sex. This real-life experience is essential for providing insight into the new sex status, allowing the patient to become accustomed to the social interactions arising from it.[1,11] Such sex reassignment, by enabling the patient to experience life as a person of the subjectively appropriate sex, reduces gen-

der dysphoria and improves social and sexual functioning.[2,18]

HORMONAL SEX REASSIGNMENT

The goals of hormonal treatment are to induce the development of the secondary sex characteristics of the new sex and to diminish those of the natal sex.[11] Prior hormonal effects on the skeleton and vocal cords cannot be reversed. No randomized trials have been conducted to determine the optimal formulations and dosages of cross-sex hormones. Treatment strategies resemble those used for hypogonadal patients[11] (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Male-to-Female Transsexuals

Hormonal therapy is prescribed for male-to-female transsexuals to induce breast formation and a more female distribution of fat and to reduce male-pattern hair growth.[19] To achieve these goals, the biologic action of androgens must be almost completely neutralized. Administration of estrogens suppresses gonadotropin output and therefore androgen production, but combining this treatment with a progestational agent, a gonadotropin-releasing-hormone (GnRH) analogue,[20] or other medications that suppress androgen action (e.g., cyproterone acetate, flutamide, nilutamide, or bicalutamide) appears to be more effective.[21]

Many estrogens are available. Ethinyl estradiol, although efficacious, should be avoided. When taken at the dosages required for sex reassignment, this agent has been associated with significantly increased risks of venous thrombosis[22] and death from cardiovascular causes,[23] as compared with 17β-estradiol.

Although progestins suppress androgen production, they have no role in the feminization of the body and may have harmful metabolic effects; consequently, progestins should be discontinued after orchiectomy.[24] In postmenopausal women, progestins combined with estrogens increase the risk of breast cancer.[25] Men undergoing androgen-deprivation treatment for prostate cancer are at increased risk for features of the metabolic syndrome.[26] Studies assessing the metabolic effects of androgen deprivation and estrogen therapy in male-to-female transsexuals have shown that increases in visceral fat are associated with increases in triglyceride levels, insulin resistance, and blood pressure.[27,28] Available data from one large practice with a median follow-up of 18.5 years have not suggested an increased risk of death from cardiovascular causes with treatment[21,23] except among current users of ethinyl estradiol. Data from larger and longer-term studies are not available.[29] The effects of treatment are listed in Table 2.

Female-to-Male Transsexuals

Treatment in female-to-male transsexuals is intended to induce virilization.[11] This includes male-pattern hair growth,[19] the development of male physical contours, and the cessation of uterine bleeding. The principal hormonal treatment is a testosterone preparation (Table 1 in the Supplementary Appendix). Concomitant progestin therapy is nearly always needed when testosterone is administered transdermally, since serum testosterone levels are lower with transdermal administration than with intramuscular administration, lessening suppression of gonadotropins.

Long-Term Treatment

After sex-reassignment surgery, including gonadectomy, hormonal therapy must be continued.[11,21] Some male-to-female transsexuals continue to have male-pattern hair growth; continued administration of antiandrogens, typically at only about half the preoperative dose, reduces male-pattern hair growth. Continued administration of cross-sex hormones is required to avoid symptoms and signs of hormone deficiency, such as vasomotor symptoms and, in particular, osteoporosis. Observational studies have shown that bone mass is generally maintained with estrogen alone in male-to-female transsexuals and with testosterone alone in female-to-male transsexuals when prescribed at the doses typically used to treat hypogonadism.[30] Sufficient intake of calcium and vitamin D is also recommended. A blood concentration of serum luteinizing hormone in the normal range is a reliable marker of adequate dosing. If sex-reassignment surgery has taken place, the usual prescribed dose of estradiol in male-to-female transsexuals is approximately 50 μg per day and that of testosterone in female to-male transsexuals is typically the same as that used preoperatively: 200 to 250 mg every 2 weeks in parenteral form or 5 to 10 g per day in gel form.[30] Table 2

lists the potential side effects of sex steroids and recommendations for monitoring.

Risks and Contraindications

A serious concern regarding long-term administration of cross-sex hormones is the possibility of an increased risk of hormone-dependent cancers.[31] There are rare case reports of prolactinomas, breast cancers, and prostate carcinomas in male-to-female transsexuals and rare reports of ovarian carcinoma, breast cancer, and vaginal cancer (one each of the latter two, to my knowledge) in female-to-male transsexuals.[31] Rare cases of hormone-dependent tumors in organs other than the reproductive organs (e.g., lung, colon, and brain [meningioma]) have also been reported in transsexuals who have undergone estrogen treatment.[31] Evidence is lacking to indicate a significantly increased frequency of cancers in association with cross-sex hormonal treatment, but the available data are from studies that involved relatively short-term exposure. Risks may become more apparent as subjects age and the duration of hormone exposure increases.[31] Because a portion of administered testosterone is aromatized to estradiol, female-to-male transsexuals who have not undergone breast removal and oophorectomy–hysterectomy should be monitored for estrogen-sensitive cancers of the breast, endometrium, and ovaries.[31] Although the addition of a progestin may help to prevent endometrial cancer, studies of postmenopausal hormone use suggest that this therapy may increase the risk of breast cancer.[25,32] It has also been reported that testosterone may contribute to the development of breast[33] and endometrial[34] cancer; therefore, monitoring of female-to-male transsexuals for such cancers is also prudent. Transsexuals may not always be forthright with physicians about their sex change, and this hesitancy can lead to delays in diagnosing cancers of organs specific to the former sex.

Table 2. Recommendations for Clinical Assessment and Follow-up during Treatment with Cross-Sex Hormones.

Male-to-female and female-to-male transsexuals
Rule out or treat coexisting conditions; address possible overdose of cross-sex hormones, substance abuse, depressive disorders
Measure bone mineral density and assess for osteoporosis at baseline with the use of dual energy x-ray absorptiometry (DEXA), repeating every 1 or 2 yr thereafter if additional risk factors develop or patient stops taking hormones; determine whether there is a personal or family history of osteoporosis (prior fractures); prescribe dosages of sex hormones that are adequate to preserve bone mineral density achieved in male-to-female transsexuals with estrogen administration and in female-to-male transsexuals with aromatization of testosterone to estrogen; use the eugonadal range of serum luteinizing hormone as an indicator of hormonal dosing adequacy
Determine whether there is a personal or family history of cardiovascular disease (combined use of estrogens and antiandrogens may increase serum levels of triglycerides, and the use of androgens may lower serum levels of high-density lipoprotein cholesterol); at follow-up, repeat measurements of body-mass index, blood pressure, and serum levels of lipids, fasting glucose, glycated hemoglobin, and liver enzymes; weight gain is typical. The metabolic syndrome or nonalcoholic fatty liver disease may develop as a result of the combination of androgen deprivation and estrogen treatment
Male-to-female transsexuals
Measure serum levels of prolactin annually to screen for prolactinoma, particularly in patients receiving high-dose estrogens
Examine breasts to detect any tumors; follow general guidelines for breast cancer screening
Examine prostate and consider measurement of prostate-specific antigen level in elderly patients, particularly those with a family history of prostate cancer; follow general guidelines for prostate cancer screening
Female-to-male transsexuals
Obtain red-cell count to assess for erythrocytosis, which is usually related to circulating testosterone levels but can also be idiosyncratic
Measure serum levels of liver enzymes
If there has been no surgical sex reassignment, examine breasts, vagina, ovaries, and uterus for cancer

SURGICAL SEX REASSIGNMENT

Male-to-female sex reassignment involves the surgical construction of a neovagina, with the penile skin or colon usually used for vaginal lining and scrotal skin used for the labia.[35] The breasts may be augmented if their development is judged to be insufficient. Masculine facial features and a prominent Adam's apple may also be surgically mitigated.

Female-to-male sex reassignment should ideally include removal of the breasts, uterus, and ovaries because the development of cancer in these organs is not easily detected.[31] In rare instances, the clitoris becomes sufficiently hypertrophied after testosterone exposure to serve as a phallus. Otherwise, the patient can undergo a metoidioplasty (see Fig. 2 in the Supplementary Appendix), which involves elongation and reconstruction of the clitoris as a small neopenis with erectile function,[36] sometimes allowing urination in a standing position. Free flaps of tissue removed from the arms or legs can be used to construct a neophallus.[37] Procedures have been developed to provide rigidity for penetration, including insertion of autologous cartilage or bone, rigid implants, or an inflatable prosthesis, but these procedures, and their outcomes, remain cumbersome. A scrotum can be constructed from the labia majora along with implantation of a testicular prosthesis. The aesthetic results of surgery depend largely on surgical skill.

Surgical treatment improves the overall quality of life for most transsexual persons. However, 1 to 2% of those who have undergone surgical sex reassignment regret it,[38] the majority being men with late-onset transsexuality. Determining eligibility for hormonal and surgical treatment is more complex with these patients than it is with those who have early-onset transsexuality. When regrets occur, they may reflect difficulties in making the transition to a different lifestyle because of appearance or limited social skills. These problems appear to be more common in patients with late-onset transsexuality, who have lived in their natal sex for a long time, underscoring the importance of actually living as the other sex before undergoing cross-sex surgery.

JUVENILE GENDER DYSPHORIA

Over the past two decades, awareness of gender identity disorder in children and adolescents has grown.[10,16] Although most juveniles with gender identity disorder are otherwise psychologically healthy, certain forms of psychiatric conditions may be present (most commonly anxiety, mood, and disruptive disorders) and can complicate accurate diagnosis and assessment of eligibility for treatment.[3,5,39] Gender identity disorder must be distinguished from conditions also associated with feelings of being different (e.g., extreme transvestic fetishism and autism spectrum disorders).[39,40] As a rule, only extreme cases of gender identity disorder persist into adolescence and beyond. An experience of the first somatic signs of hormonal puberty as alienating is diagnostically significant and a marker that that the gender identity disorder will probably persist.[41]

If diagnostic criteria for gender identity disorder are met in adolescence,[3,39] development of secondary sex characteristics may be suspended with the use of GnRH analogue treatment alone.[11] This intervention is reversible and allows time for reflection on the desire to undergo sex reassignment while pubertal development is halted.[11,42] Although correct diagnosis requires that the first signs of physical puberty be allowed to emerge, GnRH analogue administration should begin before it is too late to reverse the process. This is possible during stage B3 (breast bud extending beyond areola) in girls and during stage G3 (increase in testicular volume of ≥4 ml, with measurable nocturnal testosterone values) in boys.[42] Once daytime testosterone production commences (testicular volume ≥10 ml), virilization becomes irreversible.[43] For the duration of GnRH analogue administration, increases in bone mass cease, but there is typically no loss.[42] The goal of treatment is the same as that for the treatment of precocious puberty — returning hormone levels to prepubertal levels.[44]

GnRH analogues are expensive and progestins offer an alternative treatment that also suppresses gonadotropin secretion. In addition, the use of antiestrogens in girls and antiandrogens in boys delays the progression of puberty, although neither class of agents is as effective as GnRH analogues.[44]

If the follow-up diagnostic process confirms the diagnosis of gender identity disorder and the well-being of the patient increases with the cessation of pubertal development, cross-sex hormones may be added in a stepwise fashion in accordance with the treatment protocols for hypogonadal children.[11] The addition of cross-sex hormones usually begins at the age of legal medical competence (16 years of age in most Western countries). Parental agreement may be required, but even if it

is not, parental support is of paramount importance. Follow-up should include anthropometric measurements, assessment of bone mineral density and metabolic measures (e.g., lipid and glucose levels and bone turnover), psychometric testing, and ongoing counseling.

Limited observational data from juvenile transsexuals have indicated that gender dysphoria is reduced[45] and relationships and academic skills are improved[5,46] after early treatment for sex reassignment. Beginning treatment at the time of puberty appears to be associated with better outcomes (e.g., in psychopathologic scores) than beginning in adulthood, by which time irreversible sex characteristics may pose lifelong barriers to successful sex reassignment.[16,17,46,47]

AREAS OF UNCERTAINTY

Although several studies have shown amelioration of gender dysphoria and improvements in social and sexual functioning in transsexuals who have undergone sex reassignment, none have conclusively demonstrated that medical interventions resolve gender dysphoria.[2,5,6] Comparative studies are lacking to inform decision making regarding regimens and dosing of cross-sex hormones. Recommendations for management are based on expert opinion[11]; studies of the efficacy and safety of hormone preparations are lacking, as are dose–response studies of sex hormone preparations. Large, long-term studies are needed to provide data on the long-term risk of disease,[21,29,48] especially for cardiovascular disease[21] and cancer,[31] which are of particular concern in older patients and in those who have had prolonged exposure to sex hormones. Data are also needed on how the administration of GnRH analogues followed by cross-sex hormonal treatment affects pubertal development.[42] Unresolved questions are whether there is an age at which cross-sex hormonal treatment should be discontinued[21] and whether hormone replacement should be avoided in older male-to-female transsexuals.

GUIDELINES FROM PROFESSIONAL SOCIETIES

Guidelines for the treatment of transsexuals have been formulated by the World Professional Association for Transgender Health and are published in its 2001 report, *Standards of Care for Gender Identity Disorders*.[1] These guidelines have been elaborated, with a special focus on cross-sex hormones, in the most recent guidelines from the Endocrine Society.[11] The recommendations in this review are consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The person described in the vignette has gender dysphoria that is probably consistent with a diagnosis of gender identity disorder. The diagnosis must be verified by an experienced mental health professional, with attention to eligibility and readiness for sex reassignment. The patient needs to understand that sex reassignment brings relief of gender dysphoria only — other psychological problems may remain. Expectations about physical appearance and life after sex reassignment must also be realistic. Because real-life experience is indispensable, a prerequisite for surgical sex reassignment is at least a year of experience living entirely as a member of the new sex, with complete habituation to the new behaviors and to the responses of others. Patients who follow this procedure rarely have regrets after sex reassignment.

Persons undergoing sex reassignment can be reassured that serious short-term complications of cross-sex hormonal treatment appear to be uncommon.[21,49] However, longer-term effects on the risks of cardiovascular disease, metabolic disease, and cancer are not well charted.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

Supplement to: Gooren LJ. Care of transsexual persons. N Engl J Med 2011;364:1251-7.

Supplemental Appendix

Figures: Courtesy of Dr Stan Monstrey, Gent, Belgium

Figure 1: Surgical construction of a neovagina, using the penile skin or colon for vaginal lining and scrotal skin for the labia[35].

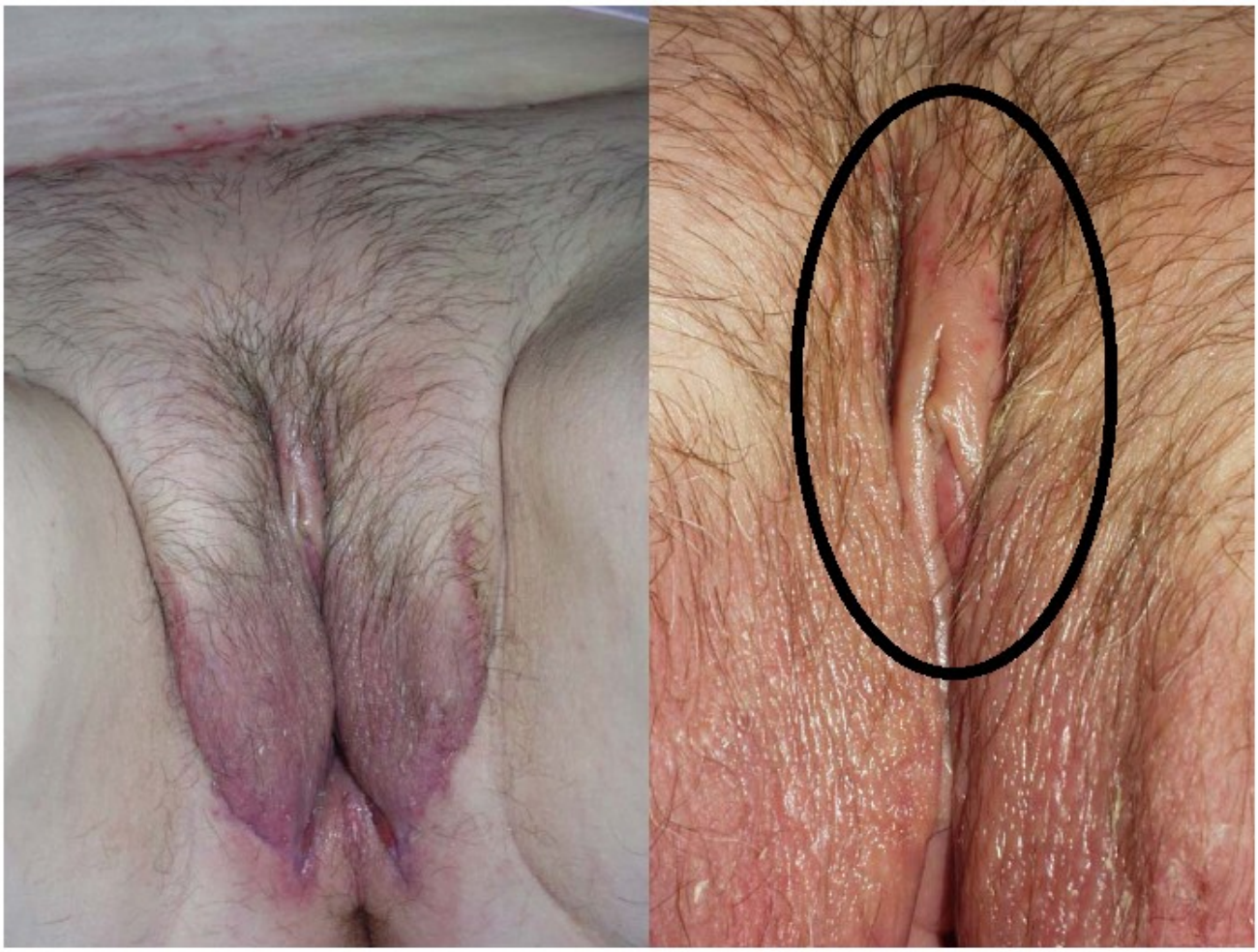


Figure 2: Metaidoioplasty involving elongation and reconstruction of the clitoris as a small neopenis with erectile function, sometimes allowing urination in a standing position. Surgical construction of a neoscrotum with use of the labia majora[36]

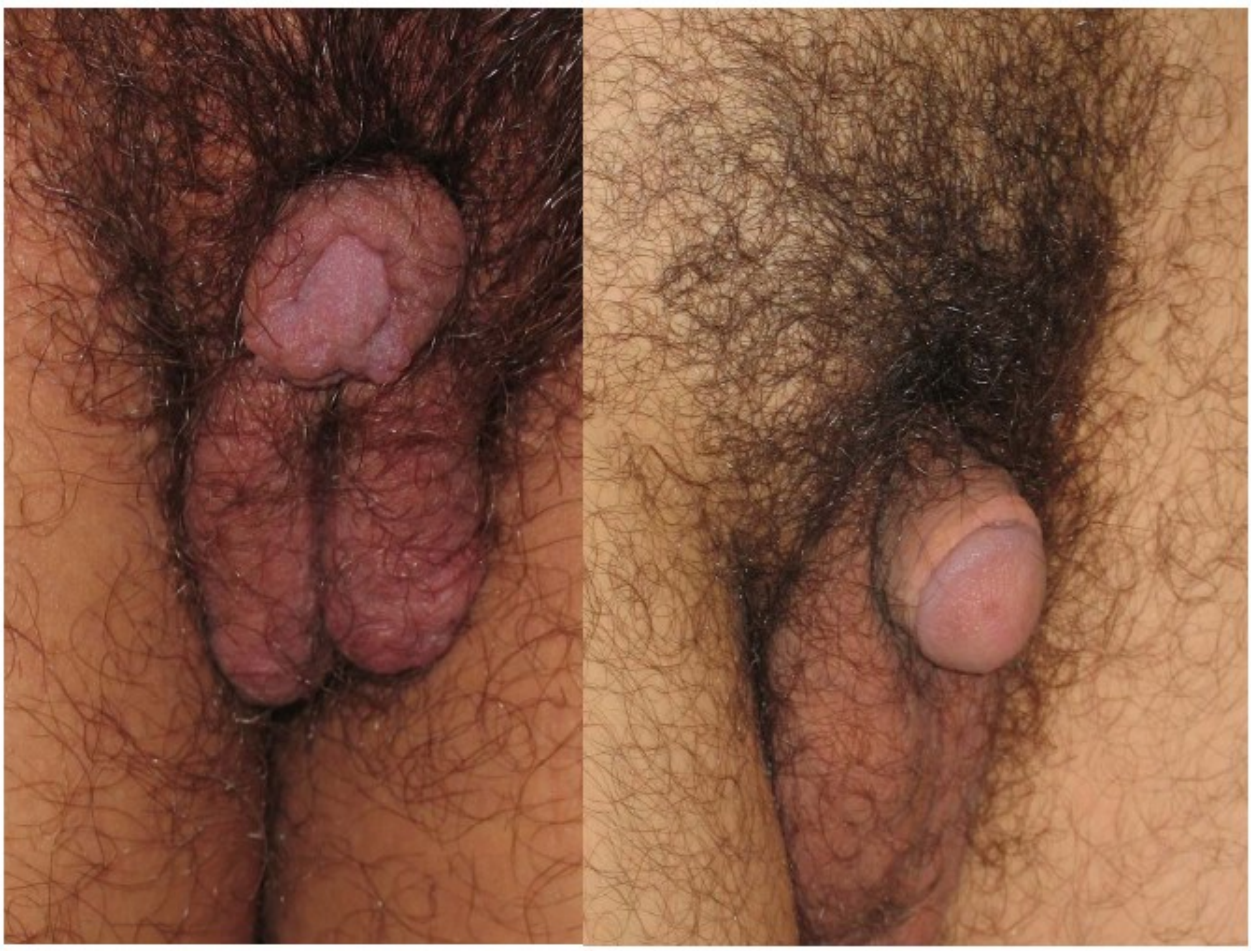
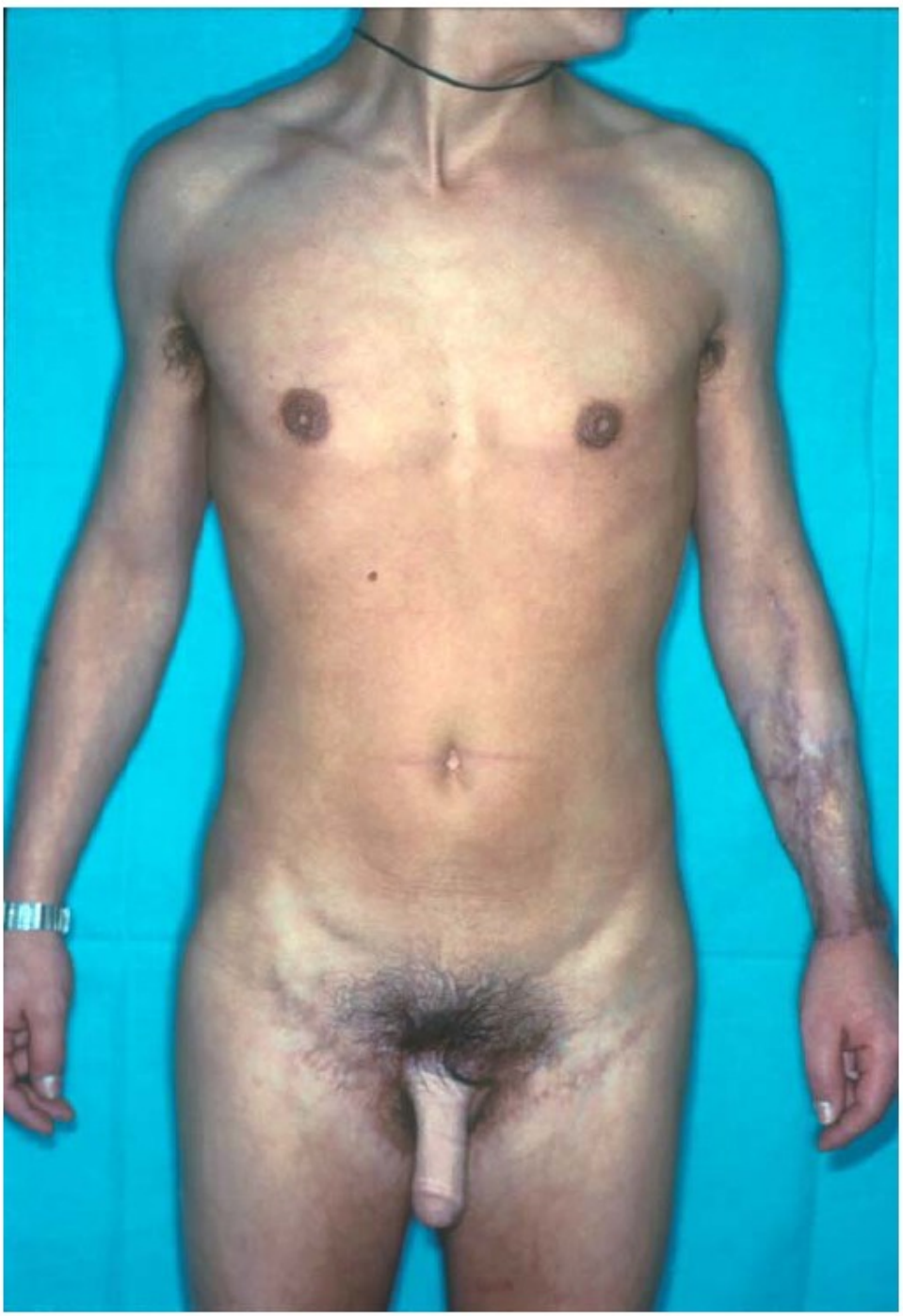


Figure 3: Surgical construction of a neophallus from pedicled flaps or free flaps removed from arms or legs. This surgical option allows for urination while standing. Surgical construction of a neoscrotum with use of the labia majora[37]



Supplemental Table 1. Cross-sex hormone administration to transsexuals		
Male-to-female transsexuals	Effects	Side effects/Contraindications
1) Drugs suppressing testosterone levels and/or testosterone action		
Cyproterone acetate 50 mgs twice daily (not available in the USA), or alternatively, medroxyprogesterone acetate, 5 to 10 mg/day.	Reduction of sexual hair, mainly on trunk, less so on face; cosmetic removal of facial hair also often necessary; minimal regrowth of hair in alopecia androgenetica	Reduced activity of sebaceous glands with dry skin and brittle nails. Hot flashes with GnRHa, less so with pure non-steroidal antiandrogens
GnRH analogues Suppression of serum testosterone levels should be to the female range (<50 ng/dL).		
Non-steroidal pure antiandrogens: flutamide 250 mg twice daily, nilutamide 150 mg twice daily, or the more recent bicalutamide 50 mg once daily (fewer side effects)		
Spironolactone 100 mg twice daily, blood minerals to be monitored		
5alpha-reductase inhibitors: finasteride 5 mg/day		
2) Estrogens		
Oral: estradiol valerate 2 mg twice daily, estradiol hemihydrate 2 mg twice daily, ethinyl estradiol 50 microgram twice daily (not advised due to risk of venous thrombosis/cardiovascular disease)	Breast formation: starting some weeks after initiation of treatment, reaching maximum potential after 2 years; breast augmentation appropriate in about 50% of cases; occasionally galactorrhea Feminized body fat distribution; in cases of weight gain also increase of visceral fat	No feminization of voice, speech training recommended; surgical shortening of vocal cords impairs range and modulation of voice Migraine Possible risk of breast or other estrogen dependent cancers Contraindications: mutations in the BRCA1/2 gene or strong family history of breast cancer; lactotroph adenoma (not microprolactinomas); cardiovascular disease, thromboembolic disease, poorly controlled diabetes mellitus, active liver disease, obesity (relative contraindication)
Transdermal patch: estradiol hemihydrate 50-100 microgram / 24 hours		
Parenteral: estradiol valerate/cypionate 5-10 mg / 2 weeks		
Serum estradiol should be maintained at the mean daily level for premenopausal women (~200 ng/mL)		

Female-to-male transsexuals	Effects	Side effects
1) Testosterone preparations		
Transdermal testosterone: testosterone gel 1%, 5-10 mg/day Parenteral testosterone: testosterone enanthate or cypionate 200-250 mg / 2 weeks, testosterone undecanoate 1000 mg /12 weeks (in the USA 750 mg / 10 weeks) Oral testosterone undecanoate 40 mg (not available in the USA) 2-3 capsules twice daily (not recommended) Aiming at serum testosterone values in the normal male range (320 – 1000 ng/dL	Increase in sexual hair growth; increase in muscle mass; redistribution of body fat with visceral fat accumulation in cases of weight gain. Breaking of voice after 8-16 weeks of androgen treatment. Cessation of menstrual bleeding, sometimes requiring addition of a progestin to androgen treatment. Increased libido	in 50% alopecia androgenetica, largely determined by genetic/racial factors. Increase in activity of sebaceous gland resulting in skin oiliness and acne, often on the back and shoulders. Vaginal atrophy/dryness, occasionally increase of secretion through aromatization of androgens to estrogens. Decrease in HDL-lipoprotein. Polycythemia. Risk of development of breast, ovaries and endometrium cancer in non-operated subjects Relative contraindications: cardiovascular disease, thromboembolic disease, poorly controlled diabetes mellitus, and active liver disease, obesity
2) Progestins		
Lynestrenol 5-10 mg/day	stop uterine bleeding	Decrease of HDL-lipoprotein, possible increased risk for breast cancer
Medroxyprogesterone oral 5-10 mg/day		