Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline

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An Endocrine Society
Clinical Practice Guideline

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Co-sponsoring Associations:
European Society of Endocrinology (ESE), The World Professional Association for Transgender Health (WPATH), Lawson Wilkins Pediatric Endocrine Society (LWPES)

This adolescent care-specific version of the original document (which included adult care guidelines) focuses on information relating to endocrine treatment of transsexual adolescents and is intended for use by families, youth and their medical providers. The adolescent-specific content is identical to the original document.

In some instances the TransActive staff provides an opinion (clearly defined as such and highlighted in purple) with regard to recommendations or conclusions stated in this Guideline.

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The Endocrine Society

Founded in 1916, The Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Society works to foster a greater understanding of endocrinology amongst the general public and practitioners of complementary medical disciplines and to promote the interests of all endocrinologists at the national scientific research and health policy levels of government.

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In August of 2006, TransActive founder Jenn Burleton realized that a gap existed not only in services offered to trans and gender non-conforming children, youth and their families, but more significantly, that children were being left out of the struggle for transgender rights, respect and inclusion. She realized that while online support groups are a valuable resource for parents, the "real world" invisibility of trans/gender non-conforming children and youth has not really changed much in the decades since she was herself, a transgender child.

TransActive has since grown into a diverse and motivated team, working together to provide these amazing children and youth a present and future in which they can achieve their dreams and express their individuality.

Vision

***E**very child and youth has a right to freely express their gender identity as they experience it.*

***F**amilies deserve access to accurate and supportive information regarding gender identity development and expression.*

***Y**outh should be assisted in experiencing pubertal development that is congruent with their gender identity, if they so desire.*

***T**ransgender and gender non-conforming identity in children and youth is no less authentic than cisgender identity.*

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Introduction

Men and women have experienced the confusion and pain resulting from simplistic, forced conformity to sexual dimorphism throughout recorded history. Aspects of gender variance have been part of biological, psychological, and sociological debates amongst humans in modern history. The twentieth century marked the beginning of a social awakening for men and women whose bodies imprisoned them in the wrong gender. Harry Benjamin and Magnus Hirshfeld, who met in 1907, pioneered the medical responses to those who sought relief and resolution of their torment, enabling the "transsexual," a term coined by Hirshfeld in 1923, to live a gender- appropriate life, occasionally facilitated by surgery.

Endocrine treatment of transsexual persons (note: In the current psychiatric classification system, the Diagnostic and Statistical Manual of Mental Disorders-IV-TR, the term *gender identity disorder* is used instead of *transsexualism* [APA, 2001]), previously limited to ineffective elixirs, creams, and implants, became reasonable with the availability of diethylstilbesterol in 1938 and following the isolation of testosterone in 1935. Personal stories of role models, treated with hormones and sex reassignment surgery, appeared in the press during the second half of the twentieth century. The Harry Benjamin International Gender Dysphoria Association (HBIGDA) was founded in September 1979; it is now known as the World Professional Association of Transgender Health (WPATH). The Association's "Standards of Care" was first published by HBIGDA in 1979 and its sixth edition is currently being revised. These carefully prepared documents have provided mental health and medical professionals with general guidelines for the evaluation and treatment of transsexual persons.

Prior to 1975, few peer- reviewed articles were published concerning endocrine treatment of transsexual persons. Since that time, more than 800 articles about various aspects of transsexual care have appeared. It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience that will enable endocrinologists to provide safe and effective endocrine treatment for individuals diagnosed with gender identity disorder (GID) or transsexualism by mental health professionals. In the future, rigorous evaluation of the effectiveness and safety of endocrine protocols is needed. What will be required is the careful assessment of 1) the effects of prolonged delay of puberty on bone, growth and development upon adolescents, 2) in adults, the effects on outcome of both endogenous and cross-sex hormone levels during treatment, 3) the requirement for and the effects of anti-androgens and progestins during treatment, and 4) long-term medical and psychological risks of sex reassignment. These needs can be met only by a commitment of mental health and endocrine investigators to collaborate in long-term, large-scale studies across countries that employ the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools.

Terminology and its use vary and continue to evolve. Table 1 (pg. 24) contains definitions of terms as they are used throughout the Guideline.

Abstract Objective: To formulate practice guidelines on the endocrine treatment of transsexual patients.

Participants: An Endocrine Society appointed Task Force of experts, methodologist, and medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence, which was generally low or very low.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society, European Society of Endocrinology, The World Professional Association for Transgender Health (WPATH), and Lawson Wilkins Pediatric Endocrine Society reviewed and commented on preliminary drafts of these guidelines.

Conclusions: Transsexual persons seeking to develop the physical characteristics of the appropriate gender require a safe and effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and 2) maintain sex hormone levels within the normal range for the person's gender. A mental health professional (MHP) must recommend endocrine treatment and participate in the ongoing care throughout the endocrine transition. The endocrinologist must confirm the diagnostic criteria the MHP used to make this recommendation and collaborate with the MHP in making the recommendation for surgical sex reassignment.

We recommend treating transsexual adolescents (Tanner stage 2) with suppression of puberty with GnRH analogues until age 16 years old, only after which time cross-sex hormones may be given. We suggest suppression of endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and surveillance for known risks and complications in adult transsexual persons.

TransActive disagrees that cross-sex hormones should be given only after 16 years of age. We recommend that cross-gender hormones should be available a maximum of 2 years after the onset of Tanner 2 pubertal suppression assuming the youth desires them and there are no medical contraindications.

The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence.

In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2.

Cross-filled circles indicate the quality of the evidence, such that ⊕OOO denotes very low quality evidence; ⊕⊕OO low quality; ⊕⊕⊕O moderate quality; and ⊕⊕⊕⊕ high quality.

The Task Force has confidence that patients who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the patient's circumstances, values, and preferences to determine the best course of action.

Summary of Recommendations

1.0 DIAGNOSTIC PROCEDURE *(see pg. 7)*

1.1 We recommend that the diagnosis of gender identity disorder (GID) be made by a mental health professional. For children and adolescents the mental health professional should also have training in child and adolescent developmental psychopathology. (1|⊕⊕OO)

1.2 Given the high rate of remission of GID after the onset of puberty, we recommend against a complete social role change and hormone treatment in pre-pubertal children with GID. (1|⊕OOO) →

1.3 We recommend that physicians evaluate and ensure that applicants understand the reversible and irreversible effects of hormone suppression (e.g., GnRH analogue treatment) and cross-sex hormone treatment before they start hormone treatment. (1|⊕OOO)

1.4 We recommend that all transsexual individuals be informed and counseled regarding options for fertility prior to initiation of puberty suppression in adolescents and prior to treatment with sex hormones of the desired sex in both adolescents and adults. (1|⊕⊕⊕O) *(see pg. 7)*

1.2
TransActive strongly disagrees with both the statement and recommendation in 1.2

By referencing "complete social role change" and "hormone treatment in pre-pubertal children" in the same sentence, the Task Force implies that one necessarily follows the other.

TransActive fully supports social gender role change for children and youth who have exhibited an expressed desire for such and who fall within the "persistent" and "consistent" diagnostic criteria.

2.0 TREATMENT OF ADOLESCENTS *(see pg. 8)*

2.1. We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development. (1|⊕OOO) *(see pg. 8)*

2.2. We recommend that suppression of pubertal hormones start no earlier than Tanner stages 2-3 and when girls and boys exhibit pubertal levels of estradiol and testosterone, respectively. (1|⊕⊕⊕O) *(see pg. 8)*

2.3. We recommend GnRH analogues be used to achieve suppression of pubertal hormones. (1⊕⊕OO) *(see pg. 9)*

2.4. We suggest that pubertal development of the desired, opposite sex be initiated at about the age of 16 years, using a gradually increasing dose schedule of cross-sex steroids. (2|⊕OOO) *(see pg. 10)* →

2.5. We recommend referring hormone-treated adolescents for surgery when 1) the real life experience has resulted in a satisfactory social role change, 2) the individual is satisfied about the hormonal effects, and 3) the individual desires definitive surgical changes (1⊕OOO) →

2.6 We suggest deferring surgery until the individual is at least 18 years old. (2⊕OOO). *(see pg. 11)*

2.4
As stated on page 3, TransActive disagrees that cross-sex hormones should be given only after 16 years of age.

2.5
It is our experience that all three of these criteria are often achieved several years prior to the Task Force recommended GRS age of 18 as stated in 2.6, which we strongly disagree with.

4.0 ADVERSE OUTCOME PREVENTION AND LONG-TERM CARE

4.1 We suggest regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly. (2|⊕⊕OO) *(see pg. 12)*

4.2 We suggest monitoring prolactin levels in male-to-female transsexual persons treated with estrogens. (2|⊕⊕OO) *(see pg. 12)*

4.3 We suggest that transsexual persons treated with hormones be evaluated for cardiovascular risk factors (2|⊕⊕OO) *(see pg. 13)*

4.4 We suggest that bone mineral density measurements be obtained if risk factors for osteoporosis exist, specifically in those who stop hormone therapy after gonadectomy. (2|⊕⊕⊕O) *(see pg. 13)*

4.5 We suggest that male-to-female transsexual persons, who have no known increased risk of breast cancer, follow breast screening guidelines recommended for biological women. (2|⊕⊕OO) *(see pg. 14)*

4.6 We suggest that male-to-female transsexual persons treated with estrogens follow screening guidelines for prostatic disease and prostate cancer recommended for biological men. (2|⊕OOO) *(see pg. 14)*

4.7 We suggest that female-to-male transsexuals evaluate the risks and benefits of including total hysterectomy and oophorectomy as part of sex reassignment surgery. (2|⊕OOO) *(see pg. 14)*

5.0 SURGERY FOR SEX REASSIGNMENT *(see pg. 15)*

5.1 Genital sex reassignment surgery should be recommended by both the physician responsible for endocrine transition therapy and the mental health professional. (1|⊕OOO) *(see pg. 16)*

5.2 We recommend that genital sex reassignment surgery be recommended only after completion of at least 1 year of consistent and compliant hormone treatment.(1|⊕OOO) *(see pg. 16)*

5.3 We recommend that the physician responsible for endocrine treatment medically clear transsexual individuals for sex reassignment surgery and collaborate with the surgeon regarding hormone use during and after surgery. (1|⊕OOO) *(see pg. 16)*

5.1
TransActive disagrees with the recommendation that another “gatekeeper” be inserted into the Genital Reassignment Surgery process. There is currently an existing requirement that a surgical candidate obtain two letters of referral prior to surgery; one from a counselor or therapist and a second letter from a Ph.D -level mental health practitioner.

Further, surgery should only be “recommended” if and when the youth expresses a consistent and persistent desire for such.

1.0 Diagnostic Procedure
Sex reassignment is a multidisciplinary treatment. It requires five processes:

- diagnostic assessment
- psychotherapy or counseling
- real-life experience
- hormone therapy
- surgical therapy.

The focus of this Guideline is hormone therapy, although collaboration with appropriate professionals responsible for each process maximizes a successful outcome. It would be ideal if care could be given by a multidisciplinary team at one treatment center, but this is not always possible. It is therefore important that caregivers be aware of the contributions of the various disciplines.

1.0
TransActive disagrees with the statement that sex reassignment "requires five processes".

Under the current WPATH Standards of Care, it is recommended that trans-identified youth receive a diagnostic assessment, counseling and be living in their target gender role as prerequisites for hormone therapy. We do not agree that desire for "surgical therapy" should be, in all cases, an expected or required diagnostic eventuality.

1.4 Evidence
Because early adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormones, consent and patient education should include parents, the referring mental health professional(s), and other members of their support group.

To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding future fertility of adolescents or adults beginning sex reassignment treatment. Prolonged pubertal suppression using GnRH analogues is reversible and should not prevent resumption of pubertal development upon cessation of treatment.

Although sperm production and development of the reproductive tract in early adolescent biological males with GID are insufficient for cryopreservation of sperm, they should be counseled that sperm production can be initiated following prolonged gonadotropin suppression, prior to estrogen treatment. It should be noted that the time required to obtain sufficient spermatogenesis to collect sperm is unpredictable and will probably be associated with physical manifestations of testosterone production.

Girls should expect no adverse effects when treated with pubertal suppression. They should be informed that no data are available regarding timing of spontaneous ovulation or response to ovulation induction following prolonged gonadotropin suppression. All referred subjects who satisfy eligibility and readiness criteria for endocrine treatment, at age 16 or as adults, should be counseled regarding the effects of hormone treatment on fertility and available options that may enhance the chances of future fertility, if desired (De Sutter 2007; De Sutter 2001).

Reports of an increased incidence of polycystic ovaries in female-to-male (FTM) transsexual persons, both prior to and as a result of androgen treatment, should be acknowledged (Spinder 1989 Baba 2007). Pregnancy has been reported in FTM transsexual persons who have had prolonged androgen treatment, but no genital surgery (Trebay 2008). Counsel from a gynecologist prior to hormone treatment regarding potential fertility preservation following ovariectomy will clarify available and future options (De Sutter 2003).

2.0 Treatment of Adolescents

Over the past decade, clinicians have progressively acknowledged the suffering of young transsexual adolescents that is caused by their pubertal development. Indeed, an adolescent with GID often considers the pubertal physical changes to be unbearable.

As early medical intervention may prevent this psychological harm, various clinics have decided to start treating young adolescents with GID with puberty-suppressing medication (a GnRH analogue). As compared to starting sex reassignment long after the first phases of puberty, another benefit of pubertal suppression is relief of gender dysphoria and a better psychological and physical outcome.

The physical changes of pubertal development are the result of maturation of the hypothalamo-pituitary-gonadal axis and development of the secondary sex characteristics. Gonadotropin secretion increases with a day-night rhythm with higher levels of LH during the night. The night time LH increase in boys is associated with a parallel testosterone increase. Girls do not show a day-night rhythm, although in early puberty, the highest estrogen levels are observed during the morning as a result of a delayed response by the ovaries (Boyar 1976).

In girls the first physical sign of the beginning of puberty is the start of budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, with menarche occurring approximately two years later. In boys the first physical change is testicular growth. A testicular volume equal to or above 4 ml is seen as the first pubertal increase. From a testicular volume of 10 ml, daytime testosterone levels increase, leading to virilization (Wennink 1989).

2.1-2.2 Evidence

Pubertal suppression aids in the diagnostic and therapeutic phase, in a manner similar to the real life experience. (Delemarre-Van de Waal 2006, Cohen-Kettenis 2008). Management of gender dysphoria usually improves. In addition, the hormonal changes are fully reversible, enabling full pubertal development in the biologic gender if appropriate. Therefore, we advise starting suppression of puberty before irreversible development of sex characteristics. →

> **2.1-2.2**
> TransActive strongly supports these clinical recommendations as they reflect our experience in working directly with pre & post adolescent trans youth.

The experience of full biologic puberty, an undesirable condition, may seriously interfere with healthy psychological functioning and well-being. Suffering from gender dysphoria without being able to present socially in the desired social role or to stop the development of secondary sex characteristics may result in an arrest in emotional, social, or intellectual development.

Another reason to start sex reassignment early is that the physical outcome following intervention in adulthood is far less satisfactory. Looking like a man (woman) when living as a woman (man) creates difficult barriers which have enormous life-long disadvantages.

Pubertal suppression maintains end-organ sensitivity to sex steroids observed during early puberty, enabling satisfactory cross-sex body changes with low doses and avoiding irreversible characteristics that occur by mid-puberty.

The protocol of suppression of pubertal development can also be applied to adolescents in later pubertal stages. In contrast to effects in early pubertal adolescents, physical sex characteristics, such as breast development in girls and lowering of the voice and outgrowth of the jaw and brow in boys will not regress completely.

Unlike the developmental problems observed with delayed puberty, this protocol requires a mental health professional skilled in child- and adolescent- psychology to evaluate the response of the adolescent with GID after pubertal suppression. *Adolescents with GID should experience the first changes of their biologic, spontaneous puberty* because their emotional reaction to these first physical changes has diagnostic value. The early treatment in puberty risks limited growth of the penis and scrotum that may make the surgical development of a vagina from scrotal tissue more difficult.

> The statement that "Adolescents with GID should experience the first changes of their biologic, spontaneous puberty" fails to take into account the life experiences of children who transitioned to their true gender role at a very young age. The majority of their socialization has been in the gender role they identify with, rather than with their biologic sex. To use "distress" as a diagnostic tool on such children is both unnecessary and cruel.

2.1-2.2.Values and Preferences

This recommendation places a high value on the increasing likelihood of a satisfactory physical change when secondary sexual characteristics have become manifest and irreversible while offering the adolescent the experience of the desired gender, and places a lower value in avoiding potential harm from early hormone therapy.

2.1-2.2 Remarks

Tanner stages of breast and male genital development are given in Table 6. Blood levels of sex steroids during Tanner stages of pubertal development are given in Table 7. Careful documentation of hallmarks of pubertal development will ensure precise timing of initiation of pubertal suppression later initiation of cross-sex hormone treatment later. Irreversible and, for transsexual adolescents, undesirable sex characteristics are in female puberty large breasts and short stature and in male puberty Adam's apple, low voice, male bone configuration such as large jaws, big feet and hands, tall stature and male hair pattern on the face and extremities.

2.3. Evidence

Suppression of pubertal development and gonadal function is accomplished most effectively by gonadotropin suppression with GnRH analogues and antagonists. Analogues suppress gonadotropins after a short period of stimulation, whereas antagonists immediately suppress pituitary secretion (Tuvemo 2006, Roth 2002). Since no long-acting antagonists are available for use as pharmacotherapy, long-acting analogues are the currently preferred treatment option.

During treatment with the GnRH analogues, slight development of sex characteristics will regress and, in a later phase of pubertal development, will be halted. In girls, breast development will become atrophic and menses will stop; in boys, virilization will stop and testicular volume will decrease (Delemarre 2006). An advantage of using GnRH analogues is the reversibility of the intervention. If, after extensive exploring of his/her reassignment wish, the patient no longer desires sex reassignment pubertal suppression can be discontinued. Spontaneous pubertal development will resume immediately (Manasco1988).

In children with central precocious puberty, bone density is relatively high for age. Suppressing puberty in these children using GnRH analogues will result in a further increase in BMD and stabilization of BMD standard deviation scores

(Neely 1995). Initial data in transsexual subjects demonstrate no change of bone density during GnRH analogue therapy. (Delemarre 2006).

GnRH analogues are expensive and not always reimbursed by insurance companies. For financial reasons, treatment with progestins can be an alternative. They suppress gonadotropin secretion and exert a mild peripheral anti-androgen effect in boys. Depo-medoxyprogesterone will suppress ovulation and progesterone production for long periods of time, although residual estrogen levels vary. In high doses, progestins are relatively effective in suppression of menstrual cycling in girls/women and androgen levels in boys/men. However, at these doses, side effects such as suppression of adrenal function and suppression of bone growth may occur (Raudrant 2003). Anti-estrogens in girls and anti-androgens in boys can be used in order to delay the progression of puberty (Mieszczak 2007, Jain 2004). Their efficacy, however, is far less than that of the GnRH analogues.

2.3 Values and Preferences

For patients who can afford the therapy, our recommendation of GnRH analogues places a higher value on the superior efficacy, safety and reversibility of the pubertal hormone suppression achieved as compared with the alternatives and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot progestin preparations may be partially effective, but not as safe; its lower cost makes it an acceptable treatment for patients who cannot afford GnRH.

2.3 Remarks

Measurements of gonadotropin and sex steroid levels give precise information about suppression of the gonadal axis. If the gonadal axis is not completely suppressed, the interval of GnRH analogue injections should be shortened. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt as well as impaired bone accretion. The clinical protocol to be used is shown in Table 8. Glucose and lipid metabolism, complete blood counts and liver and renal function should be monitored during suppression and cross-sex hormone substitution. For the evaluation of growth anthropometric measurements are well informative. To assess bone density, dual energy X-ray absorptiometry (DEXA) scans can be performed.

2.4. Evidence

In many countries, 16-year-olds are legal adults with regard to medical decision making. This is probably because, at this age, most adolescents are able to make complex cognitive decisions. Although parental consent may not be required, obtaining it is preferred since the support of parents should improve the outcome during this complex phase of the adolescent's life (Delemarre-Van de Waal 2006).

While TransActive agrees that the support of parents regarding cross-gender hormone therapy is the preferred treatment model, we don't believe that absence of parental consent should, in all cases, be grounds for denial of treatment.

For the induction of puberty, we use a similar dose scheme of induction of puberty in these hypogonadal transsexual adolescents as in other hypogonadal individuals (Table 9). We do not advise the use of sex steroid creams or patches since there is little experience for induction of puberty. The transsexual adolescent is hypogonadal and may be sensitive to high doses of cross-sex steroids, causing adverse effects of striae and abnormal breast shape in girls and cystic acne in boys.

In FTM *(female-to-male)* transsexual adolescents, suppression of puberty may halt the growth spurt. To achieve maximum height, slow introduction of androgens will mimic a "pubertal" growth spurt. If the patient is relatively short, one may treat the patient with oxandrolone, a growth-stimulating anabolic steroid also applied in women with Turner syndrome (Nilsson 1996).

We support these recommendations. It is also TransActive's position that the recommendations to the left contradict (rightfully so) the earlier recommendation to withhold cross-gender hormone treatment until age 16, by which time much of the damage mentioned at left would have been done and irreversible.

In MTF *(male-to-female)* transsexual adolescents, extreme tall stature is often a genetic probability. The estrogen dose may be increased in a faster schedule, estrogens may be started before the age of 16, or estrogens can be prescribed in growth-inhibiting doses (Delemarre-Van de Waal 2006).

We suggest that treatment with GnRH analogues be continued during treatment with cross-sex steroids in order to maintain full suppression of pituitary gonadotropin levels and, thereby, gonadal steroids. When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion (Table 7). Endogenous production of sex steroid hormone of the undesired sex can interfere with the effectiveness of the treatment. GnRH analogue treatment is advised until gonadectomy.

2.4 Values and Preferences

Identifying an age at which pubertal development is initiated will be by necessity arbitrary but the goal is to start this process at a time when the individual will be able to make informed mature decisions and engage in the therapy, while at the same time developing with his or her peers. Growth targets reflect personal preferences, often shaped by societal expectations. Individual preferences should be the key determinant, rather than the professional deciding a priori that MTF transsexuals should be shorter than FTM transsexuals.

TransActive agrees with the recommendations at left and further believes that individual preferences rather than an arbitrary age should be the determining factor as to when cross-gender hormone treatment is initiated.

2.4 Remarks

Protocols for induction of puberty can be found in Table 9.

We recommend monitoring clinical pubertal development as well as laboratory parameters (Table 10). Sex steroids of the desired sex will initiate pubertal development, which can be (partially) monitored using Tanner stages. In addition, the sex steroids will affect growth and bone development as well as insulin sensitivity and lipid metabolism as in normal puberty (Ball 2006, Reinehr 2005).

2.6 We suggest deferring for surgery until at least 18 years old.

Surgery is an irreversible intervention. The WPATH SOC (Standards of Care) (Meyer 2001) emphasize that the "threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention." If the real life experience supported by sex hormones of the desired sex has not resulted in a satisfactory social role change, if the patient is not satisfied with or is ambivalent about the hormonal effects, or if the patient is ambivalent about surgery, then the applicant should not be referred for surgery.(Monstrey 2001, Monstrey 2007)

While surgery at any age certainly should not proceed if the individual is ambivalent about the process, we believe that having a third-party subjectively evaluate whether or not a "satisfactory social role change" has occurred opens the door to stereotypical gender-role/ appearance expectations.

4.0 Adverse Outcome Prevention and Long-term Care

Cross-sex hormone therapy confers the same risks associated with sex hormone replacement therapy in biological males and females. The risk of cross-sex hormone therapy arises from and is worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones or inadequate doses of sex hormones to maintain normal physiology (Gooren 2008b, Gooren 2008a).

4.1 Evidence

Pretreatment screening and appropriate regular medical monitoring is recommended for both FTM and MTF transsexual persons during the endocrine transition and periodically thereafter (Meyer 2006, Meyer 1981). Monitoring of weight and blood pressure, directed physical exams, routine health questions focused on risk factors, medications, complete blood counts, renal and liver function, lipid and glucose metabolism should be carried out.

Female-to-male transsexual persons

A standard monitoring plan for individuals on testosterone therapy is found in Table 15. Key issues include maintaining testosterone levels in the physiologic normal male range and avoidance of adverse events resulting from chronic testosterone therapy, particularly erythrocytosis, liver dysfunction, hypertension, excessive weight gain, salt retention, lipid changes, excessive or cystic acne and adverse psychological changes (Bhasin 2006) Since oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated using parenteral or transdermal testosterone (Bird 1979, Westaby 1977). Still, periodic monitoring is recommended given that up to 15% of FTM persons treated with testosterone have transient elevations in liver enzymes (Van Kesteren 1997).

Male-to-female transsexual persons

A standard monitoring plan for individuals on estrogens, gonadotropin suppression or anti-androgens is found in Table 16. Key issues include avoiding supraphysiologic doses or blood levels of estrogen, which may lead to increased risk for thromboembolic disease, liver dysfunction, and development of hypertension.

4.2 Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term estrogen therapy (Gooren 1988, Kovacs 1994, Serri 1996). Up to 20% of transsexual women treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (Asscheman 1988). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy (Gooren 1985).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Prolactin levels should be obtained at baseline and then at least annually during the transition period and biannually thereafter. The major presenting symptoms of micro-prolactinomas (gynecomastia, and hypogonadism) are not apparent in MTF transsexual persons.

Because transsexual persons are diagnosed and followed throughout sex reassignment by a mental health professional, it is likely that some will receive psychotropic medications that can increase prolactin levels.

4.3 Evidence

Female-to-male transsexual persons

Testosterone administration to FTM transsexual persons will result in a more atherogenic lipid profile with lowered HDL cholesterol and higher triglyceride values (Giltay 1999, Elbers 2003, Berra 2006). Studies of the effect of testosterone on insulin sensitivity have mixed results (Elbers 2003, Polderman 1994). Numerous studies have demonstrated effects of cross-sex hormone treatment on the cardiovascular system. (Giltay 1998, Giltay1999, Giltay 2003, Giltay 2004) Long-term studies from the Netherlands found no increased risk for cardiovascular mortality (Van Kesteren 1997). Likewise, a meta-analysis of 19 randomized trials in men examining testosterone replacement showed no increased incidence of cardiovascular events (Calof 2005) (Haddad 2007). A systematic review of the literature found no conclusive evidence to suggest that normal physiologic replacement doses of testosterone do or do not increase cardiovascular events in FTM transsexual persons (Elamin [In Preparation].

Male-to-female transsexual persons

A prospective study of MTF subjects found favorable changes in lipid parameters with increased HDL and decreased LDL concentrations (Elbers 2003). However, these favorable lipid changes were attenuated by increased weight, blood pressure, and markers of insulin resistance. The largest cohort of MTF subjects (with a mean age of 41) followed for a mean of 10 years showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (van Kesteren 1997). Thus, there is limited evidence to determine whether estrogen is protective or detrimental in MTF transsexual persons (Elamin [In preparation]). With aging there is usually an increase of body weight and therefore, as with non-transsexual individuals, glucose and lipid metabolism and blood pressure should be monitored regularly.

4.4 Evidence

Female-to-male transsexual persons

Adequate dosing of testosterone is important to maintain bone mass in FTM transsexual persons (van Kesteren 1998, Turner 2004). In this study, serum LH levels were inversely related to bone mineral density, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol both systemically and locally in the bone.

Male-to-female transsexual persons

Studies in aging genetic males suggest that serum estradiol more positively correlates with BMD than testosterone (Amin 2000, Genari 2008a, Genari 2008b) and is more important for peak bone mass (Khosla 1998). Estrogen preserves BMD in MTF transsexuals who continue on estrogen and anti-androgen therapies (van Kesteren 1998, Ruetsche 2005, Mueller 2005).

Fracture data in transsexual men and women are not available. Gonadectomized transsexual persons may not continue consistent cross-sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss.

4.5-4.6 Evidence

Breast cancer is a concern in transsexual women. A few cases of breast cancer in MTF transsexual persons have been reported in the literature (Pritchard 1988, Ganly 1995, Symmers 1968). In the Dutch cohort of 1800 transsexual women followed for a mean of 15 years (range 1 to 30 years), only one case of breast cancer was found. The Women's Health Initiative study reported that women taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with women taking placebo (Anderson 2004). Women with primary hypogonadism (XO) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (Schoemaker 2008, Bosze 2006). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20-30 years). Long-term studies are required to determine the actual risk and the role of screening mammograms. Regular exams and gynecologic advice should determine monitoring for breast cancer.

Many transgender/ transsexual adolescents can be particularly sensitive about exposing their bodies to others. It is important to make every effort to establish a trust-based relationship with these youth.

Prostate cancer is very rare, especially with androgen deprivation therapy, before the age of 40 (Smith 2006) Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (BPH) (Wilson 1999). Although van Kesteren (1996) reported that estrogen therapy does not induce hypertrophy or pre-malignant changes in the prostate of MTF transsexual persons (van Kesteren 1996), cases of. BPH have been reported in MTF transsexual persons treated with estrogens for 20-25 years (Casella, 2005,) (Brown, 1997). Three cases of prostate carcinoma have been reported in MTF transsexual persons (van Haarst 1998, Dorff 2007, Thurston 1994). However, these individuals initiated cross-hormone therapy after age 50, and whether these cancers were present before the initiation of therapy is unknown. The limited evidence suggests that prostate cancer risk may be increased in the older individual initiating on cross-hormone therapy.

4.7 Evidence

Although aromatization of testosterone to estradiol in FTM transsexual persons has been suggested as a risk factor for endometrial cancer (Futterweit 1998), no cases have been reported. When FTM transsexual persons undergo hysterectomy, the uterus is small and there is endometrial atrophy. (O'Hanlan 2007, Miller 1986). The androgen receptor has been reported to increase in the ovaries after long-term administration of testosterone, which may be an indication of increased risk of ovarian cancer (Chadha 1994). Cases of ovarian cancer have been reported (Hage 2000, Dizon 2006). The relative safety of laparoscopic total hysterectomy argues for preventing the risks of reproductive tract cancers and other diseases through surgery (Mueller 2008).

4.7 Values

Given the discomfort that FTM transsexual persons experience accessing gynecologic care, our recommendation for total hysterectomy and oophorectomy places a high value upon eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

5.0 Surgery for Sex Reassignment

The surgical techniques have improved markedly during the past 10 years. Cosmetic genital surgery with preservation of neurological sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (Murad [In preparation]). In addition, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender identity treatment that includes hormones and surgery (Cole 1997). The person must be both eligible and ready for such a procedure. (Table 17.).

Sex reassignment surgeries available to the MTF transsexual persons consist of gonadectomy, pinectomy, and creation of a vagina.(Selvaggi 2005, Turgnet 2007). The skin of the penis is often inverted to form the wall of the vagina. The scrotum becomes the labia majora. Cosmetic surgery is used to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Most recently plastic surgeons have developed techniques to fashion labia minora. Endocrinologists should remind the patient to use their tampon dilators to maintain the depth and width of the vagina throughout the post- operative period until the neovagina is being used frequently in intercourse.

Physicians should not assume that their trans -female patients are heterosexual and therefore committed to penetrative, vaginal intercourse. The importance of post-operative dilation should be conveyed to the individual without expectation of a particular sexual orientation.

Ancillary surgeries for more cosmetic appearance are not within the scope of this guideline. When possible, less surgery is desirable. For instance, voice lessons by a speech pathologist is preferred to laryngeal shaving and other surgical methods to raise the tone of the voice (McNeill 2006).

With effective hormonal intervention beginning at Tanner 2-3, trans-female adolescents should develop a vocal tone within a typical female range.

Breast size in genetic females exhibits a very broad spectrum. For the patient to make the best-informed decision, breast augmentation surgery should be delayed until at least 2 years of estrogen therapy have been completed since the breasts continue to grow during that time with estrogen stimulation (Meyer 1981).

Another major effort is the removal of facial and masculine- appearing body hair using either electrolysis or laser treatments. Other feminizing surgery, such as surgery to feminize the face and the external genitalia, is now becoming more popular. (Becking 2006, Goddard2007, Giraldo 2004).

One of the key advantages of pubertal suppression and cross-gender hormone therapy is the elimination of the need for and expense of these reactive procedures.

Sex reassignment surgeries available to the FTM transsexual persons have been less satisfactory. The cosmetic appearance of a neopenis is now very good but the surgery is multistage and very expensive (Hage 1993, Monstrey 2003). Neopenile erection can be achieved only if some mechanical devise is imbedded in the penis, e.g., a rod or some inflatable apparatus (Chen 2007). Many choose a metadoioplasty that exteriorizes or brings forward the clitoris and allows for voiding while standing. The scrotum is created from the labia majora with a good cosmetic effect and artificial testicular-size structures can be implanted and appear as testes. Ovariectomy, vaginectomy, and complete hysterectomy are needed after a few years of androgen therapy since androgens can be responsible for ovarian tumors (Dizon 2006). These procedures are now done vaginally and with the aid of a laparoscope.

The ancillary surgery for the female to male that is extremely important is the mastectomy. Breast size only partially regresses with androgen therapy. Mastectomy should be considered at the same time or soon after androgen therapy is begun.

5.1.-5.3 Evidence

When a transsexual individual decides to have sex reassignment surgery, both the endocrinologist and the mental health professional must certify that he/she satisfies the eligibility and readiness criteria of the Standard of Care (Meyer 2001) (Table 17).

The WPATH SOC state that a candidate for gender reassignment surgery must have two letters of certification: one(1) from a licensed therapist/ counselor and one (1) from a psychiatrist. The already existing third gatekeeper is, obviously, the surgeon who will perform the procedure(s).

There is some concern that estrogen therapy causes an increased risk for venous thrombosis post surgery (Elamin [In preparation]. For this reason, the surgeon and the endocrinologist should collaborate in making a decision about the use of hormones during the month before surgery.

Although one study suggests that preoperative factors such as compliance are less important than the physical postoperative results (Lawrence 2003), other studies and clinical experience dictate that individuals who do not follow medical instructions and work with their physicians toward a common goal do not do achieve treatment goals (Liberopoulos 2008) and experience higher rates of postoperative infections and other complications (Forbes 2008, Davis 2008). It is also important that the person requesting surgery feel comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (Monstrey 2007).

Transsexual individuals should be monitored by an endocrinologist after surgery. Those who undergo gonadectomy will require hormone replacement therapy or surveillance or both to prevent adverse effects of chronic hormone deficiency.

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TABLE 1. DEFINITIONS OF TERMS USED IN THIS GUIDELINE

Sex refers to attributes that characterize biological male- or femaleness;. the best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia and secondary sex characteristics

Gender identity is used to describe a person's fundamental sense of being male, female or of indeterminate sex.

Gender identity disorder (GID) is a DSM-IV-TR diagnosis. This psychiatric diagnosis is given when a strong and persistent cross-gender identification, combined with a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex causes clinically significant distress.

Gender role is used to refer to behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as masculine or feminine, that is, more "appropriate" to or typical of the male or female social.

Gender dysphoria is the distress and unease experienced if gender identity and sex are not completely congruent.

Sexual orientation can be defined by a person's relative responsiveness to sexual stimuli. The most salient dimension of sexual orientation is the sex of the person to whom one is attracted sexually; sexual orientation is not entirely similar to *sexual identity*; a person may, for example, be predominantly aroused by homoerotic stimuli, yet not regard himself or herself to be gay or lesbian.

Sex reassignment refers to the complete treatment procedure for those who want to adapt their bodies to the desired sex.

Sex reassignment surgery refers only to the surgical part of this treatment.

Transsexual people identify as, or desire to live and be accepted as, a member of the gender opposite to that assigned at birth; the term *male-to-female (MTF) transsexual person* is often used to refer to biological males who desire to be a member of the female gender, *female-to-male (FTM) transsexual person* refers to a biological female who desires to be a member of the male gender.

Transition refers to the period of time during which a transsexual changes their physical, social and legal characteristic to the gender opposite that of their biologic sex.

Note:
In this Guideline, we have chosen to use the term "transsexual" throughout as defined by the ICD10 Diagnostic Code (see Table 3). We recognize that "transsexual" and "transgender" are terms often used interchangeably. However, since "transgender" may also be used to identify individuals whose gender identity does not conform to the conventional gender roles of either male or female and who may not seek endocrine treatment as described herein, we prefer to use "transsexual" as an adjective (e.g., when referring to persons, individuals, men, or women and, when appropriate, referring to subjects in research studies.)

TABLE 2. DSM-IV-TR
DIAGNOSTIC CRITERIA FOR GENDER IDENTITY DISORDER
(American Psychiatric Association 2001)

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex).

In children, the disturbance is manifested by four (or more) of the following:
1. repeatedly stated desire to be, or insistence that he or she is, the other sex
2. in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing
3. strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex
4. intense desire to participate in the stereotypical games and pastimes of the other sex
5. strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

Section A:
Requiring male-bodied children to merely indicate a "preference for crossdressing or simulating female attire" when female-bodied children must express an "insistence on wearing stereotypical masculine clothing" is inherently discriminatory, and can result in a "false positive" diagnosis of GID in male-bodied children.

These criteria, in general, depend on outdated gender role/ conformity expectations.

B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following:
1. in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities;
2. in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

Section B:
1-2. While we agree with the usefulness of the first half of this subsection as a diagnostic reference, TransActive believes that the references to "rough and tumble play", "stereotypical toys" and "normative feminine clothing" is, at best, antiquated as a diagnostic tool and at worst, overtly subjective and discriminatory.

C. The disturbance is not concurrent with a physical intersex condition.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Code based on current age:
302.6 Gender Identity Disorder in Children
302.85 Gender Identity Disorder in Adolescents or Adults
Specify if (for sexually mature individuals):
Sexually Attracted to Males
Sexually Attracted to Females
Sexually Attracted to Both
Sexually Attracted to Neither

TransActive strongly disagrees with the need to specify the sexual orientation of trans adolescents. Gender identity is independent of sexual orientation and sexual orientation has not been considered a pathological condition by the APA since 1973.

TABLE 3. *ICD-10* CRITERIA FOR TRANSSEXUALISM AND GENDER IDENTITY DISORDER OF CHILDHOOD (WORLD HEALTH ORGANIZATION MULTIAXIAL VERSION OF ICD10 1992)

Transsexualism (F64.0) has three criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments
2. The transsexual identity has been present persistently for at least 2 years
3. The disorder is not a symptom of another mental disorder or a genetic, intersex, or chromosomal abnormality

Gender Identity Disorder of Childhood (F46.2) has separate criteria for girls and for boys.

For girls:

1. The individual shows persistent and intense distress about being a girl and has a stated desire to be a boy (not merely a desire for any perceived cultural advantages of being a boy) or insistent that she is a boy
2. Either of the following must be present:
   a. persistent marked aversion to normative feminine clothing and insistence of wearing stereotypical masculine clothing
   b. persistent repudiation of female anatomical structures, as evidenced by at least one of the following:
      i. an assertion that she has, or will grow, a penis
      ii. rejection of urination in a sitting position
      iii. assertion that she does not want to grow breasts or menstruate
3. The girl has not yet reached puberty
4. The disorder must have been present for at least 6 months

See Table 2 for TransActive's (oppositional) position on these gender stereotypical diagnostic requirements.

For boys:

1. The individual shows persistent and intense distress about being a boy and has a desire to be a girl or, more rarely, insists that he is a girl
2. Either of the following must be present:
   a. preoccupation with stereotypic female activities, as shown by a preference for either cross-dressing or simulating female attire or by an intense desire to participate in the games and pastimes of girls and rejection of stereotypical male toys, games and activities.
   b. persistent repudiation of male anatomical structures, as evidence by at least one of the following repeated assertions:
      i. that he will grow up to become a woman (not merely in the role)
      ii. that his penis or testes are disgusting or will disappear
      iii. that it would be better not to have a penis or testes
3. The boy has not reached puberty
4. The disorder must have been present for at least 6 months

TABLE 6. TANNER STAGES OF BREAST DEVELOPMENT AND MALE EXTERNAL GENITALIA

The description of Tanner stages

For breast development:

1. Preadolescent
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:

1. Preadolescent
2. Slight enlargement of penis; enlarged scrotum, pink texture altered
3. Penis longer, testes larger
4. Penis larger, glans and breadth increase in size; testes larger, scrotum dark
5. Penis and testes adult size

Adapted from Tanner JM: Growth at adolescence, 2nd edition. Oxford, England, Blackwell Scientific Publications, 1962.

TABLE 7.

Estradiol levels (pmol/l) in female puberty during night and day [a]

Median of hourly measurements during 2400 – 0600h and 1200 – 1800h:

Tanner stage	Nocturnal estradiol	Diurnal estradiol
B1	<37	<37
B2	38.5	56.3
B3	81.7	107.3
B4	162.9	132.3
B5	201.6	196.7

[a]Adapted from Wennink JMB, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J. Luteinizing hormone and follicle stimulating hormone secretion patterns in girls throughout puberty measured using highly sensitive immunoradiometric assays. Clin Endocrinology 1990 33 333-344

Testosterone levels (nmol/l) in male puberty during night and day [b]

Median of hourly measurements during 2400 – 0600h and 1200 – 1800h:

Tanner stage	Nocturnal testosterone	Diurnal testosterone
G1	<0.25	<0.25
G2	1.16	0.54
G3	3.76	0.62
G4	9.83	1.99
G5	13.2	7.80
Adult	18.8	17.0

[b]Adapted from Wennink JMB, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J. Luteinizing hormone and follicle stimulating hormone secretion patterns in boys throughout puberty measured using highly sensitive immunoradiometric assays. Clin Endocrinology 1989 31 551-564

TABLE 8. FOLLOW-UP PROTOCOL DURING SUPPRESSION OF PUBERTY

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: LH, FSH, E2/T

Every year
Laboratory: renal- and liver function, lipids, glucose, insulin, HbA1c
Bone density using DXA
Bone age on X-ray of the left hand

TABLE 9. PROTOCOL INDUCTION OF PUBERTY

Induction of female puberty with 17-beta estradiol, increasing the dose every 6 months:
5 µg/kg/day
10 µg/kg/day
15 µg/kg/day
20 µg/kg/day
adult dose=2 mg per day

Induction of male puberty with testosterone esters increasing the dose every 6 months:
25 mg/m^2 /2 weeks im
50 mg/m^2 /2 weeks im
75 mg/m^2 /2 weeks im
100 mg/m^2 /2 weeks im

TABLE 10. FOLLOW-UP PROTOCOL DURING INDUCTION OF PUBERTY

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: endocrinology: LH, FSH, E2/T

Every year
Laboratory: renal- and liver function, lipids, glucose, insulin, HbA1c
Bone density using DXA
Bone age on X-ray of the left hand

These parameters should be measured also at long term. For bone development until the age of 25-30 years until peak bone mass has been reached.

TABLE 11. MEDICAL CONDITIONS THAT CAN BE EXACERBATED BY CROSS-SEX HORMONE THERAPY

Transsexual Female (MTF) - Estrogen
Very high risk of serious adverse outcomes
• thromboembolic disease

Moderate to high risk of adverse outcomes
• macroprolactinoma
• severe liver dysfunction (transaminases > 3x upper limit of normal)
• breast cancer
• coronary artery disease
• cerebrovascular disease
• severe migraine headaches

Transsexual Male (FTM) - Testosterone
Very high risk of serious adverse outcomes
• breast or uterine cancer
• erythrocytosis (hematocrit >50%)

Moderate to high risk of adverse outcomes
• severe liver dysfunction (transaminases > 3x upper limit of normal)

TABLE 15. MONITORING OF TRANSSEXUAL PERSONS ON CROSS-HORMONE THERAPY

Male-to-female transsexual persons

1. Evaluate patient every 2-3 months in the first year and then 1-2 times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 months.
    a. Serum testosterone levels should be <55 ng/mL;
    b. Serum estradiol should not exceed the peak physiologic range for young healthy females, with ideal levels approximately 200 ng/ml.
    c. Doses of estrogen should be adjusted according to the serum levels of estradiol.
3. For individuals on spironolactone, serum electrolytes particularly potassium should be monitored every 2-3 months initially in the first year.
4. Routine cancer screening recommended in non-transsexual individuals (breasts, colon, prostate)
5. Consider bone mineral density testing at baseline if risk factors for osteoporotic fracture are present (e.g. previous fracture, family history, glucocorticoid use, prolonged hypogonadism). In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy.

TABLE 16. MONITORING OF TRANSSEXUAL PERSONS ON CROSS-HORMONE THERAPY

Female to male transsexual persons

1. Evaluate patient every 2-3 months in the first year and then 1-2 times per year to monitor for appropriate signs of virilization and for development of adverse reactions;
2. Measure serum testosterone every 2-3 months until levels are in the normal physiologic male range:*
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured mid-way between injections. If dose is >700 ng/dl or <350 ng/dl, adjust dose accordingly;
   b. For testosterone undecanoate, testosterone should be measured just before the following injection;
   c. For transdermal testosterone, the testosterone level can be measured at any time after 1 week;
   d. For oral testosterone undecanoate, the testosterone level should be measured 3-5 hours after ingestion;
   e. Note: During the first 3-9 months of testosterone treatment, total testosterone levels may be high although free testosterone levels are normal due to high Sex Hormone Binding Globulin (SHBG) levels in some biological women.
3. Measure estradiol levels during the first 6 months of testosterone treatment or until there has been no uterine bleeding for six months. Estradiol levels should be < 50 pg/ml.
4. Measure CBC, LFTs at baseline and every 3 months for the first year then 1-2 times a year. Monitor weight, blood pressure, lipids, fasting blood sugar is family history of diabetes and hemoglobin A1c if diabetic at regular visits.
5. Consider bone mineral density testing at baseline if risk factors for osteoporotic fracture are present (e.g. previous fracture, family history, glucocorticoid use, prolonged hypogonadism). In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy.
6. If cervical tissue is present, annual pap smear is recommended by American College of Obstetricians and Gynecologists (ACOG).
7. If mastectomy is not performed, then consider annual mammograms recommended by American Cancer Society (ACS)

- Adapted from the Endocrine Society Guideline "Testosterone Therapy in Adult men with Androgen Deficiency Syndromes".

TABLE 17. SEX REASSIGNMENT SURGERY

Eligibility and readiness criteria

Individuals treated with cross-sex hormones, are considered eligible for sex reassignment surgery if they

- are of legal age of majority in the patient's nation
- have used cross-sex hormones continuously and responsibly during 12 months (if they have no medical contraindication)
- had a successful continuous full-time RLE (real-life experience) during 12 months
- (if required by the MHP) have regularly participated in psychotherapy throughout the RLE at a frequency determined jointly by the patient and the MHP
- have shown demonstrable knowledge of all practical aspects of surgery (e.g. cost, required lengths of hospitalizations, likely complications, post-surgical rehabilitation etc.)

Individuals, treated with cross-sex hormones, should fulfill the following readiness criteria prior to sex reassignment surgery:

- demonstrable progress in consolidating one's gender identity; and,
- demonstrable progress in dealing with work, family, and interpersonal issues resulting in a significantly better state of mental health