Title: Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline

Short Title: Guidelines on Gender-Dysphoric/Gender-Incongruent Persons


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**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.
Abstract

Objective: To update the guidelines for the endocrine treatment of transsexual persons published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society-appointed Task Force of nine experts, a methodologist, and a medical writer. The American Association of Clinical Endocrinologists, European Society of Endocrinology, European Society for Paediatric Endocrinology, World Professional Association for Transgender Health, and Lawson Wilkins Pediatric Endocrine Society co-sponsored this guideline.

Evidence: The Task Force developed this evidence-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Three group meetings, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, American Association of Clinical Endocrinologists, European Society of Endocrinology, European Society for Paediatric Endocrinology, World Professional Association for Transgender Health, and Lawson Wilkins Pediatric Endocrine Society reviewed and commented on preliminary drafts of these guidelines.

Conclusions: Gender-affirming treatment is a multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seeking to develop the physical characteristics of the desired gender require a safe and effective hormone regimen that will 1) suppress...
endogenous hormone secretion determined by the person’s genetic/gonadal sex and 2) maintain sex
hormone levels within the normal range for the person’s gender. A clinician who is knowledgeable
regarding the diagnostic and eligibility criteria for treatment, who has sufficient experience in assessing
psychopathology, and will participate in the ongoing care throughout the endocrine transition should be
the person who recommends Endocrine treatment. The treating clinician must confirm the diagnostic
criteria that the referring clinician used to make this recommendation and collaborate with the referring
clinician in making recommendations for gender-affirming surgery. We recommend treating gender-
dysphoric adolescents who have puberty (starting at Tanner stage 2) by suppression with gonadotropin-
releasing hormone analogues; after which, clinicians may add gender-affirming hormones. Clinicians may
initiate gender-affirming hormones in adolescents earlier when recommended by an experienced mental
health professional. In adult gender-dysphoric persons, we suggest suppressing endogenous sex
hormones, maintaining physiologic levels of gender-appropriate sex hormones, and monitoring for known
risks and complications.

Number of Words, Number of Tables and Figures

Word Count: 11,353 Abstract: 367 Tables: 16 Figures: 0

Abbreviations:

BMD = bone mineral density; CAH = congenital adrenal hyperplasia; DSD = disorder of sex
development; FTM = female-to-male; GD = gender-dysphoria; GD/gender-incongruence = gender-
dysphoria/gender-incongruence; GnRH = gonadotropin-releasing hormone; MTF = male-to-female; MHP
= mental health professional; WPATH = World Professional Association for Transgender Health

Summary of Recommendations (To Be Completed Upon Finalization)

The Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons guideline is a draft manuscript. The manuscript has not gone
through the copyediting process by a medical writer. Grammatical, references, and boilerplate items will be addressed by the medical writer
upon finalization.
Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of gender-dysphoria/gender-incongruence (GD/gender incongruence) individuals a priority area for which the current guideline needed revising and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. 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 persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the Task Force considered in making the recommendation; in some instances, there are remarks, a section in which the Task Force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the Task Force and their values and preferences; therefore, one should consider these remarks as suggestions.
In this guideline, the Task Force made several statements to emphasize the importance of shared decision-making, general preventive-care measures, and basic principles of diabetes technology. They labeled these “Ungraded Good Practice Statement”. Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to and remind providers of these principles; one should not consider these statements.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All Task Force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the Task Force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and a majority of these participants must be without any conflicts of interest. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests (e.g., stocks and stock options [excluding diversified mutual funds]); honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided all funding for this guideline; the Task Force received no funding or remuneration from commercial or other entities.
Commissioned Systematic Review

The Task Force commissioned two systematic reviews to support this guideline (To Be Completed by Dr. Murad and co-authors)
Introduction

Men and women have experienced the confusion and anguish resulting from rigid, forced conformity to sexual dimorphism throughout recorded history. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the beginning of a social awakening for men and women “trapped” in the wrong body (4). Harry Benjamin and Magnus Hirschfeld, who met in 1907, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Hirschfeld coined the term “transsexual” in 1923 to describe people who want to live a life that corresponds with their experienced gender versus their opposite natal gender (5). Besides transsexualism, other types of trans phenomena were described by Magnus Hirschfeld (6) and later by others (7,8). These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through “something in between” to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender, whereas others completely renounce any gender classification (9,10). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (11) or men who do not experience themselves as men but do not want to live as women (12,13). In some countries, (e.g., Nepal, Bangladesh, and Australia), these non-male or non-female genders are officially recognized (14). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their...
natal gender (15). The current version of the International Statistical Classification of Diseases and
Related Health Problems-10 (ICD-10) of the World Health Organization still uses the term transsexualism
when diagnosing adolescents and adults. However, the upcoming version, the ICD-11, has proposed using
the term “gender incongruence” (16). Treating persons with GD/gender incongruence (16) was previously
limited to relatively ineffective elixirs, creams, and implants. However, more effective endocrinology-
based treatments became possible with the availability of testosterone in 1935 and diethylstilbesterol in
1938. Reports of GD/gender incongruence individuals treated with hormones and gender-affirming
surgery appeared in the press during the second half of the twentieth century. The Harry Benjamin
International Gender Dysphoria Association was founded in September 1979, now known as World
Professional Association for Transgender Health (WPATH). WPATH published its first Standards of
Care in 1979. These standards have since been regularly updated, providing guidance for treating persons
with GD/gender incongruence (17).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of
transgender persons. Since that time, more than 2,000 articles about various aspects of transgender 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 treating physicians to provide safe and
effective endocrine treatment for individuals diagnosed with GD/gender incongruence. In the future, we
need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols.
Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful
assessment of the following: 1) the effects of prolonged delay of puberty on bone health, gonadal function
and the brain in adolescents, including effects on cognitive, emotional, social, and sexual development; 2)
the effects on both endogenous and cross-sex hormone levels during treatment in adults; and 3) the
requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids
during treatment. In order to successfully establish and enact these protocols requires 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 (e.g., European Network for the Investigation of Gender Incongruence) (18,19).

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

Biologic Determinants of Gender Identity Development

One’s self-awareness as male or female changes gradually during infant life and childhood. This
process of cognitive and affective learning evolves with interactions with parents, peers, and environment.
A fairly accurate timetable exists outlining the steps in this process (20). Normative psychological
literature, however, does not address if and when gender identity becomes crystallized and what factors
contribute to the development of a gender identity that are not congruent with the gender of rearing.
Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—
support the concept that gender identity and/or gender expression (21) likely reflect a complex interplay
of biologic, environmental, and cultural factors (22,23).

With respect to endocrine considerations, studies have failed to find differences in circulating
levels of sex steroids between transgender and non-transgender individuals (24). In addition, studies in
individuals with a disorder of sex development (DSD) have informed our understanding of the role that
hormones may play in gender identity outcome, even though most patients with gender dysphoria do not
have DSD. For example, while the majority of 46, XX adult individuals with virilizing congenital adrenal hyperplasia (CAH) caused by mutations in \textit{CYP21A2} reported a female gender identity, the prevalence of gender dysphoria was much greater based upon the reported prevalence of female-to-male transgenderism. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (25-27). Of note, in such patients, prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity \textit{per se} (28,29).

Researchers have made similar observations regarding the potential role of androgens in gender identity regarding other DSD persons. For example, a study of 46 XY individuals raised female with 5-
alpha Reductase-2-deficiency or 17-beta-hydroxysteroid dehydrogenase-3 deficiency reported female-to-
male (FTM) gender role changes in 56-63% or 39-64% of patients, respectively (30). Furthermore, in 46 XY individuals raised female with cloacal exstrophy and penile agenesis the occurrence of FTM gender identity change was significantly greater than expected in the general population (31,32), further implying a role for androgens in gender identity development.

With respect to genetics and gender identity, several studies have suggested heritability of gender dysphoria (33,34). In particular, a study by Heylens et al. demonstrated a 39.1% concordance rate for gender identity disorder (based on DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs (34). While numerous investigators have sought to identify specific genes associated with gender dysphoria, such studies have been inconsistent and without strong statistical significance (35-39).
Regarding neuro-anatomic factors and gender identity, several studies have suggested the existence of “gender-dimorphic” brain structures that differ not by natal sex but by gender identity (40-43). Yet, while some studies report that certain structures shift away from the natal sex in the direction of the experienced gender, others studies did not report any differences from controls (44). Important to note, most of these studies had small sample sizes, and while some studies were carried out prior to cross-sex hormone treatment, there are inconsistencies in findings between studies and often a lack of confirmation from other centers. In addition, functional brain plasticity with respect to both white and grey matter (45) makes it difficult to ascertain whether any observed brain differences between transgender and non-transgender individuals are intrinsic or a consequence of experience.

Given that ascertaining gender identity is based on psychological assessments, potential limitations of all of the above-noted studies is a person’s degree of self-awareness and willingness to disclose information.

In summary, while there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental and cultural factors, contribute to this fundamental aspect of human development.

Natural History of Children with Gender Dysphoria/Gender Incongruence

With current knowledge we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called desisters). Combining all outcome studies to date, a minority of gender-dysphoric children appears to persist in adolescence (21,46). A significant number of these desisters identify as homosexual or bisexual. It may be that mildly gender non-conforming children have
been included in the follow-up studies, because the DSM-IV-TR criteria for a diagnosis were rather broad; whereas, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (47,48). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education and diagnosis, treatment may include: mental health care, hormone therapy, and/or surgical therapy. With help from a mental health professional (MHP), clinicians should examine the psychosocial impact of the potential changes on people’s lives, including mental health, friends, family, jobs, and their role in society. At some point in the treatment process, transgender individuals should experience living in the new gender role and assess whether this improves their quality of life. The focus of this guideline is hormone therapy, although collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome. It would be ideal if care could be given in a multidisciplinary fashion, which, in addition to mental health and medical care, may also include advocacy and legal support.

**Diagnostic assessment and mental health care.** Gender dysphoria or gender incongruence may be accompanied with psychological or psychiatric problems (49-57) (Safer DL, AACE Clinical Case Rep, 2016). It is therefore necessary that clinicians are able to 1) make a distinction between GD/gender incongruence and conditions that have similar features, 2) diagnose accurately psychiatric conditions, and 3) undertake or refer for appropriate treatment.
Because of the psychological vulnerability of many individuals with GD/gender incongruence, availability of mental health care is important before, during and sometimes also after transitioning. For children and adolescents, an MHP should make the diagnosis that has training/experience in child and adolescent gender development as well as child and adolescent psychopathology.

During the diagnostic procedure, the clinician obtains information from the individual seeking gender-affirming treatment. In the case of adolescents, the clinician obtains information from the parents or guardians regarding various aspects of the child’s general and psychosexual development and current functioning. On the basis of this information the clinician:

- decides whether the individual fulfills diagnostic criteria (see Tables 2 and 3) for GD (DSM-5) or transsexualism (ICD-10),
- informs the individual about the possibilities and limitations of various kinds of treatment, including gender-affirming treatment, to prevent unrealistically high expectations;
- assesses potential psychological and social risk factors for unfavorable outcomes of medical interventions.

In cases in which severe psychopathology, circumstances, or both, seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should first manage the other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with good outcome (58-62).
For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic
assessment (63) and an assessment of the decision-making capability of the youth. A family
evaluation to assess the family’s ability to endure stress, give support, and deal with the
complexities of the adolescent’s situation should be part of the diagnostic phase (Di Ceglie D,
Development Service: Clinical Features and Demographic Characteristics, 2002
http://www.Sympoium.com/ijt/ijtvo06no01_01.htm).

**Social transitioning.** A change in gender expression and role (which may involve living part time
or full time in another gender role that is consistent with one’s gender identity) may test the person’s
resolve; the capacity to function in the affirmed gender; and the adequacy of social, economic, and
psychological supports. It assists both the individual and the clinician in their judgments about how to
proceed (17). During social transitioning, the person’s feelings about the social transformation, including
coping with the responses of others, is a major focus of the counseling. Individuals increasingly start social
transitioning long before they receive medically supervised hormone treatment.

**Eligibility Criteria.** Adolescents and adults seeking hormone treatment and surgery should satisfy
certain criteria before proceeding (17). There are eligibility criteria for hormone therapy for adults (Table
4) and eligibility criteria for adolescents (Table 5). Follow-up studies in adults indicate a high satisfaction
rate (Gijs L, Ann Rev Sex Res, 2007). Also a few follow-up studies on adolescents who fulfilled these
criteria indicate good treatment results (64-67).
Recommendations for Those Involved in the Hormone Treatment of Individuals for Sex

Reassignment

1.1 We recommend that only physicians and/or other trained healthcare providers who know the diagnostic and eligibility criteria and have sufficient experience in assessing psychopathology should diagnose GD/gender incongruence in adults. (1 |⊕OOO)

1.2 We recommend that only MHPs who have training in child and adolescent developmental psychology, known the diagnostic and eligibility criteria, and have sufficient ample experience in assessing psychopathology should diagnose GD/gender incongruence in youths. (1 |⊕⊕O)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (49-54,56,57,68,69) (Safer DL, AACE Clinical Case Rep, 2016). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. This way clinicians can accurately diagnose psychiatric conditions and ensure that these conditions are treated appropriately. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (70), or male-to-eunuch gender dysphoria (a condition in which a person is preoccupied with or engages in castration and/or penectomy for reasons that are not gender identity related) (12).
Values and Preferences

The Task Force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the strong recommendation in the face of low quality evidence.

1.3 We recommend that clinicians make decisions regarding the social transition of prepubertal youths with GD in conjunction with an evaluation by a qualified MHP. (Ungraded Best Practice)

1.4 We recommend against hormone intervention in prepubertal children with GD. (1 |⊕⊕O)

Evidence

In most children diagnosed with GD, the GD did not persist into adolescence. The percentages differed among studies, probably dependent upon which version of the DSM clinicians used to assess childhood patients, their age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain gender dysphoric in adolescence (21). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (46). Social transition is associated with the persistence of GD as a child progresses into adolescence. Rather than a cause-effect relationship, the presence of GD in children may simply be the earliest sign that a child is destined to be transgender as an adolescent/adult (21).
This recommendation, however, does not imply that children should be discouraged from showing gender variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the gender-dysphoric children to which this applies. At the present time, clinical experience suggests that persistence of GD can only be reliably assessed after the first signs of puberty.

Values and Preferences

The clinician should be cognizant of the difficulty parents may have with the ambiguity of the child’s gender. The MHP should evaluate the impact and role of parents in a child’s social transition prior to puberty.

1.4 We place a high value on avoiding harm with hormone therapy in prepubertal children with GD. This justifies the strong recommendation in the face of very low quality evidence.

1.5 We recommend that clinicians inform and counsel all individuals seeking gender-confirming medical treatment regarding options for fertility prior to initiation of puberty suppression in adolescents and prior to treatment with hormonal therapy of the affirmed gender in both adolescents and adults.

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (71,72). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent’s...
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 gender-affirming
treatment.

Treating early pubertal youth with gonadotropin-releasing hormone (GnRH) analogues will
temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of
transgender youth wish to preserve fertility potential, delaying or temporary discontinuing GnRH
analogues to promote gamete maturation is an option. This option is often not preferred, because mature
sperm production is associated with later stages of puberty and with the significant development of
secondary sex characteristics. Nevertheless, prolonged pubertal suppression using GnRH analogues is
reversible. Although sperm production and development of the reproductive tract in young adolescent
natal males with GD/gender incongruence are insufficient for cryopreservation of sperm, they should be
counseled that sperm production can be initiated following prolonged gonadotropin suppression, prior to
estrogen treatment. This sperm production can be accomplished by spontaneous gonadotropin (both LH
and FSH) recovery after cessation of GnRH analogs or by gonadotropin treatment and will probably be
associated with physical manifestations of testosterone production, as stated above. It should be noted that
there are no data in this population concerning the time required for sufficient spermatogenesis to collect
enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7-3
years after cessation of GnRH analogues (73). In adult men with gonadotropin deficiency, sperm are
noted in seminal fluid by 6-12 months of gonadotropin treatment, although sperm numbers when partners
of these patients conceive are far below the “normal range” (74,75).

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In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (76,77). Clinicians should inform natal girls that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogues or the response to ovulation induction following prolonged gonadotropin suppression.

In natal males, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis and oocyte maturation of immature tissue are currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In natal females, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender men, both prior to and as a result of androgen treatment (78-81); although these reports were not confirmed by others (82). Pregnancy has been reported in transgender men who have had prolonged androgen treatment but no genital surgery (83,84). A reproductive endocrine gynecologist can counsel patients before hormone treatment regarding potential fertility preservation after oophorectomy to clarify available and future options (85). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve (86).

2.0 Treatment of Adolescents

Over the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. For many adolescents with GD/gender incongruence, however, the pubertal physical changes are unbearable. As early medical intervention may prevent
psychological harm, various clinics have decided to start treating young adolescents with GD with
puberty-suppressing medication (a GnRH analogue). As compared with starting gender-affirming
treatment long after the first phases of puberty, a benefit of pubertal suppression is a better psychological
and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in
breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche
occurs approximately 2 years later. In boys, the first physical change is testicular growth. A testicular
volume equal to or above 4 ml is seen as consistent with the initiation of physical puberty. At the
beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early
morning with an ultra-sensitive assay. From a testicular volume of 10 ml, daytime testosterone levels
increase, leading to virilization (87). Pubic hair and/or axillary hair/odor may not reflect onset of puberty
but rather adrenarche.

2.1. We recommend that adolescents who meet diagnostic criteria for GD/gender incongruence,
fulfill eligibility criteria, and are requesting treatment, should initially undergo treatment to suppress
pubertal development. (1 |⊕⊕OO)

2.2. We recommend that clinicians begin pubertal hormones suppression after girls and boys first
exhibit physical changes of puberty (Tanner stages G/B2). (1 |⊕⊕OO)

Evidence

Pubertal suppression expands the diagnostic phase by a long period, giving the subject more time
to explore options and to live in the experienced gender before making a decision to proceed with gender-
affirming sex hormones treatments and/or surgery, some of which is irreversible (88,89). Pubertal
suppression is fully reversible, enabling full pubertal development in the natal sex, if appropriate.

However, the experience of full natal puberty is an undesirable condition for the gender-dysphoric individual and may seriously interfere with healthy psychological functioning and well being. Treatment of gender-dysphoric adolescents entering puberty with GnRH analogues has been shown to improve psychological functioning in several domains (90).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared to initiating physical transition after puberty’s completed (64,66). Looking like a man or woman when living as the opposite sex creates difficult barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (89). Thus, Tanner stage 2-3 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential affect on future surgical treatments (91).

Clinicians can also utilize pubertal suppression in adolescents in later pubertal stages. However, in contrast to the 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, and lowering of the voice and outgrowth of the jaw and brow in boys are not reversible.
This protocol requires that a MHP skilled in child and adolescent psychology and a pediatric endocrinologist or another medical provider competent in the area of pubertal development evaluate the adolescent with GD before and during pubertal suppression.

Values and Preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sexual characteristics have become manifest and irreversible. These recommendations place a higher value on psychological well being and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty progresses. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (92). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for gender-dysphoric adolescents, undesirable sex characteristics in female puberty are large breasts and short stature. In male puberty, they are a prominent Adam’s apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that clinicians use GnRH analogues to suppress pubertal hormones. (1 2828O0)
Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogues and antagonists. Analogues (which are, in fact, super-agonists) suppress gonadotropins as a consequence of GnRH receptor desensitization after an initial increase of gonadotropins during approximately 10 days after the first and, to a lesser degree, the second injection (93). Antagonists immediately suppress pituitary secretion (94,95). Long-acting GnRH analogues are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when available.

During GnRH analogue treatment, the slight development of sex characteristics may regress, and in a later phase of pubertal development, they will stop. In girls, breast tissue will become atrophic and menses will stop; in boys, virilization will stop and testicular volume may decrease (96).

An advantage of using GnRH analogues is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression, and spontaneous pubertal development will resume (97).

Recommendations 2.1-2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 male-to-female [MTF], 33 FTM) at three time points: (a) before the start of GnRH agonist (average 14.8 years at start of treatment), (b) at initiation of gender-affirming hormones (average 16.7 years at start of treatment), and (c) 1 year after “gender reassignment surgery” (average age 20.7 years) (67). Despite a decrease in depression and an improvement in general mental health functioning, GD persisted through pubertal suppression, as previously reported (90). However, following cross-sex hormone treatment and...
“gender-reassignment surgery”, GD was resolved and psychological functioning steadily improved (67).

Furthermore, well being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and underscores the benefit of the multi-disciplinary approach pioneered in the Netherlands.

**Side Effects**

The primary risks of pubertal suppression in gender-dysphoric adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with cross-sex hormone treatment), compromised fertility, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on bone mineral density (BMD) in adolescents with GD. Initial data in gender-dysphoric subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analogue therapy but a decrease in a BMD Z-score (98). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in a BMD Z-scores and of bone mineral apparent density Z-scores (which takes the size of the bone into account) in 19 transmen treated with GnRHa from age 15.0 years (±2.0) for a median duration of 1.5 years (0.3-5.2) and in 15 transwomen treated from 14.9 years (±1.9) for 1.3 years (0.5-3.8), although not all changes were statistically significant (99). There was incomplete follow-up at age 22 years after cross sex hormone treatment from age 16.6 (±1.4) for a median duration of 5.8 years (3.0-8.0) in transwomen and from age 16.4 (±2.3) for 5.4 years (2.8-7.8) in transmen. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD Z-scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating cross sex hormone treatment (69).
Additional data are available from individuals with late puberty or GnRH analog treatment for other indications. Some studies report that men with constitutionally delayed puberty have decreased BMD in adulthood (100), whereas other studies report that these men have normal BMD (101,102).

Treating adults with GnRH analogues results in a decrease of BMD (103). In children with central precocious puberty, treatment with GnRH analogues has been found to result in a decrease of BMD during treatment by some (104) but not others (40). Studies have reported normal BMD after discontinuing therapy (73,76,77,105,106). In adolescents treated with growth hormone who are short for gestational age and have normal pubertal timing, 2-year GnRH analogue treatments did not adversely affect BMD (107). Calcium supplementation may be beneficial in optimizing bone health in GnRH analogue treated individuals (108). There are not studies of vitamin D supplementation in this context, but clinicians should offer supplements to Vitamin D deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (107) and is therefore likely to be beneficial for bone health in GnRH analogue treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in gender-dysphoric adolescents (99). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (76) and body mass index and body composition comparable to those of controls after treatment (77).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (109,110). Blood pressure monitoring before and during treatment is recommended.
It is recommended that any use of pubertal blockers (and subsequent use of gender-affirming hormones, as detailed below) include a discussion about implications for fertility (see paragraph 1.3). Transgender adolescents may wish to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of gender-affirming hormones (see above).

Limited data are available regarding the effects of GnRH analogues on brain development. A single cross-sectional study demonstrated no compromise of executive function (111).

Values and Preferences

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 and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treatment of precocious puberty in papers from the 1960’s and early 1970’s (112-115). These compounds are usually safe, but some side effects have been reported (116-118). Only two recent studies involved transgender youth (119,120). One of these studies describes the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transboys who are at Tanner stage B4 or further at the start of treatment (120). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flushes, and fatigue were other frequent side effects. Progestin preparations may be an acceptable treatment for persons without access to GnRH analogues or with a needle phobia. Another alternative and less expensive agent to delay puberty that has been studied in the U.S. is the
progesterone, medroxyprogesterone. This agent is not as effective as GnRH analogues in lowering endogenous sex-hormones but may be associated with other side effects (119).

**Remarks**

Measurements of gonadotropin and sex steroid levels give precise information about suppression of the gonadal axis, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogues (92). If the gonadal axis is not completely suppressed, the interval of GnRH analogue treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone accretion. The clinical protocol to be used is shown in Table 7.

For the evaluation of growth, anthropometric measurements and X-rays of the left hand to monitor bone age are informative. To assess BMD, clinicians can perform dual energy X-ray absorptiometry scans.

2.4 In adolescents who request gender-affirming hormones treatment, we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team has confirmed the persistence of GD, as well as sufficient mental capacity to give informed consent for this partly irreversible treatment (which most adolescents have by age 16 years). (1 | ☐ ☐ OO)

2.5 We recognize that there may be compelling reasons to initiate cross-sex hormone treatment prior to the age of 16 years in some gender dysphoric/gender incongruent adolescents. As with the care of adolescents ≥16 years of age, we suggest that an expert multi-disciplinary team comprised of medical and mental health professionals manage this treatment. (1 | ☐ ☐ OO)
2.6 We recommend monitoring clinical pubertal development every 3-6 months and laboratory parameters every 6-12 months during cross-sex hormone treatment (Table 9). (1 |©©OO)

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15-16 years (121), and in many countries, 16-year-olds are legally competent with regard to medical decision making (Stultiens L, European Journal of Health Law, 2007). However, others believe that while some capacities are generally achieved before age 16 years, other abilities, such as good risk assessment, do not develop until well after 18 years (Arshagouni P, J Health Care Law & Policy, 2006). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures such as most surgical procedures (Arshagouni P, J Health Care Law & Policy, 2006). Currently available data from transgender adolescents support treatment with gender-affirming hormones starting at age 16 years (67). However, while data supporting earlier use of gender-affirming hormones in transgender adolescents do not currently exist, we recognize that some may incur potential risks by waiting until age 16. These include the potential risk to bone health if puberty is suppressed for 6-7 years before initiating gender-affirming hormones (e.g. if someone reached Tanner 2 at age 9-10 years old). In addition, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the
person has reached 16 years of age. Long-term observational studies are needed to determine the optimal age of cross-sex hormone treatment in gender-dysphoric adolescents.

The MHP who has followed the adolescent during GnRH analogue treatment plays an essential role in assessing if the adolescent is ready to start cross-sex hormone therapy and capable of consenting to this treatment. Support of the family/environment is essential. Prior to the start of gender-affirming hormones, clinicians should discuss the implications for fertility (see paragraph 1.3). Throughout pubertal induction, an MPH and a pediatric endocrinologist should monitor the adolescent.

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal gender-dysphoric adolescents as they use in other hypogonadal individuals, carefully monitoring for desired and undesired effects (Table 8). In MTF adolescents, transdermal 17-beta estradiol may be an alternative for oral 17-beta estradiol. It is increasingly used for pubertal induction in hypogonadal females. Although, the absence of low-dose estrogen patches may be a problem; individuals may need to cut patches to size themselves to achieve appropriate dosing (122).

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. Especially in MTF adolescents treated with low doses of estrogen, gonadotropin secretion and endogenous production of testosterone may resume that can interfere with the effectiveness of the estrogen treatment (123,124). Therefore, continuation of GnRH analogue treatment is advised until gonadectomy. Given that FTM gender-dysphoric adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analogue treatment. Alternatively, GnRH analogue treatment can be discontinued once an adult dose of testosterone has been reached and the individual is
well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analogue (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison to testosterone alone.

Values and Preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity to give informed consent for such partly irreversible treatment (which may be around the age of 16 years) places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of hormone treatment and to give informed consent; it places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate cross sex hormones versus the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (Money J, Johns Hopkins University Press, 1972).

Remarks

We need prospective efficacy and safety studies to better inform the optimal age for initiation of cross-sex hormone treatment in GD/gender incongruence adolescents.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are 1) to reduce endogenous sex hormone levels and, thereby, the secondary sex characteristics of the individual’s natal sex, and 2) to replace endogenous sex hormone levels consistent with the individual’s chosen gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is co-determined in collaboration with both
the person pursuing transition and the healthcare providers. The treating providers should include a 
medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender 
incongruence and the mental health concerns of transition, and a primary care provider able to provide 
care appropriate for transgender individuals. The physical changes induced by this sex hormone transition 
are usually accompanied by an improvement in mental well-being (68,125).

3.1 We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and 
the eligibility and readiness criteria for the endocrine phase of gender transition before beginning 
treatment. (I ⊗⊗O)

3.2 We recommend that clinicians evaluate and address medical conditions that can be 
exacerbated by hormone depletion and treatment with sex hormones of the chosen gender prior to 
initiation of treatment (Table 10). (I ⊗⊗O)

3.3 We recommend that clinicians measure hormone levels during treatment to insure that natal 
sex steroids are suppressed and gender sex steroids are maintained in the normal physiologic range for the 
affirmed gender. (2 ⊗O)

Evidence

It is the responsibility of the referred clinician to confirm that the person fulfills criteria for 
treatment. The referred clinician should become familiar with the terms and criteria presented in Tables 1-
5 and take a thorough history from the patient in collaboration with the other members of the treatment 
team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, 
risks, and benefits of treatment are well understood; and the desire for transition persists. They also need 
to discuss fertility preservation options (see recommendation 1.3) (71,72).
Female-to-male transgender persons. Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in FTM transgender persons (116,117,126-129 Appendix A). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (130). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (320-1000 ng/dL) (Table 11)(131). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see Section 4.0) and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in the FTM individual results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness, and increased sexual desire (132).

In FTM transgender persons, testosterone will result in: mild clitoromegaly; temporary or permanent decreased fertility; deepening of the voice; cessation of menses (usually); and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (133). Clinicians may also administer gonadotropin-releasing hormone analogues or depot medroxyprogesterone to stop menses prior to testosterone treatment and to reduce estrogens to levels found in natal males.

Male-to-female transgender persons. The hormone regimen for MTF transgender individuals is more complex than the FTM regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for natal females. Most published
clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range 

Multiple adjunctive medications are available, such as progestins with anti-androgen activity and 
gonadotropin-releasing hormone agonists (136). Spironolactone reduces testosterone by directly 
inhibiting testosterone secretion and by inhibiting androgen binding to the androgen receptor (117,128). It 
may also have estrogenic activity (137). Cyproterone acetate, a progestational compound with anti-
androgenic properties (116,127,138), is widely used in Europe. There are some data regarding with oral 
medroxyprogesterone. 5-alpha reductase inhibitors do not reduce testosterone levels effectively and have 
adverse effects (Chiraco, Andrology: 2016).

Dittrich (136) reported that monthly doses of the GnRH agonist goserelin acetate in combination 
with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 
60 MTF transgender persons. Leuprolide and transdermal estrogen were as effective as cyproterone and 
transdermal estrogen in a comparative retrospective study (139).

Patients can take estrogen as oral conjugated estrogens, transdermal 17β-estradiol, or parenteral 
estrogen esters (Table 11). They should not take ethinyl estradiol (134,140).

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular 
estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogens use. Clinicians should 
measure serum estradiol and maintain it at the level for pre-menopausal women (<200-300 pg/mL), and 
the serum testosterone level should be in the female range (<50 ng/dL). The transdermal preparations and 
injectable depo estradiol preparations may confer an advantage in older transgender women who may be 
at higher risk for thromboembolic disease (141).
Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones (e.g., persons with diabetes, liver disease, cardiovascular disease, or who smoke) should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in MTF transgender persons to avoid increased risk of thromboembolism and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (142).

Not all individuals with GD/gender incongruence seek treatment as described (e.g., male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (143). We need prospective studies to better understand treatment options for these persons.

3.4 We suggest that endocrinologists talk to their patients about the onset and time course of physical changes induced by cross-sex hormone treatment. (2 |⊕| OOO)
Evidence

**Female-to-male transgender persons.** Physical changes that are expected to occur during the first 3 months of the initiation of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice, mild clitoromegaly, and, in some individuals, male pattern hair loss (117,138,144,145) (Table 1).

**Male-to-female transgender persons.** Physical changes that may occur in the first 3-6 months of estrogen and anti-androgen therapy include decreased sexual desire and spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, breast tissue growth, and redistribution of fat mass (117,134,141,144-146) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (117,134,141,145). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in MTF persons has been studied (145), precise information about other changes induced by sex hormones is lacking (138). There is a great deal of variability between individuals, as evidenced during pubertal development.

**Values and Preferences**

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (e.g., breast, face, and body habitus). Clear expectations for the extent and timing of sex-hormone-induced changes may prevent the potential harm and expense of unnecessary procedures.
4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender man and women confers many of the same risks associated with sex hormone replacement therapy in non-transgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (126,134).

4.1 We suggest regular clinical and laboratory monitoring every 3 months during the first year of hormone therapy for FTM and MTF transgender man and women and then once or twice yearly. (27,145)

Evidence

Pretreatment screening and appropriate regular medical monitoring is recommended for both FTM and MTF transgender persons during the endocrine transition and periodically thereafter (27,145). Clinicians should monitor weight and blood pressure, conduct physical exams, pose routine health questions focused on risk factors and medication use, perform complete blood counts, and assess renal function, lipids, and glucose metabolism.

Female-to-male transgender persons. Table 15 contains a standard monitoring plan for individuals on testosterone therapy. Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (130).
Since oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (147,148). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (138,140,149).

**Male-to-female transgender persons.** Table 1 contains a standard monitoring plan for individuals on estrogens, gonadotropin suppression, or anti-androgens. Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitoring serum estradiol levels using labs participating in external quality control, as measurements of estradiol in blood can be very challenging (150).

Venous thromboembolism may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (146). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (141). The incidence decreased when clinicians stops administering ethinyl estradiol (146). Thus, the use of synthetic estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1/60 of MTF persons treated with a gonadotropin releasing hormone analog and oral estradiol (136). The one patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase. In an Austrian gender clinic, administering gender-affirming hormones to 162 MTF and 89 FTM persons was not associated with venous thromboembolism despite an 8.0% and 5.6% incidence of thrombophilia (151). A more recent multi-national study reported only 10 cases of VTE from cohort of 1,073 subjects (152). Thrombophilia screening of transgender persons.
initiating hormone treatment should be restricted to those with a personal or family history of venous thromboembolism (151). Monitoring D-dimer levels during treatment is not recommended (153).

4.2 We suggest periodically monitoring prolactin levels in MTF transgender persons treated with estrogens. (2|⊕⊕OO)

Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term estrogen therapy (154-157). Up to 20% of transgender women treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (158). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or cessation of cyproterone acetate (159) (Bunck MC, BMJ Case Rep, 2009; Nota NM, Andrologia. 2016).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and biannually thereafter. Given only a few case studies reported prolactinomas, and they were not reported in large cohorts of estrogen-treated persons, the risk of prolactinoma is likely to be very low.

Since the major presenting findings of micro-prolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in MTF persons, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels.
4.3 We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors. (2|⊕|OO)

Evidence

**Female-to-male transgender persons.** Administering testosterone to FTM persons results in a more atherogenic lipid profile with lowered HDL cholesterol and higher triglyceride and LDL cholesterol values (160-163). Studies of the effect of testosterone on insulin sensitivity have mixed results (162,164).

A randomized, open-label uncontrolled safety study of FTM persons treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (165) (The effect of sex steroids on lipids, bone health, thrombotic events, cardiovascular events and mortality in transgender individuals: a systematic review and meta-analysis). Numerous studies have demonstrated the effects of cross-sex hormone treatment on the cardiovascular system (163,166-168). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (146). Likewise, a meta-analysis of 19 randomized trials in men on testosterone replacement showed no increased incidence of cardiovascular events (169).

A systematic review of the literature found that data were insufficient, due to very low quality evidence, to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or venous thromboembolism in FTM persons (160). Future research is needed to ascertain harms of hormonal therapies (160). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (170).
The effect of sex steroids on lipids, bone health, thrombotic events, cardiovascular events and mortality in transgender individuals: a systematic review and meta-analysis

**Male-to-female transgender persons.** A prospective study of MTF subjects found favorable changes in lipid parameters with increased HDL and decreased LDL concentrations (162). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (171). 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 (146).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental in MTF persons (160). With aging, there is usually an increase of body weight and, therefore, as with non-transgender individuals, clinicians should monitor glucose and lipid metabolism and blood pressure regularly and manage them regularly according to established guidelines (170).

4.4 We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕OO)

**Evidence**

**Female-to-male transgender persons.** Baseline bone mineral levels in FTMs are generally in the normal range (172). However, adequate dosing of testosterone is important to maintain bone mass in FTM persons (173,174). In one study (174), serum LH levels were inversely related to BMD, 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 transgender persons. A baseline study of BMD reported T scores less than -2.5 in 16 percent of MTF individuals (175). In aging natal males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (176,177) and is more important for peak bone mass (178). Estrogen preserves BMD in MTF persons who continue on estrogen and anti-androgen therapies (172,174,175,179,180).

Fracture data in transgender men and women are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss.

4.5 We suggest that MTF transgender persons, who have no known increased risk of breast cancer, follow breast-screening guidelines recommended for natal women. (2 ⊕⊕OO)

4.6 We suggest that MTF transgender persons treated with estrogens follow screening guidelines for prostatic disease and prostate cancer recommended for natal men. (2 ⊕OOO)

Evidence

Breast cancer is a concern in transgender women. Studies have reported a few cases of breast cancer in MTF transgender persons (181-184). A Dutch study of 1,800 transgender women followed for a mean of 15 years (range 1-30 years) found only one case of breast cancer. 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 (132).
Women with primary hypogonadism (Turner’s syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (185,186). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20-30 years). We need long-term studies to determine the actual risk and the role of screening mammograms. Regular exams and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen-deprivation therapy (187). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (188). Although van Kesteren (189) reported that estrogen therapy does not induce hypertrophy or pre-malignant changes in the prostates of MTF transgender persons, Studies have reported cases of benign prostatic hyperplasia in MTF transgender persons treated with estrogens for 20-25 years (190,191). Studies have also reported a few cases of prostate carcinoma in MTF transgender persons (192-196).

MTF persons may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for MTF persons who transitioned after age 20 to have annual screening digital rectal exams after age 50 and PSA tests consistent with United States Preventive Services Task Force Guidelines (197).
Remarks

There have been case reports of breast cancer developing in subareolar tissue in FTM individuals (198,199).

4.7 We recommend that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (1 |OOO)

Evidence

Although aromatization of testosterone to estradiol in FTM transgender persons has been suggested as a risk factor for endometrial cancer (200), no cases have been reported. When FTM transgender persons undergo hysterectomy, the uterus is small and there is endometrial atrophy (201,202).

Studies have reported that expression of the androgen receptor increases in the ovaries after long-term administration of testosterone, which may be an indication of increased risk of ovarian cancer (203).

Studies have reported cases of ovarian cancer (204,205). The relative safety of laparoscopic total hysterectomy argues for preventing the risks of reproductive tract cancers and other diseases through surgery (206).

Values

Given the discomfort that FTM transgender persons experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on 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.
Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. In addition, the approval required to change the sex in a birth certificate for FTM transgender persons may be dependent upon having a complete hysterectomy; each patient should be assisted in researching and counseled concerning such non-medical administrative criteria. If individuals decide not to undergo hysterectomy, screening for cervical cancer is just as medically necessary as it is for natal females.

5.0 Surgery for Sex Reassignment

For many transgender adults, genital gender-affirming surgery may be the necessary step towards achieving their ultimate goal of living successfully in their desired gender role. Although surgery on several different body structures is possible during sex reassignment, the most important issue is the genital surgery and removal of the gonads. The surgical techniques have improved markedly during the past 10 years. Cosmetic genital surgery that preserves neurological sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (171). In addition, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (68,138). The person must be both eligible and ready for such a procedure (Table 16).

Surgery is an irreversible intervention. The WPATH Standards of Care (207) emphasizes that the “threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention.” If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of cross sex hormone treatment, or if the person is ambivalent about surgery, then the individual should not be referred for surgery (208,209).
Gender-affirming genital surgeries available to the MTF transgender persons consist of gonadectomy, penectomy, and creation of a vagina (210,211). Surgeons often invert the skin of the penis to form the wall of the vagina and several literatures reviews have reported on outcomes (Horbach SER, A Systematic Review of Surgical Techniques. J Sex Med 2015). Sometimes there is inadequate tissue to form a full neo vagina so clinicians have revisited using intestine and found it to be successful (91,213,214). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (215,216).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also adding a G spot to the vagina to increase sensation (217). Most recently, plastic surgeons have developed techniques to fashion labia minora.

Neo vaginal prolapse and other complications do sometimes occur (218,219). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function should be preserved following genital gender-affirming surgery (220,221).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of FTM persons (222,223). No studies have compared the effectiveness of speech therapy, surgery, or combined treatment.
Breast size in genetic females exhibits a very broad spectrum. For MTF transgender persons to make the best-informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, since the breasts continue to grow during that time (136,145).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or laser treatments. Other feminizing surgery, such as that to feminize the face, is now becoming more popular (224-226).

Gender-affirming genital surgeries available to FTM transgender persons have been less satisfactory. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (227,228). Radial forearm flap seems to be the most satisfactory procedure (213,229). Other flaps also exist (230). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (231,232), but results are inconsistent (233). Surgeons can make stiffening possible only if they imbed some mechanical device in the penis, (e.g., a rod or some inflatable apparatus) (234,235). Many choose a metadoioplasty that exteriorizes or brings forward the clitoris, which may be voided when the patient stands. (236,237).

Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (238). Patients usually have these procedures, as well as oophorectomy, vaginectomy, and complete hysterectomy, after a few years of androgen therapy. Surgeons can safely perform them vaginally with laparoscopy.
The most important ancillary surgery for the FTM is mastectomy. Breast size only partially regresses with androgen therapy (145). In adults, discussions about mastectomy usually take place after androgen therapy has started. Since some FTM transgender adolescents present after significant breast development has occurred, they may consider mastectomy before age 18. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (239,240). These often involve chest contouring (241). Mastectomy is necessary for living comfortably in the new gender (241).

5.1 We recommend that transgender individuals consider genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary. (1|⊕OOO)

5.2 We recommend that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment. (1|⊕OOO)

5.3 We recommend that the clinician responsible for endocrine treatment medically clear transgender individuals for gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (1|⊕OOO)

5.4 We recommend that clinicians refer hormone-treated adolescents for surgery when 1) the individual has had a satisfactory social role change, 2) the individual is satisfied about the hormonal effects, and 3) the individual desires definitive surgical changes. (1|⊕OOO)
5.5 We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18-year-old or legal age of majority in his or her country.

5.6 We suggest that clinicians determine the timing of breast surgery for FTM transgender persons based upon the physical and mental health status of the individual. (1 |⊕ΟΟ)

Evidence

Due to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. A systematic review does describe large numbers of studies reporting satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (242). For FTM, the outcomes are less certain although the problems are now better understood (243).

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies the eligibility and readiness criteria (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (160). For this reason, the surgeon and the hormone prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery.

Although one study suggests that preoperative factors, such as compliance, are less important for patient satisfaction than are the physical postoperative results (62), other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not do achieve treatment goals (244) and experience higher rates of postoperative
infections and other complications (245,246). 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 (208).

An endocrinologist should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.
Table 1. Definitions of Terms Used in This Guideline

| **Biological sex; biological male or female** | A term referring to physical aspects of male- and femaleness. As these may not be in line with each other (e.g. a person with XY chromosomes may have female appearing genitalia), the terms biological sex and biological (fe)male are imprecise and should be avoided. |
| **Cisgender** | Not transgender. An alternative way to describe individuals who are not transgender is simply to say non-transgender people. |
| **Gender dysphoria** | The distress and unease experienced if gender identity and assigned gender are not completely congruent. (see Table 2) In 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which replaced the entry “Gender Identity Disorder” with Gender Dysphoria, and changed the criteria for diagnosis. |
| **Gender Expression** | External manifestations of gender, expressed through one’s name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than the gender they were assigned at birth. |
| **Gender identity / experienced gender** | One’s internal, deeply held sense of one’s gender. For transgender people, their gender identity does not match the sex they were assigned at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below) gender identity is not visible to others. |
| **Gender identity disorder** | Name of the diagnosis in previous versions of DSM. See Gender Dysphoria. The name is also used for the child diagnosis in the ICD-10. The proposed name for IC-11 is gender incongruence of childhood. |
| **Gender Incongruence** | An umbrella term used when the gender identity and/or gender expression differs from what is typically associated with gender assigned at birth. Gender incongruence is also the proposed name of the gender identity related diagnoses in ICD-11. Not all gender incongruent individuals seek treatment. |
| **Gender Variance. See Gender Incongruence** | |
| **Gender reassignment** | refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and surgery. This is also called gender confirming or gender-affirming treatment. |
| **Gender reassignment surgery** | (gender confirming / affirming surgery) refers only to the surgical part of this treatment. |
| **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 associated with or typical of the social role as men or as women. |
| **Natal Sex** | refers to sex assigned at birth, usually based on genital anatomy. |
**Sex** refers to attributes that characterize biological maleness 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.

**Sexual orientation** describes an individual’s enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or gender queer.

**Transgender** *(adj.)*
An umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with the sex they were assigned at birth. Not all transgender individuals seek treatment.

**Transgender man [Trans man] (Female-to-Male, FTM)**
Individuals assigned female at birth but who identify and live as men.

**Transgender woman [Trans woman] (Male-to-Female MTF)**
Individuals assigned male at birth but who identify and live as women.

**Transition** refers to the process during which trans gender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.

**Transsexual** *(adj.)*
An older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.
### Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults (APA, 2013)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 months’ duration, as manifested by at least two of the following:</td>
</tr>
<tr>
<td></td>
<td>1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).</td>
</tr>
<tr>
<td></td>
<td>2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).</td>
</tr>
<tr>
<td></td>
<td>3. A strong desire for the primary and/or secondary sex characteristics of the other gender.</td>
</tr>
<tr>
<td></td>
<td>4. A strong desire to be of the other gender (or some alternative gender different from one’s assigned gender).</td>
</tr>
<tr>
<td></td>
<td>5. A strong desire to be treated as the other gender (or some alternative gender different from one’s assigned gender).</td>
</tr>
<tr>
<td></td>
<td>6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s assigned gender).</td>
</tr>
<tr>
<td>B</td>
<td>The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
</tr>
</tbody>
</table>

Specify if:

With a disorder of sex development.

Specify if:

Post-transition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).
Table 3. *ICD-10* Criteria for Transsexualism and Gender Identity Disorder of Childhood  
(WHO, 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, DSD, or chromosomal abnormality.

Table 4. Eligibility Criteria for Hormone Therapy for Adults (according to WPATH, 2011)  
(17)

Adults are eligible for cross-sex hormone treatment if:

1. There is persistent, well-documented gender dysphoria/gender incongruence;
2. They have the capacity to make a fully informed decision and to consent for treatment;
3. They are the age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. Mental health concerns, if present, must be reasonably well-controlled.

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Table 5. Eligibility Criteria for Hormone Therapy for Adolescents (according to WPATH)

Adolescents are eligible and ready for GnRH agonists treatment if:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);

2. Gender dysphoria emerged or worsened with the onset of puberty;

3. Any co-existing psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent’s situation and functioning are stable enough to start treatment;

4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Adolescents are eligible for cross-sex hormone treatment if they fulfill the criteria for GnRH treatment.

Readiness requires the adolescent to be capable of overseeing the consequences of this partially irreversible treatment in order to give informed consent, and should be assessed by a multidisciplinary team. At age 16 yr most adolescents are thought to have reached such capability.
### 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, testicular volume <4 ml
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4-6 ml
3. Penis longer, testes larger (8-12 ml)
4. Penis larger, glans and breadth increase in size; testes larger (12-15 ml), scrotum dark
5. Penis and testes adult size (>15 ml)

Adapted from (62)

(Copyright Pending)
Table 7. Follow-up Protocol During Suppression of Puberty

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3-6 months</td>
<td>Anthropometry: height, weight, sitting height, blood pressure, Tanner stages</td>
</tr>
<tr>
<td>Every 6-12 months</td>
<td>Laboratory: LH, FSH, E2/T, 25OH vitamin D</td>
</tr>
<tr>
<td>Every 1-2 years</td>
<td>Bone density using DXA</td>
</tr>
<tr>
<td></td>
<td>Bone age on X-ray of the left hand</td>
</tr>
</tbody>
</table>
Table 8. 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 – 6 mg per day

In postpubertal MTF adolescents the dose of 17-beta estradiol can be increased more rapidly:
- 1 mg/day for 6 months
- 2 mg/day

**Induction of female puberty with transdermal 17-beta estradiol, increasing the dose every 6 months (new patch is placed every 3.5 days):**
- 6.25-12.5 μg/24 hr (cut 25 μg patch into quarters, then halves)
- 25 μg/24 hr
- 37.5 μg/24 hr
- 50 – 200 μg/24 hr

For alternatives once at adult dose see table 11.
Adjust maintenance dose to mimic physiological estradiol levels, see table 14.

**Induction of male puberty with testosterone esters increasing the dose every 6 months (im or sc):**
- 25 mg/m²/2 weeks (or alternatively, half this dose weekly)
- 50 mg/m²/2 weeks
- 75 mg/m²/2 weeks
- 100 mg/m²/2 weeks
- Adult dose = 100 – 200 mg every 2 weeks

In postpubertal FTM adolescents the dose of testosterone esters can be increased more rapidly:
- 75 mg/2 weeks for 6 months
- 125 mg/2 weeks

For alternatives once at adult dose see table 11.
Adjust maintenance dose to mimic physiological testosterone levels, see table 15.
Table 9. Follow-Up Protocol During Induction of Puberty

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Every 3-6 months</strong></td>
<td>Anthropometry: height, weight, sitting height, blood pressure, Tanner stages</td>
</tr>
<tr>
<td>Every 6-12 months</td>
<td>Laboratory: complete blood count (in FTM), liver enzymes, lipids, prolactin (in MTF), testosterone and estradiol</td>
</tr>
<tr>
<td><strong>Every 1-2 years</strong></td>
<td>BMD using DXA</td>
</tr>
<tr>
<td></td>
<td>Bone age on X-ray of the left hand</td>
</tr>
<tr>
<td></td>
<td>BMD should be monitored into adulthood (until the age of 25-30 years or until peak bone mass has been reached).</td>
</tr>
<tr>
<td></td>
<td>For recommendations on monitoring once pubertal induction has been completed see tables 15 and 16.</td>
</tr>
</tbody>
</table>

(Copyright Pending)
Table 10. Medical Conditions that Can Be Exacerbated by Cross-Sex Hormone Therapy

<table>
<thead>
<tr>
<th>Transgender Female (MTF) – Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk of serious adverse outcomes</td>
</tr>
<tr>
<td>• thromboembolic disease</td>
</tr>
<tr>
<td>Moderate risk of adverse outcomes</td>
</tr>
<tr>
<td>• macroprolactinoma</td>
</tr>
<tr>
<td>• severe liver dysfunction (transaminases &gt;3x upper limit of normal)</td>
</tr>
<tr>
<td>• breast cancer</td>
</tr>
<tr>
<td>• coronary artery disease</td>
</tr>
<tr>
<td>• cerebrovascular disease</td>
</tr>
<tr>
<td>• severe migraine headaches</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transgender Male (FTM) – Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk of serious adverse outcomes</td>
</tr>
<tr>
<td>• erythrocytosis (hematocrit &gt;50%)</td>
</tr>
<tr>
<td>Moderate risk of adverse outcomes</td>
</tr>
<tr>
<td>• severe liver dysfunction (transaminases &gt; 3x upper limit of normal)</td>
</tr>
<tr>
<td>• coronary artery disease</td>
</tr>
<tr>
<td>• cerebrovascular disease</td>
</tr>
<tr>
<td>• hypertension</td>
</tr>
<tr>
<td>• breast or uterine cancer</td>
</tr>
</tbody>
</table>
### Table 11. Hormone Regimens in Transgender Persons

<table>
<thead>
<tr>
<th>Male-to-Female Transgender Persons*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen</strong></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>2.0 - 6.0 mg/day</td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
</tr>
<tr>
<td>Estradiol Transdermal patch</td>
<td>0.025 - 0.2 mg/day</td>
</tr>
<tr>
<td>New Patch Placed every 3 – 5 days</td>
<td></td>
</tr>
<tr>
<td>Parenteral</td>
<td></td>
</tr>
<tr>
<td>Estradiol valerate or cypionate</td>
<td>5 - 30 mg IM every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>2 - 10 mg IM every week</td>
</tr>
<tr>
<td><strong>Anti-Androgens</strong></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100- 400 mg/day</td>
</tr>
<tr>
<td>Cyproterone acetate**</td>
<td>25 - 50 mg/day</td>
</tr>
<tr>
<td><strong>Gonadotropin-releasing hormone agonist</strong></td>
<td>3.75 mg SQ (C) monthly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female-To-Male Transgender Persons</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testosterone</strong></td>
<td></td>
</tr>
<tr>
<td>Parenteral Testosterone</td>
<td></td>
</tr>
<tr>
<td>Testosterone enanthate or cypionate 100 – 200 mg IM or SQ (C) q2wks</td>
<td>or 50% per week</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone undecanoate**</td>
<td>1000 mg every 12 weeks</td>
</tr>
<tr>
<td>Transdermal testosterone</td>
<td></td>
</tr>
<tr>
<td>Testosterone gel 1.6%****</td>
<td>50 – 100 mg/day</td>
</tr>
<tr>
<td>Testosterone transdermal patch</td>
<td>2.5 – 7.5 mg/day</td>
</tr>
</tbody>
</table>

* Estrogens used with or without anti-androgens or gonadotropin-releasing hormone agonist

** Not available in the USA

*** 1000 mg initially followed by an injection at 6 weeks then at 12-week intervals

**** Avoid exposure to other individuals

(Copyright Pending)
Table 12. Masculinizing Effects in Female-To-Male Transsexual Persons

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset 1</th>
<th>Maximum 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Facial/body hair growth</td>
<td>6-12 months</td>
<td>4-5 years</td>
</tr>
<tr>
<td>Scalp hair loss</td>
<td>6-12 months</td>
<td>*</td>
</tr>
<tr>
<td>Increased muscle mass/strength</td>
<td>6-12 months</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>1-6 months</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Cessation of menses</td>
<td>2-6 months</td>
<td>**</td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Deepening of voice</td>
<td>6-12 months</td>
<td>1-2 years</td>
</tr>
</tbody>
</table>

1. Estimates represent clinical observations, Toorians et al., 2003 (141), Gooren et al., 1985 (159), Asscheman et al. 1988 (158), Wierckx et al., 2014 (247).
* Prevention and treatment as recommended for biological men.
** Menorrhagia requires diagnosis and treatment by a gynecologist.

(Copyright Pending)

Table 13. Feminizing Effects in Male-To-Female Transsexual Persons

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset 1</th>
<th>Maximum 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redistribution of body fat</td>
<td>3-6 months</td>
<td>2-3 years</td>
</tr>
<tr>
<td>Decrease in muscle mass and strength</td>
<td>3-6 months</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Softening of skin/decreased oiliness</td>
<td>3-6 months</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decreased sexual desire</td>
<td>1-3 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>1-3 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Male sexual dysfunction</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Breast growth</td>
<td>3-6 months</td>
<td>2-3 Years</td>
</tr>
<tr>
<td>Decreased testicular volume</td>
<td>3-6 months</td>
<td>2-3 Years</td>
</tr>
<tr>
<td>Decreased sperm production</td>
<td>Unknown</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>Decreased terminal hair growth</td>
<td>6-12 months</td>
<td>&gt; 3 years*</td>
</tr>
<tr>
<td>Scalp hair</td>
<td>No regrowth</td>
<td>**</td>
</tr>
<tr>
<td>Voice changes</td>
<td>None</td>
<td>***</td>
</tr>
</tbody>
</table>

1. Estimates represent clinical observations, Toorians et al., 2003 (141), Gooren et al., 1985 (159), Asscheman et al. 1988 (158).
* Complete removal of male sexual hair requires electrolysis or laser treatment or both.
** Familial scalp hair loss may occur if estrogens are stopped.
*** Treatment by speech pathologists for voice training is most effective.

(Copyright Pending)
Table 14. Monitoring of Transsexual Persons on Cross-Hormone Therapy  
Male-To-Female Persons

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Evaluate patient every 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.</td>
</tr>
</tbody>
</table>
| 2. | Measure serum testosterone and estradiol every 3 months.  
   a. Serum testosterone levels should be <50 ng/mL.  
   b. Serum estradiol should not exceed the peak physiologic range: 200 - 300ng/ml. |
| 3. | For individuals on spironolactone, serum electrolytes particularly potassium should be monitored every 2-3 months in the first year and annually thereafter. |
| 4. | Routine cancer screening recommended as in non-transgender individuals (breasts, colon, prostate). |
| 5. | Consider BMD testing at baseline (175). 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 15. Monitoring of Transsexual Persons on Cross-Hormone Therapy
Female-To-Male Persons

1. Evaluate patient every 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 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 the level is >700 ng/dl or <400 ng/dl, adjust dose accordingly. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is below 400 ng/dl, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2 hours after application).

3. Measure CBC at baseline and every 3 months for the first year and then 1-2 times a year. Monitor weight, blood pressure, and lipids at regular intervals.

4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy or who develop risks for bone loss..

5. If cervical tissue is present, an annual pap smear is recommended by the American College of Obstetricians and Gynecologists.

6. Ovariectomy should be considered after completion of hormone transition;

7. Sub- and peri-areolar annual breast exams if mastectomy performed; If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

* Adapted from Ott et al., 2010 (151), Lapauw et al., 2008 (144).

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Table 16. Gender-affirming Surgery – Eligibility and Readiness Criteria

<table>
<thead>
<tr>
<th>Individuals treated with gender-affirming hormones are considered eligible for gender-affirming surgery if they:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- are of the legal age of majority in their nation</td>
<td></td>
</tr>
<tr>
<td>- have used gender-affirming hormones continuously and responsibly during 12 months (if they have no medical contraindication)</td>
<td></td>
</tr>
<tr>
<td>- had a successful continuous full-time living in the new gender role (REL) during 12 months</td>
<td></td>
</tr>
<tr>
<td>- (if required by the MHP) have regularly participated in psychotherapy throughout the RLE at a frequency determined jointly by the patient and the MHP</td>
<td></td>
</tr>
<tr>
<td>- have shown demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals, treated with gender-affirming hormones, should fulfill the following readiness criteria prior to gender-affirming surgery:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- demonstrable progress in consolidating one’s gender identity</td>
<td></td>
</tr>
<tr>
<td>- demonstrable progress in dealing with work, family, and interpersonal issues resulting in a significantly better state of mental health</td>
<td></td>
</tr>
</tbody>
</table>

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Appendix A. Protocol Female to Male

<table>
<thead>
<tr>
<th>Trans Men Year</th>
<th>Study</th>
<th>Population</th>
<th>Age (years)</th>
<th>Medication</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Deutsch et al., 2015 (248)</td>
<td>31 FtM's</td>
<td>29 ± 6.9</td>
<td>Testosterone cypionate 200 mg/ml weekly</td>
<td>6 months</td>
</tr>
<tr>
<td>2015</td>
<td>van Caenegem et al., 2015 (172)</td>
<td>23 FtM's</td>
<td>27 ± 9</td>
<td>Nebido 1000mg/12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>van Caenegem et al...</td>
<td>20 FtM's</td>
<td>25.6 ± 8.0</td>
<td>Nebido 1000mg/12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>2014</td>
<td>Pelusj et al.2014</td>
<td>45 FtM's</td>
<td></td>
<td>testoviron 100mg/10 days; testosterone gel 50mg/day;TU 1000mg/6-12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>2014</td>
<td>Wierckx et al.2014</td>
<td>53 FtM's</td>
<td></td>
<td>Nebido 1000mg/5-12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>2010</td>
<td>Mueller et al.2010</td>
<td>45 FtM's</td>
<td>30.4 ± 9.1</td>
<td>Testosterone undecanoat 1000mg im/12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>Year</td>
<td>Study Reference</td>
<td>Participants</td>
<td>Mean Age (Range)</td>
<td>Treatment</td>
<td>Duration</td>
</tr>
<tr>
<td>------</td>
<td>--------------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>2010</td>
<td>Cupisti et al., 2010</td>
<td>45 FtM’s</td>
<td>29.9 (CI 27.8-32.0)</td>
<td>Testosterone undecanoat 1000mg/12 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>2007</td>
<td>Haraldsen et al., 2007</td>
<td>21 FtM’s</td>
<td>25.1 ± 4.8</td>
<td>Testosterone enantate 250mg/3 weeks im</td>
<td>12 months</td>
</tr>
<tr>
<td>2007</td>
<td>Mueller et al., 2007</td>
<td>37 FtM’s</td>
<td>29.6 ± 9.0</td>
<td>Nebido 1000mg/3 months</td>
<td>12 months</td>
</tr>
<tr>
<td>2006</td>
<td>Berra et al., 2006</td>
<td>16 FtM’s</td>
<td>30.4 ± 5.4</td>
<td>Testoviron 100mg/10 days im</td>
<td>6 months</td>
</tr>
<tr>
<td>2004</td>
<td>Giltay et al., 2004</td>
<td>81 FtM’s</td>
<td></td>
<td>Sustanon 250mg/2 weeks; TU 240 mg/day</td>
<td>3-4 months</td>
</tr>
<tr>
<td>2003</td>
<td>Elbers et al., 1998</td>
<td>17 FtM’s</td>
<td>23 ± 5</td>
<td>Sustanon 250mg/2 wkn</td>
<td>12 months</td>
</tr>
<tr>
<td>1998</td>
<td>Giltay et al., 1998</td>
<td>15 FtM’s</td>
<td>median 23 (range 16-33)</td>
<td>Sustanon 250mg/2 wkn</td>
<td>12 months</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Gender Reassignment</th>
<th>Age (Mean ± SD)</th>
<th>Testosterone Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Elbers et al., 1997</td>
<td>10 FtM's</td>
<td>24 ± 6</td>
<td>Sustanon 250mg/2 weeks</td>
<td>12 months</td>
</tr>
<tr>
<td>1997</td>
<td>Elbers et al., 2007</td>
<td>15 FtM's</td>
<td>23 ± 5</td>
<td>Sustanon 250mg/2 weeks</td>
<td>12 months</td>
</tr>
</tbody>
</table>

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Appended B. Protocol Male to Female - Women

<table>
<thead>
<tr>
<th>Trans Woman Year</th>
<th>Study</th>
<th>Population</th>
<th>Age (years)</th>
<th>Medication</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Deutsch et al., 2015</td>
<td>16 MtF’s</td>
<td>29 ± 9.4</td>
<td>Spironolactone 100mg/day*+N=14 17B E2 2 mg 2dd subl, N=1 Estradiol patch 100 mcg/day N=1 E2 valerate 20mg im/2 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>van Caenegem et al…</td>
<td>40 MtF’s</td>
<td>31.5 ± 12.9</td>
<td>CPA**50mg/day + N=29 estradiol valerate 4mg/day N=11 17-β estradiol patch 100 mcg/24h</td>
<td>12 months</td>
</tr>
<tr>
<td>2014</td>
<td>Wierckx et al.2014</td>
<td>40 MtF’s</td>
<td></td>
<td>CPA**50mg/day + estradiol valerate 4mg/day</td>
<td>12 months</td>
</tr>
<tr>
<td>2014</td>
<td>Wierckx et al.2014</td>
<td>13 MtF’s</td>
<td></td>
<td>CPA**50mg/day + 17-β estradiol patch 100 mcg/24h</td>
<td>12 months</td>
</tr>
<tr>
<td>2011</td>
<td>Mueller et al.2011</td>
<td>84 MtF’s</td>
<td>36.3 ± 11.3</td>
<td>3.8mg goserelin acetate/4 weeks + 10mg oestradiol-17b valerate im/10 days</td>
<td>12 months</td>
</tr>
<tr>
<td>2007</td>
<td>Haraldsen et al.2007</td>
<td>12 MtF’s</td>
<td>29.3 ± 7.8</td>
<td>50 mcg oral ethinylestradiol***</td>
<td>12 months</td>
</tr>
<tr>
<td>2003</td>
<td>Elbers et al 2003</td>
<td>20 MtF’s</td>
<td>26 ± 6</td>
<td>100 mg CPA**+ 100 mcg ethinyl estradiol</td>
<td>12 months</td>
</tr>
<tr>
<td>1999</td>
<td>Elbers et al 1999</td>
<td>20 MtF’s</td>
<td>26 ± 6</td>
<td>100 mg CPA**+ 100 mcg ethinyl estradiol</td>
<td>12 months</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Subjects</td>
<td>Age Range</td>
<td>Therapy</td>
<td>Duration</td>
</tr>
<tr>
<td>------</td>
<td>------------------</td>
<td>----------</td>
<td>-----------</td>
<td>----------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>1998</td>
<td>Giltay et al.1998</td>
<td>18 MtF's</td>
<td>median 27 (range 18-37)</td>
<td>100 mg CPA**+ 100 mcg ethinyl estradiol</td>
<td>12 months</td>
</tr>
<tr>
<td>1997</td>
<td>Elbers et al.1997(2)</td>
<td>17 MtF's</td>
<td>26 ± 7</td>
<td>100 mg CPA**+ 100 mcg ethinyl estradiol</td>
<td>12 months</td>
</tr>
</tbody>
</table>

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