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

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Objective: The aim was to formulate practice guidelines for endocrine treatment oftranssexual persons.

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

Consensus Process: Committees and members of The Endocrine Society, European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and World Professional Association for Transgender Health commented on preliminary drafts of these guidelines.

Conclusions: Transsexual persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and 2) maintain sex hormone levels within the normal range for the person's desired gender. A mental health professional (MHP) must recommend endocrine treatment and participate in ongoing care throughout the endocrine transition and decision for surgical sex reassignment. The endocrinologist must confirm the diagnostic criteria the MHP used to make these recommendations. Because a diagnosis of transsexualism in a prepubertal child cannot be made with certainty, we do not recommend endocrine treatment of prepubertal children. We recommend treating transsexual adolescents (Tanner stage 2) by suppressing puberty with GnRH analogues until age 16 years old, after which cross-sex hormones may be given. We suggest suppressing endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks in adult transsexual persons.
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Summary of Recommendations

1.0 Diagnostic procedure

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

1.2 Given the high rate of remission of GID after the onset of puberty, we recommend against a complete social

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Abbreviations: BMD, Bone mineral density; FTM, female-to-male; GID, gender identity disorder; MHP, mental health professional; MTF, male-to-female; RLE, real-life experience.

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role change and hormone treatment in prepubertal children with GID. (1 ⊕⊕○○)

1.3 We recommend that physicians evaluate and ensure that applicants understand the reversible and irreversible effects of hormone suppression (*e.g.* GnRH analog treatment) and cross-sex hormone treatment before they start hormone treatment.

1.4 We recommend that all transsexual individuals be informed and counseled regarding options for fertility prior to initiation of puberty suppression in adolescents and prior to treatment with sex hormones of the desired sex in both adolescents and adults.

2.0 Treatment of adolescents

2.1. We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development. (1 ⊕○○○)

2.2. We recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2–3. (1 ⊕⊕○○)

2.3. We recommend that GnRH analogs be used to achieve suppression of pubertal hormones. (1 ⊕⊕○○)

2.4. We suggest that pubertal development of the desired opposite sex be initiated at about the age of 16 yr, using a gradually increasing dose schedule of cross-sex steroids. (2 ⊕○○○)

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

2.6 We suggest deferring surgery until the individual is at least 18 yr old. (2 ⊕○○○)

3.0 Hormonal therapy for transsexual adults

3.1 We recommend that treating endocrinologists confirm the diagnostic criteria of GID or transsexualism and the eligibility and readiness criteria for the endocrine phase of gender transition. (1 ⊕⊕⊕○)

3.2 We recommend that medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment be evaluated and addressed prior to initiation of treatment (see Table 11: Medical conditions that can be exacerbated by cross-sex hormone therapy). (1 ⊕⊕⊕○)

3.3 We suggest that cross-sex hormone levels be maintained in the normal physiological range for the desired gender. (2 ⊕⊕○○)

3.4 We suggest that endocrinologists review the onset and time course of physical changes induced by cross-sex hormone treatment. (2 ⊕⊕○○)

4.0 Adverse outcome prevention and long-term care

4.1 We suggest regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly. (2 ⊕⊕○○)

4.2 We suggest monitoring prolactin levels in male-to-female (MTF) transsexual persons treated with estrogens. (2 ⊕⊕○○)

4.3 We suggest that transsexual persons treated with hormones be evaluated for cardiovascular risk factors. (2 ⊕⊕○○)

4.4 We suggest that bone mineral density (BMD) measurements be obtained if risk factors for osteoporosis exist, specifically in those who stop hormone therapy after gonadectomy. (2 ⊕⊕⊕○)

4.5 We suggest that MTF transsexual persons who have no known increased risk of breast cancer follow breast screening guidelines recommended for biological women. (2 ⊕⊕○○)

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

4.7 We suggest that female-to-male (FTM) transsexual persons evaluate the risks and benefits of including total hysterectomy and oophorectomy as part of sex reassignment surgery. (2 ⊕○○○)

5.0 Surgery for sex reassignment

5.1 We recommend that transsexual persons consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the MHP find surgery advisable. (1 ⊕○○○)

5.2 We recommend that genital sex reassignment surgery be recommended only after completion of at least 1 yr of consistent and compliant hormone treatment. (1 ⊕○○○)

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

Introduction

Men and women have experienced the confusion and anguish resulting from rigid, forced conformity to sexual dimorphism throughout recorded history. Aspects

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of gender variance have been part of biological, psychological, and sociological debates among humans in modern history. The 20th century marked the beginning of a social awakening for men and women "trapped" in the wrong body (1). Harry Benjamin and Magnus Hirschfeld, who met in 1907, pioneered the medical responses to those who sought relief from and resolution of their profound discomfort, enabling the "transsexual," a term coined by Hirschfeld in 1923, to live a gender-appropriate life, occasionally facilitated by surgery (2).

Endocrine treatment of transsexual persons [note: In the current psychiatric classification system, the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR), the term "gender identity disorder" is used instead of "transsexualism" (3)], previously limited to ineffective elixirs, creams, and implants, became reasonable with the availability of diethylstilbesterol in 1938 and after the isolation of testosterone in 1935. Personal stories of role models, treated with hormones and sex reassignment surgery, appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association (HBIGDA) was founded in September 1979; it is now known as the World Professional Association of Transgender Health (WPATH). The Association's "Standards of Care" (SOC) was first published by HBIGDA in 1979, and its sixth edition is currently being revised. These carefully prepared documents have provided mental health and medical professionals with general guidelines for the evaluation and treatment of transsexual persons.

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

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

TABLE 1. Definitions of terms used in this guideline

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
Gender identity is used to describe a person's fundamental sense of being a man, a woman, or of indeterminate sex.
Gender identity disorder (GID) is a DSM-IV-TR diagnosis. This psychiatric diagnosis is given when a strong and persistent cross-gender identification, combined with a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causes clinically significant distress.
Gender role is used to refer to behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as masculine or feminine, that is, more "appropriate" to, or typical of, the social role as men or as women.
Gender dysphoria is the distress and unease experienced if gender identity and sex are not completely congruent.
Sexual orientation can be defined by a person's relative responsiveness to sexual stimuli. The most salient dimension of sexual orientation is the sex of the person to whom one is attracted sexually; sexual orientation is not entirely similar to *sexual identity*; a person may, for example, be predominantly aroused by homoerotic stimuli, yet not regard himself or herself to be gay or lesbian.
Sex reassignment refers to the complete treatment procedure for those who want to adapt their bodies to the desired sex.
Sex reassignment surgery refers only to the surgical part of this treatment.
Transsexual people identify as, or desire to live and be accepted as, a member of the gender opposite to that assigned at birth; the term *male-to-female* (MTF) *transsexual person* refers to a biological male who identifies as, or desires to be, a member of the female gender; *female-to-male* (FTM) *transsexual person* refers to a biological female who identifies as, or desires to be, a member of the male gender.
Transition refers to the period of time during which transsexual persons change their physical, social, and legal characteristics to the gender opposite that of their biological sex. Transition may also be regarded as an ongoing process of physical change and psychological adaptation.

Note: In this Guideline, we have chosen to use the term "transsexual" throughout as defined by the ICD-10 Diagnostic Code (see Table 3). We recognize that "transsexual" and "transgender" are terms often used interchangeably. However, because "transgender" may also be used to identify individuals whose gender identity does not conform to the conventional gender roles of either male or female and who may not seek endocrine treatment as described herein, we prefer to use "transsexual" as an adjective (*e.g.* when referring to persons, individuals, men, or women and, when appropriate, referring to subjects in research studies).

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Etiology of Gender Identity Disorders

One's self-awareness as male or female evolves gradually during infant life and childhood. This process of cognitive and affective learning happens in interaction with parents, peers, and environment, and a fairly accurate timetable exists for the steps in this process (4). Normative psychological literature, however, does not address when gender identity becomes crystallized and what factors contribute to the development of an atypical gender identity. Factors that have been reported in clinical studies may well enhance or perpetuate rather than originate a GID (for an overview, see Ref. 5). Behavioral genetic studies suggest that, in children, atypical gender identity and role development has a heritable component (6, 7). Because, in most cases, GID does not persist into adolescence or adulthood, findings in children with GID cannot be extrapolated to adults.

In adults, psychological studies investigating etiology hardly exist. Studies that have investigated potential causal factors are retrospective and rely on self-report, making the results intrinsically unreliable.

Most attempts to identify biological underpinnings of gender identity in humans have investigated effects of sex steroids on the brain (functions) (for a review, see Ref. 8). Prenatal androgenization may predispose to development of a male gender identity. However, most 46,XY female-raised children with disorders of sex development and a history of prenatal androgen exposure do not develop a male gender identity (9, 10), whereas 46,XX subjects exposed to prenatal androgens show marked behavioral masculinization, but this does not necessarily lead to gender dysphoria (11–13). MTF transsexual individuals, with a male androgen exposure prenatally, develop a female gender identity through unknown mechanisms, apparently overriding the effects of prenatal androgens. There is no comprehensive understanding of hormonal imprinting on gender identity formation. It is of note that, in addition to hormonal factors, genetic mechanisms may bear on psychosexual differentiation (14).

Maternal immunization against the H-Y antigen has been proposed (15, 16). This hypothesis states that the repeatedly reported fraternal birth order effect reflects the progressive immunization of some mothers to Y-linked minor histocompatibility antigens (H-Y antigens) by each succeeding male fetus and the increasing effects of such immunization on the future sexual orientation of each succeeding male fetus. Sibling sex ratio studies have not been experimentally supported (17).

Studies have also failed to find differences in circulating levels of sex steroids between transsexual and nontranssexual individuals (18).

In summary, neither biological nor psychological studies provide a satisfactory explanation for the intriguing phenomenon of GIDs. In both disciplines, studies have been able to correlate certain findings to GIDs, but the findings are not robust and cannot be generalized to the whole population.

Method of Development of Evidence-based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the diagnosis and treatment of transsexual individuals a priority area in need of practice guidelines 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 (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (19). A detailed description of the grading scheme has been published elsewhere (20). The Task Force used the best available research evidence that Task Force members identified and two commissioned systematic reviews (21, 22) to develop some of 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 ⊕◯◯◯ denotes very low quality evidence, ⊕⊕◯◯ denotes low quality, ⊕⊕⊕◯ denotes moderate quality, and ⊕⊕⊕⊕ denotes 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 panelists considered in making the recommendation; in some instances, there are "remarks," a section in which panelists offer 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 panelists and their values and preferences; therefore, these remarks should be considered suggestions. Some statements in this guideline (1.3 and 1.4) are not graded. These are statements the task force felt it was necessary to make, and it considers them matters about which no sensible health-

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care professional could possibly consider advocating the contrary (*e.g.* clinicians should conduct an adequate history taking and physical examination, clinicians should educate patients about their condition). These statements have not been subject to structured review of the evidence and are thus not graded.

1.0 Diagnostic procedure

Sex reassignment is a multidisciplinary treatment. It requires five processes: diagnostic assessment, psychotherapy or counseling, RLE, hormone therapy, and surgical therapy. The focus of this Guideline is hormone therapy, although collaboration with appropriate professionals responsible for each process maximizes a successful outcome. It would be ideal if care could be given by a multidisciplinary team at one treatment center, but this is not always possible. It is essential that all caregivers be aware of and understand the contributions of each discipline and that they communicate throughout the process.

Diagnostic assessment and psychotherapy

Because GID may be accompanied with psychological or psychiatric problems (see Refs. 23–27), it is necessary that the clinician making the GID diagnosis be able 1) to make a distinction between GID and conditions that have similar features; 2) to diagnose accurately psychiatric conditions; and 3) to undertake appropriate treatment thereof. Therefore, the SOC guidelines of the WPATH recommend that the diagnosis be made by a MHP (28). For children and adolescents, the MHP should also have training in child and adolescent developmental psychopathology.

MHPs usually follow the WPATH's SOC. The main aspects of the diagnostic and psychosocial counseling are described below, and evidence supporting the SOC guidelines is given, whenever available.

During the diagnostic procedure, the MHP obtains information from the applicants for sex reassignment and, in the case of adolescents, the parents or guardians regarding various aspects of their general and psychosexual development and current functioning. On the basis of this information the MHP:

- decides whether the applicant fulfills DSM-IV-TR or ICD-10 criteria (see Tables 2 and 3) for GID;
- informs the applicant about the possibilities and limitations of sex reassignment and other kinds of treatment to prevent unrealistically high expectations; and
- assesses potential psychological and social risk factors for unfavorable outcomes of medical interventions.

In cases in which severe psychopathology or circumstances, or both, seriously interfere with the diagnostic work or make satisfactory treatment unlikely, management of the other issues should be addressed first. Literature on postoperative regret suggests that severe psychiatric comorbidity and lack of support may interfere with good outcome (30–33).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (34) and,

TABLE 2. DSM-IV-TR diagnostic criteria for GID (3)

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex).
   In children, the disturbance is manifested by four (or more) of the following:
   1. Repeatedly stated desire to be, or insistence that he or she is, the other sex.
   2. In boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing.
   3. Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex.
   4. Intense desire to participate in the stereotypical games and pastimes of the other sex.
   5. Strong preference for playmates of the other sex.

   In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.
B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.
   In children, the disturbance is manifested by any of the following:
   1. In boys, assertion that his penis or testes is disgusting or will disappear, or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities.
   2. In girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

   In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (*e.g.* request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.
C. The disturbance is not concurrent with a physical intersex condition.
D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Codes based on current age:
302.6 GID in children
302.85 GID in adolescents or adults

Specify whether (for sexually mature individuals):
Sexually attracted to males
Sexually attracted to females
Sexually attracted to both
Sexually attracted to neither

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TABLE 3. ICD-10 criteria for transsexualism and GID of childhood (29)

Transsexualism (F64.0) 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 yr.
3. The disorder is not a symptom of another mental disorder or a genetic, intersex, or chromosomal abnormality.

GID of childhood (F64.2) has separate criteria for girls and for boys.

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

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

preferably, a child psychiatric evaluation (by a clinician other than the diagnostician). Di Ceglie *et al.* (35) showed that 75% of the adolescents referred to their Gender Identity clinic in the United Kingdom reported relationship problems with parents. Therefore, 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 procedure.

The real-life experience

WPATH's SOC states that "the act of fully adopting a new or evolving gender role or gender presentation in everyday life is known as the real-life experience. The real-life experience is essential to the transition to the gender role that is congruent with the patient's gender identity. The real-life experience tests the person's resolve, the capacity to function in the preferred gender, and the adequacy of social, economic, and psychological supports. It assists both the patient and the MHP in their judgments about how to proceed" (28). During the RLE, the person should fully experience life in the desired gender role before irreversible physical treatment is undertaken. Living 12 months full-time in the desired gender role is recommended (28). Testing an applicant's ability to function in the desired gender assists the applicant, the MHP and the endocrinologist in their judgements about how to proceed. During the RLE, the person's feeling about the social transformation, including coping with the responses of others, is a major focus of the counseling. Applicants increasingly start the RLE long before they are referred for hormone treatment.

Eligibility and readiness criteria

The WPATH SOC document requires that both adolescents and adults applying for hormone treatment and surgery satisfy two sets of criteria— eligibility and readiness— before proceeding (28). There are eligibility and readiness criteria for hormone therapy for adults (Table 4) and eligibility cri-

TABLE 4. Hormone therapy for adults

Adults are **eligible** for cross-sex hormone treatment if they (28):
1. Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism (see Tables 2 and 3).
2. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
3. Demonstrate knowledge and understanding of the expected outcomes of hormone treatment, as well as the medical and social risks and benefits; AND
4. Have experienced a documented RLE of at least 3-month duration OR had a period of psychotherapy (duration specified by the MHP after the initial evaluation, usually a minimum of 3 months).

Adults should fulfill the following **readiness criteria** before the cross-sex hormone treatment. The applicant:
1. Has had further consolidation of gender identity during a RLE or psychotherapy.
2. Has made some progress in mastering other identified problems leading to improvement or continuing stable mental health.
3. Is likely to take hormones in a responsible manner.

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TABLE 5. Hormone therapy for adolescents

Adolescents are **eligible** and ready for GnRH treatment if they:

1. Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism.
2. Have experienced puberty to at least Tanner stage 2.
3. Have (early) pubertal changes that have resulted in an increase of their gender dysphoria.
4. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
5. Have adequate psychological and social support during treatment, AND
6. Demonstrate knowledge and understanding of the expected outcomes of GnRH analog treatment, cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and the social risks and benefits of sex reassignment.

Adolescents are **eligible** for cross-sex hormone treatment if they:

1. Fulfill the criteria for GnRH treatment, AND
2. Are 16 yr or older.

Readiness criteria for adolescents eligible for cross-sex hormone treatment are the same as those for adults.

teria for adolescents (Table 5). Eligibility and readiness criteria for sex reassignment surgery in adults and adolescents are the same (see *Section 5.0*). Although the eligibility criteria have not been evaluated in formal studies, a few follow-up studies on adolescents who fulfilled these criteria and had started cross-sex hormone treatment from the age of 16 indicate good postoperative results (36–38).

One study on MTF transsexual subjects reports that outcome was not associated with minimum eligibility requirements of the WPATH's SOC. However, this study was performed among a group of individuals with a relatively high socioeconomic background (39). One study investigating the need for psychotherapy for sex-reassignment applicants, based on questionnaire scores, suggests that "classical" forms of psychotherapy before medical interventions are not needed in about two thirds of the applicants (40).

Recommendations for those involved in the hormone treatment of applicants for sex reassignment

1.1 Recommendation

We recommend that the diagnosis of GID be made by a MHP. For children and adolescents, the MHP must also have training in child and adolescent developmental psychopathology. (1 ⊕⊕◯◯)

1.1 Evidence

GID may be accompanied with psychological or psychiatric problems (see Refs. 23–27). It is therefore necessary that the clinician making the GID diagnosis be able to make a distinction between GID and conditions that have similar features, to accurately diagnose psychiatric conditions, and to ensure that any such conditions are treated appropriately. One condition with similar features is body dysmorphic disorder or Skoptic syndrome, a condition in which a person is preoccupied with or engages in genital self-mutilation, such as castration, penectomy, or clitoridectomy (41).

1.1 Values and Preferences

The Task Force placed a very high value on avoiding harm from hormone treatment to individuals who have conditions other than GID and who may not be ready for the physical changes associated with this treatment, and it 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.

1.2 Recommendation

Given the high rate of remission of GID after the onset of puberty, we recommend against a complete social role change and hormone treatment in prepubertal children with GID. (1 ⊕◯◯◯)

1.2 Evidence

In most children with GID, the GID does not persist into adolescence. The percentages differ between studies, probably dependent upon which version of the DSM was used in childhood, ages of children, and perhaps culture factors. However, the large majority (75–80%) of prepubertal children with a diagnosis of GID in childhood do not turn out to be transsexual in adolescence (42–44); for a review of seven older studies see Ref. 45. Clinical experience suggests that GID can be reliably assessed only after the first signs of puberty.

This recommendation, however, does not imply that children should be entirely denied to show cross-gender behaviors or should be punished for exhibiting such behaviors.

1.2 Values and Preferences

This recommendation places a high value on avoiding harm with hormone therapy in prepubertal children who may have GID that will remit after the onset of puberty and places a relatively lower value on foregoing the potential benefits of early physical sex change induced by hormone therapy in prepubertal children with GID. This justifies the strong recommendation in the face of very low quality evidence.

1.3 Recommendation

We recommend that physicians evaluate and ensure that applicants understand the reversible and irreversible effects of hormone suppression (*e.g.* GnRH analog treat-

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ment) and of cross-sex hormone treatment before they start hormone treatment.

1.3 Remarks

In all treatment protocols, compliance and outcome are enhanced by clear expectations concerning the effects of the treatment. The lengthy diagnostic procedure (GnRH analog treatment included, because this reversible treatment is considered to be a diagnostic aid) and long duration of the period between the start of the hormone treatment and sex reassignment surgery give the applicant ample opportunity to make balanced decisions about the various medical interventions. Clinical evidence shows that applicants react in a variety of ways to this treatment phase. The consequences of the social role change are sometimes difficult to handle, increasing understanding of treatment aspects may be frightening, and a change in gender dysphoric feelings may lead to confusion. Significant adverse effects on mental health can be prevented by a clear understanding of the changes that will occur and the time course of these changes.

1.4 Recommendation

We recommend that all transsexual individuals be informed and counseled regarding options for fertility before initiation of puberty suppression in adolescents and before treatment with sex hormones of the desired sex in both adolescents and adults.

1.4 Remarks

Persons considering hormone use for sex reassignment need adequate information about sex reassignment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision about this treatment. Because early adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormones, 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 sex reassignment treatment.

Prolonged pubertal suppression using GnRH analogs is reversible and should not prevent resumption of pubertal development upon cessation of treatment. Although sperm production and development of the reproductive tract in early adolescent biological males with GID are insufficient for cryopreservation of sperm, they should be counseled that sperm production can be initiated after prolonged gonadotropin suppression, before 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. 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 adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6–12 months of gonadotropin treatment, although sperm numbers at the time of pregnancy in these patients are far below the normal range (46, 47).

Girls can expect no adverse effects when treated with pubertal suppression. They should be informed that no data are available regarding timing of spontaneous ovulation or response to ovulation induction after prolonged gonadotropin suppression.

All referred subjects who satisfy eligibility and readiness criteria for endocrine treatment, at age 16 or as adults, should be counseled regarding the effects of hormone treatment on fertility and available options that may enhance the chances of future fertility, if desired (48, 49). The occurrence and timing of potentially irreversible effects should be emphasized. Cryopreservation of sperm is readily available, and techniques for cryopreservation of oocytes, embryos, and ovarian tissue are being improved (50).

In biological males, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. Prolonged exposure of the testes to estrogen has been associated with testicular damage (51–53). Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In biological females, the effect of prolonged treatment with exogenous testosterone upon ovarian function is uncertain. Reports of an increased incidence of polycystic ovaries in FTM transsexual persons, both before and as a result of androgen treatment, should be acknowledged (54, 55). Pregnancy has been reported in FTM transsexual persons who have had prolonged androgen treatment, but no genital surgery (56). Counsel from a gynecologist before hormone treatment regarding potential fertility preservation after oophorectomy will clarify available and future options (57).

2.0 Treatment of adolescents

Over the past decade, clinicians have progressively acknowledged the suffering of young transsexual adolescents that is caused by their pubertal development. Indeed, an adolescent with GID often considers the pubertal physical changes to be unbearable. Because early medical intervention may prevent this psychological harm, various clinics have decided to start treating young adolescents

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with GID with puberty-suppressing medication (a GnRH analog). As compared with starting sex reassignment long after the first phases of puberty, a benefit of pubertal suppression is relief of gender dysphoria and a better psychological and physical outcome.

The physical changes of pubertal development are the result of maturation of the hypothalamo-pituitary-gonadal axis and development of the secondary sex characteristics. Gonadotropin secretion increases with a day-night rhythm with higher levels of LH during the night. The nighttime LH increase in boys is associated with a parallel testosterone increase. Girls do not show a day-night rhythm, although in early puberty, the highest estrogen levels are observed during the morning as a result of a delayed response by the ovaries (58).

In girls the first physical sign of the beginning of puberty is the start of budding of the breasts, followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, with menarche occurring approximately 2 yr later. In boys the first physical change is testicular growth. A testicular volume equal to or above 4 ml is seen as the first pubertal increase. From a testicular volume of 10 ml, daytime testosterone levels increase, leading to virilization (59).

2.1–2.2 Recommendations

2.1 We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development. (1 ⊕◯◯◯)

2.2 We recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2–3. (1 ⊕⊕◯◯)

2.1–2.2 Evidence

Pubertal suppression aids in the diagnostic and therapeutic phase, in a manner similar to the RLE (60, 61). Management of gender dysphoria usually improves. In addition, the hormonal changes are fully reversible, enabling full pubertal development in the biological gender if appropriate. Therefore, we advise starting suppression of puberty before irreversible development of sex characteristics.

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

Another reason to start sex reassignment early is that the physical outcome after intervention in adulthood is far less satisfactory than intervention at age 16 (36, 38). Looking like a man (woman) when living as a woman (man) creates difficult barriers with enormous lifelong disadvantages.

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

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

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

2.1–2.2 Values and Preferences

These recommendations place a high value on avoiding the increasing likelihood of an unsatisfactory physical change when secondary sexual characteristics have become manifest and irreversible, as well as a high value on offering the adolescent the experience of the desired gender. These recommendations place a lower value on avoiding potential harm from early hormone therapy.

2.1–2.2 Remarks

Tanner stages of breast and male genital development are given in Table 6. Blood levels of sex steroids during Tanner stages of pubertal development are given in Table 7. Careful documentation of hallmarks of pubertal development will ensure precise timing of initiation of pubertal suppression.

Irreversible and, for transsexual adolescents, undesirable sex characteristics in female puberty are large breasts and short stature and in male puberty are Adam's apple; low voice; male bone configuration such as large jaws, big feet, and hands; tall stature; and male hair pattern on the face and extremities.

2.3 Recommendation

We recommend that GnRH analogs be used to achieve suppression of pubertal hormones. (1 ⊕⊕◯◯)

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TABLE 6. Description of tanner stages of breast development and male external genitalia

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

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

Adapted from Ref. 62.

2.3 Evidence

Suppression of pubertal development and gonadal function is accomplished most effectively by gonadotropin suppression with GnRH analogs and antagonists. Analogs suppress gonadotropins after a short period of stimulation, whereas antagonists immediately suppress pituitary secretion (64, 65). Because no long-acting antagonists are available for use as pharmacotherapy, long-acting analogs are the currently preferred treatment option.

During treatment with the GnRH analogs, slight development of sex characteristics will regress and, in a later phase of pubertal development, will be halted. In girls, breast development will become atrophic, and menses will stop; in boys, virilization will stop, and testicular volume will decrease (61).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploring of his/her reassignment wish, the applicant no longer desires sex reassignment, pubertal suppression can be discontinued. Spontaneous pubertal development will resume immediately (66).

Men with delayed puberty have decreased BMD. Treatment of adults with GnRH analogs results in loss of BMD (67). In children with central precocious puberty, bone density is relatively high for age. Suppressing puberty in these children using GnRH analogs will result in a further increase in BMD and stabilization of BMD SD scores (68). Initial data in transsexual subjects demonstrate no change of bone density during GnRH analog therapy (61). With cross-hormone treatment, bone density increases. The long-term effects on bone density and peak bone mass are being evaluated.

GnRH analogs are expensive and not always reimbursed by insurance companies. Although there is no clinical experience in this population, financial considerations may require treatment with progestins as a less effective alternative. They suppress gonadotropin secretion and exert a mild peripheral antiandrogen effect in boys. Depomedroxyprogesterone will suppress ovulation and progesterone production for long periods of time, although residual estrogen levels vary. In high doses, progestins are relatively effective in suppression of menstrual cycling in girls and women and androgen levels in boys and men. However, at these doses, side effects such as suppression of adrenal function and suppression of bone growth may occur (69). Antiestrogens in girls and antiandrogens in boys can be used to delay the progression of puberty (70, 71). Their efficacy, however, is far less than that of the GnRH analogs.

TABLE 7. Estradiol levels in female puberty and testosterone levels in male puberty during night and day

Tanner stage	Nocturnal	Diurnal
Estradiol (pmol/liter)[a]		
B1	<37	<37
B2	38.5	56.3
B3	81.7	107.3
B4	162.9	132.3
B5	201.6	196.7
Testosterone (nmol/liter)[b]		
G1	<0.25	<0.25
G2	1.16	0.54
G3	3.76	0.62
G4	9.83	1.99
G5	13.2	7.80
Adult	18.8	17.0

Data represent median of hourly measurements from 2400–0600 h (nocturnal) and 1200–1800 h (diurnal).

[a] Adapted from Ref. 63.

[b] Adapted from Ref. 59.

2.3 Values and Preferences

For persons who can afford the therapy, our recommendation of GnRH analogs 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, a depot progestin preparation may be partially effective, but it is not as safe (69, 72); its lower cost may make it an acceptable treatment for persons who cannot afford GnRH.

2.3 Remarks

Measurements of gonadotropin and sex steroid levels give precise information about suppression of the gonadal axis. If the gonadal axis is not completely suppressed, the interval of GnRH analog injections should be shortened. 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 8.

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TABLE 8. Follow-up protocol during suppression of puberty

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: LH, FSH, estradiol/testosterone
Every year
Laboratory: renal and liver function, lipids, glucose, insulin, glycosylated hemoglobin
Bone density using dual-energy x-ray absorptiometry
Bone age on x-ray of the left hand

Glucose and lipid metabolism, complete blood counts, and liver and renal function should be monitored during suppression and cross-sex hormone substitution. For the evaluation of growth, anthropometric measurements are informative. To assess bone density, dual energy x-ray absorptiometry scans can be performed.

2.4 Recommendation

We suggest that pubertal development of the desired, opposite sex be initiated at the age of 16 yr, using a gradually increasing dose schedule of cross-sex steroids. (2 ⊕◯◯◯)

2.4 Evidence

In many countries, 16-yr-olds are legal adults with regard to medical decision making. This is probably because, at this age, most adolescents are able to make complex cognitive decisions. Although parental consent may not be required, obtaining it is preferred because the support of parents should improve the outcome during this complex phase of the adolescent's life (61).

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

In FTM transsexual adolescents, suppression of puberty may halt the growth spurt. To achieve maximum height, slow introduction of androgens will mimic a "pubertal" growth spurt. If the patient is relatively short, one may treat with oxandrolone, a growth-stimulating anabolic steroid also successfully applied in women with Turner syndrome (73–75).

In MTF transsexual adolescents, extreme tall stature is often a genetic probability. The estrogen dose may be increased by more rapid increments in the schedule. Estrogens may be started before the age of 16 (in exceptional cases), or estrogens can be prescribed in growth-inhibiting doses (61).

TABLE 9. Protocol induction of puberty

Induction of female puberty with oral 17-β estradiol, increasing the dose every 6 months:
5 μg/kg/d
10 μg/kg/d
15 μg/kg/d
20 μg/kg/d
Adult dose = 2 mg/d
Induction of male puberty with intramuscular testosterone esters, increasing the dose every 6 months:
25 mg/m^2 per 2 wk im
50 mg/m^2 per 2 wk im
75 mg/m^2 per 2 wk im
100 mg/m^2 per 2 wk im

We suggest that treatment with GnRH analogs be continued during treatment with cross-sex steroids to maintain full suppression of pituitary gonadotropin levels and, thereby, gonadal steroids. When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion (Table 7). The estrogen doses used may result in reactivation of gonadotropin secretion and endogenous production of testosterone that can interfere with the effectiveness of the treatment. GnRH analog treatment is advised until gonadectomy.

2.4 Values and Preferences

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

2.4 Remarks

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

We recommend monitoring clinical pubertal development as well as laboratory parameters (Table 10). Sex

TABLE 10. Follow-up protocol during induction of puberty

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: endocrinology, LH, FSH, estradiol/testosterone
Every year
Laboratory: renal and liver function, lipids, glucose, insulin, glycosylated hemoglobin
Bone density using dual-energy x-ray absorptiometry
Bone age on x-ray of the left hand

These parameters should also be measured at long term. For bone development, they should be measured until the age of 25–30 yr or until peak bone mass has been reached.

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steroids of the desired sex will initiate pubertal development, which can be (partially) monitored using Tanner stages. In addition, the sex steroids will affect growth and bone development, as well as insulin sensitivity and lipid metabolism, as in normal puberty (76, 77).

2.5–2.6 Recommendations

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

2.6 We suggest deferring for surgery until the individual is at least 18 yr old. (2 ⊕◯◯◯)

2.5–2.6 Evidence

Surgery is an irreversible intervention. The WPATH SOC (28) emphasizes that the "threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention." If the RLE supported by sex hormones of the desired sex has not resulted in a satisfactory social role change, if the person is not satisfied with or is ambivalent about the hormonal effects, or if the person is ambivalent about surgery, then the applicant should not be referred for surgery (78, 79).

3.0 Hormonal therapy for transsexual adults

The two major goals of hormonal therapy are: 1) to reduce endogenous hormone levels and, thereby, the secondary sex characteristics of the individual's biological (genetic) sex and assigned gender; and 2) to replace endogenous sex hormone levels with those of the reassigned sex 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 cross-sex hormones is codetermined in collaboration with both the person pursuing sex change and the MHP who made the diagnosis, performed psychological evaluation, and recommended sex reassignment. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being.

3.1–3.3 Recommendations

3.1 We recommend that treating endocrinologists confirm the diagnostic criteria of GID or transsexualism and the eligibility and readiness criteria for the endocrine phase of gender transition. (1 ⊕⊕⊕◯)

3.2 We recommend that medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment be evaluated and addressed before initiation of treatment (Table 11). (1 ⊕⊕⊕◯)

TABLE 11. Medical conditions that can be exacerbated by cross-sex hormone therapy

Transsexual female (MTF): estrogen
Very high risk of serious adverse outcomes
Thromboembolic disease
Moderate to high risk of adverse outcomes
Macroprolactinoma
Severe liver dysfunction (transaminases >3 × upper limit of normal)
Breast cancer
Coronary artery disease
Cerebrovascular disease
Severe migraine headaches
Transsexual male (FTM): testosterone
Very high risk of serious adverse outcomes
Breast or uterine cancer
Erythrocytosis (hematocrit >50%)
Moderate to high risk of adverse outcomes
Severe liver dysfunction (transaminases >3 × upper limit of normal)

3.3 We suggest that cross-sex hormone levels be maintained in the normal physiological range for the desired gender. (2 ⊕⊕◯◯)

3.1–3.3 Evidence

Although the diagnosis of GID or transsexualism is made by an MHP, the referral for endocrine treatment implies fulfillment of the eligibility and readiness criteria (see *Section 1*) (28). It is the responsibility of the physician to whom the transsexual person has been referred to confirm that the person fulfills these criteria for treatment. This task can be accomplished by the physician's becoming familiar with the terms and criteria presented in Tables 1–5, taking a thorough history from the person recommended for treatment, and discussing these criteria with the MHP. Continued evaluation of the transsexual person by the MHP, in collaboration with the treating endocrinologist, will ensure that the desire for sex change is appropriate, that the consequences, risks, and benefits of treatment are well understood, and that the desire for sex change persists.

FTM transsexual persons

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in FTM transsexual persons (80–84). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (85). Either parenteral or transdermal preparations can be used to achieve testosterone values in the normal male range (320–1000 ng/dl) (Table 12). Sustained supraphysiological levels of testosterone increase the risk of adverse reactions (see *Section 4.0*).

Similar to androgen therapy in hypogonadal men, testosterone treatment in the FTM individual results in increased

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TABLE 12. Hormone regimens in the transsexual persons

	Dosage
MTF transsexual persons[a]	
Estrogen	
Oral: estradiol	2.0–6.0 mg/d
Transdermal: estradiol patch	0.1–0.4 mg twice weekly
Parenteral: estradiol valerate or cypionate	5–20 mg im every 2 wk 2–10 mg im every week
Antiandrogens	
Spironolactone	100–200 mg/d
Cyproterone acetate[b]	50–100 mg/d
GnRH agonist	3.75 mg sc monthly
FTM transsexual persons	
Testosterone	
Oral: testosterone undecanoate[b]	160–240 mg/d
Parenteral	
Testosterone enanthate or cypionate	100–200 mg im every 2 wk or 50% weekly
Testosterone undecanoate[b,c]	1000 mg every 12 wk
Transdermal	
Testosterone gel 1%	2.5–10 g/d
Testosterone patch	2.5–7.5 mg/d

[a] Estrogens used with or without antiandrogens or GnRH agonist.

[b] Not available in the United States.

[c] 1000 mg initially, followed by an injection at 6 wk, then at 12-wk intervals.

muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness, and increased libido (86). Specific to the FTM transsexual person, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, and, usually, cessation of menses. 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, addition of a progestational agent or endometrial ablation may be considered (87, 88). GnRH analogs or depot medroxyprogesterone may also be used to stop menses before testosterone treatment and to reduce estrogens to levels found in biological males.

MTF transsexual persons

The hormone regimen for MTF transsexual individuals is more complex than the FTM regimen. Most published clinical studies report the use of an antiandrogen in conjunction with an estrogen (80, 82–84, 89).

The antiandrogens shown to be effective reduce endogenous testosterone levels, ideally to levels found in adult biological women, to enable estrogen therapy to have its fullest effect. Two categories of these medications are progestins with antiandrogen activity and GnRH agonists (90). Spironolactone has antiandrogen properties by directly inhibiting testosterone secretion and by inhibiting androgen binding to the androgen receptor (83, 84). It may also have estrogenic activity (91). Cyproterone acetate, a progestational compound with antiandrogenic properties (80, 82), is widely used in Europe. Flutamide blocks binding of androgens to the androgen receptor, but it does not lower serum testosterone levels; it has liver toxicity, and its efficacy has not been demonstrated.

Dittrich (90), reporting on a series of 60 MTF transsexual persons who used monthly the GnRH agonist goserelin acetate in combination with estrogen, found this regimen to be effective in reducing testosterone levels with low incidence of adverse reactions.

Estrogen can be given orally as conjugated estrogens, or 17β-estradiol, as transdermal estrogen, or parenteral estrogen esters (Table 12).

Measurement of serum estradiol levels can be used to monitor oral, transdermal, and im estradiol or its esters. Use of conjugated estrogens or synthetic estrogens cannot be monitored by blood tests. Serum estradiol should be maintained at the mean daily level for premenopausal women (<200 pg/ml), and the serum testosterone level should be in the female range (<55 ng/dl). The transdermal preparations may confer an advantage in the older transsexual women who may be at higher risk for thromboembolic disease (92).

Venous thromboembolism may be a serious complication. A 20-fold increase in venous thromboembolic disease was reported in a large cohort of Dutch transsexual subjects (93). This increase may have been associated with the use of ethinyl estradiol (92). The incidence decreased upon cessation of the administration of ethinyl estradiol (93). Thus, the use of synthetic estrogens, especially ethinyl estradiol, is undesirable because of the inability to regulate dose by measurement of serum levels and the risk of thromboembolic disease. Deep vein thrombosis occurred in 1 of 60 MTF transsexual persons treated with a GnRH analog and oral estradiol (90). The patient was found to have a homozygous C677 T mutation. Administration of cross-sex hormones to 162 MTF and 89 FTM transsexual persons was not associated with venous thromboembolism despite an 8.0 and 5.6% incidence of thrombophilia, respectively (94). Thombophilia screening of transsexual persons initiating hormone treatment should be restricted to those with a personal or family history of venous thromboembolism (94). Monitoring D-dimer levels during treatment is not recommended (95).

3.1–3.3 Values and Preferences

Our recommendation to maintain levels of cross-sex hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharma-

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cological doses. Those receiving endocrine treatment who have relative contraindications to hormones (*e.g.* persons who smoke, have diabetes, have liver disease, *etc.*) should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

3.1–3.3 Remarks

All endocrine-treated individuals should be informed of all risks and benefits of cross-sex hormones before initiation of therapy. Cessation of tobacco use should be strongly encouraged in MTF transsexual persons to avoid increased risk of thromboembolism and cardiovascular complications.

3.4 Recommendation

We suggest that endocrinologists review with persons treated the onset and time course of physical changes induced by cross-sex hormone treatment. (2 ⊕⊕○○)

3.4 Evidence

FTM transsexual persons

Physical changes that are expected to occur during the first 3 months of initiation of testosterone therapy include cessation of menses, increased libido, 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, clitoromegaly, and, in some individuals, male pattern hair loss (83, 96, 97) (Table 13).

MTF transsexual persons

Physical changes that may occur in the first 3–6 months of estrogen and antiandrogen therapy include decreased libido, decreased facial and body hair, decreased oiliness of skin, breast tissue growth, and redistribution of fat mass (82, 83, 84, 96, 97) (Table 14). Breast development is generally maximal at 2 yr after initiation of hormones (82, 83, 84). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in MTF transsexual persons has been studied (97), precise information about other changes induced by sex hormones is lacking. There is a great deal of variability between individuals, as evidenced during pubertal development.

TABLE 13. Masculinizing effects in FTM transsexual persons

Effect	Onset (months)[a]	Maximum (yr)[a]
Skin oiliness/acne	1–6	1–2
Facial/body hair growth	6–12	4–5
Scalp hair loss	6–12	[b]
Increased muscle mass/strength	6–12	2–5
Fat redistribution	1–6	2–5
Cessation of menses	2–6	[c]
Clitoral enlargement	3–6	1–2
Vaginal atrophy	3–6	1–2
Deepening of voice	6–12	1–2

[a] Estimates represent clinical observations. See Refs. 81, 92, and 93.

[b] Prevention and treatment as recommended for biological men.

[c] Menorrhagia requires diagnosis and treatment by a gynecologist.

TABLE 14. Feminizing effects in MTF transsexual persons

Effect	Onset[a]	Maximum[a]
Redistribution of body fat	3–6 months	2–3 yr
Decrease in muscle mass and strength	3–6 months	1–2 yr
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	3–6 months
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 yr
Decreased testicular volume	3–6 months	2–3 yr
Decreased sperm production	Unknown	>3 yr
Decreased terminal hair growth	6–12 months	>3 yr[b]
Scalp hair	No regrowth	[c]
Voice changes	None	[d]

[a] Estimates represent clinical observations. See Refs. 81, 92, and 93.

[b] Complete removal of male sexual hair requires electrolysis, or laser treatment, or both.

[c] Familial scalp hair loss may occur if estrogens are stopped.

[d] Treatment by speech pathologists for voice training is most effective.

3.4 Values and Preferences

Transsexual 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

Cross-sex hormone therapy confers the same risks associated with sex hormone replacement therapy in biological males and females. The risk of cross-sex hormone therapy arises from and is worsened by inadvertent or intentional use of supraphysiological doses of sex hormones or inadequate doses of sex hormones to maintain normal physiology (81, 89).

4.1 Recommendation

We suggest regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly. (2 ⊕⊕○○)

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4.1 Evidence

Pretreatment screening and appropriate regular medical monitoring is recommended for both FTM and MTF transsexual persons during the endocrine transition and periodically thereafter (13, 97). Monitoring of weight and blood pressure, directed physical exams, routine health questions focused on risk factors and medications, complete blood counts, renal and liver function, lipid and glucose metabolism should be carried out.

FTM transsexual persons

A standard monitoring plan for individuals on testosterone therapy is found in Table 15. Key issues include maintaining testosterone levels in the physiological normal male range and avoidance of adverse events resulting from chronic testosterone therapy, particularly erythrocytosis, liver dysfunction, hypertension, excessive weight gain, salt retention, lipid changes, excessive or cystic acne, and adverse psychological changes (85).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with the use parenteral or transdermal testosterone (98, 99). Still, periodic monitoring is recommended given that up to 15% of FTM persons treated with testosterone have transient elevations in liver enzymes (93).

MTF transsexual persons

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

4.2 Recommendation

We suggest monitoring prolactin levels in MTF transsexual persons treated with estrogens. (2 ⊕⊕◯◯)

4.2 Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term estrogen therapy (100–102). Up to 20% of transsexual women treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (103). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy (104).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Prolactin levels should be obtained at baseline and then at least annually during the transition period and biannually thereafter. Given that prolactinomas have been reported only in a few case reports and were not reported in large cohorts of estrogen-treated transsexual persons, the risk of prolactinoma is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in MTF transsexual persons, radiological examination of the pituitary may be carried out in those whose prolactin levels persistently increase despite stable or reduced estrogen levels.

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

4.3 Recommendation

We suggest that transsexual persons treated with hormones be evaluated for cardiovascular risk factors. (2 ⊕⊕◯◯)

4.3 Evidence

FTM transsexual persons

Testosterone administration to FTM transsexual persons will result in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride values (21, 105–107). Studies of the effect of testosterone on insulin sensitivity have mixed results (106, 108). A recent randomized, open-label uncontrolled safety study of FTM transsexual persons treated with testosterone undecanoate demonstrated no insulin resistance after 1 yr (109). Numerous studies have demonstrated

TABLE 15. Monitoring of MTF transsexual persons on cross-hormone therapy

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

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TABLE 16. Monitoring of FTM transsexual persons on cross-hormone therapy

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

[a] Adapted from Refs. 83 and 85.

effects of cross-sex hormone treatment on the cardiovascular system (107, 110–112). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (93). Likewise, a meta-analysis of 19 randomized trials examining testosterone replacement in men showed no increased incidence of cardiovascular events (113). A systematic review of the literature found that data were insufficient, due to very low quality evidence, to allow meaningful assessment of important patient outcomes such as death, stroke, myocardial infarction, or venous thromboembolism in FTM transsexual persons (21). Future research is needed to ascertain harms of hormonal therapies (21). Cardiovascular risk factors should be managed as they emerge according to established guidelines (114).

MTF transsexual persons

A prospective study of MTF subjects found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (106). However, these favorable lipid changes were attenuated by increased weight, blood pressure, and markers of insulin resistance. The largest cohort of MTF subjects (with a mean age of 41 yr) followed for a mean of 10 yr showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (93). Thus, there is limited evidence to determine whether estrogen is protective or detrimental in MTF transsexual persons (21). With aging there is usually an increase of body weight, and therefore, as with nontranssexual individuals, glucose and lipid metabolism and blood pressure should be monitored regularly and managed according to established guidelines (114).

4.4 Recommendation

We suggest that BMD measurements be obtained if risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (2 ⊕⊕⊕○)

4.4 Evidence

FTM transsexual persons

Adequate dosing of testosterone is important to maintain bone mass in FTM transsexual persons (115, 116). In one study (116), 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.

MTF transsexual persons

Studies in aging genetic males suggest that serum estradiol more positively correlates with BMD than does testosterone (117–119) and is more important for peak bone mass (120). Estrogen preserves BMD in MTF transsexuals who continue on estrogen and antiandrogen therapies (116, 121, 122).

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

4.5–4.6 Recommendations

4.5 We suggest that MTF transsexual persons who have no known increased risk of breast cancer follow breast

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screening guidelines recommended for biological women. (2 ⊕⊕◯◯)

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

4.5–4.6 Evidence

Breast cancer is a concern in transsexual women. A few cases of breast cancer in MTF transsexual persons have been reported in the literature (123–125). In the Dutch cohort of 1800 transsexual women followed for a mean of 15 yr (range, 1 to 30 yr), only one case of breast cancer was found. The Women's Health Initiative study reported that women taking conjugated equine estrogen without progesterone for 7 yr did not have an increased risk of breast cancer as compared with women taking placebo (126). Women with primary hypogonadism (XO) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (127, 128). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short-term (<20–30 yr). Long-term studies are required to determine the actual risk and the role of screening mammograms. Regular exams and gynecological advice should determine monitoring for breast cancer.

Prostate cancer is very rare, especially with androgen deprivation therapy, before the age of 40 (129). Childhood or pubertal castration results in regression of the prostate, and adult castration reverses benign prostate hypertrophy (130). Although van Kesteren (131) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostate of MTF transsexual persons, cases of benign prostate hypertrophy have been reported in MTF transsexual persons treated with estrogens for 20–25 yr (132, 133). Three cases of prostate carcinoma have been reported in MTF transsexual persons (134–136). However, these individuals initiated cross-hormone therapy after age 50, and whether these cancers were present before the initiation of therapy is unknown.

MTF transsexual 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 transsexual persons who transitioned after age 20 to have annual screening digital rectal exams after age 50 and PSA tests consistent with the U.S. Preventive Services Task Force Guidelines (137).

4.7 Recommendation

We suggest that FTM transsexual persons evaluate the risks and benefits of including a total hysterectomy and oophorectomy as part of sex reassignment surgery. (2 ⊕◯◯◯)

4.7 Evidence

Although aromatization of testosterone to estradiol in FTM transsexual persons has been suggested as a risk factor for endometrial cancer (138), no cases have been reported. When FTM transsexual persons undergo hysterectomy, the uterus is small and there is endometrial atrophy (139, 140). The androgen receptor has been reported to increase in the ovaries after long-term administration of testosterone, which may be an indication of increased risk of ovarian cancer (141). Cases of ovarian cancer have been reported (142, 143). The relative safety of laparoscopic total hysterectomy argues for preventing the risks of reproductive tract cancers and other diseases through surgery (144).

4.7 Values and Preferences

Given the discomfort that FTM transsexual persons experience accessing gynecological care, our recommendation for 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.

4.7 Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecological care required after transition. In addition, approval of birth certificate change of sex for FTM transsexual persons may be dependent upon having a complete hysterectomy; each patient should be assisted in researching and counseled concerning such nonmedical administrative criteria.

5.0 Surgery for sex reassignment

For many transsexual adults, genital sex reassignment surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. Although surgery on several different body structures is considered 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 yr. Cosmetic genital surgery with preservation of neurological sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (22). In addition, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender identity treatment that

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TABLE 17. Sex reassignment surgery eligibility and readiness criteria

Individuals treated with cross-sex hormones are considered eligible for sex reassignment surgery if they:
1. Are of the legal age of majority in their nation.
2. Have used cross-sex hormones continuously and responsibly during 12 months (if they have no medical contraindication).
3. Had a successful continuous full-time RLE during 12 months.
4. Have (if required by the MHP) regularly participated in psychotherapy throughout the RLE at a frequency determined jointly by the patient and the MHP.
5. Have shown demonstrable knowledge of all practical aspects of surgery (*e.g.* cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation, *etc.*).

Individuals treated with cross-sex hormones should fulfill the following readiness criteria prior to sex reassignment surgery:
1. Demonstrable progress in consolidating one's gender identity.
2. Demonstrable progress in dealing with work, family, and interpersonal issues, resulting in a significantly better state of mental health.

includes hormones and surgery (24). The person must be both eligible and ready for such a procedure (Table 17).

Sex reassignment surgeries available to the MTF transsexual persons consist of gonadectomy, penectomy, and creation of a vagina (145, 146). The skin of the penis is often inverted to form the wall of the vagina. The scrotum becomes the labia majora. Cosmetic surgery is used to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Most recently, plastic surgeons have developed techniques to fashion labia minora. Endocrinologists should encourage the transsexual person to use their tampon dilators to maintain the depth and width of the vagina throughout the postoperative period until the neovagina is being used frequently in intercourse. Genital sexual responsivity and other aspects of sexual function should be preserved after genital sex reassignment surgery (147).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. When possible, less surgery is desirable. For instance, voice therapy by a speech language pathologist is preferred to current surgical methods designed to change the pitch of the voice (148).

Breast size in genetic females exhibits a very broad spectrum. For the transsexual person to make the best-informed decision, breast augmentation surgery should be delayed until at least 2 yr of estrogen therapy has been completed, given that the breasts continue to grow during that time with estrogen stimulation (90, 97).

Another major effort 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 (149–151).

Sex reassignment surgeries available to the FTM transsexual persons have been less satisfactory. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (152, 153). Neopenile erection can be achieved only if some mechanical device is imbedded in the penis, *e.g.* a rod or some inflatable apparatus (154). Many choose a metaidoioplasty that exteriorizes or brings forward the clitoris and allows for voiding while standing. The scrotum is created from the labia majora with a good cosmetic effect, and testicular prostheses can be implanted. These procedures, as well as oophorectomy, vaginectomy, and complete hysterectomy, are undertaken after a few years of androgen therapy and can be safely performed vaginally with laparoscopy.

The ancillary surgery for the FTM transition that is extremely important is the mastectomy. Breast size only partially regresses with androgen therapy. In adults, discussion about mastectomy usually takes place after androgen therapy is begun. Because some FTM transsexual adolescents present after significant breast development has occurred, mastectomy may be considered before age 18.

5.1–5.3 Recommendations

5.1 We recommend that transsexual persons consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the MHP find surgery advisable. (1 ⊕○○○)

5.2 We recommend that genital sex reassignment surgery be recommended only after completion of at least 1 yr of consistent and compliant hormone treatment. (1 ⊕○○○)

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

5.1–5.3 Evidence

When a transsexual individual decides to have sex reassignment surgery, both the endocrinologist and the MHP must certify that he or she satisfies the eligibility and readiness criteria of the SOC (28) (Table 17).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or after surgery (21). For this reason, the surgeon and the endocrinologist should collaborate in making a decision about the use of hormones during the month before surgery.

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Although one study suggests that preoperative factors such as compliance are less important for patient satisfaction than are the physical postoperative results (39), other studies and clinical experience dictate that individuals who do not follow medical instructions and work with their physicians toward a common goal do not achieve treatment goals (155) and experience higher rates of postoperative infections and other complications (156, 157). 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 (78).

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

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