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

Short Title: Guidelines on the Endocrine Treatment of Transsexuals

Authors: Wylie C. Hembree, Peggy Cohen-Kettenis, Henriette A. Delemarre, Louis J. Gooren, Walter J. Meyer III, Norman P. Spack,Vin Tangpricha, and Victor M. Montori

Affiliations: Columbia University and New York Presbyterian Hospital (W.C.H.) New York, New York; Vrije University Medical Center (P.C-K.) Amsterdam, The Netherlands; Vrije University Medical Center (H.A.D.) Amsterdam, The Netherlands; Androgen Consultant (L.J.G.) Bangkok, Thailand; University of Texas Medical Branch (W.J.M.) Galveston, Texas; Harvard Medical School (N.P.S.) Boston, Massachusetts; Emory University School of Medicine (V.T.) Atlanta, Georgia; and Mayo Clinic (V.M.M.) Rochester, Minnesota.

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

Financial Disclosures of the Task Force: Wylie C. Hembree, M.D. (chair)—Financial or Business/Organizational Interests: Columbia University, New York Presbyterian Hospital; Significant Financial Interest or Leadership Position: Sperm Bank of New York. **Peggy Cohen-Kettenis, Ph.D.—**Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: WPATH. **Henriette A. Delemarre, M.D., Ph.D.—**Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared. **Louis J. Gooren, M.D., Ph.D.—**Financial or

Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared. **Walter J. Meyer III, M.D.**—Financial or Business/Organizational Interests: WPATH; Significant Financial Interest or Leadership Position: University of Texas Medical Branch, WPATH. **Norman P. Spack, M.D.**—Financial or Business/Organizational Interests: LWPES, American Diabetes Association; Significant Financial Interest or Leadership Position: none declared. **Vin Tangpricha, M.D., Ph.D.**—Financial or Business/Organizational Interests: Auxillium, Novartis, NIH; Significant Financial Interest or Leadership Position: none declared. ***Victor M. Montori, MD**- Financial or Business/Organizational Interests: KER Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared.

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

Abstract

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

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

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

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

Conclusions:

Transsexual persons seeking to develop the physical characteristics of the appropriate gender require a safe and effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and 2) maintain sex hormone levels within the normal range for the person's gender. A mental health professional (MHP) must recommend endocrine treatment and participate in the ongoing care throughout the endocrine transition. The endocrinologist must confirm the diagnostic criteria the MHP used to make this recommendation and collaborate with the MHP in making the recommendation for surgical sex reassignment. We recommend treating transsexual adolescents (Tanner stage 2) with suppression of puberty with GnRH analogues until age 16 years old, only after which time cross-sex hormones may be given. We suggest suppression of endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and surveillance for known risks and complications in adult transsexual persons.

Number of Words, Number of Tables & Figures

Word Count: 8,610, Abstract: 250, Tables: 17, Figures: 0

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. For children and adolescents the mental health professional should also have training in child and adolescent developmental psychopathology. (1|⊕⊕OO)

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

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

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

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|⊕OOO)

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

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

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

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

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

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|⊕⊕⊕O)

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 *(*Table 11: Medical conditions that can be exacerbated by cross-sex hormone therapy*).* (1|⊕⊕⊕O)

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

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

4.0 ADVERSE OUTCOME PREVENTION AND LONG-TERM CARE

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

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

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

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

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

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

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

5.0 SURGERY FOR SEX REASSIGNMENT

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

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

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

Introduction

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

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

Prior to 1975, few peer- reviewed articles were published concerning endocrine treatment of transsexual persons. Since that time, more than 800 articles about various aspects of transsexual care have appeared. It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience that will enable

endocrinologists to provide safe and effective endocrine treatment for individuals diagnosed with gender identity disorder (GID) or transsexualism by mental health professionals. In the future, rigorous evaluation of the effectiveness and safety of endocrine protocols is needed. What will be required is the careful assessment of 1) the effects of prolonged delay of puberty on bone, growth and development upon adolescents, 2) in adults, the effects on outcome of both endogenous and cross-sex hormone levels during treatment, 3) the requirement for and the effects of anti-androgens and progestins during treatment, and 4) long-term medical and psychological risks of sex reassignment. These needs can be met only by a commitment of mental health and endocrine investigators to collaborate in long-term, large-scale studies across countries that employ the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools.

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

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 of the steps in this process (Ruble 2006). 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 Zucker, 2004). Behavioral genetic studies suggest that, in children, atypical gender development has a heritable component (Coolidge 2002, Knafo 2005). Since, 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 Gooren 2006). Prenatal androgenization may predispose to a male gender identity development. 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 (Meyer-Bahlburg 2005, Reiner 2005), whereas 46,XX subjects exposed to prenatal androgens show marked behavioural masculinization, but this does not necessarily lead to gender dysphoria (Meyer-Bahlburg 2004, Meyer-Balburg 2006, Dessens 2005). Male-to-female (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 (Bocklandt 2007).

Maternal immunization against the H-Y antigen hypotheses (Blanchard 1997, Blanchard 2001), arising from fraternal birth order and sibling sex ratio studies have not been experimentally supported (Whitehead 2007).

Studies have also failed to find differences in circulating levels of sex steroids between transsexual and non-transsexual individuals (Gooren 1990).

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

1.0 Diagnostic Procedure

Sex reassignment is a multidisciplinary treatment. It requires five processes: diagnostic assessment, psychotherapy or counseling, real-life experience, 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 therefore important that caregivers be aware of the contributions of the various disciplines.

Diagnostic Assessment and Psychotherapy

Because GID may be accompanied with psychological or psychiatric problems (e.g., Cohen-Kettenis 2003, Cole 1997, Hepp 2005, Kersting 2003, Wallien 2007), 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 Standards of Care (SOC) guidelines of the WPATH recommend that the diagnosis be made by a mental health professional (MHP) (Meyer 2001). For children and adolescents, the MHP should also have training in child and adolescent developmental psychopathology.

Mental health professionals 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 and, in the case of adolescents, the parents/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 gender identity disorder;
- informs the applicant about the possibilities and limitations of sex reassignment and other kinds of 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 and/or circumstances 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 (Kuiper 1998, Landèn 1998, Olsson 2006, Pfafflin 1992).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment and, preferably, a child psychiatric evaluation (by a clinician other than the diagnostician). DiCeglie et al. (2002) showed that 75% of the adolescents referred to their Gender Identity clinic in the UK 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

During the real life experience (RLE), the person should fully experience life in the desired gender role before irreversible physical treatment is undertaken. The RLE is meant to test an applicant's ability to function in the desired gender, and assists both the applicant and MHP in their judgments about how to proceed. During the RLE, the person's feelings 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 experts who elaborated the Standards of Care document requires that both adolescents and adults applying for hormone treatment and surgery satisfy two sets of criteria, eligibility and readiness, before proceeding (Meyer 2001). There are eligibility and readiness criteria for hormone therapy for adults (Table 4) and eligibility criteria 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 followup studies on adolescents who fulfilled these criteria, and had started cross-sex hormone treatment from the age of 16, indicate good post-operative results (Cohen-Kettenis 1997, Smith 2001, Smith 2005).

One study on MTF transsexual subjects reports that outcome was not associated with minimum eligibility requirements of the WPATH. However, this study was performed among a group of individuals with a relatively high socioeconomic background (Lawrence 2003). One study investigating the need for psychotherapy for sex reassignment applicants, based on questionnaire scores, suggests that 'classical' forms of psychotherapy prior to medical interventions are not needed in about two thirds of the applicants (Seikowski 2007).

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

Recommendation

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

1.1 Evidence

GID may be accompanied with psychological or psychiatric problems (e.g.., Cohen-Kettenis 2003, Cole 1997, Hepp 2005, Kersting 2003, Wallien 2007). 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, accurately diagnose psychiatric conditions, and see to their appropriate treatment.

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 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.

Recommendation

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

1.2 Evidence

Although the percentages differ between studies, the GID will not persist into adolescence in the large majority of prepubertal children with a diagnosis of GID in childhood (Cohen-Kettenis 2001, Drummond 2008, Wallien and Cohen-Kettenis, 2008; for a review of seven older studies see Zucker 1995). Clinical experience suggests that only after the first signs of puberty persistent GID can be reliably assessed.

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

Recommendation

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

1.3 Evidence

In all treatment protocols, compliance and outcome are enhanced by clear expectations concerning the effects of the treatment. The lengthy diagnostic procedure (GnRH analogue treatment included, as 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 upon mental health can be prevented by a clear understanding of the changes that will occur and the time course of these changes.

Recommendation

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

1.4 Evidence

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 patient education should include parents, the referring mental health professional(s), and other members of their support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding future fertility of adolescents or adults beginning sex reassignment treatment.

Prolonged pubertal suppression using GnRH analogues is reversible and should not prevent resumption of pubertal development upon cessation of treatment. Although sperm production and development of the reproductive tract in early adolescent biological males with GID are insufficient for cryopreservation of sperm, they should be counseled that sperm production can be initiated following prolonged gonadotropin suppression, prior to estrogen treatment. It should be noted that the time required to obtain sufficient spermatogenesis to collect sperm is unpredictable and will probably be associated with physical manifestations of testosterone production. In adult men with gonadotropin deficiency, sperm are noted in seminal fluid after 6-12 months of treatment. Girls should expect no adverse effects when treated with pubertal suppression. They should be informed that no data are available regarding timing of

spontaneous ovulation or response to ovulation induction following prolonged gonadotropin suppression.

All referred subjects who satisfy eligibility and readiness criteria for endocrine treatment, at age 16 or as adults, should be counseled regarding the effects of hormone treatment on fertility and available options that may enhance the chances of future fertility, if desired (De Sutter 2007; De Sutter 2001). 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 (Seli 2005).

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 (Thiagaraj 1987 Schultz 1988 Lubert 1992). 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 female-to-male (FTM) transsexual persons, both prior to and as a result of androgen treatment, should be acknowledged (Spinder 1989 Baba 2007). Pregnancy has been reported in FTM transsexual persons who have had prolonged androgen treatment, but no genital surgery (Trebay 2008). Counsel from a gynecologist prior to hormone treatment regarding potential fertility preservation following ovariectomy will clarify available and future options (De Sutter 2003).

2.0 Treatment of Adolescents

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

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

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

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

Recommendations

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

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

2.1-2.2 Evidence

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

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

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

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

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

Unlike the developmental problems observed with delayed puberty, this protocol requires a mental health professional skilled in child- and adolescent- psychology to evaluate the response of the adolescent with GID after pubertal suppression. Adolescents with GID should experience the first changes of their biologic, spontaneous puberty because their emotional reaction to these

first physical changes has diagnostic value. The early treatment in puberty risks limited growth of the penis and scrotum that may make the surgical development of a vagina from scrotal tissue more difficult.

2.1-2.2.Values and Preferences

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

2.1-2.2 Remarks

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

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

2.3. We recommend GnRH analogues to be used to achieve suppression of pubertal hormones. (1|⊕⊕OO)

2.3. Evidence

Suppression of pubertal development and gonadal function is accomplished most effectively by gonadotropin suppression with GnRH analogues and antagonists. Analogues suppress gonadotropins after a short period of stimulation, whereas antagonists immediately suppress

pituitary secretion (Tuvemo 2006, Roth 2002). Since no long-acting antagonists are available for use as pharmacotherapy, long-acting analogues are the currently preferred treatment option.

During treatment with the GnRH analogues, slight development of sex characteristics will regress and, in a later phase of pubertal development, will be halted. In girls, breast development will become atrophic and menses will stop; in boys, virilization will stop and testicular volume will decrease (Delemarre 2006).

An advantage of using GnRH analogues is the reversibility of the intervention. If,after extensive exploring of his/her reassignment wish, the patient no longer desires sex reassignment, pubertal suppression can be discontinued. Spontaneous pubertal development will resume immediately (Manasco1988).

Men with delayed puberty have decreased bone mineral density (BMD). Treatment of adults with GnRH analogues results in loss of BMD (Mittan 2002). In children with central precocious puberty, bone density is relatively high for age. Suppressing puberty in these children using GnRH analogues will result in a further increase in BMD and stabilization of BMD standard deviation scores (Neely 1995). Initial data in transsexual subjects demonstrate no change of bone density during GnRH analogue therapy. (Delemarre 2006).

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

progression of puberty (Mieszczak 2007, Jain 2004). Their efficacy, however, is far less than that of the GnRH analogues.

2.3 Values and Preferences

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

2.3 Remarks

Measurements of gonadotropin and sex steroid levels give precise information about suppression of the gonadal axis. If the gonadal axis is not completely suppressed, the interval of GnRH analogue injections should be shortened. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt as well as impaired bone accretion. The clinical protocol to be used is shown in Table 8.

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

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

2.4. Evidence

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

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

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

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

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

2.4 Values and Preferences

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

2.4 Remarks

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

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

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

2.6 We suggest deferring for surgery until the individual is at least 18 years old. (2|⊕OOO).

2.5 -2.6. Evidence

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

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 co-determined in collaboration with both the person pursuing sex change and the mental health professional 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.

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|⊕⊕⊕O)

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

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

3.1-3.3 Evidence

Although the diagnosis of GID or transsexualism is made by a mental health professional, the referral for endocrine treatment implies fulfillment of the eligibility and readiness criteria (See Section 1) (Meyer 2001). 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. Continued evaluation of the transsexual person by the mental health professional, 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.

Female-to-male transsexual persons

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in the female-to-male (FTM) transsexual persons. (Gooren 2005, Tangpricha 2003, Levy 2003, Moore 2003, Gooren 2007a). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (Bhasin 2006). Either parenteral or transdermal preparations can be used to achieve testosterone values in the normal male range (320 – 1000 ng/dL) (Table 12. Recommended Hormone Regimens in the Transsexual Persons). Sustained supraphysiologic 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 muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness, and increased libido (Bolona 2007). 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 (Prasad 2008, Dickersin 2008). Gonadotropin releasing hormone analogues or depot medroxyprogesterone may also be used to stop menses prior to testosterone treatment and to reduce estrogens to levels found in biological males.

Male-to-female transsexual persons

The hormone regimen for male-to-female (MTF) transsexual individuals is more complex than the FTM regimen. Most published clinical studies report the use of an anti-androgen in conjunction with an estrogen (Gooren 2005, Tangpricha 2003, Levy 2003, Moore 2003, Gooren 2008b).

The anti-androgens 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 anti-androgen activity and gonadotropin-releasing hormone agonists (Dittrich 2005). Spironolactone has anti-androgen properties by directly inhibiting testosterone secretion and by inhibiting androgen binding to the androgen receptor (Tangpricha 2003, Moore 2003). It may also have estrogenic activity (Levy 1980). Cyproterone acetate, a progestational compound with anti-androgenic properties (Gooren 2005, Levy 2003) 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 (2005), reporting 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, andintramuscular 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 pre-menopausal women (~200 ng/mL) and the serum testosterone level should be in the female range <50 ng/dL. The transdermal preparations may confer an advantage in the older transsexual women who may be at higher risk for thromboembolic disease (Toorians 2003).

A 20-fold increase in venous thromboembolic disease was reported in a large cohort of Dutch transsexual subjects (van Kesteren 1997). This increase may have been associated with the use of ethinyl estradiol (Toorians 2003). 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.

3.1-3.3 Values

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 pharmacologic 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 prior to initiation of therapy. Cessation of tobacco use should be strongly encouraged in MTF transsexual persons to avoid increased risk of thromboembolism and cardiovascular complications.

Recommendation

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

3.5 Evidence

Female-to-male 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 (Meyer 1986, Moore 2003) (Table 13).

Male-to-female transsexual persons

Physical changes that may occur in the first 3-6 months of estrogen and anti-androgen therapy include decreased libido, decreased facial and body hair, decreased oiliness of skin, breast tissue growth, and redistribution of fat mass (Meyer 1986, Moore 2003) (Table 14). Breast development is generally maximal at 2 years after initiation of hormones (Meyer 1986, Moore 2003). 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 (Meyer 1986), 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.

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 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 supraphysiologic doses of sex hormones or inadequate doses of sex hormones to maintain normal physiology (Gooren 2008b, Gooren 2008a).

Recommendation

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

4.1 Evidence

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

Female-to-male transsexual persons

A standard monitoring plan for individuals on testosterone therapy is found in Table 15. Key issues include maintaining testosterone levels in the physiologic normal male range and avoidance of adverse events resulting from chronic testosterone therapy, particularly erythrocytosis, liver dysfunction, hypertension, excessive weight gain, salt retention, lipid changes, excessive or cystic acne and adverse psychological changes (Bhasin 2006)

Since oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated using parenteral or transdermal testosterone (Bird 1979, Westaby 1977). Still, periodic monitoring is recommended given that up to 15% of FTM persons treated with testosterone have transient elevations in liver enzymes (Van Kesteren 1997).

Male-to-female transsexual persons

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

Recommendation

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

4.2 Evidence

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

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

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

Recommendation

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

4.3 Evidence

Female-to-male transsexual persons

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

Male-to-female transsexual persons

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

Recommendation

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

4.4 Evidence

Female-to-male transsexual persons

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

Male-to-female transsexual persons

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

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

Recommendations

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

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

4.5-4.6 Evidence

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

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

of therapy is unknown. The limited evidence suggests that prostate cancer risk may be increased in the older individual initiating on cross-hormone therapy.

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 USPSTF Guidelines (USPSTF 2008).

Recommendation

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

4.7 Evidence

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

4.7 Values

Given the discomfort that FTM transsexual persons experience accessing gynecologic care, our recommendation for total hysterectomy and oophorectomy places a high value upon eliminating

the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

4.7 Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. In addition, approval of birth certificate change of sex for FTM transsexual persons may be dependent upon having a complete hysterectomy.

5.0 Surgery for Sex Reassignment

For many transsexual adults, genital sex reassignment surgery may be the necessary step towards achieving their ultimate goal of living successful 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 years. Cosmetic genital surgery with preservation of neurological sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (Murad [In preparation]). In addition, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender identity treatment that includes hormones and surgery (Cole 1997). The person must be both eligible and ready for such a procedure. (Table 17.).

Sex reassignment surgeries available to the MTF transsexual persons consist of gonadectomy, pinectomy, and creation of a vagina.(Selvaggi 2005, Turgnet 2007). The skin of the penis is often inverted to form the wall of the vagina. The scrotum becomes the labia majora. Cosmetic surgery is used to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Most recently plastic surgeons have developed techniques to fashion labia minora. Endocrinologists should remind the patient

to use their tampon dilators to maintain the depth and width of the vagina throughout the post-operative period until the neovagina is being used frequently in intercourse. Genital sexual responsivity and other aspects of sexual function should be preserved following genital sex reassignment surgery (Green 1998).

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

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

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

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

therapy since androgens can be responsible for ovarian tumors (Dizon 2006). These procedures are now done vaginally and with the aid of a laparoscope.

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

Recommendations

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

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

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

5.1.-5.3 Evidence

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

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

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

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

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 GRADE group, an international group with expertise in development and implementation of evidence-based guidelines. A detailed description of the grading scheme has been published elsewhere (Swiglo 2008). The Task Force used the best available research evidence that Task Force members identified and two commissioned systematic reviews (Elamin [In preparation], Murad [In preparation]) to inform 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 ⊕**OOO** denotes very low quality evidence; ⊕⊕**OO** low quality; ⊕⊕⊕**O** moderate quality; and ⊕⊕⊕⊕ high quality. The Task Force has confidence that patients who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the patient's circumstances, values, and preferences to determine the best course of action. 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 patient. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

References

American Psychiatric Association (APA) 2001 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: APA

Amin S, Zhang Y, Sawin CT, Evans SR, Hannan MT, Kiel DP, et al 2000 Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham Heart Study. Ann Intern Med 133:951-963.

Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee 2004 Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291:1701-12

Asscheman H, Gooren LJ, Assies J, Smits JP, de Slegte R 1988 Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. Clin Endocrinol (Oxf) 28:583-8

Baba T, Endo T, Honnma H, Kitajima Y, Hayashi, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T 2007 Association between polycystic ovary syndrome and female-to-male transsexuality. Hum Reprod 22:1011-1016

Balen A 2001 Polycystic ovary syndrome and cancer. Hum Reprod Update 7(6):522-5

Ball GD, Huang TT, Gower BA, Cruz ML, Shabibi GQ, Weigensberg MJ, Goran MI 2006 Longitudinal changes in insulin sensitivity, insulin secretion, and beta-cell function during puberty. J Pediatr 148:16-22

Becking AG, Tuinzing DB, Hage JJ, Gooren LJ 2007 Transgender feminization of the facial skeleton. Clin Plast Surg 34:557-564

Berra M, Armillotta F, D'Emidio L, et al 2006 Testosterone decreases adiponectin levels in female to male transsexuals. Asian J Androl 8:725-729

Bhasin S, Cunningham GR, Hayes F, Matsumoto AM, Synder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes. J Clin Endocrinol Metab 91:1995-2010

Bird D, Vowles K, Anthony PP 1979 Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. Br J Surg 66:212-213

Blanchard R 1997 Birth order and sibling sex ratio in homosexual\versus heterosexual males and females. Annu Rev Sex Res 8:27-67

Blanchard R 2001 Fraternal birth order and the maternal immune hypothesis of male homosexuality. Horm Behav 40:105-14

Bocklandt S, Vilain E 2007 Sex differences in brain and behavior: hormones versus genes. Adv Genet 59:245-66

Bosze P, Toth A, Torok M 2006 Hormone replacement and the risk of breast cancer in Turner's syndrome. N Engl J Med 355:2599-2600

Boyar RM, Wu RHK, Roffwarg H, Kapen S, Weitzman E, Hellman L, Finkelstein JW 1976 Human puberty: twenty-four hour estradiol patterns in pubertal girls. J Clin Endocrinol Metab 43:1418-1421

Brown JA, Wilson TM 1997 Benign prostatic hyperplasia requiring transurethral resection of the prostate in a 60-year-old male-to-female transsexual. Brit J Urol 80:956-957

Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S 2005 Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 60:1451-7

Casella R, Bubendorf L, Schaefer DJ, Bachmann A, Gasser TC, Sulser T 2005 Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing surgery. Urol Int 75:288-290

Chadha S, Pache TD, Huikeshoven JM, Brinkmann AO, van der Kwast TH 1994 Androgen receptor expression in human ovarian and uterine tissue of long-term androgen-treated transsexual women. Hum Pathol 25:1198-1204

Chen HC, Gedebou TM, Yazar S, Tang YB 2007 Prefabrication of the free fibula osteocutaneous flap to create a functional human penis using a controlled fistula method. J Reconstr Microsurg 23:151-154

Magdeleyns EJ, **Tans G**, **Gooren LJ**, **Rosing J**. 2007 Prolactinoma and estrogens: pregnancy, contraception and hormonal replacement therapy. Ann Endocrinol (Paris) 68:106-112

Cohen-Kettenis PT 2001 Gender identity disorder in DSM? J Am Acad Child Adolesc Psychiatry 40:391

Cohen –Kettenis PT, Delemarre-Van de Waal HA, Gooren LJG 2008 The Treatment of Adolescent Transsexuals: Changing Insights. J Sex Med 5: 1892-1897

Cohen-Kettenis PT, Gooren LJ 1999 Transsexualism: a review of etiology, diagnosis and treatment. J Psychosom Res 46:315-333.

Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ 2003 Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. J Abnorm Child Psychol 31:41-53

Cohen-Kettenis PT, van Goozen SH 1997 Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc 36:263-271

Cohen-Kettenis PT, van Goozen SH 1998 Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 7:246-248

Cole CM, O'Boyle M, Emory L E, Meyer WJ 3rd 1997 Comorbidity of gender dysphoria and other major psychiatric diagnoses. Arch Sex Behav 26:13-26

Coolidge FL, Thede L, Young SE 2002 The heritability of gender identity disorder in a child and adolescent twin sample. Behav Genet 32:251-257

Davis PJ, Spady D, de Gara C, Forgie SE 2008 Practices and Attitudes of Surgeons Toward Prevention of Surgical Site Infections: A Provincial Survey in Alberta Canada. Infect Control Hosp Epidemiol [Epub Publication]

De Sutter P 2001 Gender reassignment and assisted reproduction: present and future reproductive options for transsexual people. Hum Reprod 16:612-614

De Sutter P 2003 Donor inseminations in partners of female to male transsexuals: should the question be asked? Reprod Biomed Online 6:382-383

De Sutter P 2007 Reproduction and fertility issues for transpeople. In: Ettner R, Monstrey S, Eyler AE, eds. Principles of Transgender Medicine and Surgery. New York: The Haworth Press; 209-221

Delemarre-Van de Waal HA, Cohen-Kettenis PT 2006 Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. Eur J Endocrinol 155(Suppl 1):S131-S137

Dessens AB, Slijper FM, Drop SL 2005 Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav 34:389-97

Di Ceglie D, Freedman D, McPherson S, Richardson P 2002 Children and adolescents referred to a specialist gender identity development service: clinical features and demographic characteristics. Int J Transgenderism 6(1). Available at: http://www.symposion.com/ijt/ijtvo06no01_01.htm

Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, Zhu Q, Hallock L, Nichols J, Yalcinkaya TM; Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Research Group 2007 Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. Obstet Gynecol 110:1279-1289

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A 2005 Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes 113:586-592

Dizon DS, Tejada-Berges T, Koelliker S, Steinhoff M, Granai CO 2006 Ovarian cancer associated with testosterone supplementation in a female-to-male transsexual patient. Gynecol Obstet Invest 62:226-228

Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA 1999 Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 84(10):3469-78.

Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ 2007 Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. Clin Genitourin Cancer 5:344-346

Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ 2008 A follow-up study of girls with gender identity disorder. Dev Psychol 44:34-45

Elbers JM, Giltay EJ, Teerlink T, et al 2003 Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 58:562-571

Forbes SS, Stephen WJ, Harper WL, Loeb M, Smith R, Christoffersen EP, McLean RF 2008 Implementation of evidence-based practices for surgical site infection prophylaxis: results of a pre- and postintervention study. J Am Coll Surg 207: 336-341.

Finkelstein JS, Neer RM, Biller BM, Crawford JD, Klibanski A 1992 Osteopenia in men with a history of delayed puberty. N Engl J Med 326:600-4

Futterweit W 1998 Endocrine therapy of transsexualism and potential complications of long-term treatment. Arch Sex Behav 27:209-26

Gadducci A, Gargini A, Palla E, Fanucchi A, **Genazzani AR** 2005 Polycystic ovary syndrome and gynecological cancers: is there a link? Gynecol Endocrinol 20:200-8

Ganly I, Taylor EW 1995 Breast cancer in a trans-sexual man receiving hormone replacement therapy. Br J Surg 82:341

Genari L, Khosla S, Bilezikian JP 2008a Estrogen effects on bone in the male skeleton. IN: Principles of Bone Biology (Bilezikian JP, Martin TJ, Raisz LG, eds.) 3rd Edition, Elsevier/Academic Press, San Diego, 1801-1818.

Genari L, Khosla S, Bilezikian JP 2008b Estrogen and fracture risk in men. J Bone Min Res 23: 1548-1818.

Giltay EJ, Gooren LJ 2000 Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. J Clin Endocrinol Metab 85:2913-21

Giltay EJ, Hoogeveen E, Elbers J, Gooren L, Asscheman H, Stehouwer C 1998 Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. J Clin Endocrinol Metab 83:550-553

Giltay EJ, Lambert J, Gooren LJ, Elbers JM, Steyn M, Stehouwer CD 1999 Sex steroids, insulin, and arterial stiffness in women and men. Hypertension 34: 590-597

Giltay EJ, Toorians AW, Sarabdjitsingh AR, de Vries NA, Gooren LJ 2004 Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals. J Endocrinol 180:107-12

Giltay EJ, Verhoef P, Gooren L, Geleijnse J, Schouten E, Stehouwer C 2003 Oral and transdermal estrogens both lower plasma total homocysteine in male-to-female transsexuals. Atherosclerosis 168:139-146

Giraldo F, Esteva I, Bergero T, Cano G, Gonzalez C, Salinas P, Rivada E, Lara JS, Soriguer F; Andalusia Gender Team 2004 Corona glans clitoroplasty and urethropreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. Plast Reconstr Surg 114:1543-1550

Goddard JC, Vickery RM, Terry TR 2007 Development of feminizing genitoplasty for gender dysphoria. J Sex Med 4:981-989

Gooren L 1990 The endocrinology of transsexualism: a review and commentary. Psychoneuroendocrinology 15:3-14

Gooren L 2005 Hormone treatment of the adult transsexual patient. Horm Res 64(Suppl 2):31-36

Gooren L 2006 The biology of human psychosexual differentiation. Horm Behav 50:589-601

Gooren L 2007 Treatment of transsexualism. Published electronically on the UpToDate website.

Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H 1988 Estrogen-induced prolactinoma in a man. J Clin Endocrinol Metab 66:444-446

Gooren LJ, Giltay EJ 2008a Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. J Sex Med 5:765-776

Gooren LJ, Giltay EJ, Bunck MC 2008b Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 93:19-25

Gooren LJ, Harmsen-Louman W, van Kessel H 1985 Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. Clin Endocrinol (Oxf) 22:201-7

Green R 1998 Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. Int J Impot Res 10(Suppl 1):S22-24

Hage JJ, de Graaf FH, Bouman FG, Bloem JJ 1993 Sculpturing the glans in phalloplasty. Plast Reconstr Surg 92:157-161

Hage JJ, Dekker JJ, Karim RB, Verheijen RH, Bloemena E 2000 Ovarian cancer in female-to-male transsexuals: report of two cases. Gynecol Oncol 76:413-415

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A 2005 Psychatric comorbidity in gender identity disorder. J Psychsom Res 58:254-261

Hines M 2004 Brain Gender. New York: Oxford University Press

Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell DR 2004 Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. Contraception 70:11-18

Kersting A, Reuteman M, Gast U, Ohrmann P, Suslow T, Michael N, Arolt V 2003 Dissociative disorders and traumatic childhood experiences in transsexuals. J Nerv Ment Dis 191:182-189

Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266-2274

Knafo A, Iervolono AC, Plomin R 2005 Masculine girls and feminine boys: Genetic and environmental contributions to atypical gender development in early childhood. J Pers Soc Psychol 88: 400-412

Kovacs K, Stefaneanu L, Ezzat S, Smyth HS 1994 Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. A morphologic study. Arch Pathol Lab Med 118:562-565

Krauss DJ, Taub HA, Lantinga LJ, et al 1991 Risks of blood volume changes in hypogonadal men treated with testosterone enanthate for erectile impotence. J Urol 146:1566-70.

Kuiper AJ, Cohen-Kettenis PT 1998 Gender role reversal among postoperative transsexuals. Int J Transgendersim 2. Available at: http://www.symposion.com/ijt/ijtc0502.htm

Landen M, Walinder J, Hambert G, Lundstrom B 1998 Factors predictive of regret in sex reassignment. Acta Psychaitr Scand 97:284-289

Lawrence AA 2003 Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 32:299-315

Levy A, Crown A, Reid R 2003 Endocrine intervention for transsexuals. Clin Endocrinol (Oxf) 59:409-418

Levy J, Burshell A, Marbach M, Afilato L, Glick SM 1980 Interaction of spironolactone with oestradiol receptors in cytosol. J Endocrinol 84:371-379

Liberopoulos EN, Florentin M, Mikhailidis DP, Elisaf MS. 2008 Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. Expert Opin Drug Saf 7: 717-725.

Lindemalm G, Korlin D, Uddenberg N 1987 Prognostic factors vs. outcome in male-to-female transsexualism: a follow-up study of 13 cases. Acta Psychiatr Scand 75:268-274

Lips P, Asscheman H, Uitewaal P, Netelenbos JC, Gooren L 1989 The effect of cross-gender hormonal treatment on bone metabolism in male-to-female transsexuals. J Bone Miner Res 4:657-662

Lubbert H, Leo-Rosenberg I, Hammerstein J 1992 Effects of ethinyl estradiol on semen quality and various hormonal parameters in a eugondal male. Fertil Steril 58:603-608

Luders E, Narr KL, Thompson PM, Rex DE, Woods RP, Deluca H, Jancke L, **Toga AW** 2006 Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp 27:314-324

Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler GB 1988 Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. J Clin Endocrinol Metab 67:368-72

McNeill EJ 2006 Management of the transgender voice. J Laryngol Otol 120:521-523

Meyer WJ 3rd, Bockting W, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B, Laub D, Lawrence A, Menard Y, Monstrey S, Patton J, Schaefer L, Webb A, Wheeler CC 2001 Harry Benjamin International Gender Dysphoria Association's The Standards of Care for Gender Identity Disorders, 6th version. Int J Transgenderism 5:1-22. Available at: http://www.symposion.com/ijt/soc_2001/index.htm

Meyer WJ 3rd, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA 1986 Physical and hormonal evaluation of transsexual patients: a longitudinal study. Arch Sex Behav 15:121-138

Meyer-Bahlburg HF 2005 Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Arch Sex Behav 34:423-38

Meyer-Bahlburg HF, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI 2004 Prenatal androgenization affects gender-related behavior but not gender identity in 5-12-year-old girls with congenital adrenal hyperplasia. Arch Sex Behav 33:97-104

Meyer-Bahlburg HF, Dolezal C, Baker SW, **Ehrhardt AA**, **New MI**. 2006 Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. Arch Sex Behav 35:667-684

Mieszczak J, Eugster EA 2007 Treatment of precocious puberty in McCune-Albright syndrome. Pediatr Endocrinol Rev 4(Suppl 4):419-422

Miller N, Bedard YC, Cooter NB, Shaul DL 1986 Histological changes in the genital tract in transsexual women following androgen therapy. Histopathology 10:661-669

Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JW 2002 Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab 87:3656-61

Monstrey S, De Cuypere G, Ettner R 2007 Surgery: General Principles. In: Ettner SR,Monstrey S, Eyler AE, eds. Principles of Transgender Medicine and Surgery. New York: The Haworth Press; 89-104

Monstrey S, Hoebeke P, Dhont M, De Cuypere G, Rubens R, Moerman M, Hamdi M, Van Landuyt K, Blondeel P 2001 Surgical therapy in transsexual patients: a multi-disciplinary approach. Acta Chir Belg 101:200-209

Moore E, Wisniewski A, Dobs A 2003 Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. J Clin Endocrinol Metab 88:3467-3473

Mueller A, Dittrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, Beckmann MW 2005 High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. Eur J Endocrinol 153:107-13

Mueller A, Gooren L 2008 Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 159:197-202

Neely EK, Bachrach LK, Hintz RL, Habiby RL, Siemenda CW, Feezle L, Pescovitz OH 1995 Bone mineral density during treatment of central precocious puberty. J Pediatr 127:819-22

Nillson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, Häger A, Ivarsson SA, Karlberg J, Kriström B, Marcus C, Moell C, Ritzen M, Tuvemo T, Wattsgård C, Westgren U, Westphal O, Aman J 1996 Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab 81:635-40

O'Hanlan KA, Dibble SL, Young-Spint M 2007 Total laparoscopic hysterectomy for female-to-male transsexuals. Obstet Gynecol 110:1096-1101

Olsson SE, Moller A 2006 Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. Arch Sex Behav 35:501-506

Pfäfflin F, Junge A 1992 Geschlechtsumwandlung: Abhandlungen zur Transsexualität (Sex Change: Treatises on Transsexualism). Stuttgart: Schattauer

Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ 1994 Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 79:265-271

Prasad P, Powell MC 2008 Prospective observational study of thermablate endometrial ablation system as an outpatient procedure. J Minim Invasive Gynecol 15:476-479

Pringsheim T, Gooren L 2004 Migraine prevalence in male to female transsexuals on hormone therapy. Neurology 63:593-4

Pritchard TJ, Pankowsky DA, Crowe JP, Abdul-Karim FW 1988 Breast cancer in a male-to-female transsexual. A case report. JAMA 259:2278-2280

Raudrant D, Rabe T 2003 Progestogens with antiandrogenic properties. Drugs 63:463-492

Reinehr T, Kiess W, Andler W 2005 Insulin sensitivity indices of glucose and free faty acid metabolism in obese children and adolescents in relation to serum lipids. Metabolism 54:397-402

Reiner WG 2005 Gender identity and sex-of-rearing in children with disorders of sexual differentiation. J Pediatr Endocrinol Metab 18:549-53

Riman T, Nilsson S, Persson IR 2004 Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies. Acta Obstet Gynecol Scand 83:783-95

Rishpon-Meyerstein N, Kilbridge T, Simone J, Fried W 1968 The effect of testosterone on erythropoietin levels in anemic patients. Blood 31:453-60

Ross MW, Need JA 1989 Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. Arch Sex Behav 18:145-153

Roth C 2002 Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. Expert Opin Investig Drugs 11:1253-9

Ruble DN, Martin CL, Berenbaum SA 2006 Gender development. In: Damon W, Lerner RM, Eisenberg N, eds. Handbook of Child Psychology, 6th edition. John Wiley & Sons, New York, NY; vol. 3, 858-932

Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K 2005 Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. Osteoporos Int 16:791-8

Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA; **UK Clinical Cytogenetics Group** 2008 Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. Lancet Oncol 9:239-246

Schulze C 1988 Response of the human testis to long-term estrogen treatment: morphology of Sertoli cells, Leydig cells, and spermatogonial stem cells. Cell Tissue Res 251:31-43

Seikowski K 2007 Psychotherapy and transsexualism. Andrologia 39:248-252

Seli E, Tangir J 2005 Fertility preservation options for female patients with malignancies. Curr Opin Obstet Gynecol 17(3):299-308

Selvaggi G, Ceulemans P, De Cuypere G, VanLanduyt K, Blondeel P, Hamdi M, Bowman C, Monstrey S 2005 Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. Plast Reconstr Surg 116:135e-145e

Serri O, Noiseux D, Robert F, Hardy J 1996 Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. J Clin Endocrinol Metab 81:3177-3179

Smith RA, Cokkinides V, Eyre HJ 2006 American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin 56:11-25

Smith YL, van Goozen SH, Cohen-Kettenis PT 2001 Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry 40:472-481

Smith YL, van Goozen SH, Kuiper AJ, Cohen-Kettenis PT 2005 Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med 35:89-99

Spinder T, Spijkstra JJ, van den Tweel JG, Burger CW, van Kessel H, Hompes PG, Gooren LJ 1989 The effects of long term testosterone administration on pulsatile

hormone section and on ovarian histology in eugonadal female to male transsexual subjects. J Clin Endocrinol Metab 69:151-157

Symmers WS 1968 Carcinoma of the breast in trans-sexual individuals after surgical and hormone interference with primary and secondary characteristics. Br Med J 2:82-85

Tangpricha V, Ducharme SH, Barber TW, Chipkin SR 2003 Endocrinologic treatment of gender identity disorders. Endocr Pract 9:12-21

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

Thiagaraj D, Gunasegaram R, Loganath A, Peh KL, Kottegoda SR, Ratnam SS 1987 Histopathology of the testes from male transsexuals on oestrogen therapy. Ann Acad Med Singapore 16:347-348

Thurston AV 1994 Carcinoma of the prostate in a transsexual. Br J Urol 73:217

Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J 2003 Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 88:5723-5729

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR 2007 Current management of male-to-female gender identity disorder in the UK. Postgrad Med J 83:638-642

Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V 2004 Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. Clin Endocrinol (Oxf) 61:560-566

Tuvemo T 2006 Treatment of central precocious puberty. Expert Opin Investig Drugs 15:495-505

U.S. Preventive Services Task Force (USPSTF) 2008 Screening for prostate cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med 149:185-191

Van Coeverden SC, De Ridder CM, Roos JC, Van't Hof MA, Netelenbos JC, Delemarre-Van de Waal HA 2001 Pubertal maturation characteristics and the rate of bone mass development longitudinally toward menarche. J Bone Miner Res16:774-781

van Haarst EP, Newling DW, Gooren LJ, Asscheman H, Prenger DM 1998 Metastatic prostatic carcinoma in a male-to-female transsexual. Br J Urol 81:776

van Kesteren P, Kooistra T, Lansink M, van Kamp G, Asscheman H, Gooren L, Emeis J, Vischer U, Stehouwer C 1998 The effects of sex steroids on plasma levels of marker proteins of endothelial cell functioning. Thromb Haemost 79:1029-1033

van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J 1998 Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol (Oxf) 48:347-354

van Kesteren P, Meinhardt W, van der Valk P, Geldof A, Megens J, Gooren L 1996 Effects of estrogens only on the prostates of aging men. J Urol 156:1349-1353

van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ 1997 Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 47:337-342

von Schoultz B 2007 Androgens and the breast. Maturitas 57:47-9

Wallien MSC, Cohen-KettenisPT 2008 Psychosexual outcome of gender dysphoric children. Am J Child Adolesc Psychiatry, in press

Wallien MSC, Swaab H, Cohen-Kettenis PT 2007 Psychiatric comorbidity among children with gender identity disorder. J Am Acad Child Adolesc Psychiatry 46:1307-1314

Wennink JM, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J 1989 Luteinizing hormone and follicle stimulating hormone secretion patterns in boys throughout puberty measured using highly sensitive immunoradiometric assays. Clin Endocrinol (Oxf) 31:551-564

Wennink JM, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J 1990 Luteinizing hormone and follicle stimulating hormone secretion patterns in girls throughout puberty measured using highly sensitive immunoradiometric assays. Clin Endocrinol (Oxf) 33:333-344

Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM 1977 Liver damage from long-term methyltestosterone. Lancet 2(8032):262-3

Whitehead NE 2007 An antiboy antibody? Re-examination of the maternal immune hypothesis. J Biosoc Sci 39:905-21

Wilson JD, Roehrborn C 1999 Long-term consequences of castration in men: lessons from the Skoptzy and the eunuchs of the Chinese and Ottoman courts. J Clin Endocrinol Metab 84:4324-4331

World Health Organisation Multiaxial Version of ICD10. 1992 Clinical Descriptions and Diagnostic Guidelines. Geneva, World Health Organisation.

Zucker KJ 2004 Gender identity development and issues. Child Adolesc Psychiatric Clin N Am 13:551-568

Zucker KJ, Bradley SJ 1995 Gender Identity Disorder and Psychosexual Problems in Children and Adolescents. New York: Guilford Press

Table 1. Definitions of terms used in this guideline

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

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

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

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

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

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

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

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

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

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

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

Table 2. DSM-IV-TR Diagnostic criteria for gender identity disorder (American Psychiatric Association 2001)

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

In children, the disturbance is manifested by four (or more) of the following:

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

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

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

In children, the disturbance is manifested by any of the following:

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

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

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

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

Code based on current age:

302.6 Gender Identity Disorder in Children
302.85 Gender Identity Disorder in Adolescents or Adults

Specify if (for sexually mature individuals):

Sexually Attracted to Males
Sexually Attracted to Females
Sexually Attracted to Both
Sexually Attracted to Neither

Table 3. *ICD-10* criteria for transsexualism and gender identity disorder of childhood (World Health Organization Multiaxial Version of ICD10 1992)

Transsexualism (F64.0) has three criteria:

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

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

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

For boys:

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

Table 4. Hormone therapy for adults

Adults are eligible for cross-sex hormone treatment if they (Meyer 2001):

- fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism (See Tables 2 and 3)
- do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment
- demonstrate knowledge and understanding of the expected outcomes of hormone treatment, as well as the medical and social risks and benefits; and
- have experienced a documented real life experience (RLE) of at least 3 months duration OR had a period of psychotherapy (duration specified by the mental health professional after the initial evaluation, usually a minimum of 3 months).

Adults should fulfill the following readiness criteria prior to the cross-sex hormone treatment: the applicant

- has had further consolidation of gender identity during a RLE or psychotherapy;
- has made some progress in mastering other identified problems leading to improvement or continuing stable mental health; and
- is likely to take hormones in a responsible manner.

Table 5. Hormone therapy for adolescents

Adolescents are eligible and ready for GnRH treatment if they:

- fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism;
- have experienced puberty to at least Tanner stage 2;
- (early) pubertal changes have resulted in an increase of their gender dysphoria
- do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment;
- have adequate psychological and social support during treatment;
- demonstrate knowledge and understanding of the expected outcomes of GnRH analogue 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

- fulfill the criteria for GnRH treatment AND
- are 16 years or older.

Readiness criteria for adolescents eligible for cross-sex hormone treatment are similar to those for adults.

Table 6. Tanner stages of breast development and male external genitalia

The description of Tanner stages

For breast development:

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

For penis and testes:

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

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

Table 7.
Estradiol levels (pmol/l) in female puberty during night and day[a]
Median of hourly measurements during 2400 – 0600h and 1200 – 1800h:

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

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

Testosterone levels (nmol/l) in male puberty during night and day[b]
Median of hourly measurements during 2400 – 0600h and 1200 – 1800h:

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

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

Table 8. Follow-up protocol during suppression of puberty

Every 3 months

Anthropometry: height, weight, sitting height, Tanner stages

Laboratory: LH, FSH, E2/T

Every year

Laboratory: renal- and liver function, lipids, glucose, insulin, HbA1c

Bone density using DXA

Bone age on X-ray of the left hand

Table 9. Protocol induction of puberty

Induction of female puberty with 17-beta estradiol, increasing the dose every 6 months:

5 µg/kg/day
10 µg/kg/day
15 µg/kg/day
20 µg/kg/day
adult dose=2 mg per day

Induction of male puberty with testosterone esters increasing the dose every 6 months:

25 mg/m^2 /2 weeks im
50 mg/m^2 /2 weeks im
75 mg/m^2 /2 weeks im
100 mg/m^2 /2 weeks im

Table 10. Follow-up protocol during induction of puberty

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

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

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

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

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

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

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

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

Table 12. Hormone regimens in the transsexual persons

Male-to-female transsexual persons*

• Estrogen	
Oral Estrogens	
Estradiol	2.0 – 6.0 mg/day
Estradiol Transdermal patch	0.1 – 0.4 mg twice weekly
Parenteral Estrogens	
Estradiol Valerate or Cypionate	20 – 40 mg IM every 2 weeks
• Anti-androgens	
Spironolactone	200 – 400 mg/day
Cyproterone acetate**	50-100 mg/day
• Gonadotropin-releasing hormone agonist	3.75 mg SQ monthly

Female-to-male transsexual

• Testosterone	
Oral Testosterone	
Testosterone undecanoate** Not available in US.	160-240 mg /day
Parenteral Testosterone	
Testosterone enanthate or cypionate	100 – 200 mg IM every 2 weeks or 50% weekly.
Testosterone undecanoate**, ***	1000 mg every 12 weeks
Transdermal testosterone	
Testosterone gel 1%	2.5 – 10 g/day
Testosterone transdermal patch	2.5 – 7.5 mg/day

* 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 six weeks then at 12 week intervals

Table 13. Masculinizing effects in female-to-male transsexual persons

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

**** Prevention and treatment as recommended for biological men.
***** Menorrhagia requires diagnosis and treatment by a gynecologist.

Table 14. Feminizing effects in male-to-female transsexual persons

Effect	Onset	Maximum
Redistribution Body Fat	3-6 months	2-3 years
Decrease Muscle Mass and Strength	3-6 months	1-2 years
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 Years
Decreased Testicular Volume	3-6 months	2-3 Years
Decreased Sperm Production	Unknown	> 3 years
Decreased Terminal Hair Growth	6-12 months	> 3 years*
Scalp Hair	No Regrowth	**
Voice Changes	None	***

* Complete removal of male sexual hair requires electrolysis and/or laser treatment.
** Familial scalp hair loss may occur if estrogens are stopped.
*** Treatment by speech pathologists for voice training is most effective.

Table 15. Monitoring of transsexual persons on cross-hormone therapy
Male-to-female transsexual persons

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

Table 16. Monitoring of transsexual persons on cross-hormone therapy
Female to male transsexual persons

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

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

Table 17. Sex reassignment surgery
Eligibility and readiness criteria

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

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

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

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