

## The endocrine treatment of transsexual adolescents

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## Abbreviations

BMD	Bone Mineral Density
DSM	Diagnostic and Statistical Manual of Mental Disorders
GID	Gender Identity Disorder
GnRH	Gonadotrophin Releasing Hormone
HBIGDA	Harry Benjamin International Gender Dysphoria Association
ICD	International Classification of Diseases
MHP	Mental Health Professional
RLE	Real life experience
SOC	Standard of care
SRS	Sex Reassignment Surgery
WPATH	World Professional Association of Transgender Health

## Abstract

Hormonal treatment of transsexual adolescents is controversial. Whereas gender identity in childhood is not stable, adolescence is often a crucial phase in the development of a persons' gender identity. Hormonal treatment in transsexual adolescents may avoid the development of or a worsening of psychiatric co-morbidity, leads to superior cosmetic results, and is therefore strongly indicated. Recently, guidelines for the endocrine treatment of transsexual adolescents have been published by the Endocrine Society, leading to a de-marginalisation of transsexualism. The diagnosis of a gender identity disorder is made by a mental health professional, but its treatment is multidisciplinary. Three phases are to be distinguished during childhood and adolescence and are discussed in detail in this article: The diagnostic phase, a reversible phase of suppression of puberty with GnRH analogs and a partially irreversible phase of cross-sex hormone treatment. Throughout this time, psychological evaluation and support, by which the eligibility and readiness of the adolescent for the next treatment step is assessed, remains the basis of treatment. Sex reassignment surgery is only performed in adulthood (above the age of 18 years) and is not discussed here. Although long term outcome data are presently lacking, the first studies suggest excellent results psychologically as well as cosmetically with this treatment regimen.

## Introduction

Sexual dimorphism is - already during childhood - considered as a basic principle of our society: From birth onwards, one is regarded as male or female. However, this rigid dichotomy does not take individual variances in biological, psychological and social aspects of gender into account. A person's gender identity - a person's fundamental sense of being a

man, a woman - is somewhere on a continuum of what is considered as either typical male or typical female, and may be changing over time. When biological sex and gender identity are not fully congruent, this may result in serious psychological distress, called gender dysphoria, and / or transsexuality, defined as a desire to live and be accepted as a member of the gender opposite to that assigned at birth. According to the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR), a gender identity disorder (GID) is present 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. The diagnosis of GID and transsexualism, and the exclusion of psychiatric co-morbidities are primarily made by a mental health professional (MHP) (psychiatrist or psychologist). However, the treatment of transsexualism is multidisciplinary, and involves the MHP, (pediatric) endocrinologist, urologist, gynaecologist and plastic surgeon [1].

Guidelines for the evaluation and management of transsexual persons have been proposed since 1979 under the form of "Standards of Care" by the World Professional Association of Transgender Health (WPATH) (formerly called the Harry Benjamin International Gender Dysphoria Association (HBIGDA)). Only very recently, international consensus guidelines for the endocrine treatment of transsexual persons were proposed by the Endocrine Society [1]. These guidelines are the result of a common effort of the world's specialists in the care of transgender persons to put their individual clinical and scientific experiences together, and, although ample evidence is often lacking due to small sample size, especially in the pediatric population, these guidelines actually represent the foundation for actual transsexual patient care, and will be the basis for this article.

Historically, pediatricians have been hesitant to treat gender dysphoric children and adolescents. This is in part due to the fact that gender identity in children is age dependent, flexible and hard to examine, and secondly due to the principle of "first do no harm", which has an extra ethical dimension in children because of their immaturity and dependence on adults for decision making [2]. However, severe gender dysphoria may cause serious psychological distress and / or psychiatric co-morbidity, which is often initiated or worsened by the development of physical signs of puberty such as breast development and the occurrence of menses in girls, and facial hair growth and penis development in boys. Therefore, while living explicitly in the desired gender role during childhood is not advised, the pubertal period is now regarded as a crucial phase, where the emotional reaction on the onset of puberty and the suppression of these first pubertal signs afterwards represent an extra diagnostic tool. Because GID treatment has been marginalized for a long time, many transsexual persons have been driven to self-treatment and over-treatment, leading to inappropriate and potentially dangerous formulations. A major achievement of the recently

published guidelines is precisely to destigmatise transsexuality and make it a medical condition for which appropriate treatment can bring relief.

### **The different phases of endocrine treatment**

Although experience in the endocrine treatment of transsexual adolescents is very limited, there is a vast evidence-based knowledge on suppression of puberty and hormone replacement therapy in a variety of conditions, making the here outlined treatment safe and well-known in experienced hands.

#### *1. Diagnosis and follow-up during childhood*

The diagnosis of GID and transsexualism is based on the criteria as described in the DSM-IV-TR (Table 1) or the International classification of diseases (ICD)-10 (Table 2). There are separate criteria for children and adolescents. The diagnosis must be made by a MHP with specific training in childhood developmental psychopathology and must also include a psychiatric evaluation. Psychiatric co-morbidities and a congenital condition in which sex development is disturbed (a so-called disorder of sex development or DSD) must be excluded [1].

There is no evidence that the gender dysphoric child may benefit from adopting the desired gender role overtly already during childhood or from any hormonal therapy. Moreover, the large majority (75-80%) of prepubertal gender dysphoric children do not turn out to be transsexual adolescents. Therefore, when confronted with a prepubertal child with a possible diagnosis of GID, the MHP will put emphasis on the diagnostic work-up, the exclusion and management of (psychiatric) co-morbidities, and will support the child and his / her environment. Additionally, the child will be referred once to the pediatric endocrinologist to formally exclude a DSD [1, 3-5].

#### *2. The onset of puberty: Suppression of puberty and real life experience (RLE)*

The onset of puberty is often pivotal in children with a GID: The appearance of the first physical signs of puberty will often result in an increase of gender dysphoria. As stated above, this reaction is awaited by the MHP to finalise the diagnostic work-up. After pubertal onset, hormonal treatment can be started, but only in those adolescents who fulfil all eligibility and readiness criteria as defined by the WPATH SOC (Table 3). The final decision to start hormonal treatment is taken by the multidisciplinary team (pediatric psychologist, pediatric psychiatrist, pediatric endocrinologist). The aim of the hormonal treatment at this stage is to stop pubertal progression in a fully reversible way: This gives the adolescent the necessary time to grow older, to reflect on the impact of adolescence on his thoughts and feelings, while avoiding irreversible pubertal changes associated with the undesired sex. After the tumultuous phase of pubertal onset, hormonal suppression of puberty often brings back an emotional relief and quiescence, which again, may add to the diagnostic tableau.

From this stage on, adolescents can be encouraged to start the real life experience (RLE), in which the adolescent fully acts in the desired gender role and gender presentation in every day life. A successful RLE of at least twelve months is a necessary condition before the adolescent is eligible for irreversible cross-sex hormone therapy, which is never started before the age of 16 years (Table 3).

A major advantage of pubertal suppression with GnRH analogs is that the secondary sex characteristics of the undesired sex will not progress, with superior cosmetic results after later sex reassignment surgery (SRS) as a result. At Tanner stages 2-3, breast development in girls is (almost) fully reversible with GnRH analog use, avoiding the scars of mastectomy in the female to male (FtM) transsexual. Likewise, facial hair growth is absent or very limited in boys under GnRH analog treatment, making facial laser therapy in the male to female (MtF) transsexual unnecessary [1, 3, 4, 6].

However, many individuals with GID only seek medical attention when pubertal development is already at an advanced stage. At this point, secondary pubertal characteristics are not reversible anymore, making treatment with an GnRH analog of no use. Anti-androgens for MtF, or high-dose progestins inducing amenorrhea for FtM may bring temporarily relief, until the adolescent fulfills eligibility and readiness criteria for cross-sex hormone treatment [1].

### *3. Advanced adolescence and adulthood: Cross-sex hormones and SRS*

Adolescents are eligible for treatment with hormones of the desired sex (the so-called cross-sex hormones) when they fulfil all eligibility and readiness criteria for pubertal suppression and are at least 16 years old (Table 3). The decision to start treatment with cross-sex hormones is taken by the multidisciplinary team, and depends on a careful and individualised evaluation of all eligibility and readiness criteria [1].

Oral or transdermal estrogens are administered to MtF transsexual adolescents, intramuscular injections with testosterone derivatives are given to FtM. Doses are gradually increased, aiming to induce full pubertal development of the desired sex in about two years of time. For the transsexual adolescent and his / her environment, it is very important to realise that changes induced by cross-sex hormone treatment, e.g. breast development, female body habitus in MtF, and deepening of the voice, facial hair growth, clitoral growth in FtM, are only partially reversible. These aspects should be discussed in depth with the adolescents and his / her parents, as well as the consequences for future fertility. Cryopreservation of sperm is not possible at start of GnRH analog treatment due to the early pubertal stage at which this treatment is started, however, spermatogenesis will start after stopping this treatment for a reasonable time, e.g., before the administration of estrogens. This will of course be associated with physical signs of testosterone production. Techniques for cryopreservation of ovarian tissue are in development, but are not routinely available presently [1].

Treatment with GnRH analogs should ideally be continued until gonadectomy is performed. SRS, including gonadectomy can only be performed after the age of 18 years. A detailed description of the different SRS procedures is beyond the scope of this article.

During the different phases of hormonal treatment, regular psychological follow-up must be continued, to fully appreciate the emotional reactions and adaptations of the transsexual individual and his / her environment to the changes induced by the hormonal treatment regimen.

## **Guidelines for endocrine treatment and side effects**

### *1. Suppression of puberty*

Effective suppression of puberty is reached with the intramuscular administration of Triptoreline 3.75 mg every 4 weeks or Triptoreline 11.25 mg every 12 weeks. Treatment is never started before Tanner stage 2-3 for reasons outlined above. At this stage, physical signs of puberty are often fully reversible, and no irreversible effects on gonadal function have been described. The emotional reaction to GnRH analog treatment is considered to be a diagnostic aid (see above). The response to treatment should be assessed by a pediatric endocrinologist every 3-6 months. No serious side effects have been noticed with Triptoreline after short term use. Spontaneous pubertal development will restart after cessation of treatment. Some concern exists with regard to bone development and bone mineral density (BMD) after long-term use of GnRH analogs. Initial studies on bone density changes in transsexual adolescents during GnRH analog treatment are reassuring, but studies assessing long-term peak bone mass and BMD are still awaiting [1, 4]. The use of GnRH analogs is expensive, limiting its use substantially.

For persons seeking medical advice at a later pubertal stage, the advanced physical signs of puberty are not reversible anymore with GnRH analog treatment. Anti-androgens (Androcur®, 25 - 50 mg daily) may bring relief in MtF (decreased facial and body hair growth and sexual desire), while high-dose progestins (Orgametril® 5mg daily or Depoprovera 150 mg intramuscular once every 3 months) may cause cessation of menses in FtM [1].

### *2. Cross-sex hormone treatment*

The decision to start cross-sex hormones in patients who are at least 16 years of age is made by the multidisciplinary team. The aim of this treatment is to induce puberty of the desired sex stepwise, very similar to puberty induction in patients with hypogonadotropic hypogonadism. Meanwhile, psychological follow-up must be continued. The initial low doses of hormone replacement therapy insufficiently suppress endogenous gonadotrophin secretion; therefore it is advised to continue GnRH analogs until gonadectomy is performed. Clinical (growth, tanner stages, blood pressure) and hormonal follow-up and check of safety parameters is advised every 3-6 months. Lipid profile, bone turn-over and insulin resistance

should be checked every year, as well as BMD. Self-treatment and overtreatment should evidently be avoided. In these circumstances, hormone replacement therapy turns out to be safe and effective, but overtreatment in general results in an increased cardiovascular risk profile [1].

In MtF transsexual adolescents, estradiol can be administered orally or via transdermal route. However, experience with this last method is limited in young persons. A commonly used schedule is the administration of 17 $\beta$ - estradiol, to start with 5 $\mu$ g/kg/d, followed by a 6 monthly increase with 5 $\mu$ g/kg/d. The adult dose is 2 mg/d. The use of 17 $\beta$ - estradiol is preferred to that of ethinyl estradiol, because it can be measured in serum, and its safety profile is superior to that of ethinyl estradiol [1]. Breast development, female body habitus and body composition appear in the first year and are not fully reversible anymore. However, breast development is expected to reach its maximum only after two years of treatment with the adult dose. The increased risk of thrombo-embolism is a major concern with estrogen therapy, especially in combination with smoking or a family history of thrombo-embolic disease. In these cases, the transdermal administration route is preferred [1].

In FtM transsexuals, testosterone is frequently administered under the form of testosterone esters (Sustanon®), via intramuscular injections every 2 weeks. The initial dose is 25 mg, to be augmented with 25 mg every six months, until the adult dose of 125-250 mg/2 weeks is reached. Serum values of testosterone are best obtained before the next injection. Erythrocytosis is a major concern, and hematocrit values must be maintained within the normal range. Other side effects are liver dysfunction, hypertension, salt retention, weight gain and lipid changes and excessive acne. Smoking should be strongly discouraged. The first effects of testosterone treatment (increased libido and muscle mass, male pattern hair growth) are seen within the first months of treatment, later changes are deepening of the voice and clitoral growth [1]. No data on the use of Nebido (intramuscular testosterone undecanoate) are available in adolescents.

## **Conclusions**

Gender dysphoria and transsexualism are diagnoses primarily made by a MHP. However, treatment of transsexualism is multidisciplinary.

A discomfort with the own gender is relatively frequent during childhood, and only 10-20% of gender dysphoric children turn out to become transsexual adolescents. Therefore, therapy during childhood is only supportive, medical treatment and a complete gender role change are not indicated. During adolescence, the emotional reaction to puberty, and its suppression by GnRH analog treatment is a diagnostic tool, and aids the adolescent to avoid the development of important psychopathologic co-morbidity. Moreover, pubertal suppression of the biological sex leads to superior cosmetic results in transsexuals. Therefore, in

adolescents who fulfil all eligibility and readiness criteria, GnRH analogs and at a later stage cross-sex hormones are the treatment of choice. Although experience in transsexual adolescents is limited, the use of these medications in other indications appears to be effective and safe. Intensive psychological follow-up and a careful evaluation of the RLE throughout this period are obligatory. Under these circumstances, outcome turns out to be excellent. In a follow-up study of the Dutch cohort, treated according to the protocol as outlined above, no patients showing feelings of regret were encountered [4, 5]. Data on long-term outcome of transsexual individuals treated during adolescence are awaited.

## References

- [1] Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009 Sep;94(9):3132-54.
- [2] Houk CP, Lee PA. The diagnosis and care of transsexual children and adolescents: a pediatric endocrinologists' perspective. *Journal of pediatric endocrinology & metabolism.* 2006 Feb;19(2):103-9.
- [3] Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1997 Feb;36(2):263-71.
- [4] Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *European journal of endocrinology / European Federation of Endocrine Societies.* 2006 Nov;155 Suppl 1:S131-7.
- [5] Smith YL, van Goozen SH, Cohen-Kettenis PT. 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.* 2001 Apr;40(4):472-81.
- [6] Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *Eur Child Adolesc Psychiatry.* 1998 Dec;7(4):246-8.



**TABLE 1. DSM-IV-TR diagnostic criteria for GID**

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

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

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

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

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

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

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

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

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

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

Codes based on current age:

302.6 GID in children

302.85 GID in adolescents or adults

Specify whether (for sexually mature individuals):

Sexually attracted to males

Sexually attracted to females

Sexually attracted to both

Sexually attracted to neither

**TABLE 2. ICD-10 criteria for transsexualism and GID of childhood**

Transsexualism (F64.0) criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.

2. The transsexual identity has been present persistently for at least 2 yr.

3. The disorder is not a symptom of another mental disorder or a genetic, intersex, or chromosomal abnormality.

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

Criteria for girls:

1. The individual shows persistent and intense distress about being a girl and has a stated desire to be a boy (not merely a desire for any perceived cultural advantages of being a boy) or insists that she is a boy.

2. Either of the following must be present:

a. Persistent marked aversion to normative feminine clothing and insistence on wearing stereotypical masculine clothing.

b. Persistent repudiation of female anatomical structures, as evidenced by at least one of the following:

i. An assertion that she has, or will grow, a penis.

ii. Rejection of urination in a sitting position.

iii. Assertion that she does not want to grow breasts or menstruate.

3. The girl has not yet reached puberty.

4. The disorder must have been present for at least 6 months.

Criteria for boys:

1. The individual shows persistent and intense distress about being a boy and has a desire to be a girl or, more rarely, insists that he is a girl.

2. Either of the following must be present:

a. Preoccupation with stereotypic female activities, as shown by a preference for either cross-dressing or simulating female attire or by an intense desire to participate in the games and pastimes of girls and rejection of stereotypical male toys, games, and activities.

b. Persistent repudiation of male anatomical structures, as evidenced by at least one of the following repeated assertions:

i. That he will grow up to become a woman (not merely in the role).

ii. That his penis or testes are disgusting or will disappear.

iii. That it would be better not to have a penis or testes.

3. The boy has not reached puberty.

4. The disorder must have been present for at least 6 months.

**TABLE 3. Hormone therapy for adolescents: Eligibility and readiness criteria**

Adolescents are eligible for GnRH treatment if they:

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

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

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

Adolescents are ready for GnRH treatment if they:

1. Have had further consolidation of gender identity during a RLE or psychotherapy
  2. Have made some progress in mastering other identified problems leading to improvement or continuing stable mental health
  3. Are likely to take hormones in a responsible manner
- (Readiness criteria are the same as for adults).