

Approach to the management of children and adolescents with Gender Dysphoria

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Abstract

Over the past 20 years, the care for transgender adolescents has developed throughout many countries following the “Dutch Approach” initiated in the 90’s in pioneer countries as the Netherlands, United States and Canada, with increasing numbers of children and adolescents seeking care in transgender clinics. This medical approach has considerable positive impacts on the psychological outcomes of these adolescents and several studies have been recently published underlining the relative safety of such treatments.

This paper reviews the current standards of care for transgender children and adolescents with particular emphasis on disparities among countries and short to medium-term outcomes. Finally it highlights ethical considerations regarding categorization of gender dysphoria, timing of treatment initiation, infertility, and how to deal with the long-term consequences.

Definition of Gender Dysphoria

Gender dysphoria (GD) in children, adolescents and adults is defined in the Diagnostic and Statistical Manual of Mental Health, Fifth Edition (DSM 5) as “incongruence between one’s experienced/expressed gender and assigned gender [...] causing clinically significant distress and impairment in social, school or other important areas of functioning” (see Table 1 for DSM 5 diagnostic criteria) (1). In order to understand this definition, it seems important to call to mind such notions as gender identity and other concepts related to gender (see Table 2 for key words), and to describe how, in our clinical practice, transboys (birth-assigned female whose gender identity is male) and transgirls (birth-assigned male whose gender identity is female) present. It seems also very important to keep in mind that the terminology in this field is quite confusing, as the same term “gender dysphoria” could refer to the DSM 5 diagnosis or to the distress resulting from the incongruence between birth-assigned gender and experienced gender. In the article, when we refer to the diagnosis, we use the abbreviation “GD”; when we refer to the distress, we spell out the words in lowercase letters (gender dysphoria).

Clinical presentation

Development of gender identity (Table 2) is complex, and one’s self-awareness as male or female (or other) evolves and may change gradually during life (2, 3), under a multifactorial interplay of biological (genetic, hormonal), psychological and environmental (social, cultural) factors (2, 4) (for a detailed review on this subject see (5)). For most children, gender identity is consistent with their birth-assigned gender and remains constant across lifespan, but some children may experience an incongruence between their experienced and assigned gender (so-called gender incongruence) and exhibit persistent, consistent nonconforming or nongender-stereotypical behaviors at ages as young as 2-3 years-old (4). They can explicitly insist that they are of the other gender or that they identify with the other gender and sometimes strongly dislike their physical sexual characteristics (6). Other persons may disclose a transgender identity

later in adolescence or adulthood, and express a strong desire for the anatomy of the experienced gender and an aversion of the body characteristics of the birth-assigned gender (7) without a history of gender non-conformity in early childhood (4). If the distress resulting from this incongruence (so-called gender dysphoria) reaches clinical levels, the diagnosis of GD, according to current DSM 5, is applicable (Table 1) (1). In pre-pubertal children, presentation varies widely, often depending on environment, some experiencing feelings such as being “trapped” in the wrong body (3).

Persistence or desistence?

Young children who are gender non-conforming or who identify as transgender may or may not continue to identify as transgender as adolescents and adults and may follow different developmental pathways (4). There is evidence to suggest that for the majority of them, this gender incongruence will desist and that they will identify with their birth-assigned gender by early adolescence (4, 8, 9). According to various studies, the percentage of “persisters” appears to be between 10 and 39% (10, 11). Besides, studies that have been conducted among children and adolescents have shown that GD that persists into adolescence is unlikely to subside (2, 10, 12, 13). Therefore adolescents may be considered for medical treatment when GD persists or intensifies when puberty has started (Tanner breast or genital stage 2) (3). For those, the peripubertal and pubertal physical changes can be unbearable. In the qualitative study from Steensma et al, persisters and desisters both reported that they felt that the period between age 10 and 13 was a critical time period (10). There have been efforts to identify factors to differentiate pre-pubertal children who will persist in their transgender identity during adolescence and adulthood versus those who will desist (4) but it is currently impossible to predict persistence or desistence with certainty. Studies examining factors associated with persistence of childhood GD suggest that the likelihood of transgender identity in adolescence/adulthood may be predicted by more severe symptoms of GD and more persistent, insistent and consistent cross-gender statements and behaviors in childhood, and the tendency to assert their gender cognitively versus affectively (“I am a boy” versus “I feel like a boy”) (14).

History of transgender care in children and adolescents

The beginning of transgender care for children and adolescents is marked by the seminal paper on young gender-incongruent children by Money and Green (15). Specialized consultations for transgender children have developed steadily. The starting point was the pediatric endocrinology department at Johns Hopkins Hospital in Baltimore with John Money; there were also several other important places: Robert Stoller with Richard Green in Los Angeles; Kenneth Zucker in Toronto; Peggy Cohen-Kettenis and Henriette Delemarre-van de Waal in Amsterdam, Domenica Di Ceglie in London. The “Dutch approach” was designed by Profs Cohen-Kettenis and Delemarre-van de Waal (16) and has been proposed to transgender adolescents since the 90’s in the Netherlands (17). Today, although gender clinics for children and adolescents exist in many countries, this clinical practice and related research remains unevenly distributed around the world. Little by little since the 2000s, most specialists, owing to the contribution of the LGBTIQ community, came to the conclusion that trans-identity is not a psychiatric disorder but a singular construction of identity as everyone builds his/ her identity in a singular way. In the DSM 5, the condition of experiencing clinically significant distress is required to assert diagnosis of GD (1) so that a transgender person who feels well is not attributed any diagnosis. Currently, the debate is still continuing with the development of the ICD-11 (18). Research is ongoing on the way to facilitate access to care for transgender people, to better meet their needs, but also on educational and informational programs to reduce transphobia and discriminations that are considered to contribute to dysphoria and comorbid conditions in transgender youth (19, 20).

Epidemiological data

Few studies exist on the prevalence and incidence of GD. A recent review from Kenneth Zucker aimed to summarize actual epidemiological data among children and adolescents, based on self-identification as a transgender person or parents reporting their child as “wishing to be of opposite sex” in standardized questionnaires (21). Interestingly, from a parental point of view there seemed to be a higher prevalence of

birth-assigned girls that wished to be of opposite sex than boys (21). In the pediatric population, one study in younger children was published of a random sample of 2730 students in grade 6-8 who were asked what their gender was, of whom 1.3% answered being “transgender” (22), however it remains unclear to what extent children understood the question. Similarly, high school students from New Zealand were asked the question “Do you think you are transgender” to which 1.2% answered yes. An additional 2.5% reported not being sure about their gender and 1.7% that they did not understand the question (23). In 2016, Eisenberg et al, published a prevalence of 2.7% of transgender or gender nonconforming youth, with 3.6% of birth assigned females and 1.7% of birth assigned males considering themselves as “transgender, genderqueer, genderfluid or unsure about their gender identity” among a random sample of 81 885 high school teenagers (24). In 2017, Becker et al, asked 940 German male and female adolescents aged 10-16 years to report their current gender experience (feminine and masculine) and expression (gender role as girl or boy). Among them, 4.1% adolescents were evaluated as variant in gender experience and 3.0% as non-conforming in expression, while 0.9% adolescents demonstrated both gender variance and non-conforming expression (25).

Aside from previous studies that estimated prevalence in the general or student population, studies from adult transgender clinics throughout the world have reported a varying clinical prevalence possibly depending on accessibility to care, society and culture. The majority of those seeking treatment were birth-assigned males (between 1:3205 to 1:30000 birth-assigned males versus 1:7752 to 1:100000 birth-assigned females) (21). A recent meta-analytic review by Arcelus et al, concluded that the prevalence of ‘transsexualism’ in adult males was 1:14705 versus 1:38461 in adult females (26). In adolescents, the sex ratio also favored boys until the mid-2000s when a shift was observed to one favoring birth-assigned girls in several countries (Canada, Netherlands, Finland) (27, 28).

It is of particular interest to note that wherever a specialized transgender health care program has opened, increasing rates of children and adolescents seeking out health care have been observed, questioning whether there is a true increase in the prevalence/incidence or whether it is due to a depathologisation and destigmatisation of GD, making it easier for children/parents to seek out health care (13, 29).

Etiological Hypotheses

Most authors consider GD to have multifactorial origins: genetic, biological, psychological and social (30, 31). Animal studies show that prenatal sex hormones do not only determine the development of the internal and external genitalia but also act on the brain in the sense of sexual differentiation (32). Recently, Beking and colleagues have shown that both prenatal and pubertal testosterone affects brain lateralization in a task-specific way in boys (33). Moreover, the increased incidence of GD in the context of Differences/Disorders of Sexual Development (DSD) has led to the hypothesis that sex steroids play a role in the etiology of GD, and that mutations in the genes encoding enzymes involved in their biosynthesis or metabolism or encoding their receptors could be implicated (31).

A neurobiological theory of the origin of GD is based on the fact that during embryogenesis, genital differentiation occurs well before sexual differentiation of the brain. Since these two processes are not synchronous, and may not require similar levels of hormonal impregnation, it is possible that in relation to variable levels of androgen secretion at these two stages, sexual organs develop towards the female phenotype while the brain differentiates towards the male phenotype, or conversely (34).

Several studies support a genetic component in GD (35, 36). In a literature review of twin studies, including unpublished cases from specialized centers, it was possible to show a significantly higher concordance for GD among monozygotic twins than among same sex dizygotic twins (37, 38). Familial occurrence of GD has also been described in a non-twin siblings study (39), but in terms of absolute numbers, the likelihood for the sibling of a transgender individual to also be dysphoric is very low. Abnormal karyotype is rarely found in transgender individuals (40). Associations between GD and specific mutations or mean repetition numbers of specific polymorphisms in genes related to sex hormones have been investigated. The studies were conducted in transgender individuals without associated DSD, versus same-sex controls. The genes encoding the estrogen receptor alpha ($ER\alpha$), the estrogen receptor beta ($ER\beta$), the progesterone receptor (PR), and the enzymes CYP19, CYP17 and SRD5A2 were candidates. These studies, often conducted on a small number of individuals, were

discordant and inconclusive (Table 3) (41, 42, 43, 44, 45, 46, 47, 48). Recently, a study using whole-genome- and whole-exome-sequencing revealed a rare mutation in the *RYR3* gene, coding for a calcium transporter, in some transgender individuals (49).

Research in neuroimaging has also been performed. Anatomical studies seem to show that although the overall volume and the morphology of the gray and white matter remain close to birth-assigned gender (50), very localized areas are morphologically closer to the sex concordant with gender identity (31). More recently, functional MRI studies have shown atypical activation patterns in transgender children and adolescents, either GD specific (different from both cisgender males and females) or sex-atypical (similar to their experienced gender pattern) (51). No effect of GnRH analogue (GnRHa) treatment was found on executive function (52) but effects of gender-affirming hormone therapy on the brain have been observed (53, 54).

Regarding the psychological and environmental components, many studies have been conducted around the possible influence of parents' prenatal sex preference, but also around social reinforcement or parental emotional functioning contribution. To date, there is no evidence of an impact of the prenatal wish (55). However, parental tolerance to cross-sex behavior and parental emotional functioning may be associated with GD but there is no evidence for specificity (55). Moreover, what may seem an atypical parental reinforcement of feminine and masculine behavior that would encourage the child in transidentity may rather be an adequate parental adaptation to a child with GD. It is interesting to note that non-conforming gender identity is expressed in many cultures, including non-Western countries which suggests that particular cultural aspects may not be of major influence (56, 57, 58, 59).

Finally, a psychoanalytic hypothesis proposes to consider one's identity as constructed by a "knot" comprising several dimensions (e.g., the real body, the body image, and the symbolic dimension) (60). Transgender persons may be experiencing a discrepancy between these dimensions - that they can reduce by transitioning and with lots of creative non-normative possibilities so they can fulfill themselves as human beings (61).

Guidelines for the care of transgender youth

Transgender children and adolescents should receive multidisciplinary care from mental health professionals, physicians, surgeons and ethicists, specialized in gender identity care and working together to give youth who seek gender affirming treatment from early puberty on, the chance to develop into well-functioning young adults.

Psychological care and Social Transitioning

According to the recommendations of the World Professional Association for Transgender Health (WPATH) (62), the Endocrine Society Clinical Practice Guidelines (3), the American Academy of Child & Adolescent Psychiatry (AACAP) (63) and the American Psychological Association (64) the mental health professional should welcome the child or adolescent and his/her family and acknowledge their concerns about gender identity, possible distress and health and well-being in general. The mental health professional offers an age-appropriate assessment for GD and any coexisting mental health concern. The clinician conducts an interview with the child or adolescent and also obtains information from the parents regarding various aspects of the child's general and psychosexual development and current functioning. Hence, the Endocrine Society Guidelines recommend mental health clinicians should be trained in child and adolescent developmental psychology and psychopathology, competent in using the DSM and/or the ICD for diagnostic purposes, knowledgeable about the GD diagnostic criteria and able to make a distinction between GD and other conditions that may have similar presentation (e.g. body dysmorphic disorders). The American Psychological Association Guidelines advocates as their "Guideline 1" that psychologists should understand gender as a non-binary construct that allows for a range of gender identities and model an acceptance of ambiguity as transgender and gender non-conforming children and adolescents explore aspects of their gender (64). Assessment explores the nature and characteristics of the child's or adolescent's gender identity, emotional experience, intensity of the eventual distress, cognitive and emotional functioning, family dynamics, peer and other social relationships, school achievement, in the context of cultural values of the youth, family and community. The AACAP insists on the need for

confidentiality in the clinical alliance that is a special consideration in the assessment of sexual and gender minority youths. Similarly, according to the AACAP practice principles, the mental health professional should investigate the existence of commonly encountered circumstances in this population such as bullying, suicidal ideation, high-risk behaviors or substance abuse. Moreover, the mental health professional should be aware of the profound intersections between gender identity, gender expression and other aspects of identity as ethnicity, age, education, socioeconomic status, immigration status, occupation, disability status, relational status, and spiritual affiliation (64). The mental health professional gives information about transgender and gender non-conforming identities, offering language to help children and adolescents describe their feelings (64), about the possibilities and limitations of the different therapeutic options and proposes referral for peer support (such as support groups for parents or children) or contacts with community-based organizations that provide support and resources for youth, families and professionals. Finally, the mental health professional offers supportive psychotherapy that focuses on exploring gender identity, alleviating distress and helping youth to develop a positive personal self-concept. To promote an accepting and nurturing response, support by family but also by school, health professionals and in general all the people who surround the child or adolescent is essential (19, 65). Indeed, different studies have shown the negative impact of social stigmatization, while family and school support are protective factors (19, 66, 67, 68, 69). Health professionals do not impose any view of gender, especially of what the gender identity of this child or adolescent should be or will be in the future, trying to keep any option open. So families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes. The mental health professional strives to create a therapeutic space based on trust and offers long-term support throughout any subsequent social changes or physical interventions, helping the child and his / her family in the important decisions they have to make, facilitating communication between the child and his / her parents.

Transition refers generally to the development of a gender expression congruent with internal gender identity that may comprise changes in appearance and behavior, legal name changes, medical and/or surgical therapies, but does not require any of these modifications. Social transitioning is an adjustment in

gender expression and role (like living part or full time in the gender role that is consistent with gender identity) that may evaluate the person's ability to function in the affirmed gender, and the adequacy of social and psychological supports. Whereas it is recommended to encourage teens with GD who seek treatment to experience social transition and assess whether this improves their quality of life, this remains controversial for prepubertal children, due to the potential high rates of desistence in cross-gender identification from childhood to adolescence. One study observed an association between childhood social transition and persistence in cross-gender identification (70), and suggested that 'detransitioning' could be difficult mostly owing to fear of peer judgment. Olson *et al.* (2016) (71) conducted a study based on parental reports of a sample of 73 prepubertal transgender youth who were allowed to socially transition and showed similar levels of anxiety and depression to matched controls. Similarly, a recent cross-sectional study by Durwood *et al.* (2017) based on children and parental reports shows that socially transitioned youth have equivalent levels of depression and self-worth to their matched-control or sibling peers as well as marginally higher anxiety (72). However authors did not form a control group with transgender youth who were not permitted to socially transition. Indeed, such a study would likely be unethical (72, 73). These studies are first steps towards an evidence base for early social transition, but there is a need for further research.

The mental health professional is able to refer for appropriate treatment with knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. The mental health professional carefully evaluates the adolescent's capacity to understand treatment and social conditions that can impact gender-affirming hormone therapy, diagnoses associated psychiatric conditions and makes sure that these conditions are treated appropriately, notably when they may complicate treatment, affect its outcome, or be affected by hormone use. The multidisciplinary team confirms the persistence of GD, ensures sufficient mental capacity to give informed consent to hormonal transition and further helps in decisions regarding gender-affirming surgery in older adolescents.

Puberty suppression and gender-affirming hormone therapy

The puberty suppression protocol follows the Endocrine Society guidelines (3) and is based on the “Dutch approach” designed by Profs Cohen-Kettenis and Delemarre-van de Waal (16). The concept is to stop pubertal progression thereby attenuating the distress and anxiety linked to appearance of secondary sexual characteristics. It allows time for evaluation and may spare adolescents later gender affirming surgical procedures such as chest masculinization for transboys; ablation of adam’s apple, facial surgeries for transgirls (74), and it may prevent deepening of the voice in transgirls. GnRHa are the currently preferred treatment option and are used to suppress puberty as in precocious puberty (75). They are long acting agonists that suppress gonadotropins secretion by a desensitization of the GnRH receptor. Treatment with GnRHa should only be considered when criteria for eligibility to puberty suppression are fulfilled (Table 4) most particularly once puberty has started (Tanner stage 2: initiation of breast development in birth-assigned girls, testicular enlargement > 4 ml in birth-assigned boys (76)) to let adolescents experience some puberty, as a diagnostic marker, to ensure that GD is persistent (10). Efficacy and short-term safety of GnRHa puberty suppression in transgender adolescents is now well established (77). This treatment can be initiated from stage 2 to stage 4-5 of puberty, as well as in post-pubertal adolescents. One monthly intra-muscular or subcutaneous injection is usually preferable to the three-monthly injection at the initiation of treatment to ensure complete inhibition of LH and FSH secretion (75, 78). At the onset of puberty secondary sexual characteristics may regress, or stop at later phases of pubertal development. In birth-assigned girls menses will stop and breast tissue will become atrophic. In birth-assigned boys, subsequent virilization will discontinue; most particularly GnRHa can prevent appearance of facial hair, even at late Tanner stages. One advantage is that the effects of GnRH treatment are completely reversible, thus, if the adolescent no longer wishes hormonal transitioning, treatment can be discontinued and physiological puberty will resume (79). However, adolescent and parents must be informed of the expected side effects of treatment (transient impact on bone mineral density, transient reduced growth velocity), of the scarcity of literature concerning final adult height, peak bone mass and skeletal morphology (80) and of its impact on future surgeries (notably vaginal reconstruction in transgirls by the

penile inversion skin technique, the current most commonly used technique for vaginal lining, that could be compromised by stopping penile growth) (81) and fertility preservation possibilities (61).

In cases where puberty is well advanced, transboys may be treated by oral progestin preparation to suppress menses (82). If GnRH α are not available or in case of needle phobia, an anti-androgen can be proposed to transgirls to directly suppress androgen secretion and action (83).

If adolescents are willing to go through hormonal transitioning, gender-affirming hormones (estrogens for transgirls, androgens for transboys) can be proposed from the age of 16 years old (Table 4). Of note, the recent Endocrine Society guidelines no longer refer to a minimal age, but rather suggest an age when the adolescent has sufficient capacity to give informed consent and weigh adequately the benefit and risk of treatments, although only minimal data support earlier use of gender-affirming hormones (3). The adolescent and his/her parents should be informed of expected effects of treatment and potential side effects notably concerning fertility. Thus, options to preserve fertility must be discussed. Initiation of gender-affirming hormones should be progressive, with a gradual dose increase and monitoring of clinical pubertal development and laboratory parameters (hormone concentrations, metabolic parameters) (3).

Treatments available in Europe

In several European countries such as the Netherlands, the United Kingdom and France GnRH α are used as initial treatment for adolescents with GD as recommended in the Endocrine Society guidelines (3, 77). Several formulations are available (Table 5). However, GnRH α are not reimbursed in other countries such as Belgium and families may not be able to pay the costs out of pocket (82). Therefore some providers use anti-androgens such as cyproterone acetate to suppress endogenous sex steroids in late pubertal transgirls (from Tanner G4) and progestins in late pubertal transboys (from Tanner B4) (82, 83). Others have used spironolactone to reduce androgen-dependent hair growth in transgirls (13). For pubertal induction oral or transdermal estradiol is preferred in transgirls whereas injections or transdermal testosterone formulations are available for transboys (Table 5).

Short to medium-term outcomes

Psychological

Adolescents with GD are at an increased risk of psychiatric disorders, such as anxiety disorders (21%), mood disorders (12% to 64%), risk of attempted suicide or self-aggressive behavior (5 to 53%) and of dropping out of school (13, 28, 84). These disorders could either be comorbidities or complications of GD or might also be consequences of social impact of transidentity. In fact, a study of 218 children and adolescents (mean age = 14 yrs) conducted in a developmental perspective, highlights contexts of harassment in 49.4% of transgirls and 45.3% of transboys (85). Recently, a clinical comparison study between four gender identity clinics across Europe showed differences in emotional and behavioral issues and peer relationships problems that were most prevalent in adolescents from the UK, followed by Switzerland, Belgium and the least by adolescents from The Netherlands. More research is needed to clarify these results and determine the factors that may contribute to them (86).

Two longitudinal studies from the Netherlands were able to measure efficacy in terms of psychological outcomes and tolerance of GnRHa treatment (12) followed by gender-affirming hormones in adolescents (87). The first longitudinal prospective study concerned a cohort of 70 transgender teenagers (33 transgirls and 37 transboys) eligible to receive puberty suppression treatment, that were assessed before the onset of GnRHa (T0) and shortly before the initiation of gender-affirming hormones (T1). Results demonstrated that depressive symptoms as well as behavioral and emotional issues decreased during treatment, while general performance improved significantly. However, feelings of anxiety and anger were stable during T0 and T1. In this cohort, no adolescent chose to withdraw from puberty suppression, and all went on with gender-affirming hormone therapy (12). In the literature, a small percentage (up to 4%) of individuals who started treatment stopped because they no longer wished to undergo a gender change (13, 83) and one suicide was reported during treatment (82). The recent study by Wiepjes et al., including 6,793 transgender individuals from the Amsterdam cohort (1972–2015) showed a percentage of only 1.9% of adolescents who stopped treatment during the phase of puberty suppression, which is also used as a

prolonged diagnostic phase. However, no adolescents stopped treatment after they had started gender affirming hormone therapy (88).

The second longitudinal study, from the same team, evaluated long-term efficiency of the global care protocol at several time points: before onset of puberty suppression (T0, mean age = 13.6 yrs), at the introduction of gender-affirming hormones (T1, mean age = 16.7 yrs), and one year after re-assignment surgery (T2, mean age = 20.7 yrs). A total of 55 young adults were evaluated (22 transwomen and 33 transmen). Focusing on their psychological functioning and their global well-being in areas such as social interactions and education or quality of life, this study demonstrates that in early adulthood, after medical and surgical gender-affirming treatment, gender dysphoria was attenuated and psychological functioning had improved. Their global well-being became equivalent to same-age young adults from the general population (87).

Medical outcomes

No long-term studies are available yet on medical outcomes in adolescents but several studies have looked at efficacy and short to medium term side-effects/safety of puberty suppression and gender-affirming hormone treatments in adolescents. Treatment with triptorelin results in a decrease of testicular volume in most transgirls and cessation of menses in transboys and adequately suppresses gonadotropins and sex steroids (77). Medroxyprogesterone has also been used to suppress puberty in both transboys and transgirls but especially in transgirls with advanced puberty, suppression of testosterone levels is incomplete (89). Lynestrenol does not completely suppress gonadotropins either in transboys and is associated with metrorrhagia (82). Cyproterone acetate only partially suppresses testosterone but results in decreased shaving frequency in the majority of late pubertal transgirls (83). Oral oestradiol treatment induces breast development within three months in most transgirls and after three years Tanner breast stage 4-5 is attained (90). Waist-to-hip ratio decreases during estrogen treatment and increases during testosterone treatment (80, 90).

The following side effects have been reported during GnRHa treatment: hot flashes, fatigue, headache and mood alterations, pain from injection and sterile abscesses (3, 13). Lynestrenol treatment is frequently associated with acne, headache, hot flashes and fatigue (82), whereas medroxyprogesterone was generally well tolerated by a small group of adolescents (89). Fatigue was common during cyproterone acetate treatment (83). Estradiol led to breast tenderness, emotionality and hunger (83) whereas testosterone resulted in acne. Height SDS decreases whereas BMI SDS is stable or increases slightly during GnRHa treatment but fat percentage increases and lean body mass percentage decreases (77, 91). Testosterone leads to an increase of BMI SDS (82) whereas estradiol does not affect BMI SDS, fat or lean body mass percentage (90). Some studies found no change in blood pressure during testosterone or estradiol treatment (90, 92) but one study observed an increase in systolic blood pressure during testosterone treatment (93). Transgirls have an average adult height of +1.9 SDS. High dose estradiol treatment did not seem effective for growth reduction although this treatment has only been described in a few adolescents (90).

Bone mineral (apparent) density z-scores decrease during GnRHa treatment, especially in the lumbar spine, and increase during treatment with testosterone or estradiol (91, 94). However, they remain lower than pre-treatment z-scores, even at age 22 years after more than 5 years of treatment with gender affirming hormones (91, 94). One individual was reported to have normal BMD z-scores at age 35 years after treatment with GnRHa for 4.9 years followed by testosterone treatment from age 18.6 years (95).

No changes in HbA1c, insulin, glucose, or HOMA index have been found during treatment with lynestrenol, cyproterone acetate, testosterone or estradiol (82, 83, 90, 92). Mean HDL-cholesterol decreases and mean LDL-cholesterol increases during treatment with lynestrenol (82). Testosterone also induces a decrease of HDL-cholesterol (92, 93). It is uncertain how this affects the risk of cardiovascular complications in the long term; few cardiovascular events and deaths have been reported in transgender males but available data are insufficient to draw any conclusions (96). Total cholesterol, HDL-cholesterol and triglycerides decrease during cyproterone acetate treatment (83). Some studies found no effect of estradiol on lipid levels (83, 92) but one study reported an increase in HDL-cholesterol (93).

Testosterone treatment causes an increase of the hematocrit but rarely (0-3%) above the normal range (82, 92). Estradiol does not affect the hematocrit in transgirls (90, 92). Transient rises in liver enzymes were observed during cyproterone acetate treatment (83) while they remained within the normal range during testosterone and estradiol treatment (82, 90, 92). Cyproterone acetate treatment lowers DHEAS levels, however its effects on adrenal function warrant further study (83).

Estrogen therapy is associated with an increased risk of venous thrombo-embolism and this has been reported in 0-5% of adult transwomen (96). However, pulmonary embolism has only been described in one transgender adolescent who was overweight, smoked tobacco and used both ethinyl estradiol to stop menses and testosterone (97).

Cyproterone acetate causes an increase of prolactin (83) and hyperprolactinemia with galactorrhea has been reported in a transgirl during high-dose ethinyl estradiol treatment (90). Some studies found that estradiol treatment does not increase prolactin levels (90, 92) but others did find an increase although within the normal female range (93).

Follow-up

During puberty suppression, it is thus suggested by the Endocrine Society Guideline that the adolescent be seen every 3 to 6 months for height, weight, sitting height, blood pressure and pubertal staging evaluation (3). At each visit, satisfaction with treatment, efficacy and possible side effects should be discussed (3). Laboratory testing is suggested at least once a year to measure hormonal levels (LH, FSH, E2/T, 25 OHD). Bone mineral density using DXA should be monitored and bone age on X-ray should be proposed every 1 to 2 years if puberty was stopped at early stages (3). If puberty suppression is inadequate then adherence to therapy should be assessed and a change of dose or dose interval can be considered. In case of suspected side effects the possibilities of changing medication, stopping medication or starting gender affirming treatment need to be discussed with the adolescent. If bone mineral density shows a worrying trend then advice can be given to optimize physical activity, calcium and vitamin D intake, and an earlier start of gender affirming hormones may be considered if appropriate.

During gender affirming hormone therapy, continued evaluation of anthropometry measures and pubertal progression is suggested every 3 to 6 months (3). Prolactin, estradiol and 25 OHD levels should be checked at least once a year in transgirls on estrogens, and hemoglobin/hematocrit, lipids, testosterone and 25 OHD levels in transboys on testosterone (3). If testosterone therapy is administered intramuscularly every 2 weeks, testosterone levels should be measured midway between injections or alternatively peak and trough levels can be monitored (3). If pubertal progression is inadequate, side effects are experienced or hormone levels are outside the target range, then a change of type or dose of medication may be considered and if abnormal laboratory results are encountered, such as erythrocytosis, temporary discontinuation of hormonal therapy may be necessary. If clinically relevant, bone mineral density using DXA and bone age on X-ray should be performed at least once every two years (3).

Transition to adult care

Transition from adolescent to adult care should be envisioned and carried out by a multidisciplinary team at the appropriate moment, including both pediatric and adult endocrinologists. These young adults should be informed of the need for long-term medical monitoring.

Hormonal therapy

Gender affirming hormones aim at attaining physiological doses (table 5), in order to avoid risks of inadequate hormone plasma levels (98, 99, 100) according to published guidelines (3). In transwomen, transdermal or oral 17beta-estradiol treatment is maintained; continuation of anti-androgenic treatment is recommended until gonadectomy, since physiological doses of estrogen alone are insufficient to inhibit testosterone secretion. There is currently no evidence regarding the hypothetic beneficial role of progestogen for breast development, and further research is needed (101).

In transmen who are adequately virilized with adult doses of testosterone, GnRHa treatment can be discontinued. If uterine bleeding occurs, progestin treatment can be prescribed until potential hysterectomy.

Follow up and long term care

Clinical evaluation is recommended every 3-6 months during the first 2 years, then once a year. Satisfaction with hormonal therapy, quality of life and psychosocial outcomes should be fully discussed with these young adults. Clinicians should also monitor weight, blood pressure. Side effects of sex steroids and cardiovascular risk factors should be evaluated; cessation of tobacco use must be recommended. Questions concerning further surgical management will be addressed, as well as those surrounding medically assisted procreation, taking into account medical and country-specific legal contexts.

Blood testing should be performed at each visit, with evaluation of levels of prolactin, estradiol and lipids in transwomen, and testosterone, hemoglobin/hematocrit and lipids in transmen (3).

Estrogen therapy is associated with increased risk for thromboembolic disease, particularly with ethinyl oestradiol (which is no longer recommended) or when supraphysiological doses of estrogens are used (93, 102).

When puberty is suppressed at early stages, bone mineral density should be monitored at least until the age of 25-30 years. If treatment was initiated after puberty, bone mineral density should be assessed in individuals who are not compliant with hormone therapy or who develop risks for bone loss (3).

In transwomen, prostate cancer risk is expected to be extremely low due to gland atrophy after pubertal medical castration. Long term use of high dose anti-androgens is of concern (103). A retrospective study observed a higher incidence of meningioma in a cisgender population using cyproterone acetate, especially when higher doses were used; however, further research is warranted (104). Regarding breast-screening, guidelines are currently identical to those for cisgender females (3).

There is no existing evidence for increased risk of reproductive tract cancers in transmen. However, clinicians should inform adolescents and adults of the recommended screening if hysterectomy and oophorectomy are not considered (3) in the prevention of cervical cancer (105) or other reproductive tract

cancers (106), similar to cisgender women, and of the potential long term effects of testosterone therapy on these organs (107).

In conclusion, long-term prospective studies are required, particularly for transgender individuals who will choose not to have surgery, in order to evaluate risks associated with long-term anti-androgenic treatment in transwomen, and to propose optimal gynecologic care in transmen.

Laws/Standards of care around the world

Professional organizations have consistently recognized that medical intervention is warranted and necessary for transgender adolescents (3, 4, 62, 108). Still, transgender youth face significant health disparities related to lack of access to competent care, given location, insurance coverage and cost (4), and it appears that despite these guidelines, the actual practice for GD is quite variable, and the number of adolescents receiving the recommended medical interventions compared with the number of potentially eligible individuals is quite low (109).

Controversies and many challenges persist around clinical management of gender variant children and adolescents with specific barriers that can be identified, such as:

- social discomfort with treatment of GD in the pediatric population (109), and/or moral or philosophical objections to treating transgender adolescents with hormonal therapies;
- unfamiliarity with the clinical practice guidelines among mental health, primary care and endocrine providers (109, 110), lack of confidence in their ability to provide care to this ‘vulnerable population’;
- limited number of centers equipped to treat GD;
- disparity regarding insurance coverage for medical therapies;
- high costs of puberty suppression therapy;
- adolescents who do seek care at specialized centers often present at late pubertal stages, i.e. after Tanner stage 3, making pubertal suppression less effective (109);

- the persistent classification of GD as a psychiatric condition, as this classification may cause a lack of awareness among adolescents, parents and providers, that GD may be treated with medical interventions in early adolescence (109);
- providers may be hesitant to follow the guidelines, given limited long-term data supporting their safety and effectiveness (109).

Nevertheless, transgender care for children and adolescents has developed and is now much more widely available. Many clinics in the world now see children and adolescents with GD and use puberty suppression protocols (7). However, some differences between countries can be identified, for instance the minimum age to initiate puberty blockers and gender affirming hormones, and the possibility for reimbursement.

A recent report provides descriptions and contact information for 35 gender programs in the US and Canada (111), like the GeMS program (6). “Gender-affirming approach to care” and medical interventions for appropriately assessed children and adolescents have become the standard of care in several states (4), with protocols adapted from existing guidelines and standards for working with transgender individuals; in Michigan, Colorado, and Massachusetts, for instance, the reported practice is to consider puberty blockers at Tanner stage 2 and gender affirming hormone treatment initiation as early as age 14 years (4). According to the guidelines, genital surgeries are typically not recommended until the adolescent has reached legal age of majority, although chest surgery in transboys may be considered earlier. Despite the advances, many transgender adolescents report facing barriers to access competent and comprehensive medical and mental health services, including lack of access to trained providers and low rates of insurance coverage for medical therapies (108). Legally speaking, in Anglo-American countries, it seems easier to adopt a new first name, but registration documents are not centralized (as a result, a person can be male according to one and female according to another document) (2).

In Canada, Khatchadourian et al. (13) describes the current standard of care in the Endocrinology and Diabetes Unit at British Columbia Children’s Hospital in Vancouver. The median time between the first visit to the clinic and initiation of GnRHa was 0.2 month (range 0-3.2 months), with 12 of 27 adolescents

(44%) receiving treatment at their first visit. The age at start of gender-affirming hormones was 17 +/- 1.6 yrs for transboys, and 14.7 +/-2.2 yrs for transgirls. The median time from first visit to initiation of gender-affirming hormones was 4.6 months (range 0-42 months). These treatments are covered by provincial drug plans. The authors report that it is now standard practice to discuss fertility preservation with adolescents before initiating medical or surgical treatment, without further details.

In Europe, disparities are still marked. In the Netherlands, the timing of the various treatment steps depends on cognitive and emotional maturation, along with physical development, according to the “Dutch protocol” (16). Treatments are covered by national health insurance. It is the same in France, where the first transgender clinic for children and young adolescents only opened in 2013 (112). In UK, children and adolescents care programs are available, in line with the Dutch protocol at the Gender Identity Development Service (GIDS) of the Tavistock Center (<https://www.nhs.uk/live-well/healthy-body/how-to-find-an-nhs-gender-identity-clinic/>), but also in some private clinics (<https://www.mermaidsuk.org.uk/assets/media/17-15-02-A-Guide-For-Young-People.pdf>), with hormonal transition possible at an age younger than 16 years-old. In Italy, an article published in 2014 (113), stating that gender clinics in the country were not able to respond to the particular situations of children and adolescents with GD, underscored the need to develop and adhere to Italian Guidelines for treatment of adolescents with GD, in line with the Dutch Approach, the Endocrine Society and the WPATH guidelines. Similarly, in Spain, a position statement paper in 2015 set out recommendations for evaluation and treatment of GD in children and adolescents (114) and a recent paper, published in 2018, describes the characteristics of the process of care for adolescents with GD in the Gender Identity Treatment Unit of Asturias during the period 2007-2015 (115). In Finland, since 2011, specialized adolescent psychiatric gender identity teams are available for minors at two university hospitals (28).

Legally speaking, Germany will be this year the first European country to officially recognize a “third gender” category, as the Federal Constitutional Court gave lawmakers until the end of 2018 to either allow the introduction of a third gender category or dispense with gender altogether in public documents (<https://www.reuters.com/article/us-germany-gender/german-court-rules-in-favor-of-third-gender->

[category-idUSKBN1D82B3](#)). In many countries that derive their laws from Napoleon's Civil Code of 1804, the birth certificate is the source for all other personal documents. It is therefore essential to change the sex indication in one's birth certificate to give a person the full rights of his/her new gender (2). In France, the "Law of modernization of Justice of the 21st century", in 2017, allowed individuals, including minors, to change their first name and allowed a change of sex indication from 18 years on, without any requirement of hormonal therapy or genital surgery.

In other countries around the world, huge disparities still persist. In Australia, recent legal developments concerning treatment for GD in children and adolescents confirm that parents are lawfully able to consent to puberty blocking medication, for children as young as 10 years old. In addition, a child who is determined by a court to be "Gillick competent" (that is who is found to possess sufficient understanding and intelligence to enable her or him to understand fully what is proposed) can consent to gender affirming hormone treatment around the age of 16 years; in other cases, gender-affirming hormone therapy has to be approved by a court (116).

Little information was found on how the question of fertility preservation (FP) is addressed in different countries (61). In the US and in UK (<https://www.england.nhs.uk/wp-content/uploads/2017/04/gender-development-service-children-adolescents.pdf>), it seems that a comprehensive fertility counseling is provided in some specialized centers (4, 117, 118) but legal issues are not discussed.

In 2017, Mamoojee and Quinton reported the variation in practice in the UK, the USA, Iran, Thailand and the Netherlands, but did not mention any detail about children and adolescents, concerning disparities in legal issues, minimal age to start puberty blockers and gender-affirming hormones, or reimbursement of medical care for that specific range of age (119). A document, the Trans Rights Europe Map & Index, published on line in May 2018, summarizes detailed country information in 25 legal categories, such as legal gender recognition, non-discrimination, health and family (<https://tgeu.org/trans-rights-map-2018/>).

Ethical considerations

Treatment teams providing affirmative medical transgender care to young people are inherently faced with moral dilemmas and questions. When GD persists during adolescence, the possibility of puberty suppression and gender-affirming hormone therapy has generated a debated dimension to clinical management. The beneficial effects of hormonal treatment on the adolescents' mental health, quality of life and on physical appearance that make it possible to live unobtrusively in the desired gender role are often emphasized (12, 120). However, various ethical concerns have been raised about the risk of making the wrong (irreversible) treatment decisions, about the decision-making abilities of adolescents, and about the potential long-term adverse effects on health and on psychological and psychosexual functioning. Interestingly, these concerns are often raised outside the scientific realm, mostly in popular media and press (for example the discussions between proponents and opponents in the Dr Phil Show on gender identity disorder – Does reparative fit? Jan 14, 2009 available at www.youtube.com/watch?v=z8lq3E85-VY, or (121, 122)). In general, ethics has been a secondary consideration in the medical academic literature (123). Here we will focus on three major issues: how should we categorize GD? What is a right timing of advancement of treatment? And how should we deal with long-term treatment effects, especially infertility?

In contrast to the DSM-IV, the DSM5 (30) no longer has "gender identity disorder" as a classification, but "GD". In both the to be released ICD-11 (18) and the DSM5 (30), the main challenge has been to find a balance between concerns related to the stigmatization of mental disorders and the need for diagnostic categories that facilitate access to healthcare (124). The status of GD as a mental disorder remains the subject of heated debate (125). Part of that debate rests on the question of what should count as a 'mental disorder', what diagnostic criteria are appropriate and what it means for therapeutic interventions that GD is seen as a mental disorder. One of the reasons for having a formal (psychiatric) diagnosis is to obtain health insurance coverage and treatment on an equal footing with other medical conditions. Moreover, the existence of a formal diagnosis encourages research developments. However, psychiatric diagnoses always impose on the individual a stigmatizing label that fails to capture the existential dimension of the person's experience.

There is also a fundamental debate about the right timing for hormonal treatment and surgery. The most recent guidelines (3) recommend starting GnRH analogues at Tanner stage B2/G2 and gender-affirming hormones at age 16. Still, arguments are made both to lower and to increase the ages at which to start hormonal treatment. Two ethical concepts are important here: the best interest of the child, and the child's autonomy to decide on medical treatment. In pediatrics, the 'best interest' standard has become the prevailing standard in decision-making (126), but often proves difficult to apply (127). Proponents and opponents of early medical interventions in children with GD are often not clear on what their definition of the best interest of a child is. There have been attempts to formulate 'objective' criteria for the best interest standard. Some authors claim that every child has a right to reach adulthood with as many opportunities left open as possible, until he is a fully formed self-determining adult capable of deciding for himself. Physicians and parents would act unethically if they make choices that constrain a child's range of future options (128). At first sight, this 'right to an open future' seems reasonable, but the problem is that it could be used by opponents as well as proponents of early interventions. The right to an open future could be described as the right to postpone the decision on this far-reaching treatment until one is a capable adult (since there is no life-threatening argument to start treatment earlier). On the other hand the open future can be described as a future in which the development of secondary sexual characteristics of the undesired sex is prevented, and in which future treatment would be less invasive and painful (for example, breast removal in transboys and painful and expensive treatment for facial hair in transgirls). This way, the future child could have much more opportunities left open in the desired sex. It could also be argued that puberty suppression could support the right to a happy childhood/adolescence or to a psychologically healthy development.

As adolescents approach adulthood, their involvement in medical decision-making increases. The best interest standard then makes way for their own values and preferences. But also decision-making competence in older children proves an important point of disagreement when discussing early interventions (129). In general, in order to be valid, consent should be fully informed, competently given, and uncoerced. "Full information" may pose a challenge in the case of GD, since (long-term) risks and

benefits of available treatments are, in fact, not fully established. Although no serious side effects are reported until now, the long-term medical and psychological effects in adolescents with GD have to continuously be evaluated. It may be argued that since the risks and benefits of early gender transition cannot be fully established in advance, it is not possible to give valid informed consent. On the other hand, every new intervention has the problem of little long-term data. But for an area with such an impact on the (future) child, GD has been subject to relatively little academic research. It is the obligation of every treatment team to participate in systematic interdisciplinary and (worldwide) multicenter registries and research.

One of the most far-reaching long-term effects of transitioning is the eventual loss of fertility. Before starting treatment, sperm and oocyte retrieval and banking can be offered to those who are post pubertal, but there are significant barriers. Oocyte retrieval is an invasive procedure with limited clinical and research experience in minors. Both sperm and oocyte banking are generally not covered by insurance. Future options may shed a new light on fertility preservation and the right to procreate (61). In the future, probably also prepubertal gonadal tissue can be differentiated in tissue culture to result in mature sperm or oocytes. Also, other assisted reproductive technologies (ART), like in-vitro gametogenesis, may prove to be the solution for transgender people to have genetic offspring (130). The current experiences of trans people with ART service providers is mostly negative, even in countries where there are no legal barriers to access to ART (131). With future options on the way, an ethical and legal debate is essential, taking into account the right to equality and non-discrimination, and the right to procreate of transgender people.

Conclusion

The number of transgender children and adolescents seeking care has risen exponentially over recent years. Clinical services arise in more and more places and guidelines for treatment are available. However, important barriers to receiving appropriate care and inequality still exist. In addition, many aspects of this care are still subject to debate. The uncertainty about the nature and etiology of GD and the scarcity of data on short to middle term outcomes and absence of data on long term outcomes of gender affirming

treatment in adolescents play an important role in the ethical concerns about this treatment. Further research in these areas should help to resolve these issues and optimize the approach to children and adolescents with GD.

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Table 1: DSM-5 criteria for Gender Dysphoria (1)

In children

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following criteria (one of which must be Criterion A1) :
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender)
 2. In boys (assigned gender), a strong preference for cross-dressing or simulated female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
 3. A strong preference for cross-gender roles in make-believe play or fantasy play
 4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender
 5. A strong preference for playmates of the other gender
 6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games and activities
 7. A strong dislike of one's sexual anatomy
 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
- B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome)

In adolescents and adults

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following criteria:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome)

Specify if:

Posttransition: the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen – namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a birth-assigned male; mastectomy or phalloplasty in a birth-assigned female)

Table 2: Key terminology used in the context of Gender Dysphoria

Birth-assigned gender: the gender that is assumed on the basis of the phenotype / physical sex characteristics present at birth (110)

Gender identity is a person's own perception of their gender, that is their internal feeling of being, for example, boy or girl, male or female, a-gender, non-binary, trans-gender, gender queer...(7). Unlike gender expression (see below), gender identity is not visible to others.

Gender role: attitudes, feelings and behaviors that a society, in a given historical period, in a given culture, associates with a person's birth-assigned gender; as so, it's a social construct and varies by place and time period (e.g., men: aggressive, strong, dominant, emotionally reserved; women: nurturing, dependent, passive...)

Gender expression: how gender identity is communicated to others (e.g one's name, gender pronoun, style of dresses...), that is, external manifestations of gender. Gender expression is all about how you demonstrate your gender through the ways you act, dress, behave, and interact, whether that is intentional or unintended. Gender expression is interpreted by others perceiving your gender based on traditional gender roles (e.g., men wear pants, women wear dresses). As so, gender role or gender expression describes how a person presents themselves as masculine or feminine in the context of societal expectations.

Gender attribution describes the process whereby other observers view a person as masculine or feminine.

Gender variance refers to gender expression and/or identity inconsistent with prevailing societal expectations and norms (6).

Transgender is an umbrella term used to identify individuals whose gender identity does not conform to conventional gender roles of either male or female (13); not all trans-people necessarily experience a complete cross-gender identity, want hormone therapy as well as surgery, and want to live as the other gender permanently or completely (2).

Transgirl or transwoman or transgender female or male-to-female or MtF: term used to identify a birth-assigned male whose gender identity is female.

Transboy or transman or transgender male or female-to-male or FtM: term used to identify a birth-assigned female whose gender identity is male.

Gender dysphoria: internal distress experienced due to the discordance between gender identity and birth-assigned gender

Cisgender: when your birth-assigned gender aligns with how you identify (term introduced to describe individuals who have a gender identity congruent with or the same as their birth-assigned gender).

Transitioning: Process by which an individual begins living in their affirmed gender role (may or may not include hormonal and/or surgical treatment).

E.g, social transition: presenting in social settings as the affirmed gender

Gender identity, gender expression, birth-assigned gender, and sexual orientation are independent of one another.

Table 3: Results from principal genetic studies on transgender populations

Authors	Investigated gene	Population	Results
<i>Henningsson et al.(41)</i>	AR	MtF	Not significant
	CYP19	vs XY control males	Not significant
	ER β		Significant P= 0.03 ; OR=6
<i>Hare et al.(42)</i>	AR	MtF	Significant P= 0.04
	CYP19	vs XY control males	Not significant
	ER β		Not significant
<i>Bentz et al.(43)</i>	SRD5	MtF	Not significant
		FtM vs XX control females	Not significant
<i>Bentz et al.(44)</i>	CPY17 genotype and haplotype	MtF	Not significant
		FtM vs XX control females	Significant P= 0.01 ; OR=1.71
<i>Ujike et al.(45)</i>	AR, ER α , ER β , PR, CYP19	MtF	Not significant
	AR, ER α , ER β , PR, CYP19	FtM vs XX control females	Not significant
<i>Fernandez et al.(46)</i>	CYP17	MtF vs FtM	Significant P= 0.041
		FtM vs XX control females	Not Significant
		MtF vs XY control males	Not Significant
<i>Fernandez et al.(47)</i>	AR, ER β , CYP19	MtF	Not significant
<i>Cortes-Cortes et al.(48)</i>	ER α genotype and haplotype	MtF	Not Significant
		FtM vs XX control females	Significant P= 0.044; OR=3.96

Table 4: Criteria for eligibility to pubertal suppression and gender-affirming hormonal treatment in adolescents (adapted from (3))

Treatment by GnRH analogs for pubertal suppression can be proposed if:

- Criteria for Gender Dysphoria have been confirmed by a qualified mental health professional, and no co-existing morbidity prevents initiation of therapy
- Pubertal development has initiated (\geq Tanner stage 2), and there are no contraindication to GnRH agonist treatment
- The adolescent and the parents have been informed of the expected effects of treatment, of its potential side effects, of its impact on future surgeries and the fertility preservation possibilities.
- The adolescent has demonstrated capacity to fully understand the treatment protocol and its implications and has given his/her informed consent. Parents must also be involved in supporting the adolescent, and give their informed consent when the legal age for medical consent is not reached.
- Treatment is proposed by a multidisciplinary team qualified in transgender care

Treatment by androgens/estrogens for gender-affirming pubertal development can be proposed if:

- The above criteria are fulfilled
 - The adolescent and parents have been informed of the expected effects of treatment, of its potential side effects, and its consequences on fertility. Fertility preservation options have been discussed.
 - The adolescent as reached an age where he/she is considered in sufficient mental capacity to evaluate benefits and risks of this partly irreversible treatment (usually by age 16 years)
 - Adolescent and parents (when the legal age for medical consent is not reached) have given their informed consent
 - Treatment is proposed by a multidisciplinary team qualified in transgender care
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Table 5. Treatment available in Europe to suppress endogenous sex steroids and induce puberty consistent with the affirmed gender in transgender adolescents. Adapted from (3, 75).

Medication used to suppress endogenous sex steroids

GnRH analogues, for example

Leuprorelin	3.75 mg i.m./s.c. monthly or 11.25 mg every 12 wk
Triptorelin	3.75 mg i.m./s.c. monthly or 11.25 mg every 12 wk
Goserelin	3.6 mg s.c. monthly or 10.8 mg every 12 wk
Buserelin	6.3 mg s.c. 2-monthly
Histrelin	50 mg implant yearly

Progestins, for example

Lynestrenol	5-10 mg/day orally
Medroxyprogesterone	5-10 mg/day orally 3-monthly 150 mg i.m.

Anti-androgens, for example

Cyproterone acetate	25–50 mg/day orally
Spirolactone	100–300 mg/day orally

Medication to induce puberty

17beta-estradiol	gradually increase to adult dose 2-6 mg/day orally 25-200 mcg patch twice a week transdermal
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Testosterone	gradually increase to adult dose mixed esters 100-200 mg every 2 wk i.m./s.c. gel 50-100 mg/day transdermal
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not suitable for pubertal induction but alternative once at adult dose:
undecanoate 1000 mg every 12 wk i.m.
