Endocrinology of Transgender Medicine

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Abstract

Gender affirming treatment for transgender people requires a multidisciplinary approach in which endocrinologists play a crucial role. The aim of this paper is to review recent data on hormonal treatment of this population and its effect on physical, psychological and mental health. The Endocrine Society guidelines for transgender women include estrogens in combination with androgen lowering medications. Feminizing treatment with estrogens and anti-androgens has desired physical changes, such as enhanced breast growth, reduction of facial and body hair growth and fat redistribution in a female pattern. Possible side effects should be discussed with patients, particularly those at risk of venous thromboembolism. The Endocrine Society guidelines for transgender men include testosterone therapy for virilization with deepening of the voice, cessation of menses plus increase of muscle mass, facial and body hair. Due to the lack of evidence, treatment for gender non-binary people should be individualized. Young people may receive pubertal suspension, consisting of gonadotrophin-releasing hormone analogs, later followed by sex steroids. Options for fertility preservation should be discussed before any hormonal intervention. Morbidity and cardiovascular risk with cross-sex hormones is unchanged among transgender men and unclear among transgender women. Sex steroid-related malignancies can occur, but are rare. Mental health problems such as depression and anxiety have been found to reduce considerably following hormonal treatment. Future studies should aim to explore the long-term outcome of hormonal treatment in transgender people and provide evidence as to effect of gender affirming treatment in the non-binary population.

Précis

Review of original and recent data on hormonal treatment in transgender people, including their effect on physical and mental health

Endocrinology of Transgender Medicine

Introduction

The acceptance by society, reflected in the media, that gender identity may not always match the assigned sex at birth, has provided the option and permission for individuals to question their gender identity more freely. Consequently, in some countries, transgender health services have expanded and developed so that gender diverse people wishing physical change are able to access gender affirming medical interventions. Hormone treatment, pivotal for those who wish to transition into their affirmed gender that differs from their sex that is assigned at birth, is ideally prescribed under the supervision of endocrinologists. However, many endocrinologists may feel uneasy and unskilled when working with the transgender population since the field of transgender medicine is relatively new. This paper aims to summarize the endocrine treatment for transgender people wishing to undergo gender affirmation therapies. The paper will first describe the terminology used in the field of transgender medicine, followed by a critical review of the diagnostic criteria currently in use, and summarize the mental health difficulties that transgender people may present with and the benefits of gender affirming treatment on wellbeing. Finally, the major focus of this paper will be to provide a critical review of the published literature on the hormonal treatment and long term monitoring for transgender children and adults.

Terminology

The term “gender non-conforming” is used to describe individuals whose gender identity, role or expression differs from what is normative for their assigned sex at birth in a given culture and historical period (1). Transgender is used as an umbrella term to describe individuals, whose gender identity differs from the assigned sex at birth. Transgender males are people assigned female at birth but who self-identify as male. Transgender females are people assigned male at birth, but who self-identify as female. When a person’s identity matches the sex assigned at birth, the term “cisgender” is used. The

term “non-binary” describes people whose gender identity, role or expression does not conform to the binary understanding of gender (male or female). This can be used as an umbrella term to include people with no gender (agender), two genders (bigender), multiple genders (pangender), or with a fluid gender (gender fluid)(2,3), among others. Non-binary people prefer for people to use the pronouns of “they” and “them” when addressing them(3).

Terminology changes all the time and terms used in the past may become outdated and can be perceived as pejorative. For example, the term transsexual which has been used since 1949(4), is largely now confined to the legal and medical literature. The International Classification of Diseases and Health Related Problems (ICD-10)(5) still uses the term “transsexualism” as a diagnostic term to describe individuals whose sex assigned at birth does not match their gender identity and wish gender affirming treatment. This term is likely to change to “gender incongruence” in the forthcoming 11th edition of the ICD(6). Other terms still used but considered outdated (although they can still be found in the literature) are: “FtM” (Female to Male) to describe transgender men or “MtF” (Male to Female) to describe transgender women.

Gender dysphoria refers to a profound distress or discomfort caused by the discrepancy between a person’s assigned sex at birth and gender identity(1). Not every transgender person suffers from gender dysphoria and the urgency for medical intervention among transgender people may vary(1). For some people, social change may be enough without the need for further physical intervention. For others, due to their personal circumstances, physical intervention may not be opportune or appropriate. Many however, will access transgender health services in order to obtain gender-affirming treatment whether in the form of hormone treatment and/or through gender affirming surgery. Research in the field of transgender medicine has primarily focused on transgender people accessing transgender health services (7). Due to the requirement in certain countries, to provide funded health services only to those with a medical diagnosis, terms describing the gender related suffering of transgender people have remained part of current diagnostic criteria(5,8). In this

manuscript, the term transgender will be used throughout to describe individuals who seek access to medical treatment in order for their bodies to become more congruent to their identified gender. A summary of some of the terms used in transgender health can be found in table 1.

Methodology

Eligibility criteria

Studies were selected only if participants were described as transgender (whether self-identified or diagnosed by health professionals), and had empirical data relating to the hormonal treatment in this population. Only studies in English, published in peer reviewed journals and with more than ten participants were selected. This is a critical review with a focus on recent and original data. This paper describes and reviews the available literature since the last published review study by one of the co-authors of the current review(9).

Information Sources and Search

An electronic literature search was conducted between January 1999 and November 2017 using Medline/Pubmed, PsycINFO and Embase. Additionally, reference sections of identified articles and Google Scholar were examined for further relevant publications. The search used the following keywords: for terms referring to Transgender people (*Transsexualism, transgender, Gender Dysphoria, Gender Identity Disorder, Trans*),* for hormonal treatment*, (cross-sex hormones, Testosterone, Estrogen, Blockers, GnRH agonist).* Every term used for Transgender people was combined using the "OR" and the "AND" operate with every term used for Hormonal treatment. Articles of interest were those that included the transgender population and had empirical data relating to hormonal treatment

within this population. Articles describing the effects of treatment, side effects, risk and long-term outcome were also collected and reviewed in order to help the discussion of the paper. If information was only to be retrieved from case reports, such as oncology, both the case reports and recent reviews on the specific topic were examined. The results of the review will be presented by describing the treatment in adults (transgender women and men) first followed by the treatment in adolescents.

Diagnosis

Currently the International Classification of Disease - version 10 (ICD-10) includes the diagnosis of transsexualism as part of the diagnostic category of "Gender Identity Disorders" (F64). It is expected that the new edition of the ICD (ICD-11) will change this term and move it out of the mental health chapter. It is likely that the new term to be used will be Gender Incongruence of Adolescence and Adulthood' (GIAA)(6,10-11).

The desire to de-pathologise being transgender and the importance of securing access to healthcare has been a dilemma in both the development of the DSM-5 and the new edition of the ICD (ICD-11). The American Psychiatric Association's diagnosis in the current edition of the DSM (DSM-5), diagnoses the distress caused by the incongruence between assigned sex at birth and experienced gender as gender dysphoria. This diagnosis aims to classify the symptoms (dysphoria) and not the individual. For an individual to fulfill the diagnostic criteria for gender dysphoria they need to present with a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration (APA(8)).

If reaching a consensus to develop terms to classify transgender adults has been complicated, creating criteria for children has been even more complex. The ICD-11 is proposing the diagnosis of gender incongruence of children (10) while the DSM-5 uses the diagnosis of gender dysphoria in children.

Prevalence

More than 20 studies have aimed to investigate prevalence rates of transgender people. Although more recently prevalence rates of transgender identities have been reported using population studies, most of the available literature has extrapolated prevalence rates from people attending transgender health clinics (7).

Some of the first epidemiological studies, which focused on individuals seeking services in order to undergo gender affirming genital surgery(12), found prevalence rates of 0.40 per 100,000 people. The ratio between male assigned at birth and female assigned at birth was found to be 4 to 1(11). Other European studies, based on people attending transgender health services, provide different prevalence rates over time; 1.22 per 100,000 (1976-1980), 1.58 per 100,000 (1976-1983), 2.77 per 100,000 (1976-1986)(13). Once again rates of male assigned at birth transgender people have been found to be higher than female assigned at birth transgender people at a ratio of 3 to 1. Studies looking at more recent periods (between 1972 and 1996) provide higher prevalence rates of 3.42 per 100,000 with ratios between birth assigned females and males being more similar (1.4 to 1)(14).

Studies have also examined the number of people that have petitioned governmental agencies in order to change their gender status legally. Those studies have described prevalence rates ranging from 2.1 (15) to 16.6 (16) per 100,000 people. A recent meta-analysis found an overall prevalence for transsexualism (as this is the diagnosis and term used in the published papers) of 4.6 in 100,000 individuals; 6.8 for transgender women and 2.6 for transgender men with an increase in reported prevalence over the last 50 years(7).

However, not every transgender person wishes and/or seeks medical care to affirm their gender(1). In order to identify the overall prevalence of transgender people (including those not accessing services) population studies may be more representative of the transgender community. Population based studies have found a considerably higher prevalence rate than those reported in clinical studies. For example, a study asking a sample of community participants in the United States (28,045 aged 18-64)

as to whether they considered themselves transgender found a prevalence rate of 0.5% (17). Studies from the Netherlands and Belgium described that 0.7%(18) and 1.1%(19) of people assigned male at birth and 0.6%(18) and 0.8%(19) of people assigned female at birth reported an incongruent gender identity.

The majority of the epidemiological studies have been conducted in Western countries, particularly in Europe and the United States. Societies which are more egalitarian and open will facilitate the expression of gender diversity, hence prevalence rates in those countries may be reported higher than in more restrictive societies. Low prevalence rates in certain societies may need to be regarded with caution as it may reflect a symptom of repression. A ban on gender identity expression for personal, cultural or religious reasons, may manifest itself as distress and profound unhappiness and may lead to the development of mental health problems(20).

Mental health in transgender people and effect of hormonal treatment

Overall prevalence of mental health diagnoses

Studies investigating rates of mental health diagnoses in the transgender population, once again, have focused on those attending transgender health services(21). Most of the studies have been cross-sectional and report high rates of affective disorders (38%)(22) such as depression(23) and adjustment disorders(24) as well as anxiety disorders (17%)(25,26). Young transgender people are found to have high rates of non-suicidal self-injuries have also been found to be very high, particularly among young people (46%) as well as suicide attempts(27,28,29). The few studies that compared their findings to the general cisgender population (controlled by age and sex) found certain mental health diagnoses, such as anxiety disorders, are 3 times more prevalent among transgender people compared to cisgender people(25).

Differences in prevalence according to gender

There are some discrepancies as to whether mental health diagnoses are more common among transgender men or among transgender women. Some studies have found mental health diagnoses were not related to assigned or identified gender(30,31), while other studies have demonstrated higher rates of mood disorders(23,32), anxiety disorders(32), adjustment disorders(18), and substance abuse(24) among transgender women than transgender men. Most of those studies are biased by not controlling for factors known to influence mental health diagnoses, particularly hormone treatment. This means that people have been recruited for studies independently as to whether they are on hormone treatment or not, while research has confirmed that such treatment reduces mental health problems. Interestingly, more recent large controlled studies involving only transgender people not on treatment have found anxiety disorders were more prevalent among transgender men than among transgender women(25). A similar study also found levels of self-harm were also higher among the same group(28).

Predictors of mental health problems

Several factors have been found to predict mental health issues among the transgender population attending transgender health services, such as experiences of victimization (or transphobic experiences), low self-esteem(27), and interpersonal problems(28,33). Lack of hormone treatment for those wishing physical change has been found to be the strongest predictor of mental health diagnoses(21,25,31).

The role of hormone treatment in mental health

A number of longitudinal studies have explored the role of hormonal treatment in mental health and quality of life among transgender people wishing gender affirmation treatment. These studies, which have mainly been conducted in Europe (Sweden(34), Italy(35), Belgium(36) or Germany(37)), have all demonstrated that people's mental health (levels of depression and anxiety) significantly improved following hormone treatment. Long-term follow-up studies and studies involving large groups of people are needed to evaluate whether these improvements remain. Hence, hormone treatment for

those wishing physical change needs to be accessible, as this will reduce morbidity and improve quality of life of transgender people.

Post treatment regrets

The literature in posttreatment regret is complex to interpret. Overall satisfaction post gender-affirming treatment is high. A study from more than 20 years ago found 2% of transgender women and 1% of transgender men later regretted their decision to undergo hormonal and/or surgical treatment (38). There are many causes of regret. Frequently dissatisfaction following gender affirming surgery has been interpreted as regret regarding social and medical transition. In order to distinguish those people who express dissatisfaction following gender affirming treatment, from those who wish to de-transition and return to their sex assigned at birth, Pfäfflin (1993) differentiates minor from major regrets. In one of the largest gender clinics (Amsterdam), 2034 individuals received treatment between 1975 and 1998. Ten of these people subsequently indicated that they regretted their decision to have undergone the treatment (nine transgender women and one transgender man)(39). The reason for those regrets varied from identifying with the sex assigned at birth and wanting de-transition (n=6) (classified as major regrets) from dissatisfaction of the outcome of surgery or loss of support following gender affirming treatment (n=4) (minor regrets). Upon review in 2005 the number of major and minor regrets increased by five out of a total of 3090 subjects. In 2015 the total number of subjects treated had risen to 6793 but there was no further increase in those expressing regret. The fact that fewer people have been having doubts about their treatment decisions over time may reflect the much-improved understanding of gender incongruence both by transgender people themselves and by the medical profession, as well as much greater acceptance of transgender people in society(39).

Summary

Mental health diagnoses are common in the transgender population, possibly due to negative societal values, but do improve once gender affirming treatment is initiated. This highlights the importance of

hormone treatment and access to adequate transgender healthcare. Although state funded health services, which are primarily available in Europe, may develop services where the needs of the transgender population can be provided for, including assessment, psychological support (if needed), hormonal treatment and gender affirming surgery, other healthcare systems may not be so fortunate and transgender people may find themselves searching for professionals who are able to confidently prescribe and monitor hormone treatment.

Results

I. Hormonal treatment in transgender women

Initial evaluation of transgender women

Transgender women seek hormone therapy to change their physical appearance to better match their gender identity and expression(40,41). Furthermore, transgender women experience improved quality of life and decrease in gender dysphoria upon initiation with hormone therapy(42,43). In the United States, Canada and most of Europe, transgender women must seek medical professionals for hormone therapy since these medications are available only by prescription but there is a black market also particularly for oral contraceptives. For non-Western countries, hormone therapy is often self-prescribed without supervision by a medical professional. Available evidence from the United States and Europe suggest that hormone therapy initiated and monitored under the supervision of a medical professional is associated with very low rates of adverse events(44,45). The Endocrine Society guidelines recommend that a medical professional confirms the diagnosis of gender dysphoria and/or gender incongruence in transgender women prior to the initiation of hormone therapy. Medical professionals should document that the gender dysphoria has been persistent and that the individual is able to make an informed decision and consent for treatment(40). However, there are no validated psychological tests or imaging studies that have been clinically useful to diagnose gender dysphoria(46), this is likely due to the fact that people with gender non-conforming expression and behaviors represent a very large and heterogeneous population. There is no demonstrable biological substrate for gender incongruence. In this regard, medical professionals have been moving towards a more gender affirmative model whereby the medical professional provides a more patient centered approach to care and understands the needs of the person rather than making a diagnosis of the patient(47,48).

Screening for conditions prior to initiation of hormone therapy

Medical professionals should evaluate transgender women for conditions that can be exacerbated by hormone therapy. History of thromboembolic diseases such as deep vein thrombosis and pulmonary embolism should undergo evaluation and treatment prior to the initiation of hormone therapy(40). In addition, risk factors that can increase the risk of thromboembolic conditions should be modified such as smoking, obesity, and sedentary lifestyle. In patients with modifiable risk factors such as known thrombophilia, past history of thrombosis, or strong family history of thromboembolism, treatment with transdermal estrogen and/or concomitant treatment with anti-coagulation therapy may need to be considered; although there are limited data to guide treatment decisions (49,50). Other diseases such as hormone sensitive cancers, coronary artery disease, cerebrovascular disease, hyperprolactinemia, hypertriglyceridemia, and cholelithiasis should be evaluated prior to the initiation of estrogen therapy as these conditions can be exacerbated by estrogen.

Modalities of hormonal therapy in transgender women

There are two main classes of medications used in transgender women: 1) estrogens and 2) androgen lowering hormones therapies.

Estrogen Therapies

The synthetic estrogen ethinyl estradiol was a widely used estrogen in Europe prior to 2003. However, given recent safety concerns about its pro-thrombotic potential and its potential role in cardiovascular disease, most clinics have now switched to oral, cutaneous or intramuscular estradiol(51). A few commonly used estrogen regimens in transgender women have been reported (Appendix B of reference 40); however, there are very few head to head studies comparing the efficacy and safety of estrogen regimens. In a large multi-national cohort study (entitled European Network for the Investigation of Gender Incongruence (ENIGI)) of 4 European countries (Belgium, The Netherlands, Italy and Norway), over 300 transgender women were prescribed oral estradiol

valerate 4 mg daily or estradiol valerate 20 mg intramuscularly every two weeks or estradiol patch 100 mcg daily, each with cyproterone acetate (CPA) 50 mg daily(52). In the short-term (< 5 years), these regimens are associated with mild elevations of prolactin(53) and improvements in bone mineral density after 1 year of therapy (54). No short- or long- term adverse events have been published from this cohort using this hormone regimen.

In a German cohort, transgender women were treated with a regimen of estradiol valerate 10 mg intramuscularly every 10 days. The authors also report short term gains in bone density after 24 months of therapy along with higher BMI with an increase of fat mass and decrease of lean body mass(55).

In the United Kingdom, transgender women were previously prescribed ethinyl estradiol or conjugated equine estrogen are now changed to oral estradiol at a dose of approximately 4 mg daily(56). In a retrospective review of transgender women in the UK, transgender women prescribed oral conjugated equine estrogens had increased risk of thromboembolism compared to transgender women taking oral estradiol valerate or ethinyl estradiol. In this cohort, 4.4% of transgender women on oral conjugated equine estrogen experienced a thromboembolic event compared to <1% in transgender women or estradiol or ethinyl estradiol (p=0.026).

In the United States, estrogen therapy can be prescribed as oral tablets, intramuscular injections, and transcutaneous preparations(41). Most commonly published in the United States is the prescription of oral estradiol 4-5 mg daily(57,58). Studies that compare the long-term safety and effectiveness among the different formulations of estrogen are lacking. The Endocrine Society Guidelines recommend that the doses of estradiol be titrated to serum estradiol levels around 200 pg/mL (734 pmol/L)(40).

Androgen Lowering Therapies

Transgender women will often require the addition of a medication to lower testosterone levels into the female range(59). In most European countries, the most commonly prescribed androgen

lowering medication is oral CPA 50 mg daily (44,52,60). Cyproterone acts primarily as an androgen receptor blocker but also has some progesterone like activity(61). However, given reports of increased risk of meningiomas(62-64), association with depression(56), and increased risk of hyperprolactinemia(53) with CPA use, in the United Kingdom (UK), transgender women are now prescribed gonadotropin-releasing hormone (GnRH) agonists to lower testosterone concentrations(65). In contrast to the rest of Europe and the United States, GnRH agonists are provided free of charge to transgender women by the National Health Service in the UK (56).

Spironolactone is the most commonly prescribed testosterone lowering medication in the United States(57,58). Spironolactone is classically known as an antagonist of the mineralocorticoid receptor and a potassium sparing diuretic. It also has anti-androgen properties by directly lowering testosterone synthesis and testosterone action at the androgen receptor(40). One U.S. cohort of about 100 transgender women found estrogen therapy in combination with oral spironolactone 200 mg daily was effective in lowering serum testosterone levels in to the cisgender female range for serum testosterone after about 1 year of therapy(66).

Peripheral androgen receptor blockers such as flutamide or dutasteride have not been recommended for use in transgender women since these agents do not lower serum testosterone levels and there are limited published studies in this population(40).

Other Second Line Hormonal Therapies

Progesterone

Progesterone therapies such as medroxyprogesterone have been used as a second agent to lower testosterone concentrations in transgender girls and women(57). Some transgender women may request progesterone to enhance breast development; however, there are no clinical studies to support a positive effect of progesterone on breast development(67). Furthermore, there are concerns regarding potential increased risk of thromboembolism and stroke found in cisgender

364 women taking progesterone(68,69). Therefore, progesterone therapy is not a routinely used
365 medication in transgender women.
366
367 *5α-Reductase Inhibitors*
368 Some transgender women may experience male pattern hair loss and may seek treatments to arrest
369 hair loss and/or restore hair. In general, lowering serum testosterone levels into the cisgender
370 female range is often adequate to arrest hair loss in most transgender women; however, there are
371 still some transgender women who experience hair loss despite lowered serum testosterone levels.
372 A few case series in transgender women with androgenetic alopecia have demonstrated finasteride
373 therapy to be effective to improve hair loss without significant side effects(70,71). The routine use of
374 5α-reductase inhibitors has been limited over previous concerns of long-term sexual dysfunction and
375 depression reported to be found in cisgender men(72,73).
376
377 **Feminization in transgender women**
378 Treatment with estrogen and testosterone lowering medications will induce feminine and reduce
379 masculine physical characteristics. The most studied physical change in transgender women is the
380 development of breast tissue. An Italian cohort study found increases in breast size were the only
381 physical feature that was significantly associated with improvement in body uneasiness scores(43).
382 However, less than 20% of transgender women reach Tanner Breast stage 4-5 after 24 months of
383 hormone therapy and thus often seek mammoplasty. Early studies in transgender women indicated
384 breast development reached a maximum size by 2 years(74). However, a more recent study of 229
385 transgender women participating in the ENIGI cohort found breast development reached a plateau
386 within the first 6 months of therapy and half of the transgender women had a AAA cup size or
387 less(75). Fisher and colleagues also found testicular volume decreased by approximately 60% after 24
388 months of transfeminine hormone therapy(43).
389

Body composition

A meta-analysis of studies published prior to 2015, transfeminine hormone therapy was associated with increased body fat and decreased in lean body mass in 171 transgender women(76). More recent studies from Europe have documented that BMI increases in transgender women after transfeminine hormone therapy(43,77). Klaver et al also demonstrated increases in body weight in 179 transgender women and transfeminine hormone therapy was associated with in increase in body fat, specifically in the android, leg and gynoid regions (78). However, recent studies from the USA have demonstrated that significant changes in BMI in transgender girls and women do not occur over a short term (< 6 months)(56,79).

Voice

Transgender women will have improved self-perceived feminine quality in their voice after the initiation of hormone therapy(80). However, many transgender women still have difficulty with their voice quality and are misperceived in the wrong gender by others(81). Transgender women may undergo voice training exercises to improve their voice quality(82). Laryngeal surgical treatment has been described as an option for transgender women to improve voice quality; however, a meta-analysis failed to demonstrate significant benefit of surgical techniques to improve the quality of the voice(83).

Skin and Hair

Transgender women will also experience reduction in facial hair after transfeminine hormone therapy. Fisher et al reported that Ferriman and Gallwey scores improved after two years of transfeminine hormone therapy(43). Transfeminine hormone therapy may arrest male pattern hair loss(71). A survey of transgender women reported interest in having facial hair removal procedures however very little data on the effectiveness of such procedures have been published(84).

Safety data specific to transgender women

1. Cardiovascular and thromboembolic safety

There have been some concerns about long-term effects of transfeminine hormone therapy on cardiovascular outcomes. A single center study of over 200 transgender women from Belgium reported increased rates of myocardial infarction, venous thrombosis, and cerebrovascular disease compared to cisgender men and women(85). A recently commissioned systematic review and meta-analysis of cardiovascular outcomes in transgender individuals did not find an increased risk of myocardial infarction, stroke or venous thrombosis in transgender women due to lack of reported outcomes from 29 eligible studies(86). This systematic review also found transfeminine hormone therapy was associated with increased serum triglyceride levels of 31.9 mg/dL (95% CI: 3.9 to 59.9) in transgender women treated for greater than 24 months with no changes in serum LDL or HDL. Thrombosis risk in transgender women is likely increased given the known pro-thrombotic actions of estrogen. However, under medical supervision, the risks of transfeminine hormone therapy appears to be safer than self-prescribed transfeminine hormone therapy(45). A large study conducted in 162 transgender women treated with transdermal estrogen in Austria found only 19 had a genetic mutation associated with venous thrombosis (1 protein C deficiency and 18 with activated protein C resistance) and none developed a thrombotic event, suggesting that estrogens that avoid the hepatic first pass effect may have less pro-thrombotic risk (87). Furthermore, given the low frequency of genetic mutations associated with thrombosis (19 out of 162), the authors do not recommend routine screening for thrombophilia. There have been reports of transgender women who developed a thrombotic event and successfully treated with anti-coagulation therapy (88,89). However, there are no long time studies to guide treatment for transgender women following a thrombotic event.

2. Bone Health

The fracture rate associated transfeminine hormone therapy is unknown. Estrogen is critically important for preserving bone mineral density in post-menopausal women and in men who lack estrogen action at the bone, (e.g. mutations in the estrogen receptor or aromatase enzyme)(90,91). A recent meta-analysis of 392 transgender women found a significant increase in lumbar spine bone mineral density but no changes in hip bone mineral density. The rates of fracture were found to be low with no fractures found in 53 transgender women after 12 months in this review(92). A recent multi-center study of 231 transgender women in Europe treated with transfeminine hormone therapy found a 3.67% increase in lumbar spine bone density and a 0.97% and 1.86% increase in total hip and femoral neck bone density, respectively, after 1 year of therapy(54).

Transgender women have been found to have lower bone mineral density even prior to the start of hormone therapy(93). Van Caenegem and colleagues found 16% had T-scores at the lumbar spine <-2.5 and approximately one third of transgender women had T-scores between -1 and -2.5 at the lumbar spine or total hip. The reasons why transgender women had lower bone density than expected for age is not clear but the authors hypothesize decreased outdoor physical activity as vitamin D status was found to be low in 72% of the cohort.

3. Oncological data and mortality

The prevalence of hormone sensitive cancers such as breast and prostate cancer appears to be low among transgender women. Initial studies from a cohort of over 2000 transgender women reported no increase in breast cancer incidence compared to the expected rate of breast cancer in cisgender women(94). A large cohort of over 5000 transgender military veterans in the USA reported only 9 cases of breast cancer in transgender veterans, two in transgender women and seven in transgender men(95). All of the transgender women presented with late stage breast cancer that proved to be fatal, whereas the transgender men before or after breast ablation presented with earlier

disease(96). One the largest studies examining cancer risk in transgender women in the USA utilized data from one large healthcare system (Kaiser Permanente: Georgia, Northern and Southern California (97). Using an electronic database method to identify transgender women in this cohort, they identified 2791 transgender women subjects. Based on ICD-9 codes, the investigators found no increased risk of breast cancer or any cancer compared in transgender women to matched cisgender women. However, there was an increased risk of breast cancer and endocrine gland cancers in transgender women compared to matched cisgender men. Furthermore, there was a decreased risk of prostate cancer compared to matched cisgender men. Other studies have reported a low risk of prostate cancer in transgender women. A recent review of literature of prostate cancer in transgender women only found 10 cases reported(98).

Other Considerations

Fertility

All transgender women should be aware of the potential fertility preservation options such as sperm cryopreservation. Transgender women report that they are interested in having their own biologic children but very few transgender women utilize fertility preservation technologies(99,100), possibly due to the lack of funding for fertility preservation in many countries. Since sperm production will decline after the initiation of hormone therapy, the Endocrine Society guidelines recommend that all transgender women discuss fertility options with their healthcare team prior to the initiation of hormone therapy (40).

Monitoring of feminizing hormone therapy

Transgender women who take hormone therapy under medical supervision experience very low rates of complications (44,45). Transgender women should maintain serum estradiol and testosterone concentrations within the expected physiologic female range (40). The Endocrine Society recommends hormone measurements every 3 months in the first year of initiating hormone

492 therapy until the hormone concentrations reach the desired concentrations. Once the hormone dose
493 is achieved, the hormone concentrations of both testosterone and estrogen can be measured once
494 yearly or when there is a dose change to ensure that levels remain in the range expected for
495 cisgender females (40). Transgender women taking spironolactone should have measurement of
496 potassium and kidney function on a regular basis. Following surgery, transgender women can have a
497 final measurement of serum testosterone to confirm levels in the male range are eliminated.
498 Measurement of prolactin levels during the course of gender affirming hormone therapy has been
499 suggested by the Endocrine Society guidelines. However, recent reports indicate that elevated
500 prolactin levels seem to occur in transgender women on cyproterone acetate and not on
501 spironolactone. Defreyne et al demonstrated that prolactin levels increased in transgender women
502 receiving cyproterone but decreased after discontinuation (101). Furthermore, a recent study by
503 Fung et al demonstrated that transgender women treated with cyproterone had significant higher
504 prolactin levels compared to those treated with spironolactone (102).
505
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II. Hormonal treatment in transgender men

Initial evaluation of transgender men

During the first outpatient consultation, the same principles apply as described for transgender women above.

Screening for conditions prior to initiation of hormone therapy

Transgender men must be informed on the possibilities, consequences, limitations and risks of testosterone treatment. Fertility preservation options are to be discussed before starting a medical intervention. Pregnancy is an absolute contraindication for testosterone therapy, and relative contraindications include severe hypertension, sleep apnea and polycythemia(40). Conditions that can be exacerbated by testosterone therapy are presence of erythrocytosis, baseline high hematocrit levels (e.g. secondary to smoking or COPD), sleep apnea and congestive heart failure. Knowledge on the presence of menstruation problems prior to initiation of testosterone treatment and on sexual practices will guide the need for follow-up procedures such as pelvic ultrasounds and pap smears.

Modalities of hormonal treatment in transgender men

Testosterone

The principal hormonal treatment used to induce virilization is testosterone. Under medical supervision, testosterone therapy is safe based on short and longer-term safety studies(44,103,104). Different testosterone formulations may be available depending on geographical location. Most commonly prescribed are injectable testosterone esters (40). More recently subcutaneous administration of testosterone was shown to be effective and preferred by transgender men at a median dosage 75 mg weekly in 63 transgender men (105,106), confirming an earlier intervention

study (106). Long acting testosterone undecanoate is also being used for treatment of transgender men (107). However, in the United States, the prescription of testosterone undecanoate is limited due to the potential risk of oil pulmonary embolus and both patient and provider must undergo Risk Evaluation and Mitigation Strategy (REMS) training to receive this therapy. Other intervention studies (Appendix A of reference 40) have also used topical androgen gel or transdermal patches. The use of oral testosterone (testosterone undecanoate), axillary solutions, patches, nasal sprays, buccal tablets or pellets is rarely reported for treatment in transgender men. In one study the effects of three different testosterone formulations were evaluated at baseline and after 12 months of treatment and no differences were found regarding short-term safety, compliance, body composition, metabolic parameters and general life satisfaction (108). Androgen therapy will need to be continued lifelong to maintain the achieved virilization and to avoid symptoms of hypogonadism such as vasomotor symptoms or osteoporosis.

Progestational agents

If menstrual bleeding does not stop after initiation of testosterone, a progestational agent, such as oral lynestrenol 5-10 mg daily or medroxyprogesterone 5-10 mg, might be considered. This occurs frequently with the use of transdermal or oral testosterone undecanoate, which are both associated with lower testosterone levels compared to injectable testosterone. GnRH analogs to halt menses are theoretically possible, but rarely reported in adults given the costs of therapy. If ovariectomy is performed, the progestational medication can be discontinued (109-111).

Virilization in transgender men

Treatment in transgender men is intended to induce virilization. This includes cessation of menses, development of male physical contours, a deepening of the voice, clitoral growth, increased sexual desire and increased facial and body hair(110,112,113). Male-pattern baldness may also occur. Changes in body composition; with redistribution of body fat, increased muscle mass and strength

have been described extensively (40,44,114). The time period before cessation of menses may vary from 1-12 months after testosterone initiation, sometimes requiring the addition of a progestational agent (40,115). Mean clitoral length may reach 3.83 +/- 0.42 cm after 2 years of testosterone therapy (43)

It is important that transgender men understand the possibilities but also the limitations of testosterone treatment. Height and bone structure (broader hips) and the larger degree of subcutaneous fat remain largely unchanged when therapy is started after puberty(110). Most of the published guidelines have been developed with the Caucasian transgender person in mind, but ethnic differences may warrant tailoring of standard doses (116). Recommendations based on clinical experience are in favor of continuing testosterone treatment for elderly transgender men(117).

Body composition

Testosterone therapy will enhance a more masculine musculature, body shape and body fat distribution. Testosterone therapy will result in changes in body composition. A meta-analysis of 10 studies examining body composition changes in response to testosterone over 12 months found body weight increased by +1.7 kg (0.7-2.7), body fat decreased by 2.6 kg (-3.9; -1.4) and lean body mass increased by +3.9 kg (3.2; 4.5) (76). Another systematic review, focusing among other parameters on BMI, revealed an increase in BMI from 1.3 to 11.4% (118). Grip strength increased with 18% in a study with 23 participants and one-year parenteral testosterone undecanoate treatment (93).

Voice

Testosterone therapy at doses in the physiological range for men will induce acoustic changes occurring from effects on the larynx (119). In a cross-sectional study of 38 transgender men, acoustic voice variables and voice quality was similar between the transgender men and cisgender controls. However, 10% of the transgender men experienced issues with pitch quality, needing voice therapy and sometimes pitch-lowering surgery (120). Transgender men (n = 77) whose voices sounded more

583 congruent with their experienced gender reported greater well-being than those with less gender
584 congruent voices (121). There is very little prospective data on the voice changes in transgender men
585 upon testosterone treatment. Seven transgender men on intramuscular testosterone esters, all
586 reached a cisgender male mean fundamental frequency within 6 months of testosterone therapy. A
587 mean decrease of 49 Hz was measured (122). In the largest longitudinal study to date (n = 50, with 36
588 having data for baseline and 12-month follow-up) acoustic analysis of fundamental frequency of the
589 habitual voice showed a significant decrease after 3 (- 37 Hz), up to 12 (-67 Hz) months, with group
590 data congruent with cisgender male reference data. In 24% of participants additional voice therapy
591 was necessary. When using an adapted version of the transsexual voice questionnaire (123) for
592 transgender men (TVQ^{MtF}) looking at self-perception of voice prospectively during intramuscular
593 testosterone undecanoate therapy in 80 participants, improvements during the first 3 months were
594 attributed to the hormonal intervention (80).

595 *Skin and hair*

596 Both androgens and estrogens are known to affect the pilosebaceous unit of the skin, as in the
597 sebocytes and hair follicle dermal papilla androgen and estrogen receptors are expressed. In a study
598 of 17 transgender men, intramuscular testosterone therapy was associated with increases in the
599 Ferriman-Gallwey hirsutism scores (124). After 12 months facial and abdominal hair had not yet
600 reached diameters found in cisgender males. An increase in acne on the face and back was present in
601 94% and 88% after four months, respectively. Data on both shorter and longer term dermatological
602 effect of IM testosterone undecanoate were available from a prospective intervention study in 20
603 hormone naïve transgender men, combined with a cross-sectional part with 50 transgender men
604 with an average of 10 years on various testosterone treatments (103). The Ferriman-Gallwey score
605 (in cisgender women usually <8) increased in a time –dependent manner from median 0,5 to 12 after
606 one year, while long-term testosterone treatment resulted in a median score of 24. The presence
607 and severity of acne based on the Gradual Acne Grading Scale increased during the first year and

peaked at 6 months; facial acne was present in 82%, and back acne was present in 88%. Long-term data from this study showed 94% of transgender men had no to mild acne. In a study with 45 transgender men, 16% developed troublesome acne when treated with testosterone undecanoate for two years (125).

In a retrospective, observational study 81 transgender men treated with testosterone esters or testosterone undecanoate self-assessed the degree of male pattern baldness (MPB) using a five-point scale (i.e. type I (no hair loss) to type V (complete hair loss)). The authors found 38% of transgender men had MPB type II-V. Thinning of hair was related to the duration of androgen administration and present in half of the transgender men after 13 years (126). Wierckx et al reported that (44), 17% of participants developed androgenic alopecia based on the Norwood-Hamilton classification after 1 year of treatment. Longer-term (10 years on average) testosterone treatment was associated with 32% of mild frontotemporal hair loss and 31% moderate to severe androgenetic alopecia (103). In 10 transgender men with androgenetic alopecia, treatment with oral finasteride 1 mg daily for 12 months, induced improvement with one grade on the Norwood-Hamilton scale after a mean of 5,5 months since the start of treatment (70).

Safety data specified for transgender men

1. Cardiovascular safety

Adult cisgender men have higher cardiovascular mortality rates than women, which has been attributed to differences in sex hormone levels. However, the available cardiovascular outcome data in transgender men show that testosterone treatment does not result in adverse cardiovascular outcomes(127). Four different recent review papers (86,118,128,129) summarized the effects of testosterone on surrogate risk factors of cardiovascular disease. These studies demonstrated despite a perceived negative impact on a number of risk factors including an increase in hematocrit, a decrease in high-density lipoprotein cholesterol, increase in triglycerides, low-density lipoprotein cholesterol levels, and inflammation parameters (130), small increase in systolic blood pressure (44,125), decrease in adiponectin and leptin (131) no significant increase in cardiovascular outcomes (77). Furthermore, there have been no elevated rates of cardiovascular deaths when compared with cisgender men and women at short and medium follow-up in the larger studies (except for one study (30)). However, data on cardiovascular outcomes in older (65+ years) transgender men are mostly lacking (86). In a cross-sectional study of 50 transgender men on testosterone treatment for an average of 10 years, no subject had experienced myocardial infarction, stroke or deep venous thrombosis (132). In a similar case-control study 138 transgender men 7.4 years on average on testosterone therapy showed a low cardiovascular morbidity (85). In a prospective study with 43 transgender men, who were treated with testosterone esters every 3 weeks, there was an increased incidence of previously absent metabolic syndrome after 1 (16,3%) and 2 years (18,6%), especially in those with psychiatric comorbidity(133). Furthermore, most studies in transgender men report no adverse impact of testosterone treatment on fasting glucose or insulin sensitivity (44,108,131,133).

Many studies report an association between testosterone therapy and increased hemoglobin (+ 4.9-12.5% range) and hematocrit (+ 4.4-17.6% range) during the first year of treatment, which then

plateaus after the initial year of treatment (107,125). Clinically significant erythrocytosis has been reported but is likely very uncommon (118). In such cases, practitioners sometimes advise change of the testosterone route of administration or reduction of dosage, despite the absence of outcome data showing risk reduction of thrombotic events. In one study use of testosterone gel showed smaller increases in hemoglobin (+4%) and hematocrit (+2%) compared to injectable testosterone(108).

A prospective study of 89 transgender men treated with parenteral testosterone undecanoate and lynestrenol for about 4 years found no cases of venous thromboembolic disease despite 5 subjects who had the activated protein C mutation. The authors concluded that general screening for thrombophilic defects is not recommended (134). In a similar study, fifty transgender men followed for about 10 years found no cases of venous thromboembolism (132)

It is important to stress that most transgender men are still relatively young, at an age when the risk of cardiovascular events is low. Long-term data and data from older transgender men are needed.

2. Bone health

Sex steroid hormones play important roles in bone growth and maintenance. Men develop larger, longer and stronger bones during puberty, explained through the combination of sex steroids and mechanical loading. Testosterone therapy in transgender men preserves bone density with adequate dosing due to aromatization of testosterone to estradiol (135). There are very limited data on the risk of osteoporotic fractures in transgender men (92). Transgender men have similar BMD compared to cisgender females prior to testosterone therapy (93,136,137).

Following ovariectomy, testosterone substitution therapy appears to prevent short term (<2 years) (54,93,108,125,136,138-140) and long term (10 + years) (141-143) bone loss due to estrogen deficiency. Transgender men have larger cortical bone size compared to cisgender females in a cross-sectional study (143). An additional study confirmed the higher cortical thickness by histomorphometric bone biopsy study (145) and higher aBMD at cortical sites (139,142). This reflects

the effect of androgens on the periosteal circumference of cortical bone. The androgen-induced higher muscle mass also induces a higher mechanical load on the bone, possibly stimulating bone formation according to the mechanostat theory (146). Higher bone formation was observed in transgender men on testosterone (93,136,141,143) and both muscle mass and strength were positively associated with trabecular and cortical parameters and bone size. Nearly all studies reported a maintained aBMD, which argues against bone loss (92). However, in transgender men who underwent ovariectomy, bone loss has been described when they irregularly used or stopped androgen therapy or when dosage was inadequate (137,138,141).

3. Oncological data and mortality

Both practitioners and transgender men express concern around carcinogenicity of long-term hormonal therapy, although these concerns are not supported by the available data. Recently the published cancer case reports in transgender men were summarized (147): 1 vaginal, 1 cervical, 7 breast, 3 ovarian and 1 endometrial cancers have been described to date. The association to risk factors such as smoking and alcohol use, sexually transmitted infections and lack of adequate access to screening programs has to be acknowledged and be included in future research (147). In transgender men on testosterone treatment and not undergoing surgical interventions, breast and cervical cancer screening protocols are advised, but timing and frequency of monitoring of female internal organs in transgender men are a matter of debate.

The available data on cancer mortality are limited and based on studies on 4 different populations (Belgium, Sweden, The Netherlands and United States). Despite low statistical power, these studies demonstrate very few cancer events in the population of transgender men (30,85,94,104,132,148,149). The data on overall mortality in transgender men, specifically related to testosterone treatment, are scarce and the few available studies are underpowered (30). A study from the Dutch cohort with 122 transgender men (148), with a later follow-up on 293 (149) and 364

transgender men (104), reported mortality to be similar to those of the general population. The lack of cancer outcome data underlines the need for studies of a large and inclusive sample size and long-term follow-up from multiple specialized centers.

Other considerations

Fertility

There is a clear need to discuss reproductive option with transgender men, before starting testosterone treatment (99). From a study based on a questionnaire, 54% of the transgender men desired to have children and 37% would have banked oocytes, if this had been possible (150). Genital reconstructive surgery results in an irreversible loss of natural reproductive capacities, while testosterone therapy has an important, but partially reversible impact on fertility. In theory, embryo and oocyte cryopreservation as established techniques, and ovarian tissue cryopreservation more experimentally can be mentioned as examples of fertility preservation options (151). The necessary hormonal stimulation with multiple endovaginal ultrasound monitoring are likely to be perceived as physically and emotionally difficult, making oocyte cryopreservation not the preferred fertility preservation technique in this group and some wish to postpone this towards the time of hysterectomy and oophorectomy. A strong suppression of AMH has been described in 22 transgender men treated with a GnRH agonist, combined with testosterone gel and an aromatase inhibitor (152). Reassuringly, androgen treatment did not deplete the primordial follicles in the ovarian cortex strips and a normal distribution of cortical follicles in the ovaries remained intact in 40 transgender men after more than one year of testosterone treatment (153). However, the use of in vitro maturation without the use of xenotransplantation is far from implementation in a clinical setting (154). Once a mature oocyte is obtained, the use of partner sperm or donor sperm and a recipient uterus upon thawing of the oocytes, or a female partner or surrogate mother will enable conception.

Based on an online survey in 41 transgender men who had been pregnant, of which 25 had used

testosterone, 80% reported resuming menstruation within 6 months upon interrupting testosterone treatment, while 20% experienced no menses before pregnancy. Of note, exogenous testosterone is not an adequate mean of birth control. Testosterone has teratogen effects on the fetus; therefore transgender men should avoid pregnancy while on testosterone therapy. This is included in preconception counseling that addresses stopping testosterone while trying to conceive and during pregnancy, with the possibility of increasing gender dysphoria during and after the pregnancy. Postpartum the options for breast feeding and when to reinitiate testosterone have to be discussed (155).

Monitoring of virilizing hormone therapy

Monitoring is advised 3-4 monthly in the first year of treatment and 1 to 2 per year thereafter, according to the Endocrine Society Guidelines (40). Aiming at testosterone levels in the physiologic normal male range and measuring hematocrit or hemoglobin in order to avoid erythrocytosis are the most important parameters. Bone densitometry in transgender men should be performed if risk factors (smoking, excessive alcohol use, family history of osteoporosis, history of fracture, use of glucocorticoids, anorexia nervosa) for osteoporosis exist, and more specifically in those who stop or temporarily interrupt hormone therapy after gonadectomy. Screening for breast and cervical cancer in transgender men who do not undergo surgical interventions is advised (40).

Insert fig. 2 about here

744

745

746 III. Hormonal treatment in adolescents

747 The endocrine treatment of transgender adolescents consists of two phases: pubertal suspension or
748 gonadal suppression followed by the addition of hormones. During the first phase (further) pubertal
749 development is halted and adolescents can further explore their gender identity and prepare for the
750 next phase.

751 **Gonadal suppression in adolescents**

752 *Gonadal suppression using gonadotropin releasing hormone analogues (GnRHa)*

753 To achieve gonadal suppression generally gonadotropin releasing hormone analogues (GnRHa) are
754 used (156). GnRHa have been used since 1981 in the treatment of central precocious puberty
755 (157,158) and their benefits are well established and the use of GnRHa is regarded as both safe and
756 effective, with no long-term adverse effects (159).

757 Treatment can generally start when the adolescent is in Tanner stage 2-3. In clinical practice,
758 transgender boys usually can start when in Tanner stage Breast 2 and transgender girls when they
759 have a testicular volume of 6-8 ml. Also, adolescents who have already physically matured can use
760 GnRHa to inhibit unwanted pubertal development, such as breast formation and menses in girls or
761 further male phenotype development and erections in boys, until the adolescent's gender identity is
762 more stable (40).

763 The general safety and efficacy of GnRHa have been studied (160,161). Anthropometry and body
764 development, hormonal status and metabolic parameters were followed prospectively in 49
765 transgender girls (median age at start 13.6 years, Tanner stage Genital 4) and 67 transgender boys
766 (median age 14.2 years, Tanner Breast 4) during 12 months of GnRHa mono-therapy. Puberty was
767 adequately suppressed with a decrease of testicular volume from 13.9 ml (± 6.5) to 8.6 ml (±4.7) in

33 transgender girls. In transgender boys, who initiated GnRHa early in puberty at Tanner Breast 2 and early menarche, breast tissue fully regressed to stage 1 (n=4) and menses ceased. Effective gonadal suppression was also reflected in a decrease in gonadotropins levels after a period of three months to nearly undetectable levels and a coinciding decrease in sex hormones. Testosterone decreased from 262 ng/dL (9.1 nmol/L) to lower than 29 ng/dL (1.0 nmol/L) in transgender girls. In transgender boys, estradiol decreased from a median of 123 pmol/L to 29 pmol/L. As for anthropometry, height velocity decreased in both transgender boys and transgender girls while BMI-SDS calculated for sex assigned at birth increased significantly. Body composition and the lean body mass percentage decreased and fat percentage increased significantly. Regarding safety monitoring, glutamyl transferase, AST, ALT and creatinine levels did not significantly change from baseline to 12 months of treatment but alkaline phosphatase decreased, most likely reflecting the decrease in growth velocity (160).

GnRHa is generally well tolerated with the exception of hot flushes early in treatment (161). However, hypertension in transgender adolescents under triptorelin treatment was reported in three transgender boys in a cohort of 138 subjects. Hypertension was reversible upon cessation of triptorelin but in one case increased intracranial pressure occurred, requiring the temporary use of acetazolamide (162). GnRHa induced hypertension is an uncommon side effect and has only been reported incidentally in children (163, 164).

Gonadal suppression in adolescents using other regimes

When resources cannot provide for GnRHa alternative treatment regimens should be considered such as progestagens in transgender boys or CPA in transgender girls(40). Similar to transgender women, endogenous androgen production can be suppressed using anti-androgens such as CPA or spironolactone in late pubertal girls. The effects of prolonged CPA mono-therapy were studied retrospectively in 27 transgender girls who were in Tanner Genital stage 4. After 6 months of CPA 50

mg once daily testosterone decreased from 432 ng/dl (15.8 nmol/L) to 248 ng/dl (8.6 nmol/L) and remained stable at 226 ng/dl (7.8 nmol/L). LH and FSH however were not suppressed at 5.0 IU/L and 5.1 IU/L during this period. Prolactin increased from 318.2 pmol/L to 760.8 pmol/L but none developed galactorrhea. Clinically more than half of the subjects reported reduced shaving frequency and in approximately one third had breast development (Tanner stage Breast 2-3). There was no increase in BMI-SDS. Fatigue was the only reported side effect. As for safety monitoring, only a transient increase of liver enzymes was seen in 15% of the study subjects. The levels remained under the threshold of three times the upper limit and therefore treatment was not stopped. Metabolic parameters such as lipid profile and glucose homeostasis were not negatively affected(165).

In post-menarche adolescent transgender boys an alternative for GnRHa to stop or decrease menses frequency may be the use of progestagens. A cohort of 42 transgender boys (mean age of 15 years and in Tanner Breast 4) was retrospectively studied during 11.6 months of lynestrenol mono-therapy. After 6 months metrorrhagia occurred in 50% but reduced to 18% in the following 6 months. Subjects reported headache (12%) and hot flushes (10%). Serum LH decreased from 7.56 IU/L to 2.58 IU/L but levels of FSH and estradiol remained unchanged. Weight increased during the first 6 months but returned to baseline value after 12 months. Regarding safety monitoring hemoglobin and hematocrit increased but remained in the normal male range. Liver enzymes, lipid profile and glucose homeostasis were not negatively affected(166).

The addition of gender affirming hormones to GnRHa monotherapy

Hormone therapy in adolescents generally has two treatment regimes. In the case when GnRHa treatment is initiated in the early stages of pubertal development, the “new” puberty is induced with a dosage scheme that is also common in hypogonadal patients. Alternatively, when GnRHa treatment is initiated in late puberty and thus the duration of the hypogonadal state was limited, hormones can be given at a higher initial dose and more rapidly increased until the expected adult

dose. An additional advantage of GnRHa treatment is that hormones do not have to be administered in supraphysiological dosages, which would otherwise be needed to suppress endogenous sex steroid production (40).

The timing of starting sex hormones in transgender adolescents continues to be an issue of debate. The recommended age of 16 years (40) is based on local jurisdiction, and not on cognitive maturation or pubertal development. In most countries at age 16 one is considered to be legally adult and one can make medical decisions. Indeed, when the first studied cohort was started in the Netherlands the age of 16 was chosen for this very reason. As a consequence there is little data available on starting GnRHa at an earlier age. The Endocrine Society guidelines make a recommendation to allow hormone therapy to be initiated at ages younger than 16 when the transgender child is evaluated by a multi-specialty team with expertise in gender identity development in children. However, the need for re-evaluating the recommended age for starting GnRHa may shift in the future (1).

Transgender girls

For a pubertal induction, it is recommended to start 17-beta estradiol at a dosage of 5 mg/kg/day, followed by 6 monthly increments of 5 mg/kg until a maintenance dosage of 2 mg is reached. The second treatment regime is more suitable for transgender girls who initiated gender affirming treatment when at least 15.5 years old. After a period of gonadal suppression varying from 3 to 6 months, estrogens can be given at a daily start dosage of 1 mg and increased to 2 mg after 6 months (40).

The effects of the addition of 17-beta estradiol were studied prospectively in 28 transgender girls (158). Estrogen treatment was started at a median age of 16.0 years after median duration of 24.8 months of GnRHa mono-therapy. Breast development had started within 3 months and after 1 year median Tanner breast stage was 3 progressing to 5 after 3 years (n=16) with a variability of all breast

stages. With respect to body shape, hip circumference increased and waist circumference decreased. Although BMI increased, BMI-SDS did not. When bone age was < 15 years at the start of estradiol, median height gain was 6.8 cm after 3 years of estrogen therapy. Overall final height was 182.7 cm corresponding to +1.9 SD for Dutch adult women. When the adult dose of 2 mg estradiol daily was used during a median duration of 2 years the median serum estradiol was 27 pg/mL (100 pmol/L) (range, 6,5-103 pg/mL (24 to 380 pmol/L). A change in prolactin levels was not seen. In addition, hemoglobin, hematocrit, HbA1c, liver enzymes and creatine remained unchanged (167).

Transgender boys

For pubertal induction the use of testosterone-esters injections is recommended. The initial dose is 25 mg/m2 every two weeks IM; and is increased with 25 mg/m2 every 6 months. The maintenance dosages vary from 200 mg per two weeks for testosterone mono-esters, such as testosterone enanthate, to 250 mg per 3-4 weeks for testosterone esters mixture. For transgender boys who started treatment in late puberty, testosterone can be started at 75 mg IM every two weeks, followed by the maintenance dosage after 6 months(40). It is advised to continue GnRHa at least until maintenance dosage of testosterone is reached and preferred to continue until gonadectomy. With androgens, virilization of the body occurs: lowering of the voice, more muscular development, particularly in the upper body, facial and body hair growth and clitoral growth(40,161).

Other considerations

Bone health in transgender adolescents

During puberty the bone mass increases and peak bone mass is only achieved at the age of 20-30 years (168). Bone mass accrual is regulated by genetic factors, gonadal hormones, and environmental factors such as physical activity and adequate supply of nutrients (calcium, vitamin D). During the hypogonadal state induced by GnRHa mono-therapy bone mineral density (BMD) is affected(170-171). In transgender girls BMD of the lumbar spine remained stable but Z-score decreased during 1.5-2 years of gonadal suppression. In the femoral region BMD and Z-score

decreased but not significantly. In contrast, in transgender boys the BMD of lumbar spine and femoral region decreased together with the corresponding Z-scores(170).

When sex steroids are added, bone mass accrual reassumes. In transgender girls, absolute BMD and Z-scores in the lumbar spine but not the hip increased (170,171) but after two years of estrogen their Z-scores were still below that of age- and sex assigned-matched norms (171). In transgender boys (153,154), the bone density and Z-scores of the lumbar spine and the femoral region increased (n=42) after 2 years of testosterone therapy but were still not at pretreatment level (171).

When BMD development was assessed until young adulthood, however, it was found that the loss in Z-score was still partially present at the age of 22 implying a possible delay in or loss of peak bone mass(170). To this date only one case report has been published on long term BMD development and it was shown that absolute BMD and Z-scores of a transgender man, treated with GnRHa in his adolescence was in the normal range at age 35. However pre-treatment data was not provided(172).

The addition of gender affirming hormones to other methods of gonadal suppression

Transgender girls

Two retrospective studies reported on the addition of estrogens to anti-androgen therapies in transgender adolescents. In one study the subjects received CPA (165) and in the other study spironolactone (79) was used. The addition of estrogens to CPA mono-therapy in transgender girls resulted in either the initiation or further progression of breast development. Oral 17-beta estradiol was started at 0.5 mg daily and increased to 0.75 mg after 6 months. After 12 months of estrogen therapy 66.7 % reached Tanner Breast 3 and 9.5% reached Tanner Breast 4. After 12 months, both testosterone and LH decreased significantly to 168 ng/dl (5.8 pmol/L) and 3.2 IU/L, respectively and FSH demonstrated a declining trend to 2.8 IU/L. The mean 17-beta estradiol level was 33 pg/mL (121.1 pmol/L). The most common adverse event reported by the transgender girls was fatigue but

resolved in almost all. BMI-SDS remained stable. In addition metabolic parameters, lipid profile and glucose homeostasis did not change(165).

In a study of 44 transgender girls (mean age 18 years; range 14-25) of whom 38 received spironolactone (dosage 50 -200 mg daily) oral estrogen was added in three routes, oral (dosage between 1 to 8 mg daily), intramuscular (dosage 20 to 80 mg monthly) or transdermal (dosage 0.025 to 0.200 mg weekly). There were no changes reported in BMI, metabolic parameters, lipid profile and prolactin and there were no differences in the methods of administration. Among the 38 subjects taking spironolactone potassium levels did not change(79).

Transgender boys

Testosterone can be added to progestagens as previously described (40) The clinical effects and effects on metabolic parameters in adolescent transgender boys have been investigated retrospectively in two studies, one single center study (n=42)(166) and one multicenter study center (n=72)(79); albeit in the later study 7 subjects had received GnRHa prior to the testosterone therapy. Only the single center study reported on side effects, which were fatigue and acne. Clinically, there was a weight gain as both BMI (79) and BMI-SDS increased (166). Although testosterone preparation and dosing differed, both studies reported an increase in both hemoglobin and hematocrit. With a testosterone-ester mixture on a biweekly frequency, values remained within the normal male range(166), whereas when treated with testosterone-ester on a weekly base, hematocrit increased to supraphysiological levels of above 50% in 3% of the cohort (2 cases) with no adverse events reported(79). ALT, AST, creatinine increased but remained in the normal range. Lipid profile was more unfavorable with an increase of cholesterol and LDL and a decrease of HDL. Glucose homeostasis parameters HbA1c (79,166) and insulin, glucose, or HOMA index (157) were not affected.

Final considerations

Knowledge regarding the treatment of gender dysphoria and non-conforming has steadily advanced over the past 10 years (173). While the psychological benefits of gender affirming treatment for young adolescents with gender dysphoria using GnRHa have been established(174,175), data on long term health outcome are still sparse. GnRHa treatment in adolescents is both clinically and biochemically effective in suppressing the hypothalamic-pituitary-gonadal axis and appears to be well tolerated and safe(160). However, transgender boys may be more susceptible for the development of arterial hypertension(162). Studies regarding treatment with estrogen on pubertal development and short-term safety demonstrate feminization of the body without adverse events (167). In transgender boys, data on combined GnRHa and androgens is lacking. Retrospective reports on bone mineral density development demonstrated a loss of Z-scores in transgender boys and transgender girls during gonadal suppression, followed by an increase after the addition of hormones but at the age of 22 years Z-scores were still under pretreatment-level. Other long-term follow-up data is not available. Also the afore mentioned studies mainly describe a relatively older and mature group, mid-teens and Tanner 4 and up, which coincides with a relatively shorter duration of an induced hypogonadal state. There are currently no publications available focusing on treatment of the young and less matured (Tanner 2 or 3) adolescent with gender dysphoria and therefore the effects of prolonged gonadal suppression i.e. 3 to 4 years; short- or long-term are unknown. There needs to be investigation if the initiation of sex steroid hormones before the recommended age of 16 may prevent the negative sequelae of hypogonadism on the skeleton. Finally, when GnRHa are not available, alternative methods to suppress puberty can be used in the more sexually matured adolescent. Short-term data on the use of anti-androgens in transgender girls and progestagens in transgender boys demonstrated its efficacy and safety(165,166).

Key Conclusions and Recommendations for Future Clinical Research

The current available research is based mostly on cross-sectional studies, with limited longitudinal data. There is also paucity of information on diverse ethnic and socioeconomic populations and papers on treatment outcome in adolescents. The current literature comes from mostly Western-European and from higher income countries, where many participants undergo surgical procedures, and has at best intermediate duration follow-up. Limited data exists on the hormonal treatment in gender non-binary persons. For specific analyses such as outcome or mortality, no single center has a sufficiently large patient base to study the population with statistical rigor.

An important barrier to better care is the diversity of training and practice across providers. Health care professionals continue to face challenges in providing optimal care for the transgender population, also due to a lack of education on the topic. The improvement of formal transgender education in medical schools and among health care providers in the broadest sense is timely (176). Professionals working in health services need to understand that patients' gender identity is important and needs to be considered during any consultation. Treating people with respect requires a good understanding of people's identity regarding their gender. Transgender health care has to be included in national and international conferences of all involved specialties. We feel strong about the fact that involving the transgender community at all stages of research is vital. This patient-centered research will progressively lead towards more studies where transgender community involvement is crucial in identifying research priorities, research design, helping recruitment, dissemination of study results. Patient centered outcome priorities in endocrinology are breast development in transgender women, time to menstrual cessation in transgender men, dose-related responses to hormonal interventions, effect on sexual function and fertility among many others (177).

Transgender medicine research is finally moving away from case reports and small series. Many efforts have gone into summarizing available data in numerous recent systematic reviews, from which we have to internalize the findings, avoid repeating the same research, and take the investigations further. The collection and reporting of original good quality data through networks has to be higher on the agenda. Innovative and patient-centered long-term research with randomized controlled trials if possible, to advance of the safety and efficacy of hormonal interventions is a priority. In doing so, clinicians and academics must listen to the voices of transgender people, recognizing and respecting the internal diversity within the transgender community.

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978 References

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980

981 **1.** Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J,
982 Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor
983 AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-
984 Bahlburg H, Hall BP, Pfaefflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V,
985 van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of
986 Care for the Health of Transsexual, Transgender, and Gender-Nonconforming
987 People, Version 7. International Journal of Transgenderism 2012; 13:165-232
988 **2.** Arcelus J, Bouman WP. Language and terminology. In: Bouman WP, Arcelus J, eds.
989 The Transgender Handbook: A guide for transgender people, their familes and
990 professionals. 1 ed. New York: Nova; 2017:1-13.
991 **3.** Richards C, Bouman WP, Seal L, Barker MJ, Nieder TO, T'Sjoen G. Non-binary or
992 genderqueer genders. Int Rev Psychiatry 2016; 28:95-102
993 **4.** Cauldwell DO. Psychopathia transsexualis. Sexology 1949; 16:274-280
994 **5.** WHO. International statistical classification of diseases and related health
995 problems. 10th revision, 2nd ed. ed. Geneva: World Health Organization.
996 **6.** Beek TF, Cohen-Kettenis PT, Bouman WP, de Vries AL, Steensma TD, Witcomb GL,
997 Arcelus J, Richards C, Elaut E, Kreukels BP. Gender Incongruence of Adolescence
998 and Adulthood: Acceptability and Clinical Utility of the World Health Organization's
999 Proposed ICD-11 Criteria. PLoS One 2016; 11:e0160066
1000 **7.** Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-
1001 Aranda F. Systematic review and meta-analysis of prevalence studies in
1002 transsexualism. Eur Psychiatry 2015; 30:807-815
1003 8. Cohen-Kettenis PT, Gooren LJ. Transsexualism: a review of etiology, diagnosis and
1004 treatment. J Psychosom Res 1999; 46:315-333
1005 **9.** American Psychiatric Assocation (APA). Diagnostic and statistical manual of mental
1006 disorders, fifth edition, DSM-V. Washington, DC: American Psychiatric Association.
1007 **10.** Beek TF, Cohen-Kettenis PT, Bouman WP, de Vries AL, Steensma TD, Witcomb GL,
1008 Arcelus J, Richards C, De Cuypere G, Kreukels BP. Gender Incongruence of
1009 Childhood: Clinical Utility and Stakeholder Agreement with the World Health
1010 Organization's Proposed ICD-11 Criteria. PLoS One 2017; 12:e0168522
1011 **11.** European Parliament. on human rights, sexual orientation and gender identity at
1012 the United Nations. 2011. Accessed 18 of March, 2015.
1013 **12.** Pauly IB. The current status of the change of sex operation. J Nerv Ment Dis 1968;
1014 147:460-471
1015 **13.** Eklund PL, Gooren LJ, Bezemer PD. Prevalence of transsexualism in The
1016 Netherlands. The British Journal of Psychiatry 1988; 152:638-640
1017 **14.** Landen M, Walinder J, Lundstrom B. Incidence and sex ratio of transsexualism in
1018 Sweden. Acta Psychiatr Scand 1996; 93:261-263
1019 **15.** Weitze C, Osburg S. Transsexualism in Germany: empirical data on epidemiology
1020 and application of the German Transsexuals' Act during its first ten years. Arch Sex
1021 Behav 1996; 25:409-425
1022 **16.** Dhejne C, Oberg K, Arver S, Landen M. An analysis of all applications for sex
1023 reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets.
1024 Arch Sex Behav 2014; 43:1535-1545

17. Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. Am J Public Health 2012; 102:118-122

18. Kuyper L, Wijsen C. Gender identities and gender dysphoria in the Netherlands. Arch Sex Behav 2014; 43:377-385

19. Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. Arch Sex Behav 2015; 44:1281-1287

20. Arcelus J, Bouman WP. Prevalence: estimating the size of the transgender population. In: Bouman WP, Arcelus J, eds. The Transgender Handbook: A Guide for Transgender People, Their Families and Professionals. New York: Nova Science publishers; 2017:13-24.

21. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: A review of the literature. Int Rev Psychiatry 2016; 28:44-57

22. Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen IR, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. Br J Psychiatry 2014; 204:151-156

23. Auer MK, Hohne N, Bazarra-Castro MA, Pfister H, Fuss J, Stalla GK, Sievers C, Ising M. Psychopathological profiles in transsexuals and the challenge of their special status among the sexes. PLoS One 2013; 8:e78469

24. Gomez-Gil E, Trilla A, Salamero M, Godas T, Valdes M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. Arch Sex Behav 2009; 38:378-392

25. Bouman WP, Claes L, Brewin N, Crawford JR, Millet N, Fernandez-Aranda F, Arcelus J. Transgender and anxiety: A comparative study between transgender people and the general population. International Journal of Transgenderism 2016; 18:16-26

26. Millet N, Longworth J, Arcelus J. Prevalence of anxiety symptoms and disorders in the transgender population: A systematic review of the literature. International Journal of Transgenderism 2016; 18:27-38

27. Claes L, Bouman WP, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self-injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. J Sex Med 2015; 12:168-179

28. Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk Factors for Non-Suicidal Self-Injury Among Trans Youth. J Sex Med 2016; 13:402-412

29. Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. Int Rev Psychiatry 2016; 28:58-69

30. Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N, Landen M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011; 6:e16885

31. Gomez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godas T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology 2012; 37:662-670

32. Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. Psychiatry Clin Neurosci 2010; 64:514-519

33. Davey A, Bouman WP, Meyer C, Arcelus J. Interpersonal Functioning Among Treatment-Seeking Trans Individuals. J Clin Psychol 2015; 71:1173-1185

34. Johansson A, Sundbom E, Hojerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 2010; 39:1429-1437

35. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. Psychoneuroendocrinology 2014; 39:65-73

36. Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med 2014; 11:119-126

37. Ruppin U, Pfafflin F. Long-Term Follow-Up of Adults with Gender Identity Disorder. Arch Sex Behav 2015; 44:1321-1329

38. Pfäfflin F. Regrets after sex reassignment surgery. J Psychol Human Sex 1992; 5:69-85

39. Kuiper AJC-K, P.T. Gender role reversal among postoperative transsexuals. Int J Transgenderism 1998; 2

40. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017; 102:3869-3903

41. Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol 2017; 5:291-300

42. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 2010; 72:214-231

43. Fisher AD, Castellini G, Ristori J, Casale H, Cassioli E, Sensi C, Fanni E, Amato AM, Bettini E, Mosconi M, Dettore D, Ricca V, Maggi M. Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data. J Clin Endocrinol Metab 2016; 101:4260-4269

44. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, Kaufman JM, T'Sjoen G. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. J Sex Med 2014; 11:1999-2011

45. Weinand JD, Safer JD. Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals. J Clin Transl Endocrinol 2015; 2:55-60

46. Keo-Meier CL, Fitzgerald KM. Affirmative Psychological Testing and Neurocognitive Assessment with Transgender Adults. Psychiatr Clin North Am 2017; 40:51-64

47. Eckstrand KL, Ng H, Potter J. Affirmative and Responsible Health Care for People with Nonconforming Gender Identities and Expressions. AMA J Ethics 2016; 18:1107-1118

48. Cavanaugh T, Hopwood R, Lambert C. Informed Consent in the Medical Care of Transgender and Gender-Nonconforming Patients. AMA J Ethics 2016; 18:1147-1155

49. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime Risk of Venous Thromboembolism in Two Cohort Studies. Am J Med. 2016;129(3):339.e19-26.

50. Laidlaw E, Irwig MS. Risks and benefits of estrogen therapy for a male-to-female transsexual with a prothrombin gene mutation.Endocr Pract 2013; 19:e150-153

51. Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola MC, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren LJ. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. Andrologia 2014; 46:791-795

52. Dekker MJ, Wierckx K, Van Caenegem E, Klaver M, Kreukels BP, Elaut E, Fisher AD, van Trotsenburg MA, Schreiner T, den Heijer M, T'Sjoen G. A European Network for the Investigation of Gender Incongruence: Endocrine Part. J Sex Med 2016; 13:994-999

53. Defreyne J, Nota N, Pereira C, Schreiner T, Fisher AD, den Heijer M, T'Sjoen G. Transient Elevated Serum Prolactin in Trans Women Is Caused by Cyproterone Acetate Treatment. LGBT Health 2017; 4:328-336

54. Wiepjes CM, Vlot MC, Klaver M, Nota NM, de Blok CJ, de Jongh RT, Lips P, Heijboer AC, Fisher AD, Schreiner T, T'Sjoen G, den Heijer M. Bone Mineral Density Increases in Trans Persons After 1 Year of Hormonal Treatment: A Multicenter Prospective Observational Study. J Bone Miner Res 2017; 32:1252-1260

55. Mueller A, Zollver H, Kronawitter D, Oppelt PG, Claassen T, Hoffmann I, Beckmann MW, Dittrich R. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. Exp Clin Endocrinol Diabetes 2011; 119:95-100

56. Seal LJ, Franklin S, Richards C, Shishkareva A, Sinclaire C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. J Clin Endocrinol Metab 2012; 97:4422-4428

57. Leinung MC, Urizar MF, Patel N, Sood SC. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract 2013; 19:644-650

58. Deutsch MB, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. Obstet Gynecol 2015; 125:605-610

59. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. Arch Sex Behav 1989; 18:49-57

60. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. Clin Endocrinol (Oxf) 2016; 85:239-246

61. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmina E, American Association of Clinical E, American College of E, Androgen E, Society P. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and Pcos Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome - Part 2. Endocr Pract 2015; 21:1415-1426

62. Mancini I, Rotilio A, Coati I, Seracchioli R, Martelli V, Meriggiola MC. Presentation of a meningioma in a transwoman after nine years of cyproterone acetate and estradiol intake: case report and literature review. Gynecol Endocrinol 2017:1-4

63. Gil M, Oliva B, Timoner J, Macia MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study. Br J Clin Pharmacol 2011; 72:965-968

64. Goncalves AM, Page P, Domigo V, Meder JF, Oppenheim C. Abrupt regression of a meningioma after discontinuation of cyproterone treatment. AJNR Am J Neuroradiol 2010; 31:1504-1505

65. Mamoojee Y, Seal LJ, Quinton R. Transgender hormone therapy: understanding international variation in practice. Lancet Diabetes Endocrinol 2017; 5:243-246

66. Liang JJ, Jolly D, Chan KJ, Safer JD. Testosterone Levels Achieved by Medically Treated Transgender Women in a United States Endocrinology Clinic Cohort. Endocr Pract 2017;

67. Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. J Sex Med 2014; 11:1240-1247

68. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, Women's Health Initiative I. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523-534

69. Barsoum MK, Heit JA, Ashrani AA, Leibson CL, Petterson TM, Bailey KR. Is progestin an independent risk factor for incident venous thromboembolism? A population-based case-control study. Thromb Res 2010; 126:373-378

70. Moreno-Arrones OM, Becerra A, Vano-Galvan S. Therapeutic experience with oral finasteride for androgenetic alopecia in female-to-male transgender patients. Clin Exp Dermatol 2017; 42:743-748

71. Stevenson MO, Wixon N, Safer JD. Scalp Hair Regrowth in Hormone-Treated Transgender Woman. Transgend Health 2016; 1:202-204

72. Irwig MS. Safety concerns regarding 5alpha reductase inhibitors for the treatment of androgenetic alopecia. Curr Opin Endocrinol Diabetes Obes 2015; 22:248-253

73. Basaria S, Jasuja R, Huang G, Wharton W, Pan H, Pencina K, Li Z, Travison TG, Bhawan J, Gonthier R, Labrie F, Dury AY, Serra C, Papazian A, O'Leary M, Amr S, Storer TW, Stern E, Bhasin S. Characteristics of Men Who Report Persistent Sexual Symptoms After Finasteride Use for Hair Loss. J Clin Endocrinol Metab 2016; 101:4669-4680

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

75. de Blok CJM, Klaver M, Wiepjes CM, Nota NM, Heijboer AC, Fisher AD, Schreiner T, T'Sjoen G, den Heijer M. Breast Development in Transwomen After One Year of Cross-sex Hormone Therapy: Results of A Prospective Multicenter Study. J Clin Endocrinol Metab 2017;

76. Klaver M, Dekker M, de Mutsert R, Twisk JWR, den Heijer M. Cross-sex hormone therapy in transgender persons affects total body weight, body fat and lean body mass: a meta-analysis. Andrologia 2017; 49

77. Quiros C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gomez-Gil E, Godas T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinol Nutr 2015; 62:210-216

78 Klaver M, de Blok CJM, Wiepjes CM, Nota NM, Dekker MJHJ, de Mutsert R, Schreiner T, Fisher AD, T'Sjoen G, den Heijer M. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. Eur J Endocrinol 2018; 178:165-173

79. Jarin J, Pine-Twaddell E, Trotman G, Stevens J, Conard LA, Tefera E, Gomez-Lobo V. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 2017; 139

80. Bultynck C, Pas C, Defreyne J, Cosyns M, den Heijer M, T'Sjoen G. Self-perception of voice in transgender persons during cross-sex hormone therapy. Laryngoscope 2017; 127:2796-2804

81. Meister J, Kuhn H, Shehata-Dieler W, Hagen R, Kleinsasser N. Perceptual analysis of the male-to-female transgender voice after glottoplasty-the telephone test. Laryngoscope 2017; 127:875-881

82. Davies SP, V.G.; Antoni, C. Voice and communication change for gender nonconforming individuals: giving voice to the person inside. Int J Transgenderism 2015; 16:117-159

83. Schwarz K, Fontanari AMV, Schneider MA, Borba Soll BM, da Silva DC, Spritzer PM, Kazumi Yamaguti Dorfman ME, Kuhl G, Costa AB, Cielo CA, Villas Boas AP, Lobato MIR. Laryngeal surgical treatment in transgender women: A systematic review and meta-analysis. Laryngoscope 2017; 127:2596-2603

84. Ginsberg BA, Calderon M, Seminara NM, Day D. A potential role for the dermatologist in the physical transformation of transgender people: A survey of attitudes and practices within the transgender community. J Am Acad Dermatol 2016; 74:303-308

85. Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman JM, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. Eur J Endocrinol 2013; 169:471-478

86. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2017; 102:3914-3923

87. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertil Steril 2010; 1:1267-1272

88. Chan W, Drummond A, Kelly M. Deep vein thrombosis in a transgender woman. CMAJ 2017; 189:E502-E504

89. Laidlaw E, Irwig MS. Risks and benefits of estrogen therapy for a male-to-female transsexual with a prothrombin gene mutation.Endocr Pract 2013; 19:e150-153

90. Bilezikian JP, Morishima A, Bell J, Grumbach MM. Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med 1998; 27:599-603

91. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994; 20:1056-1061

92. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, Davidge-Pitts C, Nippoldt TB, Prokop LJ, Murad MH. Effect of Sex Steroids on the Bone Health of Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2017; 102:3904-3913

93. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman JM, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). Eur J Endocrinol 2015; 172:163-171

94. Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. J Sex Med 2013; 10:3129-3134

95. Brown GR, Jones KT. Incidence of breast cancer in a cohort of 5,135 transgender veterans. Breast Cancer Res Treat 2015; 149:191-198

96. Brown GR. Breast Cancer in Transgender Veterans: A Ten-Case Series. LGBT Health 2015; 2:77-80

97. Silverberg MJ, Nash R, Becerra-Culqui TA, Cromwell L, Getahun D, Hunkeler E, Lash TL, Millman A, Quinn VP, Robinson B, Roblin D, Slovis J, Tangpricha V, Goodman M. Cohort study of cancer risk among insured transgender people. Ann Epidemiol 2017; 27:499-501

98. Deebel NA, Morin JP, Autorino R, Vince R, Grob B, Hampton LJ. Prostate Cancer in Transgender Women: Incidence, Etiopathogenesis, and Management Challenges. Urology 2017; 110:166-171

99. T'Sjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. Curr Opin Endocrinol Diabetes Obes 2013; 20:575-579

100. Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. Low Fertility Preservation Utilization Among Transgender Youth. J Adolesc Health 2017; 61:40-44

101. Defreyne J, Nota N, Pereira C, Schreiner T, Fisher AD, den Heijer M, T'Sjoen G. Transient Elevated Serum Prolactin in Trans Women Is Caused by Cyproterone Acetate Treatment. LGBT Health 2017; 4:328-336

102. Fung R, Hellstern-Layefsky M, Tastenhoye C, Lega I, Steele L. Differential Effects of Cyproterone Acetate vs Spironolactone on Serum High-Density Lipoprotein and Prolactin Concentrations in the Hormonal Treatment of Transgender Women. J Sex Med 2016; 13:1765-1772
103. Wierckx K, Van de Peer F, Verhaeghe E, Dedecker D, Van Caenegem E, Toye K, Kaufman JM, T'Sjoen G. Short- and long-term clinical skin effects of testosterone treatment in trans men. J Sex Med 2014; 11:222-229
104. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2011; 164:635-642
105. Spratt DI, Stewart, II, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients. J Clin Endocrinol Metab 2017; 102:2349-2355
106. Olson J, Schrager SM, Clark LF, Dunlap SL, Belzer M. Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men. LGBT Health 2014; 1:165-167
107. Jacobeit JW, Gooren LJ, Schulte HM. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. Eur J Endocrinol 2009; 161:795-798
108. Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola MC. Effects of three different testosterone formulations in female-to-male transsexual persons. J Sex Med 2014; 11:3002-3011
109. Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 2008; 93:19-25
110. Gooren LJ. Management of female-to-male transgender persons: medical and surgical management, life expectancy. Curr Opin Endocrinol Diabetes Obes 2014; 21:233-238
111. Lynch MK, MM; Meyer, MJ. Retrospective study of the management of childhood and adolescent gender identity disorder using medroxyprogesterone acetate. Int J Transgenderism 2015; 16
112. Irwig MS. Testosterone therapy for transgender men. Lancet Diabetes Endocrinol 2017; 5:301-311
113. Gooren LJ. Clinical practice. Care of transsexual persons. N Engl J Med 2011; 364:1251-1257
114. Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. Clin Endocrinol (Oxf) 2015; 83:597-606
115. Ahmad S, Leinung M. The Response of the Menstrual Cycle to Initiation of Hormonal Therapy in Transgender Men. Transgend Health 2017; 2:176-179
116. Gooren LJ. Should cross-sex hormone treatment of transsexual subjects vary with ethnic group? Asian J Androl 2014; 16:809-810
117. Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. J Sex Med 2014; 11:2012-2019
118. Velho I, Fighera TM, Ziegelmann PK, Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. Andrology 2017; 5:881-888
119. Evans S, Neave N, Wakelin D, Hamilton C. The relationship between testosterone and vocal frequencies in human males. Physiol Behav 2008; 93:783-788
120. Cosyns M, Van Borsel J, Wierckx K, Dedecker D, Van de Peer F, Daelman T, Laenen S, T'Sjoen G. Voice in female-to-male transsexual persons after long-term androgen therapy. Laryngoscope 2014; 124:1409-1414

121. Watt SO, Tskhay KO, Rule NO. Masculine Voices Predict Well-Being in Female-to-Male Transgender Individuals. Arch Sex Behav 2017;

122. Irwig MS, Childs K, Hancock AB. Effects of testosterone on the transgender male voice. Andrology 2017; 5:107-112

123. Dacakis G, Oates J, Douglas J. Associations between the Transsexual Voice Questionnaire (TVQMtF) and self-report of voice femininity and acoustic voice measures. Int J Lang Commun Disord 2017; 52:831-838

124. Giltay EJ, Gooren LJ. Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. J Clin Endocrinol Metab 2000; 85:2913-2921

125. Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, Cupisti S, Beckmann MW, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sex Med 2010; 7:3190-3198

126. Giltay EJ, Toorians AW, Sarabdjitsingh AR, de Vries NA, Gooren LJ. Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals. J Endocrinol 2004; 180:107-112

127. Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. Eur J Endocrinol 2014; 170:809-819

128. Gooren LJ, Giltay EJ. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. Andrologia 2014; 46:570-575

129. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf) 2010; 72:1-10

130. Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. Fertil Steril 2010; 94:2647-2653

131. Berra M, Armillotta F, D'Emidio L, Costantino A, Martorana G, Pelusi G, Meriggiola MC. Testosterone decreases adiponectin levels in female to male transsexuals. Asian J Androl 2006; 8:725-729

132. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med 2012; 9:2641-2651

133. Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. J Psychosom Res 2015; 78:399-406

134. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertil Steril 2010; 93:1267-1272

135. Van Caenegem E, T'Sjoen G. Bone in trans persons. Curr Opin Endocrinol Diabetes Obes 2015; 22:459-466

136. Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. Horm Behav 2007; 52:334-343

137. Miyajima T, Kim YT, Oda H. A study of changes in bone metabolism in cases of gender identity disorder. J Bone Miner Metab 2012; 30:468-473

138. Goh HH, Ratnam SS. Effects of hormone deficiency, androgen therapy and calcium supplementation on bone mineral density in female transsexuals. Maturitas 1997; 26:45-52

139. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. Clin Endocrinol (Oxf) 2004; 61:560-566
140. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. J Sex Med 2008; 5:2442-2453
141. van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol (Oxf) 1998; 48:347-354
142. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. Osteoporos Int 2005; 16:791-798
143. Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, Kaufman JM, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. J Clin Endocrinol Metab 2012; 97:2503-2511
144. Schlatterer K, Auer DP, Yassouridis A, von Werder K, Stalla GK. Transsexualism and osteoporosis. Exp Clin Endocrinol Diabetes 1998; 106:365-368
145. Lips P, van Kesteren PJ, Asscheman H, Gooren LJ. The effect of androgen treatment on bone metabolism in female-to-male transsexuals. J Bone Miner Res 1996; 11:1769-1773
146. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol 2003; 275:1081-1101
147. Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in Transgender People: Evidence and Methodological Considerations. Epidemiol Rev 2017; 39:93-107
148. Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 1989; 38:869-873
149. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997; 47:337-342
150. Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. Hum Reprod 2012; 27:483-487
151. De Roo C, Tilleman K, T'Sjoen G, De Sutter P. Fertility options in transgender people. Int Rev Psychiatry 2016; 28:112-119
152. Caanen MR, Soleman RS, Kuijper EA, Kreukels BP, De Roo C, Tilleman K, De Sutter P, van Trotsenburg MA, Broekmans FJ, Lambalk CB. Antimullerian hormone levels decrease in female-to-male transsexuals using testosterone as cross-sex therapy. Fertil Steril 2015; 103:1340-1345
153. De Roo C, Lierman S, Tilleman K, Peynshaert K, Braeckmans K, Caanen M, Lambalk CB, Weyers S, T'Sjoen G, Cornelissen R, De Sutter P. Ovarian tissue cryopreservation in female-to-male transgender people: insights into ovarian histology and physiology after prolonged androgen treatment. Reprod Biomed Online 2017; 34:557-566
154. Lierman S, Tilleman K, Braeckmans K, Peynshaert K, Weyers S, T'Sjoen G, De Sutter P. Fertility preservation for trans men: frozen-thawed in vitro matured oocytes collected at the time of ovarian tissue processing exhibit normal meiotic spindles. J Assist Reprod Genet 2017;
155. Obedin-Maliver J, Makadon HJ. Transgender men and pregnancy. Obstet Med 2016; 9:4-8

156. Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 1998; 7:246-248
157. Crowley WF, Jr., Comite F, Vale W, Rivier J, Loriaux DL, Cutler GB, Jr. Therapeutic use of pituitary desensitization with a long-acting lhrh agonist: a potential new treatment for idiopathic precocious puberty. J Clin Endocrinol Metab 1981; 52:370-372
158. Laron Z, Kauli R, Zeev ZB, Comaru-Schally AM, Schally AV. D-TRP5-analogue of luteinising hormone releasing hormone in combination with cyproterone acetate to treat precocious puberty. Lancet 1981; 2:955-956
159. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Group E-LGACC, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnukainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M, Wit JM. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009; 123:e752-762
160. Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. J Sex Med 2016; 13:1125-1132
161. Delemarre-van de Waal HC-K, PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. European Journal of Endocrinology 2006; 155:131-137
162 Klink DB, A. Dekker, C; Rotteveel J. Arterial hypertension as a complication of triptorelin treatment in adolescents with gender dysphoria. Endocrinol Metab Int J 2015; 2:8
163 Calcaterra V, Mannarino S, Corana G, Codazzi AC, Mazzola A, Brambilla P, et al. Hypertension during therapy with triptorelin in a girl with precocious puberty. Indian J Pediatr 2013; 80:884-885
164 Siomou E, Kosmeri C, Pavlou M, Vlahos A, Argyropoulou M, Siamopoulou A. Arterial hypertension during treatment with triptorelin in a child with Williams-Beuren syndrome. Pediatr Nephrol 2014; 29:1633-1636
165. Tack LJW, Heyse R, Craen M, Dhondt K, Bossche HV, Laridaen J, Cools M. Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. J Sex Med 2017; 14:747-757
166. Tack LJ, Craen M, Dhondt K, Vanden Bossche H, Laridaen J, Cools M. Consecutive lynestrenol and cross-sex hormone treatment in biological female adolescents with gender dysphoria: a retrospective analysis. Biol Sex Differ 2016; 7:14
167. Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. J Clin Endocrinol Metab 2017; 102:2356-2363
168. Berger C, Goltzman D, Langsetmo L, Joseph L, Jackson S, Kreiger N, Tenenhouse A, Davison KS, Josse RG, Prior JC, Hanley DA, CaMos Research G. Peak bone mass from longitudinal data: implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. J Bone Miner Res 2010; 25:1948-1957
169. De Schepper J, Derde MP, Van den Broeck M, Piepsz A, Jonckheer MH. Normative data for lumbar spine bone mineral content in children: influence of age, height, weight, and pubertal stage. J Nucl Med 1991; 32:216-220
170. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab 2015; 100:E270-275
171. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers

and bone mineral apparent density (BMAD) in transgender adolescents. Bone 2017; 95:11-19

172. Cohen-Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre-van de Waal HA. Puberty suppression in a gender-dysphoric adolescent: a 22-year follow-up. Arch Sex Behav 2011; 40:843-847

173. Cohen-Kettenis PT, Klink D. Adolescents with gender dysphoria. Best Pract Res Clin Endocrinol Metab 2015; 29:485-495

174. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med 2011; 8:2276-2283

175. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014; 134:696-704

176. Davidge-Pitts C, Nippoldt TB, Danoff A, Radziejewski L, Natt N. Transgender Health in Endocrinology: Current Status of Endocrinology Fellowship Programs and Practicing Clinicians. J Clin Endocrinol Metab 2017; 102:1286-1290

177. Feldman J, Brown GR, Deutsch MB, Hembree W, Meyer W, Meyer-Bahlburg HF, Tangpricha V, T'Sjoen G, Safer JD. Priorities for transgender medical and healthcare research. Curr Opin Endocrinol Diabetes Obes 2016; 23:180-187

1513 Table 1: Terminology used in transgender health

Cisgender- A person whose identity matches the sex assigned at birth.
Gender affirming treatment- Physical treatment that some transgender people access in order for their bodies to be adapted to the bodies of their experienced gender or gender identity by means of hormones and/or surgery.
Gender dysphoria- A profound distress or discomfort caused by the discrepancy between assigned sex at birth and gender identity. This is the same term as the current diagnostic term of the DSM-5.
Gender expression- The external manifestations of someone's gender, which can include name, pronouns, clothing, haircut, behavior, voice, or body characteristics.
Gender identity / experienced gender- A person's internal sense of gender. Unlike gender expression, gender identity is not visible to others.
Gender identity disorder- Diagnostic term used in previous versions of the DSM. The term is still used for the child diagnosis in the ICD-10, but the proposed name for ICD-11 is gender incongruence of childhood. Currently this term is not preferred given the term "disorder".
Gender Incongruence- The proposed diagnostic term to be used in the new edition of the ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek gender-affirming treatment.
Gender reassignment- Previously used term to describe what is known now as gender-affirming treatment.

Gender role- The behaviors, attitudes, and personality traits that a society, in a historical period, designates as masculine or feminine.
Natal sex- The term "sex assigned at birth", which is usually based on genital anatomy, is more appropriate.
Sex- Attributes that characterize biological maleness or femaleness. They can include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia and secondary sex characteristics.
Sexual orientation - An individual's physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), or be bisexual, asexual, pansexual, etcetera.
Transgender *(adj.)* - An umbrella term to describe individuals, whose gender identity differs from the sex assigned at birth based on their sexual characteristics.
Transgender male - A person whose sex was assigned female at birth (based on their sexual characteristics) but self-identifies as male.
Transgender female - A person who self-identifies as female, but whose sex was assigned male at birth.
Transition - The process during which transgender people change their physical, social, and/or legal characteristics consistent with their gender identity.

Transsexual *(adj.)*- A diagnostic term used in the ICD-10. The term is currently used in some of the medical literature when discussing diagnoses. The term transgender should now be used instead except when referring to the current ICD-10 diagnosis.

Legends

Figure 1

Effects of estrogen and antiandrogen treatment in transgender women, reproduced with permission from (41)

Figure 2

Effects of testosterone treatment in transgender men, reproduced from (112)