

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

57

58 **Introduction**

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

74

75 **Terminology**

76 The term “gender non-conforming” is used to describe individuals whose gender identity, role or
77 expression differs from what is normative for their assigned sex at birth in a given culture and historical
78 period (1). Transgender is used as an umbrella term to describe individuals, whose gender identity
79 differs from the assigned sex at birth. Transgender males are people assigned female at birth but who
80 self-identify as male. Transgender females are people assigned male at birth, but who self-identify as
81 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.

155 **Prevalence**

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

160 Some of the first epidemiological studies, which focused on individuals seeking services in order to
161 undergo gender affirming genital surgery(12), found prevalence rates of 0.40 per 100,000 people. The
162 ratio between male assigned at birth and female assigned at birth was found to be 4 to 1(11). Other
163 European studies, based on people attending transgender health services, provide different
164 prevalence rates over time; 1.22 per 100,000 (1976-1980), 1.58 per 100,000 (1976-1983), 2.77 per
165 100,000 (1976-1986)(13). Once again rates of male assigned at birth transgender people have been
166 found to be higher than female assigned at birth transgender people at a ratio of 3 to 1. Studies looking
167 at more recent periods (between 1972 and 1996) provide higher prevalence rates of 3.42 per 100,000
168 with ratios between birth assigned females and males being more similar (1.4 to 1)(14).

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

175 However, not every transgender person wishes and/or seeks medical care to affirm their gender(1). In
176 order to identify the overall prevalence of transgender people (including those not accessing services)
177 population studies may be more representative of the transgender community. Population based
178 studies have found a considerably higher prevalence rate than those reported in clinical studies. For
179 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

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

260

261

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 on 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

women taking progesterone(68,69). Therefore, progesterone therapy is not a routinely used medication in transgender women.

5 α -Reductase Inhibitors

Some transgender women may experience male pattern hair loss and may seek treatments to arrest hair loss and/or restore hair. In general, lowering serum testosterone levels into the cisgender female range is often adequate to arrest hair loss in most transgender women; however, there are still some transgender women who experience hair loss despite lowered serum testosterone levels. A few case series in transgender women with androgenetic alopecia have demonstrated finasteride therapy to be effective to improve hair loss without significant side effects(70,71). The routine use of 5 α -reductase inhibitors has been limited over previous concerns of long-term sexual dysfunction and depression reported to be found in cisgender men(72,73).

Feminization in transgender women

Treatment with estrogen and testosterone lowering medications will induce feminine and reduce masculine physical characteristics. The most studied physical change in transgender women is the development of breast tissue. An Italian cohort study found increases in breast size were the only physical feature that was significantly associated with improvement in body uneasiness scores(43). However, less than 20% of transgender women reach Tanner Breast stage 4-5 after 24 months of hormone therapy and thus often seek mammoplasty. Early studies in transgender women indicated breast development reached a maximum size by 2 years(74). However, a more recent study of 229 transgender women participating in the ENIGI cohort found breast development reached a plateau within the first 6 months of therapy and half of the transgender women had a AAA cup size or less(75). Fisher and colleagues also found testicular volume decreased by approximately 60% after 24 months of transfeminine hormone therapy(43).

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 an 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

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

Insert Fig. 1 about here

509

510 II. Hormonal treatment in transgender men

511 **Initial evaluation of transgender men**

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

514

515 **Screening for conditions prior to initiation of hormone therapy**

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

524

525 **Modalities of hormonal treatment in transgender men**

526 *Testosterone*

527 The principal hormonal treatment used to induce virilization is testosterone. Under medical
528 supervision, testosterone therapy is safe based on short and longer-term safety studies(44,103,104).
529 Different testosterone formulations may be available depending on geographical location. Most
530 commonly prescribed are injectable testosterone esters (40). More recently subcutaneous
531 administration of testosterone was shown to be effective and preferred by transgender men at a
532 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

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

Skin and hair

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

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

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

623

624

625 **Safety data specified for transgender men**

626 1. Cardiovascular safety

627 Adult cisgender men have higher cardiovascular mortality rates than women, which has been
628 attributed to differences in sex hormone levels. However, the available cardiovascular outcome data
629 in transgender men show that testosterone treatment does not result in adverse cardiovascular
630 outcomes(127). Four different recent review papers (86,118,128,129) summarized the effects of
631 testosterone on surrogate risk factors of cardiovascular disease. These studies demonstrated despite
632 a perceived negative impact on a number of risk factors including an increase in hematocrit, a
633 decrease in high-density lipoprotein cholesterol, increase in triglycerides, low-density lipoprotein
634 cholesterol levels, and inflammation parameters (130), small increase in systolic blood pressure
635 (44,125), decrease in adiponectin and leptin (131) no significant increase in cardiovascular outcomes
636 (77). Furthermore, there have been no elevated rates of cardiovascular deaths when compared with
637 cisgender men and women at short and medium follow-up in the larger studies (except for one study
638 (30)). However, data on cardiovascular outcomes in older (65+ years) transgender men are mostly
639 lacking (86). In a cross-sectional study of 50 transgender men on testosterone treatment for an
640 average of 10 years, no subject had experienced myocardial infarction, stroke or deep venous
641 thrombosis (132). In a similar case-control study 138 transgender men 7.4 years on average on
642 testosterone therapy showed a low cardiovascular morbidity (85). In a prospective study with 43
643 transgender men, who were treated with testosterone esters every 3 weeks, there was an increased
644 incidence of previously absent metabolic syndrome after 1 (16,3%) and 2 years (18,6%), especially in
645 those with psychiatric comorbidity(133). Furthermore, most studies in transgender men report no
646 adverse impact of testosterone treatment on fasting glucose or insulin sensitivity (44,108,131,133).

647 Many studies report an association between testosterone therapy and increased hemoglobin (+ 4.9-
648 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 reinstitute 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 (\pm 6.5) to 8.6 ml (\pm 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

793 mg once daily testosterone decreased from 432 ng/dl (15.8 nmol/L) to 248 ng/dl (8.6 nmol/L) and
794 remained stable at 226 ng/dl (7.8 nmol/L). LH and FSH however were not suppressed at 5.0 IU/L and
795 5.1 IU/L during this period. Prolactin increased from 318.2 pmol/L to 760.8 pmol/L but none
796 developed galactorrhea. Clinically more than half of the subjects reported reduced shaving frequency
797 and in approximately one third had breast development (Tanner stage Breast 2-3). There was no
798 increase in BMI-SDS. Fatigue was the only reported side effect. As for safety monitoring, only a
799 transient increase of liver enzymes was seen in 15% of the study subjects. The levels remained under
800 the threshold of three times the upper limit and therefore treatment was not stopped. Metabolic
801 parameters such as lipid profile and glucose homeostasis were not negatively affected(165).

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

811

812 **The addition of gender affirming hormones to GnRHa monotherapy**

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

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

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

831

832 *Transgender girls*

833 For a pubertal induction, it is recommended to start 17-beta estradiol at a dosage of 5 mg/kg/day,
834 followed by 6 monthly increments of 5 mg/kg until a maintenance dosage of 2 mg is reached. The
835 second treatment regime is more suitable for transgender girls who initiated gender affirming
836 treatment when at least 15.5 years old. After a period of gonadal suppression varying from 3 to 6
837 months, estrogens can be given at a daily start dosage of 1 mg and increased to 2 mg after 6 months
838 (40).

839 The effects of the addition of 17-beta estradiol were studied prospectively in 28 transgender girls
840 (158). Estrogen treatment was started at a median age of 16.0 years after median duration of 24.8
841 months of GnRHa mono-therapy. Breast development had started within 3 months and after 1 year
842 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.

917 *Final considerations*

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

940

941

942

943 **Key Conclusions and Recommendations for Future Clinical Research**

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

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

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

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1512

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.

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1518 Legends

1519 Figure 1

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1521 Effects of estrogen and antiandrogen treatment in transgender women, reproduced with permission

1522 from (41)

1523 Figure 2

1524 Effects of testosterone treatment in transgender men, reproduced from (112)

1525