Hormone Therapy in the Transgender Patient

15

Mary O. Stevenson and Vin Tangpricha

Introduction and Terminology

People who have a gender identity that differs from the gender assigned at birth have existed for centuries. The term used to describe the discomfort with having a gender identity that differs from the gender assigned at birth is gender dysphoria [1]. Transgender has been used as the term to describe people who do not express a gender identity that fits their assigned gender and/or societal norms for accepted gender expression [2]. Most but not all transgender people will have gender dysphoria. Transgender people may differ in their approach in handling their gender dysphoria, which may range from a social transition (living in the gender role of the affirmed gender), hormone therapy, and gender-affirming surgery [2].

The previous terms, transsexual or transsexualism, are no longer preferred since they imply a more negative connotation and that transgender people only had a "binary" gender identity, meaning only male or female. Terminologies such as gender nonconforming or gender incongruence have been proposed as terms that recognize the broad spectrum of gender identity and expression.

There are other entities that share some overlap with transgender and gender-nonconforming people. Persons with differences of sexual differentiation or disorders of sex development (DSD) or intersex often represent a separate entity of people from transgender persons. Some people with DSD may have gender dysphoria and seek therapies to align their external appearance to match their gender identity. However, some people with DSD reject the notion that they have a gender dysphoria and/or that surgery is required to align with their gender expression [3]. People that cross-dress (dress in the clothes of a different gender than their birth-assigned gender) represent an understudied population of people who may or may not fall under the terminology of transgender. Some people that initially cross-dress may be exploring different gender expressions, while others have a solidified gender expression but cross-dress for enjoyment. Other entities that may overlap with transgender and gender nonconforming include eunuchs and people with body dysmorphic syndrome. Sexual orientation is often confused with gender identity. There are a number of sexual orientations, and these occur independently from a person's gender identity. One cannot assume a person's sexual orientation based on their gender identity or sex assigned at birth.

The purpose of this chapter is to focus on the hormonal and surgical treatment of people who identity as transgender and gender nonconforming. The criteria for diagnosis, available guidelines on the initiation and monitoring of hormone therapy, and the criteria for referral for gender-affirming surgery will be discussed.

Diagnosis and Guidelines

Specific criteria for the diagnosis for gender dysphoria are available in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [1]. In brief, the criteria establish that there exists a marked incongruence of greater than 6-month duration between the affirmed gender and the sex assigned at birth that causes significant psychosocial stress which impairs functioning. There is controversy over the classification of gender dysphoria under the category of sexual dysfunctions. Professionals and transgender stakeholders are proposing to move gender dysphoria under the category of sexual health in the next revision of the International Classification of Diseases (ICD) [4]. The qualifications of professionals making the diagnosis of gender dysphoria and the timing and eligibility of hormone therapy for children and adults are proposed by the World Professional Association for Transgender Health's Standards of Care, version 7 (SOC7) [2]. In brief, gender-nonconforming adults can start on hormone therapy if they

M. O. Stevenson · V. Tangpricha (✉)
Division of Endocrinology, Metabolism and Lipids, Emory University Department of Medicine, Atlanta, GA, USA
e-mail: MOSTEVE@emory.edu; vin.tangpricha@emory.edu

F. Bandeira et al. (eds.), *Endocrinology and Diabetes*, https://doi.org/10.1007/978-3-030-90684-9_15

have a "persistent, well-documented gender dysphoria," have the "capacity to make a fully informed decision and can consent for treatment," "are of age [an adult] in a given country," and have "significant medical concerns" well-controlled prior to the initiation of hormone therapy [2]. For gender-nonconforming children, hormone therapy can be initiated once the child has reached the age of consent (typically 16 years old in most countries) but ideally also with parental consent, has documented a long period of gender dysphoria during childhood, or emerges or is exacerbated by the initiation of puberty, and has had all psychological, medical, and social issues addressed prior to hormone therapy. The hormone regimens used in children and adults differ according to the stage of puberty which will be addressed in the following sections.

Once the diagnosis of gender dysphoria has been established and the person is deemed eligible and ready to initiate hormone therapy, the 2017 Endocrine Society provides specific evidence-based and consensus recommendations on the initiation, monitoring, and long-term follow-up of hormone therapy and criteria for referral for gender-affirming surgery [5, 6]. The guidelines reaffirm that special expertise in children and adolescent psychology and psychopathology is required to make the diagnosis of gender dysphoria in children and that a multispecialty of medical and mental health providers participates in the management of children prior and during the treatment with hormone therapy. The guidelines reaffirm that the DSM-V should be used when diagnosing gender dysphoria.

Gender-Affirming Hormone Therapy in Children

Once the multispecialty team of medical and mental health providers endorses that a child is eligible for hormone therapy, the regimens used in children depend on the stage of puberty. For pre-pubertal children, no hormone therapy is recommended. During this stage, the child should work with a mental health care professional and/or mental health team regarding issues on social role change (e.g., name and pronoun change, gender role change at school, etc.). For children who are in the earliest stages of puberty, gonadotropin-releasing hormone (GnRH) agonists are recommended initially to halt puberty until the time that the expert multispecialty team deems that sex hormone therapy should be started. Earlier studies have suggested that children have not yet affirmed their adult gender identity prior to the age of 16 [7, 8]. However, more recent studies have suggested that selected children who have intense gender dysphoria prior to the age of 16 may be good candidates for earlier hormone therapy [9]. For children presenting in later stages of puberty, GnRH agonists can be started along with sex hormone therapy for the desired gender once deemed appropriate by the expert multispecialty team.

Long-term data for pubertal suppression along with hormone therapy in children do not currently exist. The longest published follow-up time was 22 years in a transboy started on hormone therapy at age 13 [10]. In this reported case, there were no reported long-term medical or mental health consequences from the hormone therapy. Recent studies have indicated that trans-children ($n = 55$) cared by a multidisciplinary team had improvements of psychosocial functioning after pubertal suppression, hormone therapy, and gender-affirming surgery [11]. Important to consider are the impacts of therapies on fertility especially if puberty is blocked making future retrieval of gametes difficult for fertility preservation therapies [12]. Other considerations include the lower doses of hormones used in children compared to adults as children have not yet reached full adult size. Finally, the continuation of GnRH agonists in transgender children into adulthood should be reassessed. The GnRH agonist therapy may be stopped particularly in transboys on testosterone. However, in transgirls, GnRH agonists still act as very effective testosterone-lowering agents [13].

Transfeminine Hormone Therapy and Long-Term Monitoring

Endocrinologists should discuss individual expectations and the time course of physical and emotional changes with each individual to ensure that these two align (Fig. 15.1). Transfeminine hormone therapy refers to hormone regimens provided to a person who is sex assigned at birth as male who is wishing to transition into the affirmed gender of a female. Some individuals may not wish to develop all of the primary and secondary sex characteristics of a female; therefore, it is important to discuss these expectations with each individual. For transfeminine hormone therapy, the Endocrine Society guidelines recommend that physicians target blood sex steroid levels in the reference normal range for females, estradiol levels 100–200 pg/mL and testosterone levels <50 ng/dL [5]. Two major classes of medications are required for transgender women: estrogen and testosterone-lowering drugs.

Estrogens can be given as an oral pill, transcutaneous gel, skin patch, or intramuscular injection. The choice of estrogen depends on the local pharmacy coverage, the individual's comorbidities, and patient preference. Estradiol is considered the safest form of estrogen to be given orally as opposed to other formulations of estrogen including ethinyl estradiol and conjugated estrogens, which have been associated with increased thromboembolism [14]. Oral estradiol preparations have the advantage that estradiol can be measured in blood to ensure adequate therapeutic concentrations and to avoid supraphysiologic levels, providing an advantage

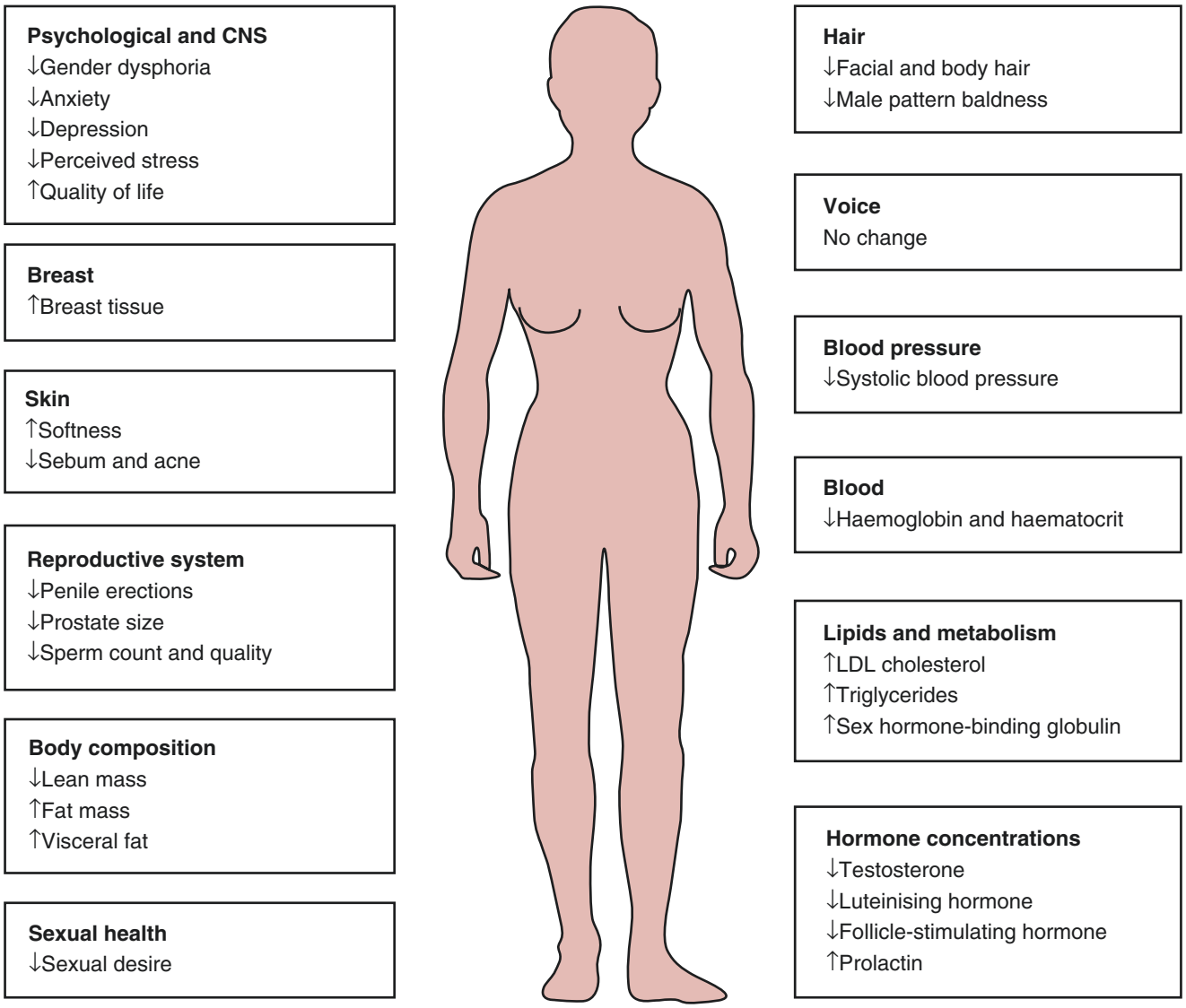

Fig. 15.1 Expected changes in response to transfeminine hormone therapy. (From Tangpricha and Den Heijer [16] Reprinted with permission from Elsevier)

over other oral formulations of estrogen. Estradiol patches have the advantage of avoiding the first-pass liver effect and thus have less stimulation on blood-clotting proteins. Estradiol patches and gels appear to have a better safety profile in terms of thromboembolism [15]. Intramuscular estrogen can be given as estradiol ester, typically estradiol valerate or cypionate [5]. Intramuscular estrogen can be given every 1–2 weeks and also has the advantage of avoiding the first-pass liver effect; however, supraphysiologic levels of estradiol can occur if levels are not carefully monitored and the dose of estrogen is not adjusted accordingly. In general, all forms of estrogen should be initiated at a low dose and titrated up over a few months until the target estradiol level is reached.

In general, a testosterone-lowering agent is also required to lower serum testosterone levels into the female range, at least initially. In the USA, the most commonly prescribed testosterone-lowering medication is spironolactone, which antagonizes androgen activity at the androgen receptor and has additional testosterone-lowering action by an unclear mechanism [5]. Given spironolactone's properties as a potassium-sparing diuretic, potassium levels and kidney function should also be monitored. In Europe, cyproterone is used as a testosterone antagonist which also has progestin-like properties. However, recent reports suggest that cyproterone is associated with increased risk of hyperprolactinemia and meningiomas which has limited its use, especially in the UK [16]. In the UK, GnRH agonists are preferred as the

testosterone-lowering medication in adults [14]. GnRH agonists are very effective in lowering testosterone levels but are largely limited in their use because of the high cost of the medication.

Other second-line medications used for transgender women include progesterones. However, the data demonstrating its effectiveness in inducing feminine characteristics (primarily breast) are very sparse. Studies conducted in older cis-gender women suggest increased risk of stroke in users of progesterones [17, 18]. 5-Alpha-reductase inhibitors, e.g., finasteride, are not considered first-line agents as a testosterone-lowering medication since they are associated with sexual dysfunction and depression [19]. In addition, they do not lower serum testosterone levels but rather decrease the conversion of testosterone to DHT. These agents may be useful in transgender women who are suffering from androgenic alopecia [20].

Long-term monitoring in transgender women should ensure that estradiol and testosterone levels remain in the normal female range. Conditions that can be exacerbated by estrogens such as thromboembolic disease, hypertriglyceridemia, gallstones, and hyperprolactinemia should be monitored periodically. Bone density testing should be obtained in those with risk factors for osteoporosis and those who undergo gonadectomy. Finally, cancer screening should be initiated based on the hormone-sensitive organs present (breast, prostate) according to national guidelines based on age and risk factors [5].

Transmasculine Hormone Therapy and Long-Term Monitoring

Transmasculine hormone therapy refers to the hormone therapy provided to a person who is sex-assigned female at birth and wishes to transition into the affirmed gender of male. As compared to transfeminine hormone therapy, transmasculine therapy is more straightforward as it requires the administration of only one medication, testosterone, to achieve secondary sex characters of male. The expected time course of changes should be discussed with each individual (Fig. 15.2). The concept of transmasculine therapy, including the preparations and hormone laboratory goals, follows the general approach of treating male hypogonadism [21]. The Endocrine Society guidelines recommend a goal to achieve testosterone values in the normal male range, typically 400–700 ng/dL [5].

Testosterone can be given transdermally, as a patch or gel, or as an injection, either subcutaneously or intramuscularly. Again, the choice of regimen depends on patient preference and insurance factors. Transdermal gel preparations require daily application, and androgen can be inadvertently transferred to close contacts if patients are not mindful of application site and do not wash their hands after application. Testosterone patches may cause local skin irritation but alleviate the potential risk of transferring testosterone to others. Testosterone enanthate or cypionate may be given as parenteral or subcutaneous injections every 1–2 weeks. Transdermal preparations have the advantage of avoiding the peak and trough levels that are seen with injections that some patients report as bothersome. For testosterone given by injection, levels of testosterone should be measured midway between injections; alternatively, peak and trough levels can be obtained to ensure levels are maintained within normal male range [5]. For monitoring of transdermal testosterone, testosterone levels should be measured once a steady state of testosterone is expected, at least a week after initiation of therapy [5].

Other medications used for transgender males include oral progesterone, GnRH analogs, and depot medroxyprogesterone, all used to stop menses in those patients who are beginning hormone therapy with testosterone or in those who do not desire testosterone therapy but have dysphoria related to menstruation. The time course of menses cessation on testosterone is variable, and several retrospective reviews have reported cessation as early as 1 month but more often seen between 6 and 12 months on testosterone therapy [22–24].

Long-term monitoring of transmasculine treatment should focus on maintaining testosterone levels within normal male range. Adverse events associated with testosterone therapy include erythrocytosis, sleep apnea, hypertension, weight gain, and lipid changes [25]. Bone density testing should be considered in patients who are at risk of osteoporosis such as those patients who stop or are noncompliant with testosterone therapy and have undergone gonadectomy. Cancer screening should again follow national guidelines for the remaining hormone-sensitive organs (breast tissue, cervix) [5].

Surgical Considerations

There are many surgical options for both transgender women and men to align their primary and secondary sex characteristics with their affirmed gender. The Endocrine Society guidelines identify two main types of surgeries, those that affect fertility and those that do not [5]. Surgeries that do not affect fertility have less stringent criteria for approval. For transwomen, these would include surgeries such as breast augmentation, facial feminization surgeries, as well as removal of facial or body hair by electrolysis or laser treatments. For transmen, a mastectomy is an example of fertility sparing surgery that may be desired.

Gender-affirming surgery, formerly known as sex reassignment surgery, affects fertility and is irreversible. Because of this, the Endocrine Society guidelines propose several criteria for gender-affirming surgery: "(1) persistent, well-

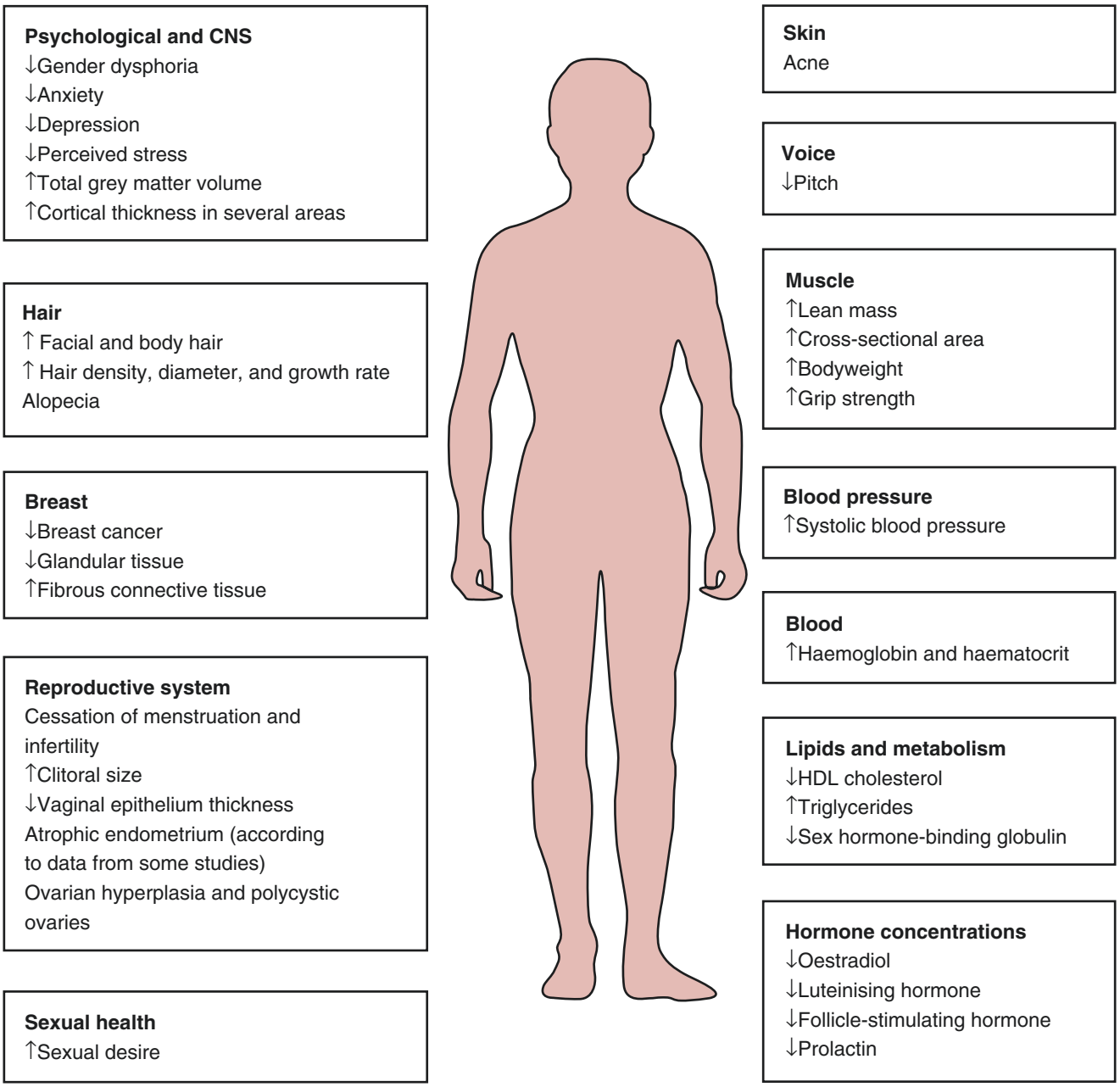

Fig. 15.2 Expected changes in response to transmasculine hormone therapy. (From Irwig MS. Testosterone therapy for transgender men. Lancet Diabetes Endocrinol. 2017;5(4):301–11. Reprinted with permission from Elsevier)

documented gender dysphoria, (2) legal age of majority in a given country, (3) having continuously and responsibly used gender-affirming hormones for 12 months, and (4) successful continuous full-time living in the new gender role for 12 months" in addition to good control of any existing medical or mental health conditions and proficiency in the practical aspects of surgery [5].

These surgeries are typically under the regulation of the state or country in which they are performed, and most surgeons require at least one letter of recommendations from a mental health provider. Examples of gender-affirming surgeries for transgender women include penectomy, gonadectomy, and creation of a neovagina. For transgender men, hysterectomy, oophorectomy, vaginectomy, and creation of a neopenis and scrotum are all considerations.

For all transgender patients considering gender-affirming surgery, fertility preservation should be offered and discussed prior to referral for surgical procedures. Fertility preservation should be offered for all patients initiating hormone therapy as well as those patients already on medical therapy. The duration and dosages of hormone therapy that will affect fertility are not known though it is reasonable to

expect that the longer a patient has been on hormone therapy, the more challenging the retrieval of gametes may be.

Conclusions

The fields of transgender medicine and surgery have grown immensely over the past decade. Terminology is evolving. Medical professionals are becoming increasingly aware of the need for competent care of transgender persons. Standards of care are available from several professional organizations, including the WPATH and Endocrine Society guidelines referenced here. There is a great need for ongoing research regarding long-term effects of hormone therapy in both transgender youth and adults.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Coleman E, et al. Standards of care for the health of transsexual, transgender and gender-nonconforming people, version 7. Inter J Transgenderism. 2012;13(4).
3. Fisher AD, Ristori J, Fanni E, Castellini G, Forti G, Maggi M. Gender identity, gender assignment and reassignment in individuals with disorders of sex development: a major of dilemma. J Endocrinol Investig. 2016;39(11):1207–24.
4. Beek TF, Cohen-Kettenis PT, Bouman WP, de Vries AL, Steensma TD, Witcomb GL, Arcelus J, Richards C, De Cuypere G, Kreukels BP. Gender incongruence of childhood: clinical utility and stakeholder agreement with the World Health Organization's proposed ICD-11 criteria. PLoS One. 2017;12(1):e0168522. https://doi.org/10.1371/journal.pone.0168522. eCollection 2017.
5. Hembree WC, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(11):3869–903.
6. Tangpricha V, Hannema SE, Irwig MS, Meyer WJ 3rd, Safer JD, Hembree WC. 2017 American association of clinical endocrinologists/endocrine society update on transgender medicine: CASE discussions. Endocr Pract. 2017;23(12):1430–6.
7. Steensma TD, Kreukels BP, de Vries AL, Cohen-Kettenis PT. Gender identity development in adolescence. Horm Behav. 2013;64(2):288–97.
8. Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. J Am Acad Child Adolesc Psychiatry. 2008;47(12):1413–23.
9. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013;52(6):582–90.
10. 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(4):843–7.
11. 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(4):696–704.
12. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. J Clin Endocrinol Metab. 2014;99(12):4379–89.
13. Mamoojee Y, Seal LJ, Quinton R. Transgender hormone therapy: understanding international variation in practice. Lancet Diabetes Endocrinol. 2017;5(4):243–6.
14. 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(12):4422–8.
15. 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(4):1267–72.
16. Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol. 2017;5(4):291–300.
17. Manson JE, Hsia J, Johnson KC, et al, for the Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003;349:523–534.
18. 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;126:373–8.
19. Irwig MS. Safety concerns regarding 5α reductase inhibitors for the treatment of androgenetic alopecia. Curr Opin Endocrinol Diabetes Obes. 2015;22(3):248–53.
20. Stevenson MO, Wixon N, Safer JD. Scalp hair regrowth in hormone-treated transgender woman. Transgend Health. 2016;1(1):202–4.
21. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91(6):1995–2010.
22. Ahmad S, Leinung M. The response of the menstrual cycle to initiation of hormonal therapy in transgender men. Transgender Health. 2017;2(1):176–9. https://doi.org/10.1089/trgh.2017.0023.
23. Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. J Sex Med. 2014;11:3002–11.
24. Deutsch MB, Bhakri V, Kubicek K, et al. Effects of cross-sex hormone treatment on transgender women and men. Obstet Gynecol. 2015;125:605–10.
25. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2006;91(6):1995–2010.