The Transgender: Endocrinological Assessment

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21.1 Introduction

In the past, gender identity has always been conceived through a binary perspective, including only two possible choices: male or female. This conceptualization—named gender binarism—has been extended also to the transgender experience. Transgender represents an umbrella term used to describe those people who transiently or permanently identify with a gender different from the assigned one (AMAB for those assigned male at birth and AFAB for those assigned female at birth) [1, 2]. Contrastingly, the term cisgender refers to individuals whose gender identity matches with the assigned gender at birth. Since gender identity can be described as a spectrum with many possibilities, a complete identification with the opposite gender should not be considered as the only available option for transgender people. In line with that, recent studies highlighted a relevant prevalence of non-binary gender identity among transgender individuals [3, 4]. Thus, professionals dealing with transgender health should explore gender identity and desired body changes of each person, in order to guarantee an individualized approach during gender-affirming path [5]. This applies also to gender-affirming hormonal treatment, which should be tailored to the individual needs.

21.2 Initial Evaluation in Trans AFAB and AMAB People

Prior to start hormonal treatment, the endocrinologist should collect a detailed family and personal medical history, in order to assess pre-existing health risks and evaluate the presence of criteria for prescribing hormonal treatment (reported in Table 21.1) [6]. In particular, hormonal treatment in trans AMAB people is contraindicated in case of history of oestrogen-sensitive cancers, cholelithiasis, macroprolactinoma, cardiovascular/cerebrovascular disease, severe hypertriglyceridemia, if not recovered [6]. History of venous thromboembolism (VTE) should undergo evaluation and treatment before the start of hormonal treatment. Current guidelines do not routinely recommend screening for hereditary thrombophilia in all trans AMAB people [6]. In trans AFAB people, absolute contraindications for testosterone (T) treatment include pregnancy, whereas relative contraindications include erythrocytosis, sleep apnoea, and congestive heart failure [6, 7].

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Table 21.1 Eligibility criteria for gender-affirming hormonal treatment in adult transgender people

Criteria for gender-affirming hormonal treatment
1. Persistent gender dysphoria/gender incongruence
2. Capacity to make a fully informed decision and to give consent for treatment
3. The age of majority in a given country
4. Mental health concerns, if present, must be reasonably well-controlled

Considering the partial lack of data regarding long-term cardiovascular safety of hormonal treatment, all the modifiable risk factors (i.e. hypertension, dyslipidemia, obesity, tobacco use, sedentary lifestyle) should be managed before the start of hormonal treatment.

Furthermore, transgender people should be adequately informed by clinicians regarding the expected body changes during hormonal treatment and their timing, in order to avoid potential anxiety due to high expectations.

Since fertility may be affected, clinicians must inform all transgender people about the potential impact of medical treatment and discuss at that time the available fertility preservation options.

21.3 Full Masculinization in Trans AFAB People

21.3.1 Hormonal Treatment Strategies

Virilizing hormonal treatment in trans AFAB people is based on T administration. To date, clinicians can opt for several available T formulations, including parental injections (T esters or undecanoate), transdermal or oral T (as detailed in Table 21.2). At the present moment, relevant differences regarding short-term safety and satisfaction have not been observed among different preparations. However, injectable short-term T esters are associated with significant fluctuations of T levels, which may be associated with mood swings and higher risk of haematocrit increase [8, 9]. On the contrast, transdermal and long-acting intramuscular T allow to maintain more stable T levels simulating male production rate and rhythm. Oral T is usually not recommended because of the gastrointestinal absorption variability leading to multiple daily administrations need.

Table 21.2 Hormonal treatment regimens in transgender people requesting full virilization or full de-virilization and feminization

Requested effect	Hormonal compounds	Administration route and recommended dosage
Full virilization	Mixed T esters preparations	Intramuscularly, 250 mg every 3 weeks
	T enanthate	Intramuscularly, 250 mg every 2–4 weeks
	T undecanoate[a]	Intramuscularly, 1000 mg every 12 weeks
	T gel 1–2%	Transdermal, 50 mg/day (available in dispenser pump or as single-dose sachets)
Full de-virilization	Cyproterone acetate	Oral, 10–50 mg/day
	Spironolactone	Oral, 100–200 mg/day
	GnRH agonist (leuprolide, triptorelin)	Intramuscularly or subcutaneously, 3.75 mg monthly or 11.25 mg every 3 months
Full feminization	Estradiol valerate	Oral, 2–6 mg/day
	Estradiol	Transdermal, patch 25–100 μg/24 h twice or once weekly
	Estradiol hemihydrate	Transdermal, gel 1.5–3 mg/day

[a]One thousand milligrams initially followed by an injection at 6 weeks then at 12 weeks

If a full virilization is required, T treatment should follow the principles of hormonal replacement treatment in hypogonadal cisgender men, achieving T levels within the adult cisgender men range (depending on the specific assay, but typically from 320 to 1000 ng/dL, or 11.1 to 34.7 nmol/L) [6].

In trans AFAB people undergoing oophorectomy, T treatment should be continued in order to avoid consequences of premature loss of hor-

monal support, such as osteoporosis, cardiovascular events, and cognitive impairment.

21.3.2 Virilizing Effects

Masculinizing effects include increase in facial and body hair, body composition and fat distribution changes, and voice deepening, which usually occur in the first 6 months of treatment [10–12]. Among dermatological effects, also increased skin oiliness, acne and—in genetically predisposed individuals—androgenetic alopecia have been reported [13]. T treatment results in clitoromegaly and amenorrhea. All T formulations lead to amenorrhea in the first 12–18 months of treatment, but transdermal T resulted associated with higher rates of persistent vaginal bleeding in the first months of treatment compared to T undecanoate [14]. If vaginal bleeding persists, clinicians may consider the addition of progestins or gonadotropin-releasing hormone analogues (GnRHa) [6]. Regarding sexual well-being, a transient increase in sexual desire has been reported in literature, probably due to the initial increase of T levels, as well as an improvement of sexual well-being in the mid-term [15, 16].

21.3.3 Safety Concerns

If full virilization is requested, clinicians should maintain T levels in the physiologic normal male range avoiding adverse effects resulting from T excess [6]. Regarding safety profile, T treatment leads to a more atherogenic lipid profile with increased triglycerides and low-density lipoprotein cholesterol (LDL-c) levels and decreased high-density lipoprotein cholesterol levels (HDL-c) [17–20]. This may lead to increased cardiovascular risk [20], even if a recent systematic review of the literature stated that definitive conclusions on rates of cardiovascular/cerebrovascular events cannot be drawn due to very low-quality evidence [21]. Furthermore, data on cardiovascular outcomes in older trans AFAB people are mostly lacking. For this reason, long-term data on cardiovascular safety of T treatment are needed. A recent study showed an increase in haemoglobin and haematocrit levels during T treatment within the range for cisgender AMAB people, reaching a plateau after the first year [9]. However, clinically significant erythrocytosis appears really uncommon [9].

With respect to bone health, T treatment may exert a protective effect on bone mediated by the peripheral conversion to oestradiol. Baseline bone mineral (BMD) levels in trans AFAB people are usually in the expected range for their birth-assigned gender [22]. No relevant changes of BMD seem to occur during T treatment unless adequate dosages and compliance are guaranteed [23]. Limited data on osteoporotic fracture risk of are available in trans AFAB people.

Long-term T treatment may be associated with some concerns around cancer incidence and mortality, although not supported by literature. The available data showed very few cancer events in trans AFAB people with cancer mortality rates similar to those of the general population [24–28]. Nevertheless, breast and cervical cancer screening protocols are advised in trans AFAB people not undergoing gender-affirming surgeries [6].

21.3.4 Monitoring During Hormonal Treatment

Periodical monitoring is advised in trans AFAB people after the start of T treatment, with a frequency of 3–4 monthly in the first year and 1 or 2 per year thereafter [6]. The monitoring aims both to identify possible side effects of T treatment and to monitor the development of desired body changes. Haematocrit and haemoglobin represent the most important biochemical parameters, due to the risk of erythrocytosis associated with T treatment. Furthermore, lipid profile, weight, waist, and blood pressure should be checked at regular intervals. Clinical and instrumental-suggested monitoring is summarized in Table 21.3. Dual-energy X-ray absorptiometry (DXA) should be performed at baseline only in case of anamnestic relevant risk of osteoporosis

Table 21.3 Periodical monitoring in trans AMAB and AFAB people before and after the start of hormonal treatment

	Baseline	First year of hormonal treatment (every 3 months)	After the first year of hormonal treatment (every 6–12 months)
Trans AMAB people	Clinical evaluation LH, FSH, total testosterone, estradiol, prolactin levels, blood counts, renal and liver function, lipid, and glucose profile BMD in older than 60 years or in those who are not compliant with hormone therapy	Clinical evaluation Testosterone, estradiol levels, LH (every 3 months); prolactin levels (once a year). Liver function, lipid, and glucose profile (every 3 months) Serum electrolytes (every 3 months in case of spironolactone use)	Clinical evaluation Testosterone, estradiol (every 6–12 months) levels; prolactin levels (every 2 years), blood counts, liver function, lipid, and glucose profile (every 6–12 months) Serum electrolytes (every 12 months, in case of spironolactone use) BMD evaluation after 60 years or in case of discontinuation of therapy after gonadectomy
Trans AFAB people	Clinical evaluation LH, FSH, total testosterone, estradiol, prolactin levels, blood counts, renal and liver function, lipid, and glucose profile BMD in older than 60 years or in those who are not compliant with hormone therapy	Clinical evaluation Testosterone, estradiol levels, LH (every 3 months); haematocrit, lipid, and glucose profile (every 3 months)	Clinical evaluation Testosterone, estradiol (every 6–12 months) levels; hematocrit, lipid, and glucose profile (every 6–12 months) BMD evaluation after 60 years or in case of discontinuation of therapy after gonadectomy

(smoking, excessive alcohol use, family history of fractures/osteoporosis, glucocorticoids use, and anorexia nervosa) and after gonadectomy in case of low compliance to hormonal treatment [6]. As stated before, periodical oncological screening of all present tissues is recommended, even if the adequate timing has not been yet elucidated.

21.4 Full Feminization and De-Masculinization in Trans AMAB People

21.4.1 Hormonal Treatment Strategies

In trans AMAB people, oestrogens are necessary to induce female secondary sexual characteristics. Among them, in the past ethinyl oestradiol was widely used especially through self-prescription. Given safety concerns due to the increased thromboembolic and cardiovascular risk, current guidelines recommend the use of oestradiol [6, 29]. Among oestrogen options, patients and clinicians can opt for oral micronized esterified (valerate) oestradiol or transdermal 17β-oestradiol (treatment regimens reported in Table 21.2). Transdermal formulations (patches or gel) do not undergo first hepatic metabolism, which may reduce the risk of prothrombotic effect. For this reason, transdermal compounds should be preferred in cases of higher thromboembolic risk (i.e. age >40 years, smoking, obesity, liver disease, diabetes mellitus with complications). If full feminization is desired, oestrogen is prescribed at dosages two or three times higher than the recommended doses for hormonal replacement treatment in postmenopausal cisgender women. In this case, the goal is to reach and maintain serum oestradiol and T in the normal range for premenopausal cisgender women (100–200 pg/mL and 50 ng/dL, respectively) [6].

Trans AMAB people often require the addition of anti-androgen therapies to achieve desired body changes (Table 21.2). In many European countries, cyproterone acetate (CPA) represents the most commonly prescribed androgen lowering compound. CPA is an anti-androgenic progestational compound with both peripheral and central action. Recently, its use

has been limited by evidences of hepatotoxicity, increased incidence of depression and hyperprolactinemia, and association with multifocal meningiomas, which is a hormone-sensitive tumour expressing progesterone receptors [30–34]. According to a recent multicentric study, a daily dose of 10 mg is effective (equally to 50 mg/daily) in lowering testosterone concentrations in trans women, while showing fewer side effects [35].

Among androgen-lowering therapies, GnRHa may be considered as a valuable alternative due to their efficacy and safety profile. GnRHa reduce T levels through the downregulation of pituitary GnRH receptor. GnRHa are considered extremely safe and in one recent comparative study they showed a better metabolic profile with respect to CPA [36]. The main limitation to their use is represented by the high cost.

Spironolactone (100–300 mg/daily) is an antagonist of mineralocorticoid receptor with anti-androgen properties, frequently used in the United States where CPA is not available. Spironolactone 200 mg daily proved effective in reducing T levels in trans AMAB people into the cisgender female range [37]. However, spironolactone use is limited by the risk of hyperkalaemia, hypotension, and gastrointestinal bleeding [38].

Peripheral androgen receptor blockers such as flutamide (50–75 mg/daily) or bicalutamide (25–50 mg/daily) are not recommended in trans AMAB people, due to the lack of data regarding their efficacy and safety and the risk of hepatotoxicity described in cisgender women [39].

21.4.2 Feminizing and De-Virilizing Effects

Body changes occurring in the first months include dermatological effects such as a significant reduction of terminal facial and body hair—although often not satisfying—and a decreased skin oiliness [12]. During the first year of treatment, body composition changes occur, with increased body fat mainly in the gynoid regions and decreased lean body mass, in line with a more feminine body composition [40]. Breast development becomes relevant after 6 months and reaches a maximum at 2 years after the start of feminizing treatment [41]. Increase in breast size is strictly associated with decrease in body uneasiness [12]; however, less than 20% of trans AMAB people reach Tanner breast stage 4–5 after 24 months of hormonal treatment [12], with most people seeking mammoplasty. To date, data supporting a beneficial effect of progestins on breast development are scarce and do not allow to recommend their use, also considering the potential increase of cardiovascular risk [42, 43]. Testicular volume decreased by approximately 60% after 24 months, along with a reduction of spontaneous erections [12]. Voice frequency does not modify in trans AMAB people under hormonal treatment [44].

Regarding sexuality, hormonal treatment in trans AMAB people is associated with a transient decrease in sexual desire in the first 3–6 months of hormonal treatment [16], whereas sexual well-being increases in the mid-term, probably because of the improvement of body image perception [15].

21.4.3 Safety Concerns

In relation to safety profile, hormonal treatment in trans AMAB people resulted associated with favourable changes in lipid profile, with increased HDL-c and decreased LDL-c concentrations [19, 20]. A recent meta-analysis found only changes in triglycerides, whose levels were higher in trans AMAB people after 24 months of hormonal treatment [21]. Concerns raised about long-term effects of feminizing hormonal treatment on cardiovascular outcomes. A study conducted in Belgium over 200 trans AMAB people reported higher rates of myocardial infarction, venous thrombosis, and cerebrovascular disease compared to cisgender men and women [25]. Other studies confirmed higher rates of ischemic stroke in trans AMAB people compared to cisgender one [45], whereas myocardial infarction rates resulted higher in trans AMAB people with respect to matched cisgender AFAB indi-

viduals and similar to those found in cisgender AMAB people [46]. Furthermore, oestrogens have a known pro-thrombotic action. The incidence rate of VTE in trans AMAB people under feminizing hormonal treatment appeared to be 2.3 per 1000 person-year [47]. However, the previous use of ethinyl oestradiol may lead to overestimation of the rate of VTE. Besides, hormonal treatment under medical supervision can be considered safer than self-prescribed therapy.

Trans AMAB people have a lower baseline BMD with respect to age-matched cisgender men, probably because of lower outdoor physical activity leading to reduced levels of vitamin D [22]. Estrogen treatment in trans AMAB people seems to be associated with improvement of BMD, especially at the lumbar spine [48–50]. However, fracture rate during long-term hormonal treatment in trans AMAB people is unknown.

Regarding oncological risk, oestrogens and progestogens can play a role in the pathogenesis of some brain tumours. Since oestrogens can stimulate the growth of pituitary lactotroph cells, an increased risk of prolactinoma has been demonstrated in trans AMAB people [51]. For this reason, guidelines recommend periodical monitoring of prolactin levels, although a moderate increase during feminizing hormonal treatment is expected [6]. Furthermore, higher risk of meningioma has been described in trans AMAB people compared to cisgender AFAB people [51], thus CPA discontinuation after gender-affirming surgery and lower dosages in case of long-term treatment are suggested [29, 35]. Rates of incidence of hormone-sensitive cancers, such as breast and prostate cancers, seemed to be low among trans AMAB people. A large study reported no increase in breast cancer incidence in trans AMAB people compared to cisgender women [52]. Another large study conducted in USA found no increased risk of any cancer in trans AMAB people compared to cisgender women, whereas an increased risk of breast cancer was reported with respect to cisgender men [53].

21.4.4 Monitoring During Hormonal Treatment

As stated before, periodical monitoring is recommended also in trans AMAB people after the start of feminizing/de-virilizing hormonal treatment, with a frequency of 3–4 monthly in the first year and 1 or 2 per year thereafter [6]. The aims are to monitor for appropriate signs of feminization and for development of adverse reactions. Serum T and oestradiol should be checked every 3 months, adjusting dosages if appropriate range for full feminization is not reached. In case of spironolactone administration, serum electrolytes should be monitored every 3 months in the first years and then annually [6, 29]. Table 21.3 shows the suggested clinical and biochemical monitoring. As for trans AFAB people, routine cancer screening of all present tissue should be performed. DXA should be performed at baseline only in individuals at high risk of osteoporosis, whereas in individuals at low risk screening for osteoporosis should be conducted after 60 years [6].

21.5 Partial De−/Masculinization and/or De-/Feminization

21.5.1 Partial Virilization and/or De-Feminization in Trans AFAB People

Some trans AFAB people may desire only partial masculinization. In this case, T dosages can be adjusted or other hormonal compounds could be added in order to shape androgens' effect on the body [5, 29]. Particularly, T could be prescribed at lower dosages, without achieving normal male T levels, although metabolic and bone safety of these treatment strategies are not elucidated. If the desired effect is represented by body composition changes and voice deepening without male body hair distribution, 5α-reductase inhibitors can be added to T [5]. In fact, by reducing 5α-dihydro-testosterone (DHT) levels through 5α-reductase type 2 inhibition, finasteride use

(1 mg/daily) resulted effective in the treatment of androgenetic alopecia and hirsutism [54, 55]. Other options besides 5α-reductase inhibitors can be proposed, such as definitive hair removal or eflornithine [54].

Conversely, in trans AFAB people requesting partial body shape changes with greater beard development, topical minoxidil application can be added to variable dosages of T [56].

Furthermore, low T dosages cannot be able to stop menses. For this purpose, when partial virilization and amenorrhea are both required, progestins, GnRHa, progesterone-releasing intrauterine devices, or endometrial ablation can be used to obtain amenorrhea [5, 57].

21.5.2 Partial Feminization and/or De-Virilization in Trans AMAB People

Some trans AMAB people may desire feminization and no/partial de-masculinization. For this purpose, the endocrinologist could prescribe only oestrogens or oestrogens plus lower dosages of CPA (such as 10 mg/daily or 10 mg on alternative days) [5].

On the contrast when de-virilization with little or no feminization is requested, only androgen lowering compounds can be proposed. Despite the absence of long-term safety data, the main criticality of this approach is represented by BMD loss due to androgen deprivation [58]. To prevent this, administration of low oestrogen dosages or selective oestrogen receptor modulators should be discussed with clients [5]. Other options to reduce male or induce female body characteristics can be discussed, such as permanent methods of hair reduction, breast augmentation, and lipofilling.

21.6 Conclusions

Transgender health—and therefore the endocrinological management—has become a topic of growing interest in the medical and scientific community in recent years. Research in this field moved away from case reports and small series, with an increased number of large longitudinal studies and systematic reviews/metanalysis. Increasing evidences regarding efficacy and safety of standardized hormonal treatment protocols are available in literature, even if there are still some open questions and long-term data remain sparse. The clinical approach also changed in recent years. In fact, endocrinologists dealing with transgender health care should explore gender identity and desired body changes in each person, actively involving the person in decisions regarding hormonal treatment and providing a real personalized clinical approach. The lack of information about non-standardized therapies for non-binary people should be kept in mind, thus benefits and risks should be extensively discussed with patients.

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