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SPECIAL ARTICLE

Clinical practice guidelines for transsexual, transgender and gender diverse minors☆

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Abstract Some people, including minors, have a gender identity that does not correspond to the sex assigned at birth. They are known as trans* people, which is an umbrella term that encompasses transgender, transsexual, and other identities not conforming to the assigned

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Gender incongruence;
Gender dysphoria;
Gender identity;
Non-binary;
Pubertal blockade;
Puberty suppression;
Hormone cross therapy;
Gender-affirming hormonal treatment;
Fertility

gender. Healthcare units for trans* minors require multidisciplinary working, undertaken by personnel expert in gender identity, enabling, when requested, interventions for the minor and their social–familial environment, in an individualized and flexible way during the gender affirmation path. This service model also includes hormonal treatments tailored as much as possible to the individual's needs, beyond the dichotomic goals of a traditional binary model. This guide addresses the general aspects of professional care of trans* minors and presents the current evidence-based protocol of hormonal treatments for trans* and non-binary adolescents. In addition, it details key aspects related to expected body changes and their possible side effects, as well as prior counselling about fertility preservation.
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PALABRAS CLAVE
Transgénero;
Incongruencia de género;
Disforia de género;
Identidad de género;
No binario;
Bloqueo puberal;
Supresión de la pubertad;
Terapia hormonal cruzada;
Terapia hormonal de afirmación de género;
Fertilidad

Guía clínica de atención a menores transexuales, transgéneros y de género diverso

Resumen Algunas personas, también las menores de edad, tienen una identidad de género que no se corresponde con el sexo asignado al nacer. Se les conoce como personas trans*, que es el término paraguas que engloba transgénero, transexual y otras identidades no conformes con el género asignado. Las unidades de asistencia sanitaria a menores trans* requieren un trabajo multidisciplinario, realizado por personal experto en identidad de género, que permita, cuando así lo soliciten, intervenciones para el menor y su entorno sociofamiliar, de forma individualizada y flexible durante el camino de afirmación de género. Este modelo de servicio también incluye tratamientos hormonales adaptados en la medida de lo posible a las necesidades del individuo, más allá de los objetivos dicotómicos de un modelo binario tradicional. Esta guía aborda los aspectos generales de la atención profesional de menores trans* y presenta el protocolo actual basado en evidencia de tratamientos hormonales para adolescentes trans* y no binarios. Además, detalla aspectos clave relacionados con los cambios corporales esperados y sus posibles efectos secundarios, así como el asesoramiento previo sobre preservación de la fertilidad.
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Introduction

The expressions *trans youth* or *trans people* are used as an umbrella term that reflects the experience of individuals that may or may not define themselves as trans, transexual, transgender, nonbinary, gender-fluid etc. In some instances, the term *trans* is followed by an asterisk to refer to the diversity in the conception of identity, the body and/or experiences outside the culturally defined norms.[1]

Gender variance may manifest in childhood with non-normative gender expression, which does not mean that the child has a gender identity (identifying as male, female or nonbinary) different from the sex assigned at birth.[2] The development of gender identity is a multifactorial process that involves self-identification, which is different for each individual, will fit or deviate from the natal gender to a varying degree, and which individuals may be aware of from an early age.

Although gender identity can be fluid in some cases, prepubertal children that assert a trans identity know their own gender as clearly and coherently as peers of the same age that identify as cisgender (gender matching the sex assigned at birth) and benefit from the same level of social acceptance.[2,3] When it comes to development, rather than focusing on who the child will become, valuing who they are, even at a young age, fosters secure attachment and resilience.[2] The gender identity, gender expression and needs of the minor must not be invalidated, but it is also important not to anticipate them or project the path the individual should take. There needs to be a change in social perception to allow the free expression of the full diversity spectrum and free personality development, promoting safe spaces that allow exploring identity and diverse expressions. In the prepubertal age, family counselling and/or psychological support, if needed, are the only interventions that should be taken.

Guidelines on medical treatment for trans children and adolescents call for the management of these minors by multidisciplinary teams of specialists experienced in gender health that may include paediatricians, psychologists, endocrinologists and social workers, among others. Ideally, care would be delivered through a shared decision-making model where families would be informed by a health professional with specialised training in gender identity and the available treatments, their effects, repercussions and limitations to generate realistic expectations, develop an individual plan for the gender confirmation process and, if needed, prescribe endocrine therapy, initially with the aim

of suppressing endogenous puberty (puberty blocking) and later, once the perceived identity is clearly asserted, to induce the desired secondary sex characteristics (gender-affirming or cross-sex hormone therapy).[4]

Although the experience with the management of hormone therapies and surgical interventions keeps growing, the scientific evidence on the subject is not rigorous and is relatively scarce due to the lack of studies with appropriate methodology assessing long-term outcomes, especially of treatments initiated in the peripubertal period; nevertheless, there is evidence that supports the benefits of both puberty blocking and gender-affirming treatment on the health of trans individuals.[5–8] Thus, if these treatments are unduly delayed or there is no social affirmation supporting these minors, there may be an overall increase in psychiatric disorders and other unfavourable outcomes, including stigmatization and bullying, dysthymia, depression, anxiety, phobias, low self-esteem, self-medication, poor academic performance, risk behaviours (increase in sexually transmitted diseases, drug abuse), self-harm, suicidal ideation and eating disorders.[9–13]

This guideline focuses on the most current hormone therapy protocol for trans minors and highlights key points regarding expected body changes and potential side effects in addition to general aspects to take into account in order to provide adequate care.

Health care guideline

Desired physical goals may range from changes that do not require any treatment to all the classic physical changes, hormone therapy and surgeries. Although it is rare,[5] some individuals may choose to detransition back to the sex assigned at birth or end up identifying as non-binary, in most cases without regret for the initial transition, and there are also trans individuals that stop medication because they feel they no longer need it at a given point in their lifespan.[14] For the purpose of treatment planning, the key is to focus on expressed needs after providing adequate information about the possible courses of action. In other cases, trans individuals detransition due to the loss of employment opportunities and lack of social support, choosing to revert to the sex assigned at birth due to psychosocial factors.

General guidelines

Table 1 presents the general recommendations for the care of trans minors.[15] Other aspects to consider include:

- Contemplate pubertal suppression with gonadotropin-releasing hormone (GnRH) analogues from Tanner stage 2 and subsequent gender-affirming therapy with testosterone or oestrogen. Health professionals should not assume that trans individuals feel aversion toward their genitalia, so it is recommended that information about potential future surgeries (Appendix B, Table S1) be given only if it is necessary. Before age 16 years, proxy informed consent should be signed by the legal guardians of the minor in adherence to the law.
- Inform of the possibility, when feasible, of saving genetic material for fertility preservation (ovarian tissue, gametes), ideally before treatment initiation.
- Take care of the general health of the minor, including healthy lifestyle habits, prevention of substance use, contraception and appropriate vaccination, especially administration of the vaccine against papillomavirus, which is recommended in every trans person under 26 years.
- In the case of suspected abuse due to rejection of the gender identity and/or sexual orientation of the minor by one or both parents or any other social factors with an impact on health, the physician should consult make a social work consultation.[16]

History taking, physical examination and initial tests

An interview (Table 2)[5–7,15,17,18] should be conducted to establish the needs of the minor and the family following the recommendations we have just presented.

Anthropometric measurements should be recorded (weight, height, growth velocity, body mass index and waist circumference if applicable), in addition to blood pressure and the Tanner pubertal stage. The physical examination should explore possible signs suggestive of disorders of sexual development (DSDs).

The physical examination of the trans individual can be a delicate juncture, as some may feel that they need to have a physical appearance fitting a binary model category to be affirmed in their perceived identity, so it is important to develop trust and never force this examination on the patient. In some cases, the examination reveals lesions in the chest and genital areas due to the use of bandages and/or tape to conceal certain primary and/or secondary sex characteristics.[19]

Table 3[4,15,20] lists the tests that should be ordered.

Pubertal suppression therapy

If at onset of puberty or during puberty the child develops or experiences exacerbation of dysphoria due to the development of secondary sex characteristics, pubertal suppression therapy may be indicated, and it is always important to consider that it should not be delayed so avoid irreversible changes that the child does not want. Thus, puberty blocking is not always indicated, but the individual and their family must be adequately informed of its potential benefits and risks so that they can ask for it if needed.

At present, the eligibility criteria for pubertal suppression established by the World Professional Association for Transgender Health (WPATH)[17] are not being applied, and puberty blocking is performed in individuals under the age threshold used to define a mature minor, typically set at 12 years. Table 4 presents the drugs used for puberty blocking.[4,15,20–23] The standard of care is administration of gonadotropin-releasing hormone (GnRH) analogues monthly or every 3 months. In the initial months, puberal suppression is better guaranteed with monthly administration of GnRH analogues, although there have been no differences in effec-

Table 1 General recommendations for the provision of medical care to trans minors.

- Interview in an environment that offers privacy and confidentiality.
- Address the minor using their chosen name and respecting the expressed gender identity. In the case of a nonbinary identity, ask the minor their preferred name and pronouns. Asking or sharing without consent the name with which the trans minor was registered in the Registro Civil (official register of births, marriages and deaths) is not recommended.
- Address the needs of the trans minor, encourage family to respect and support the minor to facilitate their acceptance and the free development of their personality, thus preventing feelings of rejection, anxiety or isolation.[15] At present, social transition, defined as the moment that the trans individual starts to openly express their gender identity in society, is carried out by the trans individual at their own pace.
- Family members undergo a process or secondary transition of their own. This process is akin to the stages of grief, shock, denial, anger, bargaining and acceptance. This process of transition in family members or the close social circle is different and personal for each individual, with differences in duration and even disagreements, and counselling and/or support may be requested to aid the transition of the minor and of the near social circle, which in some cases is coordinated by the school.
- Psychological support should be offered as part of the transition or developmental process, except to trans minors that do not need it, especially those who transitioned in childhood and have a protective environment. It is usually very helpful to the minor and the family and is actually requested in most cases. It must be provided by experienced professionals that do not negate the identity of the minor and with a respectful and depathologising approach. It should not entail postponing a potential treatment and its aim should not be diagnostic, that is, in no case can the minor be subjected to an evaluation or any other intervention involving the determination of the minor's identity by a third party, and support should be individualised. In the presence of concomitant mental health disorders, mainly those derived from problems with self-acceptance (internalised transphobia) or rejection from the environment (family, school, society), mental health professionals play a key role.
- Inform the minor of the possibility of changing the name featured in the public health card following the procedures established for the purpose by the regional government.
- Discuss the resources available in the community that could be useful to the trans minor and recommend socialization of the minor with peers.
- Produce the pertinent medical reports requested by the minor or legal guardians to carry out the administrative procedures required by current law.
- Take the necessary steps to ensure that medical forms and administrative documentation fits the circumstances of LGBTIQ individuals. For example, including a nonbinary gender option for the sex of the patient in questionnaires.

LGBTIQ, lesbian, gay, bisexual, trans, intersexual, queer.

tiveness in studies that compared administration of monthly doses versus 2 trimestral doses.[24]

The effects of pubertal suppression therapy and its ongoing management after initiation of treatment are presented in Appendix B of the online supplemental material.[4–6,15,20,24–28]

Gender-affirming hormone therapy

The factors to consider for initiation of hormone therapy are the wishes, physical and emotional wellbeing, height, bone age and sex assigned at birth of the minor, and the age at initiation of puberty blocking. Gender-affirming hormone therapy is partially irreversible, a fact that must be stated in the specific informed consent that has to be signed before its initiation.

As regards the age at initiation of gender-affirming hormone therapy, initiation before 16 years is becoming increasingly frequent in current clinical practice to help physical development to correspond to that of peers of the same age and promote the development of desired secondary sex characteristics. At present, an individualised approach is recommended, as there is no empirical evidence to support recommendations regarding the optimal age for initiation of oestrogen or testosterone therapy.

Pubertal suppression therapy poses risks to bone health if it lasts for many years without initiation of gender-affirming hormone therapy. Furthermore, mental health may deteriorate if the emergence of the secondary sex characteristics of the self-identified gender is delayed in adolescents who are inherently vulnerable due to their sex status, as they may be subject to abuse and stigmatization because of their physical appearance. The unavailability of hormone therapy for those who wish a physical change is a powerful predictor of mental health disorders.[5]

Treatment of trans female adolescents

Use of oral estradiol valerate or oral or transdermal 17ß-estradiol is recommended in the doses presented in Table 5.[4,20,21] The following are aspects to consider:

There is broad variability in the feminising effects of oestrogen therapy. A higher dose of oestrogen does not necessarily translate to an increase in breast size.

The transdermal route is associated with a lesser hepatotoxicity and a lower risk of thrombosis compared to the oral route, and it achieves concentrations closer to physiological levels. It is the recommended route in patients with liver disease and/or risk factors for cardiovascular disease, such as diabetes mellitus or smoking, or in patients that prefer this route.[4,15] In patients with known thrombophilia, a history

Table 2 History-taking in the trans minor.

Collect the following clinical information:
- Gender identity and sex assigned at birth, preferred name and pronouns.
- Degree of support from family, the environment and the school. Presence or absence of emotional or social problems.
- Desire for physical changes, knowledge and expectations regarding treatment options, reproductive desires.
- Lifestyle.
- Relevant family and personal history.

Family history

Emphasis on family history of early cardiovascular disease, hormone-dependent cancer and, in trans women, thromboembolism and hypertriglyceridemia.

Personal history

Although evidence has been published suggesting an association between autism and a transgender identity, it is of low quality.[18] Possible signs suggestive of DSDs must be explored, and particular attention devoted to the presence of diseases that, if not adequately controlled, could contraindicate future pharmacological treatment (more frequent in adults) or require special consideration during treatment, the main of which, while infrequent in children and adolescents, are:
- Presence of risk factors for cardiovascular disease.
- Pregnancy, which is an absolute contraindication for testosterone therapy and drugs that suppress the hypothalamic-pituitary-gonadal axis. The relative contraindications for testosterone include sleep apnoea and polycythaemia.[5,15]
- For oestrogen therapy, a known personal history of thrombophilia or of thrombosis. Other diseases such as hyperprolactinemia, hypertriglyceridemia and cholelithiasis must be evaluated before initiation of oestrogen therapy, as these conditions can be exacerbated by oestrogen.[5] Hormone therapy may be contraindicated in patients with active liver disease (transaminase elevation above 3 times the upper limit of normal).

If adequately controlled, the presence of a mental disorder is not a contraindication for treatment.[17] Initiation of hormone therapy improves anxiety and depression, especially if the adolescent seeks the treatment to improve their physical appearance.[5–7]

DSD, disorders of sex development.

Table 3 Initial work-up in trans minors.

- Initial blood tests: complete blood count, comprehensive metabolic panel including renal, liver and electrolyte panels, blood glucose and lipid profile (total cholesterol, LDL, HDL, triglycerides), 25(OH)D, FSH, LH, estradiol, testosterone, TSH and free T4.
- Bone age if appropriate.
- Depending on the evaluation and as deemed necessary:
  - Prolactin in trans girls, measure PTH and SHBG.
  - Bone density scan with DEXA if pubertal suppression therapy is expected to last longer than 1 year or for the same indications that apply to the general population, such as anorexia nervosa.[a]
  - Abdominopelvic ultrasound only required to verify anatomical integrity in trans boys, mainly in anticipation of possible surgeries, or if biliary lithiasis is suspected in trans girls undergoing oestrogen therapy.
  - Karyotype: in the case of suspected DSD or incomplete puberty or in trans boys that did not experience menarche before puberty blocking, as it may mask possible warning signs of DSDs.
  - Baseline adrenal androgen profile: DHEA-S, androstenedione and 17-OH-progesterone.
  - In trans girls, rule out hypercoagulability in the case of a personal history or family history in first-degree relative of thrombosis.[4]

DEXA, dual energy X-ray absorptiometry; DHEA-S, dehydroepiandrosterone sulphate; DSD, disorder of sexual development; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; SHBG, sex hormone-binding globulin; T4, thyroxine; 25(OH)D, 25-hydroxyvitamin D3.

[a] Eating disorders may be related to the pursuit of gender-affirming goals (seeking amenorrhoea and/or decrease in breast size in trans male youth).

of thrombosis or a family history of thromboembolism, use of transdermal oestrogen and/or concomitant anticoagulant therapy may need to be considered, although the available data are insufficient to recommend a specific therapeutic approach.[5]

If bone mineral density deteriorates, bone mineralization is not progressing or the goal is to reduce the final height, the oestrogen dose can be escalated faster, higher doses used, or oestrogen therapy initiated before the planned age.[20]

The dose should be adjusted over time based on the clinical response and plasma levels of oestradiol, although usually, at the beginning of treatment, the dose of oestrogen can only be adjusted based on the clinical response since most hospitals are not equipped with ultrasensitive

Table 4 Drugs used for pubertal suppression in trans youth.

a) GnRH analogues used for first-line treatment in Spain: recommended treatment with triptorelin acetate or leuprolide in the form of the 1-month 3.75 mg depot formulation (if weight < 20 kg: 70-100 μg/kg) through the IM route every 28 days or the 84-day (12-week) 11.25 mg depot formulation. If the patient does not respond (progression of secondary sex characteristics, persistence of menses and/or detectable plasma LH levels), the interval between monthly doses can be shortened to 21-25 days, the monthly dose increased to up to 160 μg/kg/28 days, or the interval between trimestral doses reduced.

b) Alternative drugs:

- 6-month triptorelin formulation (22.5 mg IM every 6 months) or 6-month leuprolide formulation (30 and 45 mg IM every 6 months). There is less evidence on these drugs, and they are seldom used.
- Histrelin, a synthetic LHRH analogue administered through a subcutaneous implant that secretes 50 or 65 μg of histrelin daily, approved for use in the United States from age 2 years. It is not currently distributed in Spain.

c) Alternative drugs for pubertal suppression in late stages:

- Antiandrogenic drugs (only in postpubertal trans women):

- Spironolactone 25-50 mg/d with a progressive increase to 100-300 mg/d orally as a single dose or divided into several doses. Some guidelines[15] recommend a maximum dose of 200 mg/d. The tablets should be taken with food. If the dose exceeds 100 mg/d, it should be divided into 2-4 smaller doses administered throughout the day.
- Cyproterone acetate: the risk of meningioma must be taken into account for, while low, it increases with the cumulative dose (high doses and prolonged duration of treatment), so its use is only recommended when other options are not possible or are ineffective, and only for short periods, with a recommended maximum dose of 25 mg/d for trans individuals. Cyproterone acetate is more effective than GnRH analogues in reducing spontaneous erection, acne and hirsutism.[20]

- Progestogens (norethisterone acetate 5-15 mg/d orally, dienogest 2 mg/d orally, micronized progesterone 100-300 mg/d orally, among others) for quicker achievement of amenorrhoea during induction of puberty with testosterone if the patient has needle phobia. Medroxyprogesterone is a more potent progestogen compared to others, but it has more adverse effects.[22]
- Finasteride (2.5-5 mg/d orally).[20] It is a 5-alpha reductase inhibitor and does not reduce testosterone levels. It can cause adverse events such as depression and sexual dysfunction. It is also used to halt hair loss at a dose of 1 mg/d delivered orally.[21,23]

GnRH, gonadotropin-releasing hormone; IM, intramuscular; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.

systems capable of detecting plasma concentrations of less than 5 pg/mL.

Table 6 presents alternative drugs that can be used in the maintenance phase of treatment.[4,15,17,20]

In transgender girls, the doses of oestrogen need to be at least doubled, with the risks that this entails, to ensure the development of desired secondary sex characteristics and the suppression of endogenous testosterone, unless GnRH analogues, cyproterone acetate or spironolactone are administered concomitantly.[4] For this reason, these drugs must be maintained until performance of gonadectomy, if the patient desires it, once the age of majority is reached.

Some clinicians[29] advocate for administration of oral micronized progesterone based on its beneficial effects in cisgender women (optimal breast maturation in Tanner stages 4-5, among others), but there is a lack of rigorous evidence supporting that these effects extend to trans women.

Recommendations for management and diagnostic testing in the follow-up of trans female adolescents after initiation of hormone therapy are presented in Table S2 in Appendix B of the supplemental material online.[4,15,17,19–21,30–32]

Table 7[4,5] shows the time that can be expected to elapse before the physical changes achieved with gender-affirming hormone therapy start to become apparent in trans female adolescents, and the time that can be expected to elapse before treatment achieves the maximum effect.

Clinicians are encouraged to help trans female adolescents to have realistic expectations about the physical changes that will take place with hormone therapy, especially if it is initiated at an advanced Tanner stage. When it comes to breast development, there is a lack of studies in minors that received pubertal suppression therapy in the early stages, but studies in adult trans women have shown a modest increase in breast volume in most women.[33,34]

Adverse effects had seldom been described during adolescence, and the most frequent are headaches or exacerbation of existing migraines, mood swings and fatigue, the latter in association with cyproterone acetate. There are cases of hyperprolactinaemia, liver dysfunction or thromboembolism, adverse events associated with higher doses and reported in adults.[5,6,20]

The goal is to maintain oestrogen and testosterone levels within the physiological range of cisgender women to avoid adverse effects like thromboembolism and liver dysfunction.[4] The risks associated with hormone therapy are presented in Table 8.[4,15,17,31,32,35,36]

Treatment of trans male adolescents

Table 5 presents the dosage of testosterone esters for induction of male puberty.[4,20]

Testosterone is usually delivered intramuscularly with doses given every 2 or 3 weeks due to a greater body of clinical evidence, but it can also be delivered subcutaneously in weekly doses. One study found more stable levels of testosterone, frequent patient preference for this route of delivery compared to intramuscular or transder-

Table 5 Induction of puberty in trans adolescents. A: trans female; B: trans male.

A) Trans female adolescents (based on the timing of initiation of puberty blocking)	
Oral 17β-oestradiol[a] *in early Tanner stages*	*Dose escalation*
5 μg/kg/d (usually 0.5 mg)	Every 6 months
10 μg/kg/d (usually 1 mg)	
15 μg/kg/d (usually 1.5 mg)	
20 μg/kg/d (usually 2 mg)	
Maintenance dose: 2-4 mg/d	
Transdermal 17β-oestradiol[b] *in early Tanner stages*	*Dose escalation*
12.5 μg/24 h	Every 6 months
25 μg/24 h	
37.5 μg/24 h	
Maintenance dose: 50-200 μg/24 h	
Oral 17β-oestradiol[a] *in Tanner stages 4-5*	*Dose escalation*
1 mg/d for 6 months	Every 6 months
2 mg/d	
Maintenance dose: 2-4 mg/d	
Transdermal 17β-oestradiol[b] *in Tanner stages 4-5*	*Dose escalation*
25 μg/24 h	Every 6 months
50 μg/24 h	
Maintenance dose: 50-200 μg/24 h	
B) Trans male adolescents	
Testosterone dose in the case of prior puberty blocking in early Tanner stages	*Dose escalation*
25 mg/m^2/2 weeks (usually 50 mg IM every 2-3 weeks)	Every 6 months
50 mg/m^2/2 weeks (usually 100 mg IM every 2-3 weeks)	
75 mg/m^2/2 weeks (usually 150 mg IM every 2-3 weeks)	
100 mg/m^2/2 weeks (maintenance dose: usually 150-200 mg; maximum 250 mg IM every 2-3 weeks)	
Testosterone in Tanner stages 4-5	*Dose escalation*
75 mg IM every 2-3 weeks	Every 6 months
125 mg IM every 2-3 weeks	
Maintenance dose: 100-200 mg/2 weeks (usually 150-250 mg IM every 2-3 weeks)	

IM: intramuscular.
[a] There are also oral oestradiol valerate formulations.
[b] Half a 25 μg/24 h patch, replaced twice a week, is equivalent to 12.5 μg/24 h of transdermal oestradiol or 0.5 mg/d of oral oestradiol.

mal delivery, fewer local reactions and a greater efficacy in the suppression of menses with subcutaneous administration of testosterone cypionate.[37] Subcutaneous administration of testosterone undecanoate is less well tolerated, as it causes greater pain.[38]

Table 6 presents treatment alternatives for the maintenance phase.[4,15,17,20]

Recommendations for management and diagnostic testing in the followup of trans male adolescents after initiation of hormone therapy are presented in Table S2 in Appendix B of the supplemental material online.[4,6,9,15,17,20,32,35,39,40]

Uterine bleeding can be a source of anxiety for trans male youth. Clinical experience shows that depressive symptoms and self-harm behaviours can peak with menstrual bleeding.[22] When it comes to the induction of amenorrhoea:

- In adolescents, the standard of care is administration of GnRH analogues for adequate inhibition of the hypothalamic-pituitary-gonadal axis. The interval between doses can be shortened if needed.
- If the patient refuses GnRH analogues and menstruation persists after 3-6 months of androgen therapy at adequate doses, a progestogen can be added in patients without underlying gynaecological abnormalities[15,22]: norethisterone acetate, 5-15 mg/d orally, among other options.
- Combine with oral contraceptives if the patient does not refuse administration of oestrogens. If dysphoria persists in adulthood, endometrial ablation or surgery may be required.[22]

Table 7 shows the time that can be expected to elapse before the physical changes achieved with gender-affirming hormone therapy start to become apparent in trans male adolescents, and the time that can be expected to elapse before treatment achieves the maximum effect.[4,5]

The literature reports an incidence of adverse events in adolescents of 30%, chiefly acne, and much less frequently dyslipidaemia, androgenetic alopecia, mood disorders, fatigue and local reactions at the injection site, with rare development of side effects that are typically found in adults.[6,20]

The goal is to maintain testosterone levels in the physiological range of cisgender men to avoid development of adverse events (Table 8) associated with chronic androgen

Table 6 Alternatives for maintenance gender-affirming therapy. A) trans women; B) trans men.

A) Trans female adolescents

- Oestradiol spray,[a] 1.53 mg/dose: 1-3 puffs on the forearm (1 puff contains 1.58 mg of oestradiol hemihydrate, with a variable absorption).
- Oestradiol gel,[a] 0.6% oestradiol, applied once a day (it comes with an applicator that delivers 2.5 g of gel, equivalent to 1.5 mg of oestradiol hemihydrate, also with a variable absorption).

The use of oral ethinylestradiol is associated with an increased risk of oestrogen-related thromboembolic events, so its use is not recommended in trans individuals.[4]

B) Trans male adolescents

- Testosterone undecanoate (1000 mg/4 mL): 1 g IM every 10-14 weeks. It achieves more stable levels. If needed, adjust the dose interval.[4]
- Transdermal[b]:

- Gels: 2% (20 mg/g), 1.6% (16 mg/g) and 1% (50 mg/5 g). Maintenance dose: 50-100 mg/d (usually 50 mg/d) applied topically in the morning on both thighs or the abdomen. It is transferred to women and infants through direct contact.

Testosterone 2% gel: 1 pump = 0.5 g gel = 10 mg de testosterone.
Testosterone 16.2 mg/g: 1 pump = 1.25 g gel = 20.25 mg testosterone.
Testosterone 1% packets: one 5 g packet = 50 mg testosterone.

- Patches: not distributed in Spain. Maintenance dose: 2.5-7.5 mg/24 h, changed every 48 h. Skin irritation develops frequently as a side effect.

Measurement of plasma levels of testosterone:

- Testosterone undecanoate: measure prior to next dose.
- Transdermal formulations: measurement can be taken at any time, starting from week 2 of treatment and at least 2 hours after topical application.[4,15]

IM, intramuscular.
[a] Since the absorption of these drugs is highly variable and depends on the individual, their use is only recommended if no other dosage forms are available, starting with the lowest dose (single puff) and measuring plasma levels of oestradiol in 1-2 months.
[b] Testosterone administered through the transdermal or intramuscular route achieves similar masculinising effects, although the process may be slower with transdermal formulations.[17]

Table 7 Effects of gender-affirming hormone therapy. A: trans female; B: trans male.

A) Feminising effects in trans women	**Start**	**Peak**
Body fat redistribution	3-6 months	2-3 years
Decreased muscle mass and strength	3-6 months	1-2 years
Softer skin/decreased fat accumulation	3-6 months	Unknown
Decreased libido	1-3 months	3-6 months
Decreased spontaneous erections	1-3 months	3-6 months
Breast development	3-6 months	2-3 years
Decreased testicular volume	3-6 months	2-3 years
Decreased sperm production	Unknown	> 3 years
Decreased terminal hair growth[a]	6-12 months	> 3 years
Decreased scalp hair loss[b]	Variable	-----
Voice changes[c]	No change	-----
B) Masculinising effects in trans men	**Start**	**Peak**
Skin oiliness/acne	1-6 months	1-2 years
Growth of facial/body hair	6-12 months	4-5 years
Scalp hair loss[d]	6-12 months	—
Increased muscle mass/strength	6-12 months	2-5 years
Redistribution of fat	1-6 months	2-5 years
Cessation of menses[e]	1-6 months	—
Clitoral enlargement[f]	1-6 months	1-2 years
Vaginal atrophy	1-6 months	1-2 years
Voice deepening	6-12 months	1-2 years

Adapted from Hembree et al (2017).[4]
[a] Complete removal of male sexual hair will require cosmetic treatment (laser).
[b] Scalp hair loss may occur if administration of oestrogen is discontinued.
[c] The patient can work with a speech therapist and/or undergo surgery followed by speech therapy.
[d] Can be treated with the same approach as alopecia in cisgender men.
[e] If uterine bleeding continues, consider the addition of a progestational agent or endometrial ablation.
[f] The length of the clitoris can increase to a mean of up to 3.83 ± 0.42 cm after 2 years of testosterone therapy.[5]

Table 8 Risks associated with gender-affirming hormone therapy. A: trans women; B: trans men.

A)	**Risks of hormone therapy in trans women**
Cardiovascular[32]	Venous thrombosis
	CNS and cardiovascular disease[a]
	Cardiovascular disease risk factors[b]: hypertriglyceridemia, ↑ BMI, ↓ lean mass, ↓ insulin sensitivity, possible increase in risk of type 2 diabetes and possible high blood pressure
Gastrointestinal	Nausea and vomiting. Cholelithiasis. Hypertransaminasaemia
Other	Hyperprolactinaemia
	Prolactinoma
	Decreased libido
	Headache
	Infertility
Antiandrogens	Cyproterone acetate: fatigue, hyperprolactinaemia, prolactinoma, Meningioma and hypertransaminasaemia[c]
	Spironolactone: ↑ K, fainting spells and gastrointestinal symptoms
B)	**Risks of hormone therapy in trans men**
Cardiovascular[32]	Polycythaemia
	Cardiovascular disease risk factors:
	-Changes in lipid profile: ↑ Triglycerides, ↑ LDL, ↓ HDL
	-Weight gain (increased lean mass)
	-High blood pressure[d]
Gastrointestinal	Hypertransaminasaemia[e]
Genitourinary	Polycystic ovary syndrome[d]
Cutaneous	Facial acne and androgenetic alopecia
Other	Mood swings, aggressive behaviours and psychosis[f]
	Increased libido
	Obstructive sleep apnoea syndrome
	Headache
	Infertility
	Local reaction
	pulmonary oil microembolism[g]

BMI, body mass index; CNS central nervous system; HDL, high-density lipoprotein; K, potassium; LDL, low-density lipoprotein.
[a] In the presence of risk factors.
[b] Increases in HDL and decreases in LDL, both protective factors against cardiovascular disease, have also been described.
[c] Hepatotoxicity described with doses of 100 mg.[31]
[d] Contradictory data.[35,36]
[e] The risk of severe liver disease is minimal with the use of transdermal testosterone.[4]
[f] Infrequent, seemingly associated with doses above the physiological range.[17]
[g] Infrequent, associated with intramuscular administration.

therapy,[4,15,17] chiefly erythrocytosis, liver dysfunction, high blood pressure, excess weight, lipid profile changes, severe acne and psychological disorders.[4]

Partial feminization/masculinization. Nonbinary individuals

Nonbinary individuals are less likely to seek surgery, and while partial feminization or masculinization is most frequently sought by nonbinary individuals, it may be requested by any trans person.

Clinicians must provide individualised and adaptable care, including hormone therapy, tailored to the extent possible to the needs of the individual and beyond the dichotomous goals of the traditional binary gender model. Specifically, nonbinary individuals or trans men may seek partial masculinization and nonbinary individuals or trans women may seek partial feminization without affecting sexual function. In addition, nonbinary individuals assigned female at birth may seek a mastectomy prior to the potential initiation of hormone therapy.[23] Other individuals may not require any endocrinological and/or surgical care, but may request psychological care due to the lack of understanding and the discrimination they endure, as do other trans individuals, in their case compounded by the lack of awareness of nonbinary identities in the general population. Appendix B of the online supplemental material[23] summarises different endocrinological approaches.

Recommendations for potential fertility preservation

Clinicians should counsel their patients about fertility before initiation of treatment with GnRH analogues or gender-affirming hormone therapy. In Spain, fertility preservation is subject to national law 14/2006 on assisted reproduction techniques (BOE-A-2006-9292) with techniques that are covered by the public health system for trans individuals that

remain able to conceive (BOE-A-2021-18287). Trans women can choose to undergo sperm cryopreservation and trans men oocyte cryopreservation. Experimental options in prepubertal trans children include cryopreservation of ovarian or testicular tissue for in vitro maturation.[28,41]

Although the collection of sperm for cryopreservation should ideally take place prior to initiation of gender-affirming hormone therapy, some studies show that it can be attempted later, with reports of successful outcomes in some trans women.[28,41]

Similarly, testosterone therapy has variable effects on ovarian function, female organs and future fertility. There are trans men that become pregnant after discontinuing treatment with testosterone, and in some cases even while in treatment, with the added risk that testosterone is a teratogen.[28]

Closing commentary

The care of trans children and youth requires a multidisciplinary approach and delivery by professionals specialised in gender identity capable of adapting to the emerging needs of the patients and embracing the diversity of trans individuals in the perception of the body, gender identity or gender expression outside the social norm. Research efforts must focus on optimising treatments and minimising their potential adverse effects. On the other hand, efforts must be made in society to fight against the stigmatization of transgender and gender-diverse people.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.anpede.2022.02.002.

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