

Endocrine Management of Transgender and Gender-Diverse Adolescents: Expert Opinion of the ESPE Working Group on Gender Incongruence and the Endo-ERN Main Thematic Group on Sexual Development and Maturation.

Title: Endocrine Management of Transgender and Gender-Diverse Adolescents: Expert Opinion of the ESPE Working Group on Gender Incongruence and the Endo-ERN Main Thematic Group on Sexual Development and Maturation.

Publication year: 2026

Journal: Hormone research in paediatrics

Authors: Department of Paediatric Endocrinology, Amsterdam UMC Location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, s.e.hannema@amsterdamumc.nl.

Society: ESPE Working Group

Origin country: Belgium

Target countries: Belgium

DOI: 10.1159/000542904

PMID: 39622214

Source: <https://pubmed.ncbi.nlm.nih.gov/39622214/>

Hormonal treatment in transgender and gender-diverse adolescents needs a proper indication, and benefits need to be balanced against dependency on medical treatment, side effects, and risks of treatment. It is important to also consider if alternative forms of support may be equally helpful, such as suppression of menstrual bleeding and psychological support. In all individuals with associated mental health problems, these should be addressed in parallel with medical and/or psychological or psychiatric support for gender incongruence.

Given the limited long-term outcome data, treatment with GnRH agonists and gender-affirming sex hormones should ideally be provided by centres of expertise with a multidisciplinary team consisting of qualified and experienced mental health professionals (such as psychologists, psychiatrists) and somatic healthcare providers (such as [paediatric] endocrinologists, gynaecologists, fertility specialists, plastic surgeons, audiologists/speech therapists, nurses or nurse practitioners), where treatment is only started after careful clinical and in-depth psychological assessment and support, and where clinical care is combined with research and long-term data collection. Adolescents and their parents/caregivers should receive information about the different options for hormonal treatment and their long-term consequences, including effects on fertility and options for fertility preservation, in a way that is suitable for their age, developmental stage, and cultural background.

After starting hormonal treatment in adolescents, long-term follow-up is recommended. Therefore, it is important to ensure optimal transition to adult healthcare providers, including an endocrinologist and mental health professional. Apart from monitoring hormone treatment, many other issues may require attention during the transition phase including education, employment, romantic relationships, sexual functioning, contraception, family building, and lifestyle.

Evidence-based long-term data on somatic and psychosocial outcomes including quality of life may over time provide the basis of guideline revision. However, evidence from clinical research alone will likely not be able to provide answers to all raised uncertainties about hormone treatment for transgender and gender-diverse adolescents and ethical dilemmas will therefore remain. Moral case deliberation is a relatively well-established form of clinical ethics support and may help clinicians deal with ethical and moral challenges more effectively.

Increasing numbers of transgender and gender-diverse adolescents (TGDA) seek endocrine treatment to align their body to their gender identity. A rise in referrals, especially of adolescents registered female at birth (RFAB), is seen in Europe, the USA as well as Australia [1]. The cause of the rising demand for transgender care is unclear but more awareness, for example, through media coverage, and increased acceptance and availability of care are thought to play a role, among others [2]. Guidelines describing evaluation, counselling, and treatment of TGDA have been issued by the Endocrine Society [3] and the World Professional Association for Transgender Health (WPATH) [4]. In addition, several national guidelines and quality standards exist [5 – 9]. In this relatively young field of medicine, there is a limited body of evidence for many recommendations, and the available evidence generally is of low quality. The National Institute for Health and Care Excellence (NICE) graded the quality of evidence as very low in 2020, and the recent final report of the Cass review concluded there is a lack of high-quality research assessing the outcomes of hormone interventions in TGDA [10 , 11]. This has led to more restrictive medical care for TGDA in several European countries (Sweden, Finland, UK). In other countries, there is also public debate whether the benefits of treating this vulnerable group of adolescents outweigh the risks. There is a need for more rigorous high-quality studies [12]. However, double-blind, placebo-controlled, randomised clinical trials are not considered feasible. The effects of sex hormones are clinically obvious so that blinding is not possible, and it is likely that many adolescents will refuse to participate or withdraw from a randomised study if they are allocated to the placebo group [13 , 14]. In the absence of randomised trials, much can be learned from prospective observational studies that are ongoing in several continents; the first results of these studies are now becoming available [15 – 17]. Many retrospective studies and a few prospective studies have shown that hormonal treatment with gonadotropin-releasing hormone (GnRH) agonists (GnRHa) to suppress sex steroid production, followed by gender-affirming hormone treatment (GAHT) with testosterone or oestradiol, is associated with improved appearance congruence (i.e., better alignment of physical appearance with gender identity) and self-perception, reduced gender incongruence (GI), and improved well-being [17 – 22]. However, other studies did not confirm all positive effects [23 , 24]. At the same time, it is important to realise that medical treatment cannot solve all mental health problems and that common psychiatric morbidity such as depression or anxiety may persist during treatment [17 , 20 , 25]. Minority stress, defined as stress due to stigmatisation and discrimination, may play an important role in the persistence of symptoms [26].

While evidence on somatic outcomes has increased in recent years [27 – 37], for areas that have not yet been investigated, current care relies on expert opinion. In order to reduce practice variation in paediatric endocrine care for transgender adolescents, we describe endocrine care for TGDA in Europe in this statement, based on the available evidence as well as the experience of experts from the European Society for Paediatric Endocrinology (ESPE) Working Group on Gender Incongruence and from the European Reference Network on Rare Endocrine Conditions (Endo-ERN), main thematic group “Sexual Development and Maturation.” This document aims to provide practical information and tools for clinical care and in addition includes a paragraph on ethical considerations regarding this care.

This document was prepared on behalf of ESPE and Endo-ERN – Project ID No. 101084921. It was written by the paediatric endocrinologists from the Steering Committee of the ESPE Working Group on Gender Incongruence (all authors), which consists of experts from nine European countries, and from the Endo-ERN main thematic group on Sexual Development and Maturation from centres that reported seeing >20 transgender adolescents per year (SEH, HLC-vdG, MC, DTK). Each section was prepared by 1–2 authors who reviewed the relevant literature. Our main aim was to update evidence published since 2017 [3]. A literature search was conducted using PubMed, Embase, and Web of Science Core Collection between January 2022 and December 2023. We retained English-written articles. Sections were then discussed with all authors during online and face-to-face meetings and adapted where necessary until final approval. The draft document was further edited for formatting and references and subsequently circulated to all authors as well as to representatives from Transvisie, Acceptess-T, and Transgender Europe for review. The subsequent version of the manuscript was reviewed by the ESPE Clinical Practice Committee. All

comments and suggestions were discussed and implemented as appropriate by the working group.

Terminology quickly evolves, and recent changes aim to depathologise. Whereas the diagnostic term gender dysphoria (GD) is used in the DSM-5, the ICD-11 uses GI and has moved the diagnosis from the Chapter on Mental and Behavioral Disorders into the chapter on Sexual Health. Preferences for certain terms can vary between individuals. In Table 1, the terms used in the current manuscript are explained.

Terms and abbreviations used in the current manuscript

Providing endocrine care for TGDA differs from other types of endocrine care. The initial diagnostic procedure or assessment must be done by a qualified mental health professional (MHP) within or outside a specialised gender clinic. A broad exploratory individual approach is recommended, which in addition to exploration of gender questions includes a more general evaluation of the needs of the adolescent. A diagnosis of GI does not necessarily imply that hormonal treatment should be started or is relevant or wanted. Furthermore, the timing and nature of the treatment may depend on the social and cultural background and legislation which may differ between countries.

Gender transitioning is a complex trajectory which involves many psychosocial and somatic factors. The standard of care is to provide integral care and treatment for TGDA with a specialised team consisting of qualified and experienced MHPs (such as psychologists, psychiatrists) and somatic healthcare providers (such as [paediatric] endocrinologists, gynaecologists, fertility specialists, plastic surgeons, audiologists/speech therapists, nurses or nurse practitioners). A multidisciplinary team (MDT) is indeed available in most European specialised centres [1]. Where this is not yet available, forming such teams should be prioritised. Close collaboration between the various team members is essential because many hormonal and surgical treatments are interdependent, and treatments can influence mental well-being. For example, early puberty suppression may affect later options for vaginoplasty, and suppression of endogenous sex steroid synthesis may affect mood.

There is a great diversity in questions regarding their gender from children, adolescents, and parents, when they seek professional help. Some have socially transitioned at a young age and feel certain about their gender identity, while others are still exploring their gender identity even in (late) adolescence. Ideally, general counselling to those with questions about their gender identity is provided by primary care providers and general psychologists. If there is a wish for medical gender-affirming treatment, adolescents can then be referred to a specialised centre or in countries where this is not available to a network of practitioners experienced in transgender care.

An MHP is often the first point of contact in the TGDA care pathway. Over multiple consultations with the adolescent and the parents/caregivers jointly or separately, the gender identity development and specific questions and/or aims are explored. The sessions are focused on gaining a general perspective of the psychosocial, cognitive, and emotional development. Additionally, in adolescents, psychosexual development is addressed. Family background is taken into account [38]. Coexisting mental health problems, such as anxiety and depression, self-harm, suicidal ideation or behaviours, and autism spectrum disorders, are more prevalent in TGDA [39 , 40]. Therefore, the diagnostic sessions are also aimed at addressing these possible coexisting problems. Internalising problems may be related to feelings of GI, social stigma, and/or minority stress. Many adolescents report a history of peer problems such as being bullied [41].

Once it is clear that the adolescent meets the diagnostic criteria of GD/GI and that this experience is marked and sustained over time, a medical intervention can be considered if treatment criteria are met (see paragraphs on pubertal suppression and GAHT) but treatment may not be desired or appropriate for all TGDA. The WPATH Standards of Care 8th version and Endocrine Society guideline describe criteria to start treatment taking into consideration coexisting psychologic and/or psychiatric problems, which should be addressed but need not necessarily be (fully) resolved (see

paragraph on GnRHa treatment) [3 , 4]. A very important prerequisite is that the adolescent must understand the consequences of treatment in the short and the long term and must be able to provide informed consent/assent for the treatment. It is recommended to involve parent(s)/guardian(s) in the assessment and informed consent process, and the MDT should make efforts to do so, unless their involvement is not feasible. Legal requirements with regard to parental consent vary between countries. TGDA with developmental delay, specific cognitive impairments, or psychiatric conditions may need more detailed consideration within the MDT as to their ability to provide informed consent/assent. In complex cases with ethical dilemmas, for example, in the case of adolescents with diminished capacity to consent, moral deliberation can be useful (see section on Ethical Considerations).

Careful counselling on the effects and risks of treatment by experienced healthcare providers is essential. Gender-affirming medical treatment is a multifaceted process and should be individualised and tailored to the needs of the adolescent (and their family). Hormonal treatment is only one part of the transition process and must be placed within the entire psychosocial context of the adolescent. It is therefore important that each adolescent's situation is discussed within the MDT so that all perspectives are taken into account before deciding on a course of treatment. The criteria for hormonal treatment (discussed in paragraphs on pubertal suppression and GAHT) should be reviewed during the MDT meeting. Consequences of starting or not starting treatment (discussed in the paragraphs on treatment) should be carefully balanced. Each next step or medical intervention has its own trajectory of counselling, obtaining informed consent and decision-making.

The discussion of adolescents' situation and their treatment plan typically takes place during regularly scheduled MDT meetings. The participants of the MDT meeting may vary depending on the type of medical interventions discussed. However, for an MDT providing endocrine care, it is recommended to have at a minimum a child psychologist, a child/adolescent psychiatrist, and a paediatric endocrinologist participating. The psychologist or psychiatrist will usually be the MHP who performs the assessment, as discussed above, and assesses the adolescents' capacity to provide genuine informed consent. A psychiatrist can help assess and advise on appropriate care for any coexisting psychiatric problems. Decisions are usually reached jointly by the MDT, with each specialty ensuring considerations from their respective field are taken into account (i.e., a paediatric endocrinologist would consider aspects such as pubertal development, somatic morbidity). Exchange of information and frequent discussions with specialists from all involved disciplines (e.g., surgeons, adult endocrinologists, fertility specialists) and patient representatives is highly recommended.

The healthcare provider who prescribes hormonal treatment to suppress endogenous hormones and/or sex steroid treatment should be experienced in the field of hormonal treatment, growth and puberty, and preferably a paediatric endocrinologist. Puberty is a critical phase of development, with major physical as well as psychosocial and neurocognitive changes. This maturation (e.g., brain development and bone mass accrual) does not stop after puberty but continues until the mid-20s. Pharmacokinetics, pharmacodynamics, and hormonal homeostasis are different in adolescence compared to adulthood. We do not recommend that hormonal treatment is initiated by the primary care physician or paediatricians who are not part of an MDT.

The paediatric endocrinologist takes a medical and family history, carries out a physical examination including height, weight, and blood pressure, to assess the presence of risk factors for adverse treatment outcomes, and evaluates Tanner stage [3]. Baseline investigations consist of laboratory investigations (haematocrit [Hct], LH, FSH, testosterone/oestradiol, lipids, 25OH-vitamin D), bone age (depending on pubertal stage), and bone densitometry. Performing a karyotype is only indicated if there is clinical suspicion of a disorder/difference of sex development, for example, because of abnormal pubertal development [42]. In addition, the paediatric endocrinologist or other healthcare provider who is knowledgeable in this area should provide information on the benefits of the endocrine treatment and the potential risks (see paragraphs on pubertal suppression and GAHT) and give advice about a healthy lifestyle (see paragraph on lifestyle). The reproductive effects, including the potential loss of fertility, of the endocrine and potential subsequent surgical

treatment are important. These must be discussed early in the counselling process, in the context of the adolescent's stage of pubertal development and mental maturity. Further information on the available options to preserve fertility should be given by a fertility physician (see paragraph on fertility) or other healthcare provider who is knowledgeable in this area.

Once hormonal treatment has started, both ongoing psychological support and endocrine monitoring are required. During follow-up appointments every 3–6 months, the effects of the treatment and satisfaction with these effects are evaluated, as well as possible side effects. Height, weight, and blood pressure are monitored; laboratory and radiological investigations are repeated as discussed in the paragraphs on puberty suppression and GAHT. Any concerns are discussed during regular MDT meetings. Furthermore, based on the treatment wishes of the adolescent, counselling about further treatments can be provided. For each treatment step, the indication, possible contraindications, and the capacity to understand long-term consequences and to make balanced decisions are assessed by the MDT. This is a continuous process with interplay of all parties (the adolescent, their family, the paediatric endocrinologist, MHP, and other team members that may be involved).

Support groups can provide essential information and support for adolescents and their families [43 , 44]. They provide advice and organise meetings where adolescents and their families can meet each other and some support groups offer practical help, for example, with coming out at school. Such groups can include the following: Youth clubs run by NGOs or LGBTI organisations

Advocacy groups for ethnic minority groups who have GI

An overview of transgender organisations in European countries can be found at <https://tgeu.org/our-members/> .

Adolescents and their parents/caregivers should receive information about hormonal treatment and surgical options, including their long-term consequences in a way that is suitable for their age, developmental stage, and cultural background. This presents a considerable challenge, as healthcare can be provided over many years and may involve different treatments at different times. Information should be repeated both before and during treatment and should be given by professionals with experience or formal training in adolescent healthcare and communication with adolescents. The same information provided to parents and guardians may be interpreted differently by the young adolescent, even causing conflicts. It is therefore paramount that information is offered individually as well as jointly in a neutral and compassionate environment with the option of asking questions and repeated meetings.

Over time, the young transgender person is expected to participate increasingly in the decision process and informed consent, supported by the parents or guardians. In many countries, adolescents from the age of 15 to 16 years can legally decide about their personal healthcare even against the advice of their guardians. Although this may be beneficial for some, it may put them at risk of losing their support network with potential serious consequences for a successful transition process.

Early choices may have an impact on later treatment possibilities and affect the whole life span. For example, early intervention with GnRH agonists (GnRHa) to avoid masculinisation in those registered male at birth (RMAB) affects options for fertility preservation and for later genital surgery. This dilemma highlights the importance of a thorough informed consent procedure including discussion of the benefits and limitations or potential risks of the different treatment options, or refraining from treatment, both in the near and far future.

The healthcare provider needs to ensure that the adolescent has a realistic expectation of what is achievable with hormonal treatment and gender-affirming surgery. A lot of unreliable and subjective information, including manipulated photos, is freely accessible through the media and may need to

be put into perspective. Written information (leaflets), podcasts, and websites of specialist centres may be useful supplements to individual face-to-face consultations.

While GI is neither a somatic nor a mental disease, any hormonal or surgical treatment needs to have a proper indication and aims at improving quality of life in both the short and the longer terms. This needs to be balanced against the inconvenience of life-long dependency on medical treatment (if continued effects of sex hormones are desired and/or if gonadectomy is performed), the side effects of treatment, and risks of surgical procedures. It is therefore important to also consider if alternative forms of support may be equally helpful, such as psychological support. This support should not aim to alter one's gender identity but could help explore if a non-medical approach may eventually suit the individual situation of the TGDA. As gender-affirming medical treatment is an intensive and demanding process, psychosocial support should be ensured during the entire treatment period as well. It is also important to continue the support of adolescents who develop doubts about their treatment or wish to discontinue treatment and/or de-transition.

It may be helpful for the team to develop a standardised algorithm for the information process which the healthcare provider shares with the young transgender person. This can serve as a "working paper" between them that can be revisited over time. Such a list may also be useful for the adolescent to review at home for reflection and discussion with people they trust (Table 2). This may facilitate shaping questions for the next visit and clarify issues that need to be addressed. Although an adolescent usually wants to speed up the transition process, time needs to be given for reflection and repeated information. In TGDA who present with significant mental health issues, the information process and decision taking may need a longer time.

Suggested topics for initial and ongoing conversations: goals, experiences, obstacles, and expectations

This checklist does not contain specific areas related to mental health which are covered by conversations with the MHP of the team.

Fertility is an important topic to discuss when considering medical gender-affirming treatment. Studies have found that many TGDAs want to become parents, but few make use of fertility preservation although this varies between clinics [45 – 50]. This contrasts with surveys in adults, reporting that they would like to have taken up fertility preservation options if they had been available. TGDA may change their minds about the importance of fertility later in life, and fertility preservation options must be discussed and re-evaluated throughout follow-up.

While the effect of a GnRHa on gonadal function is reversible, i.e., activity of the hypothalamus-pituitary-gonadal axis is restored after discontinuation, most RMAB adolescents who start GnRHa treatment will subsequently start GAHT without wanting to interrupt their hormonal treatment trajectory to allow for gamete cryopreservation. Therefore, it is recommended to provide fertility counselling before starting GnRHa to TGDA and their parents/caregivers. Several studies have highlighted a risk of reduced fertility due to GAHT treatment, most particularly effects of oestrogens on spermatogenesis [51 , 52]. Semen quality may also be negatively affected by specific lifestyle factors, such as a low frequency of masturbation or having the testes tight against the body through "tucking" or tight underwear [51]. Some early pubertal TGDAs decide to delay the start of treatment in order to pursue semen cryopreservation or testicular sperm extraction. A testicular volume of at least 10 mL seems to be the best predictor of successful sperm retrieval with a testicular biopsy [53 , 54]. Psychological support is essential as the period of waiting until puberty has sufficiently progressed may be difficult, with anxiety about irreversible physical changes arising before successful preservation of gametes is possible [55]. These considerations also apply to the situation where TGDAs decide to temporarily interrupt their treatment to pursue fertility preservation. GnRHa treatment may need to be interrupted for a considerable period of time to allow fertility preservation. A study of nine boys treated with a GnRHa for precocious puberty reported that the time between discontinuation of GnRHa and spermatarche, as assessed by spermaturia, varied from 0.7 to 3.0 years [56].

Overall, the results concerning the influence of testosterone on reproductive organs in RFAB adolescents and their function appear to be reassuring, with no negative effect of testosterone treatment on the number of oocytes or the yield of oocyte retrieval after ovarian stimulation [57]. However, there have been no prospective studies to date evaluating the effect of long-term GAHT (i.e., started in adolescence) on fertility or the effect in those treated with GnRHa in early puberty followed by testosterone therapy. In addition, TGDA may wish to pursue a gonadectomy which will make them infertile. It is thus essential to discuss infertility risk and fertility preservation options by a fertility counsellor (see Table 3) with TGDA and their families prior to initiating any of these treatments and to continue discussing this topic during follow-up [3 , 4]. If the adolescent is interested in further fertility counselling, referral to a provider with expertise and knowledge of the different available techniques should be offered. The emotional burden of discussing such questions at a young age, along with the fertility preservation procedure itself, should not be underestimated, and counselling as well as psychological support addressing these specific issues is recommended.

Individualised care should be provided in the context of each person's parenthood goals, taking into account that adolescents may not be fully aware of their future wishes. Whereas the use of mature oocytes and sperm has proven to be efficacious in assisted reproduction, cryopreserved gonadal tissues would require either future retransplantation aimed at obtaining fully functional gametes or in vitro maturation techniques. In vitro maturation of spermatogonia is still under development in basic science research settings [60]. It is also important to discuss regulations regarding later use of preserved gametes, which vary between countries and may change over time. In addition, TGDA should receive information about other ways to become a parent so that they have a realistic idea of the various options.

In TGDA, the undesired development of pubertal characteristics can lead to an increase of feelings of GD, leading to depression, impaired psychological functioning, and isolation. In the Netherlands, the first transgender adolescent was treated with GnRHa to prevent further pubertal development which was published in 1998 [61 , 62]. Since then, treatment with GnRHa has become common clinical practice as a first step in treatment of adolescents in many expert centres [19 , 63]. Preventing the development of secondary sex characteristics by the use of GnRHa may enable the adolescent to further explore gender identity and carefully consider further treatment wishes before irreversible gender-affirming treatment is started without the distress caused by physical changes incongruent with the gender identity. Multiple though not all studies described a positive effect on psychological outcomes including quality of life [18 , 63 – 66]. The great majority of those using GnRHa subsequently start GAH which they continue to use in adulthood suggesting high treatment satisfaction and very low rates of regret or detransition [67 , 68].

GnRHAs are synthetic analogues of the hypothalamic hormone GnRH. The continued stimulation of the GnRH receptor by GnRHa after injection leads to desensitisation of the gonadotropic pituitary cells. As a result, the ovaries and testes are no longer activated and stop producing sex hormones [29]. The suppression of the HPG axis by GnRHa is considered to be fully reversible as endogenous puberty will be reactivated when the treatment is stopped. However, there may be risks associated with a prolonged hypogonadotropic period before gender-affirming treatment is started, and long-term outcomes of GnRHa treatment in TGDA are still not fully known (see paragraph on outcomes).

Most knowledge about long-term outcome of GnRHa treatment comes from studies in children treated for precocious puberty. In these patients, the treatment is deemed safe although limited long-term outcome data are available [69]. In precocious puberty, suppression of the HPG axis with GnRHa occurs at an age where it is physiological to have low sex steroids, whereas in TGDA GnRHAs are used to induce low sex hormone levels at an age where puberty normally takes place. This may result in different side effects [70]. There is some experience with GnRHa in older adolescents for other indications such as in those with growth disorders, alongside growth hormone treatment [69].

Given the limited long-term outcome data, treatment with GnRHa should ideally be provided by centres of excellence, where treatment is only started after in-depth psychological assessment and support, and clinical care is combined with research and long-term data collection. In some countries, centres of excellence may not be available and providers may not have resources to perform research themselves. However, if they ensure careful follow-up, then clinical outcome data can be shared for research purposes through platforms such as the European Registries for Rare Endocrine Conditions (EuRRECa) of Endo-ERN.

All TGDA and parents should be carefully counselled about the advantages and disadvantages of GnRHa (see Table 4) [71]. For RFAB adolescents who have completed puberty (Tanner stage 4/5), GnRHas are of limited benefit; alternative options to suppress menstrual bleeding are available, and adolescents should be advised about the pros and cons of each option (see paragraph on alternatives to GnRHa to manage menstruation and Table 5). Adolescents RMAB at Tanner stage 4/5 will also have undergone most pubertal changes, and the main benefits of GnRHa in this group are prevention of (further) development of facial and body hair and suppression of erections; alternative treatment options are discussed in paragraph “Managing Hair Growth and Erections in RMAB Adolescents.” GnRHa treatment is not recommended for TGDAs who at the time of counselling do not have a wish for GAHT because of the health risks of prolonged hypogonadism.

Advantages and disadvantages of GnRH agonists

Methods for contraception and/or to reduce menstrual bleeding in adolescents RFAB

Injectable medroxyprogesterone acetate (progestin)

Etonogestrel subdermal implant (progestin)

Levonorgestrel intrauterine device (progestin)

Low for combined oestrogen/progestin with continuous use

Moderate for injection, implant, and intrauterine device

NB: Several oral progestins are not contraceptives

In TGDA requesting GnRHa treatment, prior to any hormonal treatment a comprehensive evaluation should be carried out by an experienced MHP who can determine the indication for treatment, together with the MDT. The following criteria are recommended for GnRHa treatment [3]: 1. The presence of GD/GI has been confirmed by an experienced MHP [73 , 74]

Clinical evidence of puberty, at least Tanner stage G2 (testicular volume >4 mL) or B2

No medical, psychiatric, or psychosocial contraindications, i.e., coexisting problems that could interfere with treatment or that might worsen due to treatment, have been addressed such that the adolescent's situation and functioning are stable enough to start treatment

TGDA and parents/caregivers understand the consequences of treatment and have provided informed consent in accordance with regional/national legislation

Continuing support during treatment by an experienced MHP and a paediatric endocrinologist.

Nowadays, mostly long-acting GnRHs are used. Various doses are available that are administered every 4 weeks (3.75 mg), 10–12 weeks (11.25 mg), or 20–24 weeks (22.5 mg) intramuscularly or subcutaneously (see Table 6). In most centres, a 4 or 12-weekly formulation is used as starting dose; if the adolescent is satisfied with the treatment, a longer acting formulation can be used. In RMAB adolescents who are post-menarche, GnRHs are of limited benefit and progestins should be considered instead for menstrual suppression (see paragraph “Alternatives to Suppress Endogenous Sex Steroids in Late Adolescence”).

When GnRHa treatment is started at an early pubertal stage (Tanner stage 2/3), breast development is significantly reduced in RFAB adolescents, and mastectomy either is not required or can be achieved using a less invasive approach [75]. In RMAB adolescents, the mean penile length is significantly shorter in those treated with a GnRHa compared to those who started treatment in adulthood [75]. As previously discussed, this has implications for later options for vaginoplasty should the adolescent wish to undergo such surgery. The penis inversion techniques may not be possible due to the limited penis size, and an alternative approach may be needed [75].

Several studies performed in TGDA, but not all, showed an improvement of body dissatisfaction, behavioural and emotional problems, and a decrease in depression and suicidality with GnRHa treatment, although not all changes were significant and there are methodological limitations of the studies [18 , 20 , 22 , 63]. In the study of Brik et al. [76] of 143 TGDA starting with GnRHa, 87% continued with gender-affirming hormones, suggesting that most adolescents are satisfied with the treatment, at least on the shorter and medium term. Similarly, in Butler et al. [77] 92% starting GnRHa continued to GAHT and onwards into adult care. A recent study by van der Loos et al. [67] reported that 1.6% of 882 TGDA who had started GnRHa discontinued this treatment. The high percentage of treatment continuation may be due to careful assessment prior to treatment of those highly likely to continue to experience GD and/or to the informed consent procedure. However, no studies have been performed to compare numbers of TGDA who discontinue treatment as adolescents or in adulthood between clinics.

Although GnRHs are generally well tolerated, some side effects are commonly reported such as hot flushes, especially in the first year of treatment, headache, emotional changes, and local pain after the injection [23 , 29]. Hypertension after the start of GnRHa treatment which was reversible after stopping the medication has been reported in a few cases [78]. RFAB adolescents must be informed that vaginal bleeding can occur after the first injection especially in adolescents with advanced pubertal development [29].

In children treated with GnRHa for central precocious puberty, BMI-SDS increased during treatment with GnRHa in girls, but not in boys. However, this increase was temporary and reversed 1 year after stopping treatment for the group as a whole [79]. GnRHs do not appear to increase the risk of developing obesity in adolescence or adulthood or the risk of polycystic ovarian syndrome [69]. In TGDA, GnRHa treatment is associated with an increase in fat mass and a decrease in lean mass compared to peers [80].

During GnRHa treatment, growth velocity diminishes in most adolescents, but catch-up growth occurs once GAHT is started. A recent retrospective study in 161 RMAB adolescents did not show any (stimulating or inhibiting) effect of GnRHa followed by GAHT on adult height [27]. In a retrospective study in 146 RFAB adolescents, GnRHa followed by GAHT did not have a negative impact on adult height but even led to a slightly taller adult height, especially in those who started GnRHa at a younger age [32]. A recent study shows that even when administered from early puberty onwards, and for over 2.5 years before adding gender-affirming hormones, GnRHa did not alter final height in either RFAB or RMAB adolescents [81]. Further prospective, longitudinal studies must be performed to confirm these results.

Among the most common concerns about the use of GnRHa are possible negative effects on bone mass accrual as sex hormones are necessary to stimulate adequate bone mineralisation especially

during adolescence. During treatment with GnRHa, bone mineral density (BMD) remains stable rather than showing the physiological pubertal increase, resulting in a decrease in BMD Z-scores over time. If GAHT is subsequently started, complete recovery of BMD Z-scores is seen in RFAB adolescents in their late twenties, whereas in individuals RMAB BMD Z-scores at the hip recover but Z-scores at the lumbar spine remain low also during adulthood [82].

RMAB adolescents present with BMD Z-scores below zero, already before the start of any medical treatment [30 , 83 , 84]. A recent cross-sectional study found a negative association between BMD Z-scores and age in RMAB adolescents, which was partly mediated by height-adjusted lean mass Z-score [85]. This suggests that lifestyle factors such as physical exercise, previously found to be lower in TGDA with low BMD than those with normal BMD [81], and underweight may play a role. Other risk factors for low BMD such as low calcium intake and vitamin D deficiency that are often present in TGDA might contribute to impaired BMD too [84]. Therefore, besides psychological follow-up, lifestyle counselling is important to prevent long-term morbidity (see paragraph on Lifestyle Counselling).

TGDA should be informed that it is recommended to use GnRHa monotherapy only for a limited period because it reduces bone mineral accrual. This is especially important in non-binary persons who wish to use GnRHa but do not wish to start with GAHT. Few data about the safety of prolonged use of GnRHa especially on bone mineralisation are available although they have been used for up to nearly 5 years [30 , 61]. Regular monitoring with dual-energy X-ray absorptiometry scans is recommended to detect changes in bone mineralisation over time. There are currently no data available on how changes in BMD Z-scores translate into health risk including fractures in adult life.

The effect of GnRHa on the HPG axis is reversible, but other subsequent treatments that TGDA may wish to pursue may affect fertility in an irreversible manner so that fertility counselling is recommended prior to the start of GnRHa treatment (see paragraph on fertility). As indicated above, the topic of fertility can be revisited at any time during the treatment trajectory and fertility counselling should be repeated if an adolescent wishes to start GAH or, in adulthood, wishes to undergo gonadectomy.

Few studies are available on the impact of GnRHa treatment on the brain. Gender-affirming medical treatment including GnRHa treatment was found not to negatively affect the association between IQ and educational achievement [86]. The influence of GnRHa on psychosexual development in this critical period of mental development also deserves further study. One study showed an increase of romantic and sexual experiences of TGDA after GnRHa, GAHT, and surgical treatment [87].

For RFAB adolescents in whom pubertal development is almost complete, the benefits from GnRHa are limited. Breast growth will decrease only minimally, and unwanted menstruation can be suppressed by alternative treatment such as continuous progestins or oral contraceptives (see Table 5). Progestins lower oestrogen levels without fully suppressing them and seem to have less impact on BMD than GnRHa in the short term [36], but they do affect lipid profile and lifestyle advice should still be given. Progestins may be safe and cheap alternatives to GnRHa in late-pubertal RFAB adolescents who are planning to start GAHT. Patients should be informed that most progestins are not contraceptives.

RMAB adolescents with advanced puberty can be treated as an alternative with anti-androgens (cyproterone acetate, spironolactone) to lower androgen levels and/or antagonise androgen action and inhibit further unwanted hair growth and unwanted erections. This medication may also induce variable degrees of gynaecomastia, which is often welcomed by RMAB adolescents [37]. However, they should be informed that a visible effect on hair growth may require at least 6 months of treatment. In addition, it is important to note that the use of cyproterone acetate is associated with an increased risk of meningioma, which is cumulative dose dependent [88]. If used, it is important to minimise risk by using the lowest effective dose for a limited period of time. Furthermore, cyproterone can increase prolactin levels [89]. Cyproterone acetate also has many

side effects, such as fatigue and depression [37]; spironolactone may induce electrolyte disturbances. The place for these medications as an alternative to GnRHa in the treatment of RMAB adolescents is therefore less clear. Although there are some reports of use of other agents such as bicalutamide or medroxyprogesterone in RMAB adolescents or adults, evidence is also insufficient to recommend their use [90 – 92]. Bicalutamide can cause liver toxicity [93].

GAHT with sex hormones (testosterone/oestradiol; see Table 6) aims to induce secondary sex characteristics that are in line with the gender identity and thereby decrease GI and improve well-being. Indeed, several studies have shown that characteristics such as breaking of the voice and an increase in facial hair with testosterone treatment, and breast development with oestrogen treatment can be induced within the first year of GAHT [28 , 31]. In addition, body shape (waist-to-hip ratio) and body composition develop in line with the gender identity although this may take a considerably longer time and may not be completely achieved [33 , 94]. Along with these physical changes, appearance congruence improves, and this is associated with improved mental health [17 , 19 , 20 , 22]. However, it is important to note that some TGDA continue to experience serious mental health problems despite GAHT. Continued support from the MDT including an MHP is thus essential [17 , 25].

Options for sex steroid suppression and GAHTs in adolescents

Various preparations of long-acting GnRH agonists are available such as triptorelin and leuporelin

Available doses are 3.75 mg every 4 weeks, 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks

Progestins with some androgenic effects may be preferable for transmasculine TGDA, such as lynestrenol or norethisterone

Consider a starting dose of 5 mg per day

Consider increasing the dose to 10 mg per day in case of continued menstrual bleeding; in case of a breakthrough bleed, the dose can be increased to 15 mg for 3–5 days

Cyproterone acetate is a progestin with anti-androgenic effects, which is generally only used when GnRH agonists are not available or affordable on account of the known dose-related risks

It is important to note that the use of cyproterone acetate is associated with an increased risk of meningioma, which is cumulative dose dependent [84]. Because of the potential side effects/risks, the place of cyproterone acetate in treatment of TGDA is less clear and if used, the lowest effective should be used, for a limited period of time

Tablet sizes 10 mg and 50 mg are available

Consider a dose of 10 mg or 12.5 mg (50 mg tablets can be split in quarters), as this is equally effective and has less side effects compared to higher doses [95]

Oestradiol can be taken orally once daily

Tablet sizes 0.5 mg, 1 mg, 2 mg are available

Consider a starting dose of 0.5 mg for pubertal induction

Consider a starting dose of 1 mg in a post-pubertal, larger individual

Maximum dose is 6 mg before detailed review

Oestradiol transdermal patches are applied and changed twice per week

Patch sizes 25 µg, 37.5 µg, 50 µg, 75 µg, and 100 µg are available

Consider a starting dose of 12.5 µg for pubertal induction (cut 25 µg patch in half or use ¼ of 50 µg patch)

Consider a starting dose of 25–50 µg in a post-pubertal, larger individual

Maximum dose is 100 µg patch before detailed review

Different brands deliver 0.5 mg, 0.75 mg, or 1.53 mg oestradiol per pump

There is no experience using transdermal gel for pubertal induction

Consider a starting dose of one pump in a post-pubertal, larger individual

Maximum dose is 3 pumps per day before detailed review

Monitor clinical response every 3–6 months, i.e., breast growth, emotional response, and titrate over 12–24 months to attain concentrations within the middle of the adult female reference range for the mid-follicular phase of the local laboratory

Monitor oestradiol concentrations every 6–12 months

Continue the GnRHa throughout: may be continued until gonadectomy

NB: combined treatment with a progestin is not indicated

Testosterone enanthate can be used for subcutaneous or intramuscular injections every 1–4 weeks; a mix of esters can be used for intramuscular injection every 2–4 weeks

100 mg/mL and 250 mg/mL solutions are generally available

Manufacturers recommend against the use of mixed testosterone esters in the case of peanut or soy allergy because it contains (refined) peanut oil so testosterone enanthate is preferred instead, although uneventful use of mixed testosterone esters in a boy with peanut allergy has been described [96]

Consider a starting dose of 50–75 mg every 3–4 weeks for pubertal induction

Consider a starting dose of 75 mg every 2 weeks or 125 mg every 3 weeks (or an equivalent dose every 1 or 4 weeks) in a post-pubertal, larger individual

Typical adult dose schedule is 250 mg intramuscularly/subcutaneously every 3–4 weeks

Total dose equivalent may be divided and administered every 1–2 weeks

Once established on shorter acting testosterone (either IM or SC) or gel, a transfer to the long-acting testosterone undecanoate can be considered. The starting dose is 500–1,000 mg (intramuscularly only) every 12 weeks. A booster dose is recommended after the first 6 weeks

Typical adult dose is 1,000 mg every 12 weeks

This can be considered first-line treatment in an older, mature, post-pubertal individual

Testosterone gel is applied once per day

Different brands deliver 10 mg, 20 mg, 20.25 mg, or 23 mg per pump. Sachets of 50 mg are available

Consider a starting dose of 10 mg per day (or 20 mg every other day) for pubertal induction

Consider a starting dose of 20–23 mg in a post-pubertal, larger individual

Monitor clinical response every 3–6 months, i.e., deepening of voice, hair growth, emotional response, and titrate over 12–24 months to attain testosterone concentrations in the adult male range according to the local laboratory

Measure testosterone concentration according to the manufacturer's instruction; aim for testosterone levels in the middle of the local adult male range

Do not take blood samples on the same arm on which testosterone gel is applied to avoid contamination of the blood sample if gel is applied on upper arm

For midway concentration measure testosterone midway between injections; aim for testosterone level towards the middle-upper end of the local adult male range

For trough concentration measure immediately before an injection; aim for testosterone level towards the low-normal end of the local adult male range

Continue the GnRHa or progestin until normal male testosterone concentration has been achieved

Monitor Hct/haemoglobin, lipids, and testosterone concentration every 6–12 months during testosterone treatment

Information about the expected effects of GAHT and timing of these effects should be provided so that TGDAs have realistic expectations. Some effects occur relatively quickly (within months) such as increased hair growth on the limbs and voice change with testosterone, but others occur over a longer period, such as full breast growth in RMAB and facial hair growth in RFAB adolescents which continues over several years [28 , 31]. The adolescent should be capable of providing informed consent for this partially irreversible treatment. Fertility should be (re)addressed before starting GAHT, and there should be no medical or psychosocial contraindications for GAHT.

The type of testosterone formulations, either gel or injection, is a matter of personal choice. There does not appear to be an advantage of one over the other in terms of efficacy.

A gradual increase in dose over time is recommended as per local/national and the Endocrine Society guidelines [3]. There is little information as to whether starting directly on a higher dose of testosterone is advantageous or has a higher incidence of mental health and emotional issues in adolescents who have completed endogenous puberty. An overview of options is provided in Table 6 .

Current evidence suggests that injections of testosterone enanthate can be given either intramuscularly or subcutaneously [97]. TGDA can learn to self-administer if taught the no-touch clean injection technique [97]. With transdermal gel, bioavailability can differ between individuals

and testosterone concentrations may rise directly into the adult male range and should be monitored according to the manufacturer's instruction to obtain the required effect. If unexpectedly high concentrations are measured, contamination of the blood sample with testosterone gel should be considered, especially if the gel is applied to the same side shoulder/upper arm where the blood sample was drawn. It is important to provide instructions to avoid contamination of others with the gel; it is best recommended that the gel is applied several hours prior to direct skin-to-skin contact with another person.

During testosterone treatment, regular monitoring of serum testosterone concentration is recommended with dose adjustments made to attain a concentration in the male reference range. Different manufacturers recommend blood withdrawal at different time intervals after gel application, but serum testosterone is actually quite stable throughout the day with once daily application [98]. Potential side effects and recommendations for safety monitoring are discussed in a separate section below.

Treatment with GnRHa or progestin may continue until the target testosterone concentration is achieved; with adult male testosterone concentrations, menstrual bleeding usually stops without additional medication. Those who started GnRHa treatment in early puberty (at Tanner stage B2/3) can also discontinue GnRHa without experiencing breast growth as long as testosterone is continued in an adequate dose.

It is in general preferable to use unconjugated 17 β -oestradiol preparations instead of the synthetic oestrogen ethinyl oestradiol as they are physiological and readily available in different forms such as transdermal patches, gels, or tablets and sprays in some countries. The various options are listed in Table 6 . The administration form of oestradiol is a matter of personal choice. There does not appear to be an advantage of one over the other in terms of efficacy although transdermal treatment is preferable in those at increased risk of venous thromboembolism [99]. There is insufficient evidence on potential differences in effect on bone age advancement or BMD. Oestrogen gels or sprays have the advantage over patches that they are not visible, which some TGDA may prefer, but the lowest dose that can be administered is usually half of the recommended dose for adults so this may not be suitable for TGDA who have not yet completed endogenous puberty.

Other forms of conjugated oestrogens or the synthetic ethinyl oestradiol are not recommended as they come in dose increments that are not easily adjustable and do not allow monitoring of serum oestradiol levels. Furthermore, there is a higher incidence of venous thromboembolic events with both.

A gradual increase in dose over time is recommended as per local/national and the Endocrine Society guidelines (see Table 6) [3]. The eventual long-term dosage regimen should be adjusted so the oestradiol concentration falls within the middle of the adult female reference range for the mid-follicular phase of the local laboratory. Doses of 3–4 mg of oral 17 β -oestradiol are required on average. Lower doses may result in suboptimal bone mineral accrual [100] and perhaps suboptimal breast development. Individual sensitivity to sex hormones may vary greatly [101], with some adolescents showing major bodily changes over the course of some months, and others may experience very little effects and require individualised dose adjustments.

Concern about excessive growth may be expressed by RMAB adolescents who are already tall at treatment start with GnRHa especially if their target height is high. A bone age X-ray may be conducted to attempt adult height prediction, using birth-sex references. Current evidence suggests that GnRHa treatment slows the height velocity whereas introducing oestradiol causes growth acceleration but adult height does not seem to be altered by hormonal treatment compared to birth-registered sex [27 , 81]. Preliminary evidence suggests that higher doses of 6 mg oral oestradiol do not reduce the total growth attained. Treatment with high doses of ethinyl oestradiol (100–200 μ g/day) may be associated with some height reduction but has associated risks such as venous thromboembolism, and hyperprolactinemia has been reported as a side effect [27 , 28].

Epiphysiodesis may be a good alternative to reduce final height when performed timely. Indications for epiphysiodesis and its efficacy (depending on timing) and potential risks are well described; adolescents should be counselled about the advantages and disadvantages of this intervention [102]. No data are currently available on the effect on adult height of introducing oestradiol before age 15–16 years, the age limit used in most current European protocols and published studies. The primary and indispensable criterion to start GAHT is that the adolescent has the capacity to make an informed decision.

In RFAB adolescents, adult height is not affected by GnRHa and testosterone treatment either, although those starting GnRHa treatment early in puberty may reach a slightly taller adult height than expected for their birth-registered sex without any hormonal treatment [32 , 81]. As yet, there is no evidence-based treatment to augment growth in RFAB adolescents. Growth hormone has not been investigated. Theoretically, an aromatase inhibitor could be used in parallel with the GnRHa and/or testosterone treatment, but there is no current clinical evidence for this and there may be associated risks in lowering BMD and side effects due to increased testosterone levels.

Based on the joint authors' extensive clinical experience with pubertal induction in girls with hyper- or hypogonadotropic hypogonadism, and in RMAB adolescents, the best practice to ensure optimal breast growth requires mimicking physiological puberty and gradually increasing the oestradiol dose according to local guidelines or the Endocrine Society guidelines [3]. This same approach is also recommended for girls who require pubertal induction because of congenital pituitary or gonadal reproductive hormone deficiency [70]. Increasing the oestrogen dose too rapidly may result in abnormal breast growth and shape [103]. Some RMAB adolescents with broad chests complain about the wider separation of their breasts due to the anatomical variation between the male and female chests [104 , 105]. Suppression of testosterone secretion into the female range is required as any form of androgen is antagonistic to breast growth. There is currently no evidence that the addition of a progestin will augment breast growth or later breast shape, but studies are ongoing [106]. With oestradiol treatment, areolar growth will take place as per typical cis-female development (Tanner stage B4) although not all seem to achieve Tanner stage B4–5 within the first 3 years of treatment and modest breast volumes have been observed after 3 years of oestrogen treatment in transfeminine adults [28 , 104]. Treatment can be adjusted according to clinical response in discussion with the young woman. However, final breast size has a significant biological variation, also in cis-women, and was not found to be associated with serum oestradiol concentrations [104]. Body composition, in particular fat mass, may also have an impact on final breast size [107].

The existence of both physical and psychological conditions that could form a contraindication for GAHT will need to be reviewed on an individual basis. This could include physical conditions that induce cachexia, or psychological/psychiatric conditions such as an eating disorder which may reduce the response to GAHT in terms of muscle development with testosterone and breast growth and hip fat redistribution with oestradiol. Most medical conditions that may be exacerbated by GAHT (for overview, see [3]) are rare in adolescents.

Oestrogen metabolism can be altered by medication that induces liver enzymes, including certain anti-epileptic medication and some antibiotic and antiviral agents. Oral oestradiol increases the concentration of hormone-binding proteins such as sex hormone-binding globulin, cortisol-binding globulin, and thyroxin-binding globulin, thus affecting hormone bioavailability. Changes in oestrogen status can affect mood and possibly efficacy of antidepressant medication [108 , 109].

Clinical evaluation every 3–6 months is recommended to evaluate if the adolescent is satisfied with the treatment and to monitor side effects. The most common side effects of GAHT are acne (with testosterone), breast tenderness (with oestradiol), fatigue, and emotional changes [31 , 35 , 37].

For RFAB adolescents, Hct/haemoglobin and lipids should be monitored because of the risk of polycythaemia and dyslipidaemia [3]. In adolescents, a Hct >0.5 L/L may spontaneously resolve but in case of persistent erythrocytosis TGDA should be advised to quit smoking, in case of

(relatively) high serum testosterone concentrations to reduce the testosterone dose, to switch to a transdermal administration route, and, in case of overweight/obesity, to lose weight [110 , 111]. The most frequently observed changes in lipid profile associated with testosterone are increases in LDL cholesterol and triglyceride concentrations and a decrease in HDL cholesterol [112]. This may put RFAB adolescent at greater risk of cardiovascular events in the long term. Mortality is increased in transgender adults but mainly due to non-hormone-related causes of death (suicide, lung cancer, HIV-related disease) [113]. No correlation between testosterone therapy and cardiovascular morbidity or mortality has been shown in this population [114]. Nonetheless, lifestyle counselling is important to prevent long-term morbidity (see paragraph on Lifestyle Counselling).

Many countries do not offer gender-affirming surgery prior to the age of 18 years; therefore, this is not discussed in this document. Some, however, do offer masculinising chest surgery prior to age 18. Both GnRHa and testosterone may reduce breast volume to some degree. Some surgeons request a minimal period of testosterone treatment (if such treatment is desired by the adolescent) prior to considering chest surgery as this also affects development of chest muscles. Individual discussions with the relevant surgeon will need to take place.

Many non-binary adolescents may not desire hormonal treatment, and our knowledge about the safety of long-term treatment in non-binary TGDA and adults, as well as on the long-term (gender identity) outcome of non-binary TGDA, is sparse or even absent. Many countries thus have no local guidelines for this group and do not offer hormonal treatment.

In individuals whose dysphoria increases during menstruation, suppression of menstruation can be achieved by the combined oral contraceptive pill taken continuously. Allowing a break for a planned menstrual bleed 1 to 4 times per year may avoid breakthrough bleeding (Table 6). Those young people not wishing to use oestrogen may prefer a progestin such as norethisterone (5–10 mg/day), lynestrenol (5–10 mg/day), or medroxyprogesterone acetate (10 mg daily or injections) which can be taken continuously. However, some progestins adversely affect lipid profiles and BMD in the long term [35 , 115]. Longer term management may be achieved by an intrauterine device containing a progestogen or an etonogestrel implant, which have the additional advantage of offering effective contraception, if needed. Some may wish chest reconstruction surgery in combination with progestins or as a stand-alone treatment. Evaluation by the team's adolescent psychologist/psychiatrist is required, and availability of such treatment depends on local healthcare guidelines and the willingness of the surgeon.

Full reduction in testosterone secretion is difficult to achieve other than by complete suppression with a GnRHa and is not recommended for long-term treatment due to the well-known side effects of prolonged hypogonadism. Slight reductions in testosterone but with clinical effects of facial hair growth reduction, muscle mass reduction, and decreased erections may be achieved by anti-androgen treatments such as spironolactone in low dose, for example, 25 mg/day, or progestogens such as cyproterone acetate 10 mg, but no long-term data on benefits and safety are available [37]. These treatments may be associated with direct side effects of the medication. In addition, continued use of GnRHa or cyproterone acetate will have a deleterious effect on bone mass accrual, body composition, lipid profile, and perhaps also metabolism and bone marrow adipose tissue and is therefore not recommended for this indication [36]. There is also a reported higher incidence of meningioma with cyproterone acetate use (see above).

Local treatment by ablation of the hair follicles can be achieved by laser treatment although this may not be permanent. Surgical procedures to change the prominence of the laryngeal cartilage (Adam's apple) and on the jaw and brow line can be done in discussion with individual surgeons, depending on local availability, but are generally not offered to minors.

After starting hormonal treatment in TGDA, long-term follow-up is recommended as for those who start treatment in adulthood [3 , 4]. Therefore, it is important to ensure optimal transition. If the adolescent wishes gender-affirming surgery, transition to an adult MHP and endocrinologist often takes place within a gender clinic that offers such surgery. If the adolescent does not wish genital

surgery, follow-up of hormonal treatment may also take place locally, with an endocrinologist experienced in monitoring this treatment. Contact between the paediatric and adult healthcare provider allows exchange of information on treatment protocols, which may differ between paediatric and adult clinics, to ensure a smooth transition for the adolescent without unexpected treatment changes.

Transition to adult care is a critical event, when many adolescents who receive endocrine care become lost to follow-up [116]. A joint appointment with the paediatric and adult provider may be helpful. Adolescents should otherwise be instructed to contact the service if they do not receive an appointment with the adult provider.

The adolescent needs to be prepared for transition to adult care. Tools are available to help with this preparation (<https://www.endocrine.org/improving-practice/transitions#th>). These focus on ensuring adolescents are well informed and have the necessary practical skills to take responsibility for their treatment, i.e., being able to arrange an appointment, to contact a doctor outside working hours, and to order and collect repeat prescriptions. It should be clear to the adolescent who their new doctor is and how they can contact this doctor.

The paediatric healthcare provider should inform the physician who will perform further follow-up of the medical history, including past and present endocrine and surgical treatments related to GI and other conditions, results of previous laboratory investigations and dual-energy X-ray absorptiometry scans. It is helpful to explicitly state which organs are in situ as this is important to be aware of in the assessment of complaints such as abdominal pain but also to determine potential cancer risks and relevant screening programmes such as those for cervical cancer or breast cancer. This information is also helpful for a GP and other healthcare providers that may be involved. Adolescents themselves should also be informed about appropriate cancer-screening programmes, even if they would not be eligible until they are older. Indeed, they may not receive an automatic invitation to certain cancer-screening programmes based on their registered sex. Given the time lapse of several decades until these may be required, this information needs to be repeated in the adult care unit.

During follow-up, monitoring of sex steroids is recommended to ensure levels within the physiological range for the affirmed gender [3]. In addition, in RFAB adolescents, continued monitoring of the Hct is recommended as this can increase above the reference range even after many years of testosterone treatment [117]. For Hct, haemoglobin, and creatinine, the male reference range should be used for those on testosterone, whereas the female reference range should be used for those on feminising hormone treatment with suppressed testosterone [118]. However, for prostate-specific antigen and cardiac troponin, the reference range of the sex registered at birth is appropriate [118]. Ideally, laboratories provide both the male and female reference ranges for such parameters to facilitate interpretation but this service usually is not available [119]. For other laboratory tests, the local laboratory should advise if there are differences between the male and female reference ranges.

For those treated with GnRHa during adolescence, it is recommended to monitor BMD until peak bone mass has been achieved [3]. For the calculation of BMD Z-scores, the International Society for Clinical Densitometry recommends using the reference range for the affirmed gender (<https://iscd.org/learn/official-positions/adult-positions/>). However, height should then be taken into account as adult height is similar to that of the sex registered at birth [27 , 32]. A relatively tall height compared to the female population will result in overestimation of BMD in RMAB adolescents, whereas a relatively short height compared to the male population will result in underestimation of BMD in RFAB adolescents. In case of delayed bone maturation, such as during/after GnRHa treatment, this should also be taken into account when interpreting the results of bone densitometry. If BMD in young adulthood is found to be low, lifestyle and hormone treatment should be optimised and further monitoring may be indicated, although it is currently unclear if and to what extent low BMD in TGDA translates into an increased risk of fractures.

Apart from monitoring hormone treatment, many other issues may require attention during the transition phase and young adulthood including education, employment, romantic relationships, sexual functioning, contraception, family building, and lifestyle. Adolescents should be informed where they can find help with questions on these topics.

Treatment wishes may change for various reasons, for example, because of dissatisfaction with the effects of treatment, experienced side effects, or changed gender identity. Several studies show that a high percentage of TGDA who start GnRHa continue onto gender-affirming treatment [67 , 76 , 77] and that most of those starting GAHT continue to use hormones, although these percentages vary between clinics [17 , 68 , 120]. Our knowledge about the true prevalence of de-transitioning for any reason, or about other reasons for stopping hormone treatment, is still very limited. Adolescents should be offered continued support and advice if they wish to change or stop treatment, also during healthcare at an adult gender unit. After cessation of treatment, recovery of endogenous hormone production, if applicable, should be monitored, alongside the effect that the physical changes have on the adolescent's well-being. In addition, evaluation of fertility should be offered to RMAB who have discontinued GAHT. BMD assessment is also part of follow-up. Given the lack of data on outcomes after cessation of treatment, research in this area is a priority.

In general, counselling about a healthy lifestyle is not different from the general population but it deserves special attention given the fact that long-term (i.e., in adults >30 years) bone, metabolic, and cardiovascular outcome of endocrine treatment for TGDA is currently not known. To minimise risks, the adolescent should be advised and encouraged to adhere to a balanced nutrition, sufficient physical activities, and to refrain from smoking or other recreational drugs.

A balanced nutrition should contain adequate calcium intake and must be appropriate for the energy expenditure. Indeed, obesity not only may increase the risk of long-term health complications but can also impede or complicate surgical procedures. Vitamin D intake should be optimised to support bone health and development.

Sport has many beneficial effects on global health, well-being, weight, strength, glucose and lipid metabolism, and bone mineralisation. The positive, direct effects of engaging in regular physical activity are particularly apparent in the prevention of chronic non-communicable diseases, such as cardiovascular disease, type 2 diabetes mellitus, cancer, hypertension, obesity, depression, and osteoporosis. To improve bone health, weight-bearing exercise is most effective.

It is important to help TGDA find physical activities that they feel safe and comfortable with. TGDA may prefer sports with mixed teams or individual training. Sports segregated by gender could cause dysphoria or may lead to problems with eligibility especially at a competitive level [121]. Practical issues such as use of changing rooms may need attention. Binder use might cause discomfort, pain, or shortness of breath during sport activities.

Smoking and alcohol are associated with increased cardiovascular and thromboembolic disease risks. It is highly recommended not to smoke or to quit smoking or vaping before starting GAHT. Also wound healing is severely impaired due to smoking and alcohol abuse; thus, those seeking gender-affirming surgery should be encouraged to stop smoking or vaping and reduce excessive alcohol consumption and to be offered referral to smoking cessation programmes when indicated [4]. Some surgeries where neovascularisation is critical, such as phalloplasty, may not be performed in smokers.

With TGDA, as with any adolescent, it is important not to assume sexuality. It is recommended to provide information about the prevention of sexually transmitted diseases, such as condom use and HPV vaccination programme, and testing for such diseases. TGDA should also be informed that GnRHa treatment and GAHT are not contraceptive methods and should be counselled about the available options for contraception (Table 5).

Some surveys have shown a high prevalence of sexual abuse and assault among transgender people [122]. In a US Transgender Survey, 19% of transgender youth reported sexual abuse [123]. It is recommended that healthcare professionals screen for abuse to recognise and respond to ongoing maltreatment of TGDA.

Teams providing medical care to TGDA inevitably face moral dilemmas. As discussed above, hormonal treatment has beneficial effects on mental health, quality of life, and physical appearance in TGDA that make it possible to live unobtrusively in the desired gender role. However, various ethical concerns have been raised about the risk of making the wrong (irreversible) treatment decisions, about the decision-making abilities of adolescents, the sustainability of such life-changing decisions over time, and the potential long-term adverse effects on health and on psychological and psychosexual functioning. Since the introduction of endocrine treatment for TGDA, these ethical challenges have been acknowledged by the professionals providing such healthcare [124 , 125]. Moreover, others outside these teams are critical [126 – 130].

Here, we will focus on four major issues: (1) what is the right time to begin treatment? (2) Do TGDAs have the medical decision-making competence to decide about treatment? (3) How should we deal with long-term treatment effects, especially infertility? And (4) what can be the role of moral case deliberation (MCD) sessions within the treatment teams?

There is debate about the right timing for hormonal treatment and surgery. The most recent guidelines recommend starting GnRHa from Tanner stage B2/G2 and GAHT from around age 16 although the most recent WPATH Standards of Care 8 do not provide an age limit [3 , 4]. Still, arguments are made both to lower or to increase the age at which to start GAHT. Two ethical concepts are important here: the best interest of the child and the child's autonomy to decide on medical treatment. In paediatrics, the "best interest" standard has become the prevailing standard in decision-making [131], but often proves difficult to apply [132]. Proponents and opponents of early medical interventions in TGDA are often not clear on what their definition of the best interest of a child is. There have been attempts to formulate "objective" criteria for the best interest standard. Some authors claim that every child has a right to reach adulthood with as many opportunities left open as possible, until he/she is a fully formed self-determining adult capable of deciding for himself. Physicians and parents would act unethically if they make choices that constrain a child's range of future options [133]. At first sight, this "right to an open future" seems reasonable, but the problem is that it could be used by opponents as well as proponents of early interventions. The right to an open future could be described as the right to postpone the decision on this far-reaching treatment until one is a capable adult. On the other hand, the open future can be described as a future in which the development of undesired secondary sexual characteristics of the sex registered at birth is prevented, and in which future treatment would be less invasive and painful, for example, breast removal in RFAB adolescents and painful and expensive treatment for facial hair removal in RMAB adolescents. This way, the future child could have more opportunities left open in the experienced gender. Importantly, observational data suggest that the traditional paradigms "In dubio abstine" (when in doubt, refrain) and "Primum non nocere" (first, do no harm) must be placed in a contemporary context. Withholding treatment may not be a neutral act and can potentially have significant consequences for the individual. Progressive development of secondary sex characteristics may increase distress, and the continued experience of GI may negatively impact mental health [17].

As adolescents approach adulthood, their involvement in medical decision-making increases. The best interest standard then makes way for their own values and preferences. In general, the right balance needs to be struck between protecting minors who are not fully capable of making the decision themselves to start or refuse a medical treatment and respecting minors' evolving autonomy. According to the international transgender guidelines, an important prerequisite to start treatment is that TGDAs are competent to give informed consent [3 , 4]. But even in older adolescents, decision-making competence proves an important point of disagreement when discussing early interventions [134]. There is increasing public discussion whether any adolescent is truly competent to decide on treatment, especially because the treatment has far-reaching

long-term consequences [135 – 137 , 135 , 136]. Furthermore, adolescents' competence appears to be a recurring and increasingly important issue in case law [138 , 139].

Recently, a study was conducted that aimed to determine whether the TGDAs who were eligible to start puberty suppression were competent to make that decision. The MacArthur Competence Assessment Tool for Treatment (MacCAT-T), a validated semi-structured interview, modified for minors was used [140]. The results of this study are reassuring, showing that the majority (about 90%) of the adolescents participating in this study have thoroughly thought about puberty suppression, understand what the treatment involves, and are deemed competent to decide, in line with a recent review [141].

An ethics support tool, the “Competence Consultant,” has been developed to support clinicians when dealing with moral challenges around the competence of TGDA to make decisions [58]. To be valid, consent should not only be competently given and uncoerced, but also fully informed. “Full information” may pose a challenge in the case of care for TGDA. As early choices may have an impact on later treatment possibilities and affect the whole life span, teenagers have to gain biological knowledge and develop an opinion about topics that they under different circumstances may not yet have addressed, i.e., sexual relationships and sexual health or parenthood. The healthcare provider may address topics that are premature and uncomfortable for the young person and their families. Such information may even be experienced as inappropriate and traumatic. Furthermore, (long-term) risks and benefits of available treatments are, in fact, not fully established. Although no serious side effects are reported until now, the long-term medical and psychological effects in gender dysphoric adolescents must be evaluated continuously. It may be argued that since the risks and benefits of early gender transition cannot be fully established in advance, it is not possible to give valid informed consent. On the other hand, every new intervention has the problem of few long-term data. It is the obligation of every treatment team to participate in systematic interdisciplinary and (international) multicentre registries and research.

One of the most far-reaching long-term effects of transitioning is the potential loss of fertility. Before starting treatment, sperm and oocyte retrieval and banking can be offered to those who are post-pubertal, but there are significant barriers, as described in the paragraph on fertility. Oocyte retrieval is an invasive procedure with limited clinical and research experience in minors. Both sperm and oocyte banking are in many jurisdictions not covered by insurance. Future options may shed a new light on fertility preservation and the right to procreate [59]. In the future, it may become possible for prepubertal gonadal tissue to be differentiated in tissue culture to result in mature sperm or oocytes. Also, other assisted reproductive technologies (ARTs), like in vitro gametogenesis, may prove to be the solution for transgender people to have genetic offspring [142]. The current experiences of trans people with ART service providers are mostly negative, even in countries where there are no legal barriers to access ART [95]. With future options on the way, an ethical and legal debate is essential, considering the right to equality and non-discrimination, and the right to procreate for trans people.

Questions will probably always be raised on whether it is appropriate to treat a condition that is not considered a disease with potent hormones that have irreversible effects at an age where the involved individual may not be capable of fully understanding and appreciating all consequences. Evidence from clinical research alone will likely not be able to provide answers to all raised uncertainties. Ethical dilemmas will therefore remain in this sensitive field of care, and healthcare providers need continuous mutual support and supervision including time for discussing ethical challenges.

MCD is a relatively well-established form of clinical ethics support and may help clinicians deal with ethical and moral challenges more effectively [96]. MCD is a facilitator-led, collective moral inquiry by clinicians that focuses on a concrete moral question connected to a real clinical case [143]. Research shows that MCD helps more effectively deal with ethical and moral challenges [144]. It improves mutual understanding, respect, and communication among team members. It also strengthens the ability of teams to make decisions and act when managing ethically difficult

circumstances. As such, MCD can be seen as an additional tool that can be used in complex cases [145].

Hormonal treatment in TGDA needs to be provided by a specialised MDT, only after careful assessment and extensive counselling about its effects, possible side effects and risks, and uncertainty about long-term outcomes. We urge clinicians to combine clinical care with data collection for research to improve knowledge in this field and governments to facilitate such activities. International networks such as Endo-ERN and registries such as the EuRRECa registry should help achieve this goal and further improve care.

We would like to thank the representatives from Transvisie, Acceptess-T, and Transgender Europe who reviewed the manuscript.

SEH and HLC-vdG have received a lecture fee from Pfizer and Sandoz, and KMM received a lecture fee from Novo Nordisk and an advisory board fee from Lundbeck. None of the other authors have a potential conflict of interest to declare.

This study was not supported by any sponsor or funder.

S.E.H., K.B., G.B., H.L.C-vdG., M.C., A.M.G.-S., D.K., K.M.M., L.M., A.R.-U., N.S., and M.C.dV. contributed to the design of the manuscript and the drafting and reviewing of the work and approved the final version.