Approach to the Patient: Pharmacological Management of Trans and Gender Diverse Adolescents

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Grants of Fellowships supporting the work:

KCP is supported by the Hugh Williamson Trust and Royal Children’s Hospital Foundation.

Disclosures:

Nil.
ABSTRACT

Internationally, increasing numbers of children and adolescents with gender dysphoria are presenting for care. In response, gender affirming therapeutic interventions that seek to align bodily characteristics with an individual’s gender identity are more commonly being employed. Depending on a young person’s circumstances and goals, hormonal interventions may aim to achieve full pubertal suppression, modulation of endogenous pubertal sex hormone effects and/or development of secondary sex characteristics congruent with their affirmed gender. This is a relatively novel therapeutic area and, while short-term outcomes are encouraging, longer-term data from prospective longitudinal adolescent cohorts are still lacking, which may create clinical and ethical decision-making challenges. Here we review current treatment options, reported outcomes, and clinical challenges in the pharmacological management of trans and gender diverse adolescents.

Keywords: Transgender, Gender dysphoria, Gender diverse, Hormone therapy, Adolescents
CASE PRESENTATIONS

Case 1

R.C. is 12 years old. Her female gender expression commenced in early childhood when she began to describe herself as a girl, express that her body was ‘wrong,’ and ask for her penis to be removed. At the age of 8 years, she socially transitioned to living as a girl, with improvement in her wellbeing and psychological distress, and her female gender identity has been consistent and persistent for many years. In recent months, she started puberty and is now experiencing distressing erections as well as an intense fear of developing a deeper voice, facial hair and an Adam’s apple. She has been assessed by mental health clinicians as meeting DSM-5 criteria for Gender Dysphoria (GD)(1) (Table 1). R.C. is keen to access pubertal suppression (PS) to prevent further masculinizing changes. She also expresses a longer-term goal to feminize her body and therefore envisages progression not only to gender affirming hormone (GAH) therapy with estrogen but also feminizing surgery. Baseline examination and investigation findings are shown in Table 2.

Case 2

H.G. is a 15 year old adolescent. He describes not thinking much about gender as a young child, but reports feeling different from age ~10 years in the context of early pubertal changes. Thereafter he reported increasing discomfort in relation to his body, with significant escalation in distress in the last 2-3 years. He describes his gender identity as ‘definitely not female’, with progression to consistent feelings of a more masculine identity over time. Menarche occurred at age 12.5 years. His chest, voice, menstruation and misgendering as female are the predominant sources of his GD. In the past 2 years his mental health has deteriorated with heightened anxiety around school and social engagements. His mood is low, with intermittent deliberate self-harm. He has been assessed as meeting DSM-5 criteria for Gender Dysphoria(1) and is seeking hormonal intervention. His
gender-affirming goals are to ‘pass’ as male with a deeper voice, flat chest appearance and facial hair. He reports no desire for future pregnancy or parenting but recognizes that his views on this may change over time and has been counselled on the potential effects of testosterone on fertility. Baseline examination and investigation findings are shown in Table 2.

INTRODUCTION

Internationally, presentations of trans and gender diverse (TGD) children and adolescents seeking support and therapeutic intervention from specialist clinics have significantly increased in recent decades(2-4), consistent with recent population-based surveys suggesting that TGD individuals comprise 1.2 to 2.7% of all young people(5, 6). Key terminology continues to evolve in this area and is summarised in Table 3. Gender incongruence is characterized by a marked and persistent mismatch between an individual’s experienced gender and their assigned sex(7). This may be associated with gender dysphoria (GD)(1), although not all TGD individuals experience dysphoria. TGD youth are a vulnerable population, with a higher prevalence of social isolation, harassment, mental health problems (notably mood and anxiety disorders), self-harm and suicidality compared to the general population(2, 3, 8-12).

Therapeutic interventions that aim to more closely align bodily features with an individual’s gender identity have evolved over the past few decades. Gender affirming hormonal interventions were first initiated for TGD adolescents by clinicians in the Netherlands >30 years ago(13). Today, various clinical guidelines(3, 14-16) recommend hormonal interventions for adolescents with GD who meet defined criteria (Table 4). A multidisciplinary approach to management is important(3, 14, 15), and the involvement of an experienced mental health clinician is critical, not just to assess GD but also to determine readiness for and provide monitoring during hormonal therapy.
A range of different pharmacological options exist for the management of adolescents with GD (Table 5) and are described below.

**Pubertal suppression**

While dysphoria is not universal, the development and progression of secondary sex characteristics incongruent with one’s gender identity are recognised precipitants of increasing GD and worsening mental health in TGD adolescents (3, 17, 18). PS aims to temporarily suspend sex hormone production and the development of secondary sex characteristics incongruent with an individual’s gender identity. Gonadotrophin-releasing hormone agonists (GnRHa) are the recommended means of PS for those in early or mid-puberty (14, 15), reflecting their efficacy in achieving biochemical and clinical PS (19).

GnRHa act via reversible desensitization of the GnRH receptor, with spontaneous resumption of the hypothalamic-pituitary-gonadal axis expected within months if therapy is discontinued (15, 20, 21). Treatment temporarily prevents further pubertal progression, allowing a TGD adolescent more time to explore their gender identity without experiencing ongoing incongruent pubertal development. As such, GnRHa are a therapeutic intervention in their own right and, although recent data indicate that a majority of TGD adolescents who undergo PS proceed to GAH or surgery in due course (22, 23), these subsequent treatment pathways should not be regarded as a *fait accompli* once PS has been initiated. TGD young people on GnRHa should continue to be counselled, with ongoing assessment and discussion of their desire to continue to PS as well as their longer-term therapeutic goals.
A variety of GnRHa agents and formulations are currently available and there are no reported differences in efficacy in the context of treating TGD adolescents(24). Formulations differ predominantly in their mode of administration and duration of effect, with depot preparations that afford longer suppression often preferred. Choice of a particular GnRHa agent depends on patient and physician preference, local therapeutic agency approval, and cost. In practice, effective PS may extend beyond the approved dosing schedule(25). Given the high cost of GnRHa and need for removal/replacement procedures with implants, it is not uncommon for clinicians to monitor for pubertal re-awakening before administering the subsequent dose.

Modulation of endogenous pubertal hormone effects

A variety of other agents are used in TGD adolescents to modulate the effects of endogenous pubertal hormones. Agents with anti-androgenic properties may have beneficial effects for TGD individuals with a feminine identity, while high dose progestogens can achieve menstrual suppression in transmasculine or gender non-binary youth. These agents modulate potentially distressing symptoms of incongruent puberty without causing full PS, and therefore are not typically considered first-line if PS is indicated. They may however be used when affirming care is sought at Tanner 4+ (when the higher likelihood of adverse effects from abrupt hormonal withdrawal(23) arguably outweighs the more marginal effects on physical development) or where GnRHa therapy is unavailable, precluded by cost, or undesirable (e.g. needle phobia)(15).

Anti-androgens with reported use in TGD populations include cyproterone acetate (CPA), spironolactone, medroxyprogesterone acetate and bicalutamide(26). Of these, spironolactone and CPA are most commonly used(27, 28), although outcome data specific to TGD adolescents are
limited. Spironolactone has well documented anti-androgenic effects\cite{29, 30}. CPA has been found to effectively reduce facial and body hair in a majority of late pubertal trans-girls, with fewer spontaneous erections also reported by some\cite{31}. Choice of agent may be influenced by availability (CPA is not available in the USA due to safety concerns), clinician experience, cost, patient preference and tolerability. Some anti-androgens contribute to breast development \cite{26, 31, 32}. This may arise due to lower testosterone levels (hence altered circulating estrogen:testosterone ratio), as a progestogenic effect or a combination of mechanisms; however the relative roles of different hormones or agents in promoting breast growth are not well established in TGD populations \cite{33}. Optimal dosing strategies are unknown but much lower doses of agents such as CPA (e.g.12.5mg daily) than were initially studied (up to 100mg daily) are currently employed.

For transmasculine youth, suppression of menses is often desired, not only to help relieve menstruation-associated GD, but also given prevalent safety concerns in accessing bathrooms\cite{34}. Options include a progestogen, such as medroxyprogesterone (orally or injectable depot), oral lynestrenol or norethisterone, either alone or in a continuous combined oral contraceptive pill (although many transmasculine youth may decline this due to concerns regarding estrogen use)\cite{35, 36}. Highest rates of amenorrhoea are reported with depot medroxyprogesterone\cite{35}, although concerns regarding adverse impacts on bone health limit its use as a first-line choice. The levonorgestrel-containing intra-uterine device (IUD) is another option, particularly if contraception is desired. Pelvic ultrasound to confirm sufficient uterine cavity size may be beneficial in such cases, especially in individuals presenting soon after menarche, and some TGD adolescents will require light sedation or a short anaesthetic to tolerate insertion. Irregular, unpredictable bleeding may occur with all progestogens, which may lead to discontinuation\cite{36}. Ultimately, for those who use testosterone as masculinizing GAH therapy, circulating testosterone levels in the adult male range
will induce menstrual suppression in >90% of cases(35). Involvement of pediatric gynecology services is very useful for gynecological, reproductive and sexual health aspects of TGD care.

**Gender-affirming hormone therapy**

Exogenous estrogen or testosterone may be prescribed to adolescents wishing to feminize or masculinize respectively(3, 14, 15). The principal goal of GAH therapy is to induce desired secondary sex characteristics congruent with an individual’s identity; however specific goals and priorities for gender affirmation vary between individuals.

Where PS is commenced in early puberty and the adolescent is relatively naïve to sex hormone, GAH is conventionally introduced at a low dose with gradual incremental dose increases timed to mimic the tempo of typical puberty. For adolescents already in well-established puberty (Tanner 4+), introduction and escalation of GAH therapy can be more rapid(3, 15).

Medications that contain 17 ß-estradiol are most commonly recommended for feminization. Use of ethinyl estradiol-containing medications should be avoided due to higher thrombo-embolic risks(15, 37). Oral and transdermal agents are the most commonly used routes in many countries, with injectable and sublingual options available in some jurisdictions. Published dosing strategies(15) are largely based on experience and expert opinion, and prospective controlled studies comparing different regimens are lacking(37, 38).

While exogenous estrogen therapy will provide some hypothalamic-pituitary-testicular axis suppression, experience in adult cohorts indicates that estrogen alone is unlikely to provide
sufficient suppression without use of supra-physiological doses (and attendant increase in risk of adverse effects). Concomitant GnRHa therapy can therefore be beneficial, but use of an anti-androgen is a common alternative if GnRHa is not available (15, 37). Ultimately, some transfeminine individuals elect to undergo gender affirming surgery including orchiectomy, which will remove the need for GnRHa or an anti-androgen; however, this is generally not performed until age >18 years (3, 14, 15).

Testosterone regimens in TGD adolescents seeking to masculinize reflect those used in hypogonadal cisgender males. International guidelines recommend use of short-acting injectable preparations (2-4 weekly) and these are the most commonly reported agents in adolescent cohorts (3, 15, 37, 38). However, if unavailable or unacceptable (e.g. due to frequent injections), alternative regimens and routes may also be employed (3, 15). Longer-acting injectable testosterone preparations are more typically reserved for use in those with well-established pubertal hormone exposure. Dose modulation is more easily undertaken with short-acting injectable testosterone esters or topical preparations. PS or alternative therapies to modulate the effects of endogenous pubertal hormones (e.g. progestogens) are typically continued until adult testosterone levels are consistently established.

**THERAPEUTIC EFFECTS OF HORMONAL INTERVENTION**

**Gender affirming physical changes**

Physical outcomes more congruent with gender identity have also been reported among TGD adults who received PS as compared with those who completed endogenous puberty (39, 40). Desired masculinizing effects reported in testosterone-treated TGD cohorts include voice deepening, increased facial and body hair growth, clitoral growth and cessation of menses (9, 15, 41). Many of
these effects become established within 6-12 months and continue to develop thereafter (15). In transfeminine adolescents treated with estrogen, the main gender affirming physical changes include breast development (starting within 3-6 months and continuing to Tanner 4+ in >80% at 3 years (42)) and feminization of body shape and fat distribution (42-44). Studies comparing different GAH regimens head-to-head are currently unavailable. As many gender affirming physical effects are gradual and may take years to become fully established, open discussion of the estimated timelines involved (see Endocrine Society Guidelines 2017 (15)) is important to ensure realistic expectations, especially for adolescents whose long-term and abstract thinking is still developing.

**Mental health**

Most empirical studies have reported improved mental health outcomes in TGD youth using hormonal therapies. However, the overall quality of evidence is low with studies limited by small sample sizes which may preclude the ability to determine statistically significant effects in some outcomes (23, 45-50). Suboptimal study design (e.g. cross-sectional (51), retrospective (45, 52), or lacking a well-matched control group (23, 45-48, 50, 52-54)), and use of various non-diagnostic screening tools (23, 47, 50, 51, 53) are additional methodological limitations. Whilst studies with prospective/longitudinal designs (23, 46-51, 53, 54) have emerged, randomised controlled trials are lacking. Studies assessing outcomes in socioeconomic and ethnically diverse populations or gender nonbinary adolescents are also scarce. Despite these limitations, as outlined below, improvements have been noted across most empirical studies following use of both PS alone and GAH (either alone or with PS) in the outcomes of overall psychological functioning, depressive symptoms, self-harm and suicidal ideation. Additionally, improvements in GD and body image with use of GAH have been reported.
Overall psychological functioning

General psychological wellbeing, assessed using Youth Self Report [YSR](23, 47, 49-51), the Child behaviour checklist [CBCL](23, 47, 49, 50) or the Children’s Global Assessment scale [CGAS](47, 50, 53), significantly improved from baseline following PS alone in three studies(50, 51, 53) but was unchanged in another cohort, where notably, 57% were Tanner 4+ prior to PS(23).

Improved psychological functioning, with follow-up outcomes comparable to the general population, has also been reported following use of PS(53) and GAH and/or gender-affirming surgery(47, 49).

GD and body image

GnRHa therapy alone has not been associated with a subsequent change in GD or body dissatisfaction in adolescents(17, 23). However as neither one’s incongruent primary sex characteristics nor the absence of desired secondary sex characteristics are influenced by GnRHa therapy, this is not unexpected(38). Complete resolution of GD and significant improvements in body satisfaction with subsequent introduction of GAH and/or surgery have been documented(47, 54).

Depression and anxiety

Depressive symptoms decreased significantly from baseline after PS in a prospective longitudinal study of Dutch TGD adolescents(50), with no further significant change in symptoms noted after GAH / surgery(47). Two additional longitudinal studies also found self-reported depressive symptoms decreased from baseline in TGD youth receiving endocrine interventions (PS and/or GAH)(48, 54).
Longitudinal studies have shown anxiety is largely unchanged with PS alone (50, 54). Anxiety symptoms improved significantly among those who received either PS or GAH in one study (n=102), while the decreases seen in another study (n=32) were not statistically significant (47).

Self-harm and suicidal ideation

Five studies of PS and GAH documented significantly reduced rates of self-harm and suicidal ideation (45, 46, 48, 51, 52) and, importantly, in one of these, TGD adolescents undergoing PS had similar rates of self-harm/suicidality as cisgender controls (51). Another study (n=44) reported no significant effect of PS alone (23).

POTENTIAL SIDE EFFECTS OF HORMONAL INTERVENTION

Available data indicate that hormonal treatments for TGD adolescents are generally safe (19, 42, 43). Nonetheless, it is important to consider the possibility of unwanted effects, described below.

General physical, haematological and biochemical effects

GnRHa are typically well-tolerated (55), although hot flashes, headaches, emotional lability and mood changes are described (15, 19, 23, 45), particularly early in treatment (56) and in those in more advanced puberty at GnRHa initiation (23). Similar symptoms have been described with CPA use (31). Transmasculine adolescents should also be counselled that the transient stimulatory effects of GnRHa may induce a menstrual bleed in the initial weeks after the first dose.
Electrolyte monitoring is recommended with spironolactone use but hyperkalemia has not been documented in TGD youth\(^{(57)}\). CPA is not approved for use in USA due to concerns regarding hepatotoxicity and meningioma\(^{(37)}\); additional reported side-effects include low mood, hyperprolactinemia and less favourable cardiovascular profiles\(^{(15, 27, 58)}\).

Testosterone therapy is commonly associated with acne, particularly in the first year\(^{(41, 45, 59)}\). Erythrocytosis in association with exogenous testosterone use is also recognized\(^{(37, 60)}\), with higher haemoglobin and haematocrit levels observed in adolescents on testosterone\(^{(43)}\). Evaluation and attention to concomitant secondary causes (e.g. smoking, obstructive sleep apnoea) is important. Data from adult cis\(^{(61)}\) and TGD\(^{(62)}\) cohorts suggest erythrocytosis is highest with short-acting injectable preparations and lower with transdermal preparations. Therapeutic phlebotomy or change of testosterone dose, interval or preparation may also be considered. Androgenic alopecia\(^{(45)}\), higher blood pressure\(^{(63)}\) and mild reductions in HDL\(^{(63, 64)}\) have also been documented in some TGD adolescents using testosterone; a higher prevalence of obesity prior to and during testosterone therapy is also reported\(^{(64)}\).

Estrogen-specific health risks relate predominantly to pro-thrombotic effects\(^{(37)}\), although reports in adolescents are rare\(^{(65)}\). To reduce this risk, use of 17β-containing estrogens is recommended, while ethinylestradiol should be avoided\(^{(15)}\). Transdermal delivery may also be helpful \(^{(66-68)}\). Elevation in prolactin following estrogen therapy is also recognized\(^{(15, 37)}\), likely exacerbated by CPA\(^{(27, 58, 69)}\). Current guidelines recommend prolactin monitoring \(^{(15)}\), but clinically relevant hyperprolactinemia has not been found in adolescent cohorts\(^{(42)}\) and an individualized approach based on additional risk factors and medications is taken by many.
To date, no significant differences in cardiovascular risk factors have been observed in association with hormonal therapies in TGD youth treated from adolescence to early adulthood (64). Nonetheless, encouraging universally endorsed lifestyle measures that promote cardiovascular health – such as physical activity, healthy BMI, and avoidance of smoking and prolonged immobility – and ongoing clinical monitoring are recommended. Long term assessment of cumulative risk in those who commence hormonal therapies in adolescence will be important.

**Bone health**

Sex hormones drive the significant pubertal increase in bone mineral density [BMD] accrual, which is critical for optimising peak bone mass in early adulthood and mitigating against osteoporosis and fractures later in life (70, 71). Unsurprisingly, PS affects BMD accrual and monitoring of bone health is recommended for all GnRHa-treated TGD adolescents (3, 14, 15). Interestingly, low BMD including high rates of BMD < 2 SD below the median (72-75) have been reported in TGD adolescents even prior to commencement of PS. The underlying reasons are unclear but may reflect low rates of physical activity. While longitudinal assessment in GnRHa-treated youth has documented either stable (72, 74) and/or slightly reduced mean group BMD (23, 73) relative to peers, approximately half of reported GnRHa-treated subjects appear to have lost absolute BMD during PS, which is concerning (76). Longitudinal data indicate improvement with GAH therapy, albeit with incomplete catch-up (73) and persistently low bone mineral apparent density z-scores in transfeminine individuals (77). Additional longer-term follow-up studies will be required to assess the impact, if any, on functional outcomes such as fracture risk. In the meantime, promoting measures that optimise bone health, such as weight-bearing exercise and vitamin D sufficiency, is encouraged.
Fertility

Clinical guidelines underscore the importance of fertility counselling for TGD adolescents considering hormonal interventions, given their potential impact on reproductive function (3, 14, 15). In particular, concerns relate to the adverse effects of prolonged GAH on spermatogenesis and oocyte development (15, 78), and the reader is referred to comprehensive recent reviews for more details on this subject (79, 80). Nonetheless, counselling should address both the option of gamete cryopreservation prior to hormone commencement, as well as the alternative (with documented success) of interrupting GAH treatment for a sustained period in future to restore reproductive function (81-85). The associated implications of an interruption in GAH – which might include the development of undesired physical characteristics and an exacerbation of GD – may, however be unacceptable to many TGD individuals (86). Although use of GnRHa is not expected to permanently affect fertility, the high rates of progression from PS to GAH (22, 23) mean fertility counselling is recommended prior to PS (3, 14, 15). Oocyte cryopreservation from a transmale adolescent using GnRHa therapy from early puberty has also been reported (87). Additionally, transmasculine young people should be counselled that although it may induce amenorrhea, testosterone does not provide reliable contraception and, in the event of a pregnancy, is teratogenic (15, 35). The need for an alternative means of effective contraception if engaging in vaginal intercourse should be emphasised (88).

Growth

In TGD adolescents with open epiphyses, GnRHa therapy will delay the pubertal sex hormone-dependent increase in growth velocity (GV) and prolong overall duration of growth. Subsequently, additional growth is expected following GAH initiation, with a higher GV than during PS. The cumulative impact of hormonal interventions on final height will vary depending on an individual's
genetic height potential, bone age at the initiation of therapy, duration of PS and tempo of GAH dose escalation (15). Modulation of estrogen regimens to prevent excessive height in transfeminine adolescents has been attempted, albeit with unclear success and safety (42).

**Impact on feminizing surgery options**

By limiting genital growth, the use of PS in early-mid puberty may restrict future feminizing surgical options, in particular penile inversion techniques for neovaginal formation (89, 90). Consequently, alternative surgical methods, such as peritoneal flaps or intestinal grafts, may be required but are surgically more complex and can be problematic (e.g., due to unwanted intestinal tissue mucous production (91)(92)). A recent Dutch study found that among those deemed to have insufficient genital skin for penile inversion, stretched penile length was <8 cm (91). Counselling prior to GnRHa therapy should include discussion of locally available surgical options when considering optimal timing to initiate PS, while bearing in mind that surgical techniques are continuing to evolve as greater numbers of people treated with GnRHa seek feminising surgery.

**Cognition**

Adolescence is associated with increasing maturity, cognitive gains and ongoing neurodevelopment; however, the precise roles of sex hormones in these processes are not well established. Available data have not demonstrated any adverse impact of PS on executive function in TGD youth; however, the sample size of this study was small and likely underpowered (93). A recent systematic review and meta-analysis of data in post-pubertal TGD young adults reported no adverse impact of GAH on any cognitive domain assessed and significant improvement in visuospatial abilities following testosterone treatment (94).
Unwanted psychosocial impacts

A common concern when discussing gender-affirming interventions is the potential for future regret in the face of irreversible physical effects. To date, the largest study to systematically examine regret comes from the Netherlands and followed 6,793 TGD individuals who attended a single gender identity clinic from 1972-2015. Regret rate among those 5,433 individuals who first presented as adults was 0.5%, and no cases of regret were observed among the 1,360 individuals who were first seen before the age of 18 years. Although duration of follow-up varied, the cohort included adolescents aged 12-18 years and children <12 years from 1981 and 1984 onwards, respectively; overall numbers of both children and adolescents increased significantly from 2003. Ongoing, long-term follow-up of this and other adolescent cohorts who receive hormonal interventions in adolescence is required. While GAS is uncommonly performed in adolescents aged <18 years, regret rates in those who undergo GAH in the presence or absence of subsequent GAS may also differ, and it will be important for future studies to assess this.

Data in adults also suggest testosterone may have a short-term impact on increasing aggression but not anger; however these effects have not been well-studied in adolescent TGD cohorts. Ongoing review with an experienced mental health clinician over the course of medical transition is therefore important.

Although GAH can assist with development of desired secondary sex characteristics, they will not reverse established anatomical features (e.g. phenotypically male external genitalia). Ensuring realistic expectations and acceptance of the limitations of hormonal interventions prior to commencement is a critical part of counselling.
Sexual function and well being

Sexual maturation is one of the hallmarks of adolescence, and the use of hormonal interventions in TGD young people can potentially impact sexual function and satisfaction.

Psychologically, the unwanted changes of a TGD adolescent’s endogenous puberty can increase body and genital aversion, and thus influence their approach to sexual experiences and satisfaction(47). TGD adolescents have lower self-esteem and poorer body image, and are less romantically and sexually experienced than their cisgender peers(98). Since body image, self-esteem, psychological wellbeing and sexual anxiety are all critical aspects of sexual health and satisfaction(99, 100), hormonal interventions have the potential to positively influence sexual wellbeing by improving GD(101, 102).

Physically, vaginal atrophy and dryness are common in postmenopausal women and other hypoestrogenic states,(103) and might therefore be expected with GnRHa therapy in transmasculine individuals,(104) but to date have not been reported. Testosterone can increase libido, induce clitoral growth, and cause vulvovaginal atrophy and dryness (that usually respond well to topical oestrogen or lubricant therapy), while anti-androgens and estrogen typically reduce libido, erections, semen production and ejaculate volume(15).

Taken together, hormonal interventions for TGD adolescents can be expected to affect desire, arousal and/or sexual interest as well as the ability to orgasm(105). However, it is important to note that some of the apparent disturbances or changes in sexual function do not necessarily translate to sexual dysfunction, since they may not be accompanied by distress. For example, TGD individuals may interpret increased or decreased sexual desire
differently. Thus, heightened libido is welcomed by some transmasculine people, but perceived by others as stressful\(^{(100)}\); similarly, reduced libido is undesirable for some transfeminine individuals, but is a reported relief for the majority\(^{(106, 107)}\).

Data systematically assessing sexual function and wellbeing in TGD adults, let alone adolescents, are sparse. To date, the few studies have focused on outcomes in adults following both GAH and gender-affirming surgery and, although they report improved sexual function and satisfaction\(^{(101, 108)}\), the relative contribution of hormonal or surgical interventions is not known. Longitudinal studies assessing sexual function before and after hormone treatment in TGD individuals, including adolescents, are therefore needed.

**CHALLENGES, AREAS OF UNCERTAINTY AND FUTURE DIRECTIONS**

A number of controversies exist in this field, most of which are driven by understandable concerns that individuals may come to regret decisions they made about hormonal treatments as adolescents and be left with unwanted irreversible effects\(^{(109, 110)}\). As mentioned above, existing evidence suggests low rates of regret, but further studies are required to further establish or refute these findings.

A principal challenge centres on the capacity of an adolescent to fully understand the implications of hormonal treatment as well as related decisions regarding the optimal timing of hormonal therapies. Internationally, practices pertaining to both the age and/or developmental stage at which these treatments might be prescribed, as well as circumstances relating to obtaining consent for their use from legal minors, differ. On one hand, some advocate for earlier introduction of GAH in order for younger adolescents to avoid being physically “out of sync” with their age-matched peers and have started GAH in individuals as young as 11 years\(^{(111)}\). Conversely, others argue that hormonal
treatments in minors require greater restrictions. Indeed, in countries such as Australia (112, 113) and the UK (114), concerns relating to the capacity of adolescents to give fully informed consent have resulted in judicial oversights which limit the ability of minors to consent autonomously to GnRHa and GAH. The specific situations where this applies differ between jurisdictions but in such scenarios either parents may give consent on the adolescent’s behalf or court authorisation may be required.

Such legal restrictions appear to be based on various concerns. For example, an important goal of PS is to allow additional time for a TGD young person to further explore decisions about potential GAH use without the associated distress of ongoing incongruent pubertal development. Whether typical cognitive maturity and decision-making capacity is achieved in TGD adolescents in the absence of pubertal sex hormones (115) is unclear, although it should be noted that no impact of PS on cognition has been demonstrated in cisgender cohorts treated with GnRHa for either precocious puberty (116) or short stature (117). Another concern relates to the perception that hormonal interventions reflect the start of a ‘pathway’ that an adolescent may find it difficult to get off (118). Specifically, some worry that early PS may change the trajectory of gender diverse adolescents by limiting the potential for their endogenous pubertal hormones to reinforce their assigned gender identity (110). Potentially consistent with this, older reports suggest low rates of persistence of gender incongruity from childhood into adolescence (119, 120) and these studies seemingly conflict with more recent data indicating that the vast majority of TGD young people who commence PS progress onto further GAH or surgery (22, 23). However, this discrepancy most likely reflects methodological issues (121), including changes in diagnostic criteria over this timeframe. Previously, gender non-conforming behaviour alone was sufficient to warrant a diagnosis without requiring actual distress as is now the case, with the implication being that earlier reports were based on subjects who were not actually transgender (121). Consistent with this, ‘persistence’ of GD has been
most closely linked to the intensity of the GD in childhood and the amount of reported ‘cross-gendered behaviour’ (122).

It is also important to recognise that terms such as ‘persistence’ and ‘desistence’ tend to imply binary male/female outcomes in relation to gender identity (123). However, for many young people, gender identity is fluid, dynamic and/or not exclusively male or female (i.e., non-binary) (124). Thus, some may elect not to have hormonal therapies in adolescence but to pursue this later in life (123). Equally, some adolescents may choose to discontinue GAH therapy, not because they regret using these therapies but because they are satisfied with the physical changes already attained (124). Future studies of “desistence” should therefore take into account possible gender fluidity and non-binary identities. Similarly, when ‘de-transition’ is assessed as an outcome, it should be noted that this does not necessarily imply a change of gender identity or indeed regret. Indeed, in the US Transgender study 2015, only 5% of those who had ever de-transitioned (0.4% of the overall sample) reported that they had done so because they realised gender transition was not for them; in contrast the vast majority (82.5%) reported that the decision to de-transition was driven by external pressures (most commonly family pressure and social stigma) (125).

Looking ahead, it is essential that more research be conducted to improve the available evidence base and better guide the hormonal treatment of TGD adolescents. Although existing data indicate positive outcomes, the overall quality of evidence relating to hormonal therapies in TGD youth is low (37, 38). In particular, questions remain regarding optimal pharmacological strategies (e.g., timing, dose, agent) to maximize psychological and physical benefit while minimizing unwanted effects; studies specifically assessing regret as well as interventions/outcomes for gender non-binary youth are also required. Ethical concerns regarding the withholding of hormonal therapy have
precluded randomized controlled trials in TGD adolescents, and studies with relevant control groups (e.g., those unable to access hormones or matched for existing mental health problems) are challenging to perform. Nonetheless, further studies directly assessing different hormonal treatment strategies are necessary and feasible, as are large prospective cohort studies comparing long-term physical and mental health outcomes (including bone health, fracture risk, cardiovascular outcomes, depression, anxiety, self-harm, and suicidality) between TGD adolescents who access hormonal treatments and contemporaneous age-matched, population-based samples (111, 126).

BACK TO OUR CASES

Case 1

Given her puberty-related distress, R.C. expressed a strong desire for GnRHa therapy and all her clinicians and family members supported this. However, R.C. and her parents opted to initially defer PS for several reasons. Firstly, R.C. indicated a desire to access feminizing surgery as an adult and therefore wished to delay PS to optimise her chances of having penile inversion surgery, although she was aware that this could not be guaranteed. Secondly, R.C.’s parents saw potential benefits in delaying PS to minimise adverse bone health effects. Thirdly, although R.C. was unsure about her future parenting desires, she and her parents were keen to preserve her fertility by cryopreserving sperm, and delaying PS increased the likelihood of this being successful. Finally, as R.C. was already quite tall and concerned about excessive final female height, although height outcomes were more difficult to predict, it was agreed that delaying PS (but introducing prior to peak GV) was a reasonable approach.
Initiation of PS was therefore deferred with planned commencement at a stretched penile length of ~9-10 cm and testicular volumes of ~10 ml. However, the option of starting PS earlier was also provided should R.C.’s distress regarding her endogenous pubertal development become intolerable. In the meantime, vitamin D supplementation and lifestyle advice were provided to optimise her bone health, and regular mental health, medical and hormonal monitoring continue.

Case 2

H.G.’s principal gender affirmation goals were ‘passing’ as male, altering his chest appearance, masculinizing his body and menstrual suppression. Potential options (either alone or in combination) that were discussed with him and his parents included: (i) chest binding and eventually reconstruction surgery; (ii) hormonal modulation for menstrual suppression; and (iii) testosterone. While GnRHa therapy might induce some minor reduction in breast volume(23), a female chest appearance would nonetheless remain and the potential for adverse effects was felt likely to outweigh any positive impact of PS at Tanner 5. In the first instance, H.G. trialled the oral progestogen norethisterone (commencing 5mg bd) for menstrual suppression, with good response. H.G. was keen to pursue chest surgery but this was not available locally until >18 years of age, so options and resources for safe chest binding were discussed as an interim measure. Finally, information in relation to the potential affirming, unwanted and unknown effects of testosterone – as well as its limitations – was shared with H.G. and his parents, with further detailed discussions planned for future sessions.

H.G., whose current (likely final) height is more than -2SD below the median for adult males in the general population, was also counselled that his bone age indicated no capacity for further linear growth; this was frustrating for him due to the likelihood it would negatively impact on his ‘passing’
as male. In light of his high BMI, dietary and lifestyle modification with a view to weight loss and stabilisation were also encouraged. He continues to see both medical and mental health clinicians, who are further evaluating his potential desire for and capacity to consent to testosterone.

CONCLUSION

The increasing use of hormone therapies for TGD adolescents reflects a significant increase in demand for services from TGD youth that has occurred in the broader context of improved understanding and community support for gender diversity. Endocrine practice in this area remains relatively new with sparse medium- and long-term outcome data. Clinicians can therefore face many moral and ethical challenges when providing such care(109, 110). For example, choosing not to provide hormonal interventions to a young person with GD may itself cause harm, especially given previous observations that lack of access to hormonal therapies is a known predictor of adverse mental health among TGD adults(18). Clinicians must act in the best interests of the young person, while armed with the best available evidence. That the evidence base is still emerging and not yet robust is not an adequate rationale to withhold treatment from TGD adolescents. Instead, in direct consultation with community stakeholders, evaluation of the effectiveness and safety of current treatment approaches should be considered an essential part of clinical service provision moving forwards. TGD adolescents are marginalised and vulnerable in many ways and ongoing efforts to optimise their wellbeing, physical and mental health outcomes must continue to be a priority.

ADDITIONAL INFORMATION

Data sharing: Data sharing is not applicable to this article as no data sets were generated or analyzed in the preparation of this manuscript.
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Table 1 - Definition and criteria for a diagnosis of Gender Dysphoria

The DSM-5(1) defines gender dysphoria as a marked incongruence between an individual’s experienced/expressed gender and their assigned gender that has been present for at least 6 months and is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

In **adolescents and adults**, this is manifested by at least **two** of the following:

- A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics
- A strong desire to be rid of one’s primary and/or secondary sex characteristics (or in young adolescents, a desire to prevent the development of anticipated secondary sex characteristics)
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender
- A strong desire to be treated as the other gender
- A strong conviction that one has the typical feelings and reactions of the other gender

In **children**, gender dysphoria is manifested by at least **six** of the following (one of which **must** be the first criterion):

- A strong desire to be of the other gender or an insistence that one is the other gender
- A strong preference for wearing clothes typical of the opposite gender
- A strong preference for cross-gender roles in make-believe play or fantasy play
- A strong preference for the toys, games or activities stereotypically used or engaged in by the other gender
- A strong preference for playmates of the other gender
- A strong rejection of toys, games and activities typical of one’s assigned gender
- A strong dislike of one’s sexual anatomy
- A strong desire for the physical sex characteristics that match one’s experienced gender
Table 2 – Clinical details of case illustrations

|                      | Case 1                          | Case 2                          |
|----------------------|---------------------------------|---------------------------------|
| **Sex assigned at birth** | Male                            | Female                          |
| **Gender identity**   | Female                          | Masculine                       |
| **Current age**       | 12y 2mo                         | 15y 3mo                         |
| **Pubertal development** | Testicular volumes: 6-8ml       | Tanner staging: B5             |
|                      | Stretched penile length: 6.5cm  | Age of menarche: 12.5y          |
| **BP**               | 104/58                          | 138/84                          |
|                      | Centile                         | Centile                         |
| **Height**           | 161.4cm                         | 158.4cm                         |
|                      | 93.0                             | 28.5                            |
|                      | 89.4                             | 6.0                             |
| **Weight**           | 52.1kg                           | 71.9kg                           |
|                      | 86.0                             | 92.4                            |
|                      | 82.8                             | 87.6                            |
| **BMI**              | 20.0 kg/m²                       | 28.7 kg/m²                      |
|                      | Assigned                        | Assigned                        |
|                      | Affirmed                        | Affirmed                        |
| **Baseline lx:**     | Reference *:*                    | Reference *:*                    |
| **LH**               | 1.7 IU/L                         | 8.3 IU/L                        |
|                      | 1.0-10.0 IU/L                    | 0.8-15.5 IU/L                   |
| **FSH**              | 3.9 IU/L                         | 6.5 IU/L                        |
|                      | 0.0-6.0 IU/L                     | 0.0-15.0 IU/L                   |
| **Testosterone**     | 3.4 nmol/L                       | 0.6 nmol/L                      |
|                      | Normal                           | 0.4 – 2.5 nmol/L                |
| **Estradiol**        | <18 pmol/L                       | 330 pmol/L                      |
|                      | Normal                           | 70 -936 pmol/L                  |
| **LFT**              | Normal                           | ALT 52;                         |
|                      |                                 | others normal                    |
| **Lipid profile**    | Normal                           | Normal                           |
|                      |                                 | 1.0-3.0 nmol/L                  |
| **FBE**              | Normal                           | Normal                           |
| **HbA1c**            | 4.7%                             | 4.5 – 5.7%                      |
|                      | Normal                           | 5.4 %                           |
| **25(OH) vitamin D** | 28 nmol/L                        | 38 nmol/L                       |
|                      | 50-150 nmol/L                    | 50-150 nmol/L                   |
| **Bone Age**         | 12y                              | 16y                             |
|                      | L-spine: -1.4SD                  | N/A                             |
|                      | Hip: -1.8SD                      | N/A                             |

* Relative to birth assigned sex reference; # Greulich and Pyle assessment; N/A – not available
### Table 3 - Commonly used terminology in transgender health

| Term                          | Definition                                                                                                                                                                                                 |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Affirmed gender               | The gender with which one identifies (which may or may not match that assigned at birth).                                                                                                             |
| Birth assigned male           | A person who was recorded as male at birth (typically based on external genital appearance) and initially raised as a boy.                                                                                  |
| Birth assigned female         | A person who was recorded as female at birth (typically based on external genital appearance) and initially raised as a girl.                                                                                |
| Cisgender                     | A term for someone whose gender identity aligns with the sex they were assigned at birth.                                                                                                               |
| Gender affirming hormone therapy | A term used to describe hormonal interventions that aim to reduce endogenous pubertal sex hormone production and induce secondary sex and physical characteristics congruent with gender identity. |
| Gender affirming surgery      | A term that describes surgical procedures that may be undertaken by individuals who want to adapt their bodies to better align with their gender identity. Current international guidelines recommend genital surgery is delayed until age 18 years or older, while chest surgery may be appropriate at a younger age (assessed individually). |
| Gender diverse                | A term to describe people whose gender identity differs from culturally defined expectations of masculine or feminine ‘norms’. Being transgender is one way of being gender diverse, but not all gender diverse people are transgender. |
| Gender dysphoria              | Clinically and/or functionally significant distress arising from the incongruence between one’s birth-assigned sex and gender identity.                                                                    |
| Gender expression             | The outward presentation of a person’s gender, which may include name, pronouns, clothing, hairstyle, behaviour or voice. Gender expression may or may not reflect a person’s inner gender identity based on traditional and cultural expectations. |
| Gender identity               | A person’s innermost concept of self as male, female, a blend of both or neither. One’s gender identity is not visible to others and can be the same or different from the sex assigned at birth. |
| Gender incongruence           | A term used for a marked and persistent incongruence between an individual’s experienced gender and their assigned sex. Diagnostic term in ICD 11.                                                            |
| Gender non-binary             | A term to describe someone who doesn’t identify exclusively as male or female, but whose identity falls in-between or outside of this typical gender binary.                                                 |
| Medical transition            | The process by which a person uses hormonal intervention(s) and/or surgery to change their physical appearance and sex characteristics to more closely align with their gender identity. |
| Puberty suppression / ‘blockers’ | The process of temporarily inhibiting endogenous pubertal sex hormone production to prevent progression of secondary sex characteristics.                                                               |
| Sex assigned at birth         | Refers to the sex designated and recorded at birth (typically based on external genital appearance).                                                                                                       |
| Sexual orientation:           | An individual’s physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of gender identity, an individual may be attracted to women or men, both or neither. |
| Social transition             | The process by which a person changes their gender expression to more closely align with their gender identity.                                                                                              |
| Transfemale                   | A person who was assigned male at birth but identifies as female.                                                                                                                                         |
| Transfeminine                 | A person who was assigned male at birth but identifies as feminine or gender non-binary but closer to the female end of the gender spectrum.                                                           |
| Transmale                     | A person who was assigned female at birth but identifies as male.                                                                                                                                        |
| Transmasculine                | A person who was assigned female at birth and who identifies as masculine or gender non-binary but closer to the male end of the gender spectrum.                                                     |
Table 4 – Typical criteria for hormonal interventions in TGD adolescents*

| Criteria                                                                 |
|--------------------------------------------------------------------------|
| Confirmation of diagnosis of GD by an experienced mental health professional |
| Adolescent is in established puberty and experiencing heightened symptoms of dysphoria with onset of puberty (for GnRHa only) |
| Adolescent has been given comprehensive information as to the expected, possible and unknown effects of the proposed therapy (including implications for fertility and options to preserve fertility) |
| Psychological, social and medical circumstances are stable enough to commence treatment and no medical contra-indications exist |
| The adolescent, their parent / guardian(s) and treating clinicians (both medical and mental health) agree that the proposed treatment is in the adolescent’s best interests |
| Informed consent has been given for treatment to commence** |

*The exact criteria that appear in various published guidelines and position statements (3, 14-16) differ. Those listed here are a representative amalgam. Clinicians should be aware that where reimbursement for gender affirming therapy may be accessed through private health insurance, the insurance company may require that particular criteria be met or that particular guidelines (e.g. WPATH) be used in order for treatment to be covered.

**Many older adolescents may have capacity to give their own consent to treatment and indeed this is often considered preferable, particularly for estrogen and testosterone where effects are partially irreversible; however, issues pertaining to consent differ in different jurisdictions (see text).
Table 5 – Gender affirming pharmacological interventions – examples of agents used, mechanism of action, effects and suggested monitoring.

| Indication                  | Examples of agents and dosing* | Mode & frequency of administration* | Mechanism(s) of action                                                                 | Effects considered reversible# | Potentially irreversible effects# | Monitoring §                           |
|-----------------------------|--------------------------------|-------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|--------------------------------------|
| Puberty suppression         | GnRH analogues (GnRHa)         |                                     | Central suppression of HPG axis (GnRH receptor desensitization)                          | Suppression of HPG axis       | Bone health – reduced BMD accrual may not fully revert; long term effect unclear. | 3-6mo: Growth: ht, wt BP, Puberty; 6-12mo: LH, E2/T, 25OHD Annual DXA |
|                             | Leuprolide 7.5/22.5/30/45 mg    | IM 4/12/16/24 wkly IM 3 /6 monthly IM 3/6 monthly SC 4 / 12 wkly SC annually |                                                                                 |                               |                                   | Electrolytes (S) LFTs (B)            |
|                             | Triptorelin 11.25 /22.5 mg      |                                     | Central suppression of HPG axis (GnRH receptor desensitization)                          | Suppression of HPG axis       | Bone health – reduced BMD accrual may not fully revert; long term effect unclear. | 3-6mo: Growth: ht, wt BP, Puberty; 6-12mo: LH, E2/T, 25OHD Annual DXA |
|                             | Goserelin 3.6 / 10.8 mg         |                                     | Central suppression of HPG axis (GnRH receptor desensitization)                          | Suppression of HPG axis       | Bone health – reduced BMD accrual may not fully revert; long term effect unclear. | 3-6mo: Growth: ht, wt BP, Puberty; 6-12mo: LH, E2/T, 25OHD Annual DXA |
|                             | Histrelin 50mg                  |                                     | Central suppression of HPG axis (GnRH receptor desensitization)                          | Suppression of HPG axis       | Bone health – reduced BMD accrual may not fully revert; long term effect unclear. | 3-6mo: Growth: ht, wt BP, Puberty; 6-12mo: LH, E2/T, 25OHD Annual DXA |
| Modulation of androgen effect| Cyproterone acetate (CPA) 50-100mg** | PO; daily (or alt daily**) PO; daily or bd PO: daily | AR antagonist: B, CPA, S PR agonist: CPA, S HPG suppression: CPA Inhibition of steroidogenic pathway (T production): S | Reduction of body and facial hair; Decreased oiliness of skin; Reduced libido | Unclear; If it arises, breast development (B, S) may not fully revert |                                      |
|                             | Spironolactone (S) 50-100mg     |                                     | AR antagonist: B, CPA, S PR agonist: CPA, S HPG suppression: CPA Inhibition of steroidogenic pathway (T production): S | Reduction of body and facial hair; Decreased oiliness of skin; Reduced libido | Unclear; If it arises, breast development (B, S) may not fully revert |                                      |
|                             | Bicalutamide (B) 50mg           |                                     | AR antagonist: B, CPA, S PR agonist: CPA, S HPG suppression: CPA Inhibition of steroidogenic pathway (T production): S | Reduction of body and facial hair; Decreased oiliness of skin; Reduced libido | Unclear; If it arises, breast development (B, S) may not fully revert |                                      |
| Suppression of menstruation  | Progestogens:                   |                                     | Altered endometrial angiogenesis; inhibition of endometrial proliferation                | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Medroxyprogesterone (M):        |                                     | Altered endometrial angiogenesis; inhibition of endometrial proliferation                | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | 150mg implant /104mg injxn / 10-20mg tablet |                                     | Altered endometrial angiogenesis; inhibition of endometrial proliferation                | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Lynestrenol                     |                                     | Altered endometrial angiogenesis; inhibition of endometrial proliferation                | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Norethisterone 5-20mg           |                                     | Altered endometrial angiogenesis; inhibition of endometrial proliferation                | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Levonorgestrel                  |                                     | Central GnRH inhibition (higher dose M)                                                 | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Combined OCP **                 |                                     | Central GnRH inhibition (higher dose M)                                                 | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | Testosterone                    |                                     | Central GnRH inhibition (higher dose M)                                                 | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
|                             | See below                       |                                     | Central GnRH inhibition (higher dose M)                                                 | Suppression of menses         | Unclear – reduced BMD accrual (with depot M implant) may not fully revert. | Depot M – bone health **~ Bone BP |
| Feminisation                | 17ß Estradiol / estradiol valerate |                                     | Stimulation of estrogen receptor                                                        | Softening of skin; Body fat   | Breast tissue; Epiphyseal fusion / | 3-6mo: Growth: ht, wt BP, reported |
|                             | Oral: 5mcg/kg/day- 2mg/day;     |                                     | Stimulation of estrogen receptor                                                        | Softening of skin; Body fat   | Breast tissue; Epiphyseal fusion / | 3-6mo: Growth: ht, wt BP, reported |

*Examples of agents and dosing include both oral and injectable forms.

§Monitoring may include regular physical examinations, blood tests, and radiographic studies.

#Effects may be reversible or irreversible, depending on the specific intervention and the individual's responses.

**Medications marked with an asterisk are approved for use in the United States.

†††Depot medications are administered at intervals depending on the specific preparation and the target effect.

‡‡‡Monitoring frequency may vary based on the specific intervention and the individual's response.

§§§Monitoring may include additional tests as indicated by clinical assessment.
| Masculinisation | **Testosterone cypionate or Testosterone enanthate** 12.5-50mg increasing to 200-250mg (higher dose less frequently) | **Testosterone undecanoate** ≥ | **Testosterone gel 1% (12.5-50mg)** | **Testosterone pellets** ≥ |
|----------------|-------------------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------|
| **IM 1000mg 12 weekly (once adult dosing established)** | **SQ: 1-4wkly or IM 2-4 weekly** | | **Topical (1-4 pumps / day metered dose pump); 2-4mg pellet** | |
| **Central suppression of HPG axis §** | **Acne / skin changes; Increased libido; Increased muscle mass; Menstrual suppression; Body fat redistribution;** | **Central suppression of HPG axis §** | **Voice lowering; Alopecia; Facial hair; Genital changes / clitoral growth; Vaginal mucosal thinning** | **3-6mo: FBE (haematocrit); lipids; T Growth: ht, wt BP, reported virilisation 6-12mo (once stable): T, FBE, lipids, 25OHD 1-2 yearly: BMD with DXA** |

HPG – hypothalamic-pituitary-gonadal; BMD – bone mineral density; PBM – peak bone mass; IM – intramuscular; SC: subcutaneous; PO.: by mouth; IUD: intra-uterine device; CPA – cyproterone acetate; S – spironolactone; B – bicalutamide; AR – androgen receptor; PR – progestogen receptor; b.d. - twice daily

* Relates to reports in the literature in TGD populations; note - use in this context may be off-label and not all agents have reported data in adolescent TGD populations

** Optimal dosing of anti-androgenic agents is unknown; studies of smaller and less frequent doses of agents such as CPA are underway

# Either gender-affirming or potentially unwanted effects

§ Ongoing monitoring of potential unwanted / adverse effects (e.g. drug reaction, mood effects, fatigue / altered energy, fluid retention, headaches)
Titrate to response - may need 5mg bd tds or 10mg bd to achieve amenorrhoea; use lowest effective dose

Consider DXA if additional bone health risk factors e.g. low 25-OHD, or history of low impact fracture

Reiteration of need for preventative measures to reduce thromboembolic risks. Need for prolactin monitoring can be individualised (e.g. if also on CPA).

numerous combined oral contraceptive pills (cOCP) are available, commonly containing a synthetic estrogen and progestogen. First or second generation OCP contain more androgenic progestins which may be more acceptable in TGD youth; however higher thromboembolic risk profile

- through negative feedback – greater effect when used in supra-physiological doses

Limited data in adolescent TGD cohorts