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Transgender medicine - puberty suppression

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Abstract
Puberty suppression is the reversible first step of endocrine medical treatment in transgender youth, and allows for two very important aspects of transgender management. Firstly, it buys the patient, family and their medical team time to fully evaluate the presence and persistence of gender dysphoria. Secondly, it successfully prevents the development of cis-gender unwanted secondary sexual characteristics. The latter, when present, almost certainly increase the burden of psychological co-morbidity for any transgender person. This management is modelled from treatment of gonadotropin-dependent precious puberty, with use of GnRH agonists at its core. With the increasing number of transgender youth treated, and the changing demographics of patients seeking medical care, providers are faced with the decision to start puberty blockade at younger ages than previous decades. This article will review the rationale behind puberty blockade for transgender children, the providers' options for achieving this goal, the emerging literature for potential adverse effects on such an approach, as well as identify directions of potential future research.

Keywords Puberty suppression · Puberty blockade · Transgender · GnRH agonists · Bone health · Endocrine transgender care

1 Rationale for treatment

From the early reports of young transgender adults treated in the mid-twentieth century [1] to our current state of endocrine transgender care, society and physicians have had to adapt to an increasing demand for pediatric endocrine care for youth with gender dysphoria [2]. This is reflected in the exponentially growing number of dedicated multidisciplinary centers, an illustrative example being the North America subcontinent, where such centers have exponentially increased from only four 20 years ago [3] to thirty six centers in a relevant recently published report [4]. Furthermore, in the last decade there has been a flourish of studies in transgender adult populations and, to a lesser extent, transgender youth. As such, professional bodies and academic societies are frequently revising clinical practice guidelines [5]. This article will review our current practice regarding puberty blockade in transgender youth.

It has been a long standing requirement, that for a youth to be eligible for medical treatment, they must have experienced gender dysphoria, with the most recent definition outlined in the DSM 5 [6]. Although, this can be seen in children as young as toddlerhood [7], for the majority of very young children with gender dysphoria, this pathology will not still be present in adolescence [8, 9] or young adulthood [10]. Furthermore, gender dysphoria might only appear later on in early adolescence, without any previous evidence during childhood [11]. It is now recognized that the dysphoria specifically produced by early pubertal physical changes, defined as breast budding in natal females [12] and testicular/phallic enlargement in natal males [13], is one of the key factors in determining the need for medical intervention [14]. The rational for treatment initiation is to prevent formation and progression of unwanted secondary sexual characteristics that endogenous sex steroids would produce (Table 1).

A critical age that is emerging as the time window for desistance versus persistence of gender dysphoria is 10–13 years old [9]. During this period, the severity of gender dysphoria intensifies [15], corresponding to the average age of pubertal onset in natal females [16] and males [17]. Moreover, it is well documented, that, once present, psychiatric comorbidities in untreated adolescents with persistent gender dysphoria continue to increase [18]. Therefore, for adolescents with intense gender dysphoria, it is recommended that pubertal suppression be initiated as soon as physical signs of puberty are present [5, 19, 20]. Despite previously reported benefits and the clear rationale behind this management plan, there has been a paucity in *new* data regarding the benefits of

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Table 1 unwanted sexual characteristics and their typical age of presentation

Unwanted male secondary sexual characteristics		Unwanted female secondary sexual characteristics	
Type	Tanner stage of development (Typical age in years)	Type	Tanner stage of development (Typical age in years)
Lower pitch voice	T3 (13–14)	Breast enlargement (requiring compression clothing)	T3–5 (11–14)
Adam's apple	T4 (14–16)	Female body habitus	T4–5 (12–14)
Prominent jaw	T4–5 (15–18)	Menstruation	T5 (12–13)
Larger hands and feet			
Broadened shoulders			
Coarser facial and body hair			

such as approach. In the recent past, successful early puberty blockage has been demonstrated to allow time for the proper psychological evaluation of patients as they first present to medical care [21], improve functioning in several cognitive and social domains in gender dysphoric adolescents undergoing treatment [22], and facilitate achieving more desirable cosmetic results after full physical transition [23].

2 Treatment options

Treatment for puberty suppression should start as early as one achieves Tanner 2 staging on pubertal exam (i.e. breast budding for natal females and testicular enlargement more than 4 cm in natal males) and detectable LH levels [24]. First line treatment for pubertal suppression are GnRH analogs [24, 25], much due to their success in treating gonadotropin-dependent precocious puberty [26]. Initiation of therapy produces a decrease in gonadotropins (Luteinizing Hormone and Follicle Stimulating Hormone) and eventually endogenous sex steroid levels [27], an effect that is reversible upon discontinuation of treatment [28]. An alternative approach involves the use of GnRH antagonists. Despite their more rapid effect on decreasing gonadotropin levels [29], they are not commonly chosen due to the need for much higher dosage [30], which contributes to the most impactful obstacle in using them: their cost [31]. A different and the most cost effective option is the use of progestins, similarly to how they were used prior to the development of GnRH analogues for precocious puberty [32–34]. There have been only two recent studies investigating the use of progestins for endogenous puberty blockage in transgender youth, with participants having been enrolled at a late-pubertal stage [35, 36]. The efficacy of gonadotropin reduction was not as good as that seen with GnRH analogues, but progestins were suggested to be a cost-effective alternative for patients presenting at pubertal Tanner 4 stage or beyond. It is unknown how effective progestins might be in stopping puberty at its earlier phases (Tanner 2 or 3) in younger transgender individuals.

Current treatment with parenteral GnRH agonists is offered in a variety of ways, from yearly surgically implanted subcutaneous device, to injectable versions given either monthly or every 3 months or twice a year [37–39]. Benefits of the intramuscular (IM) injectable GnRH agonists compared to the surgically implanted one include ease of administration, avoidance of anesthesia complications, as well as relatively quick recovery of the Hypothalamic Pituitary Gonadal (HPG) axis upon discontinuation. The advantages of the implantable GnRH agonists are the avoidance of repeated IM injections, less frequent need for administration, and the extended suppression of the HPG axis past the licensed approved duration of 1 year (reports suggest one implant can inhibit the axis for up to 2 years) [40]. It is noteworthy that a newer version of an intramuscular depot GnRH agonist given twice a year has been FDA approved for use in central precocious puberty [41]. The efficacy of this dose has not yet been compared with the monthly or three-monthly depot preparations, and to-date there have been no published data regarding its use in the transgender population. Table 2 is listing typically prescribed regiments of GnRH agonists [37–39].

Monitoring of therapy while on GnRH agonists includes a careful monitoring of anthropometric measurements, clinical pubertal staging and measurement of LH and natal sex steroids [27, 42]. Although early pubertal changes have been noted to reverse with treatment, in children that have more mature pubertal characteristics the aim is to stop further progression rather than induce regression of Tanner staging [42]. Biochemically suppressing LH level to undetectable or at least <0.60 IU/L seems to be sufficient to halt puberty in its tracks [27].

3 Side effects of pubertal suppression

Pubertal suppression in precocious puberty is a relatively safe medical intervention with little acute and chronic side effects [41, 43, 44]. Most frequently, adverse effects involve problems with the injection site itself. Redness and swelling can be

Table 2 formulations and doses of typically prescribed GnRH agonists

Histrelin:	
SubQ	*Supprelin LA:*
	50 mg implant; surgically changed yearly
Leuprolide:	
IM	*Lupron Depot-Ped (monthly):*
	≤25 kg: 7.5 mg every month
	>25 to 7.5 kg: 11.25 mg every month
	>37.5 kg: 15 mg every month
	Lupron Depot-Ped (3 month):
	11.25 mg or 30 mg every 12 weeks
SubQ	*Leuprolide acetate:*
	Initial: 50 mcg/kg/day

seen in up to 9% of patients, and local pain is reported by 10–20% of patients [45]. The use of GnRH agonists, although effective in suppressing puberty as described above, transiently will promote pubertal changes since the first dose will be stimulating the gonadotrophs [46]. As such, the onset of treatment might produce emotional lability, mood changes, testicular pain, worsening acne, even vaginal bleeding in Tanner 4 natal females [47]. For the older adolescent patients with already robust sex steroid levels managed with puberty blockers, inhibition of the HPG axis induces symptoms of hypogonadism [48], some of which may be desired (e.g. less erections and frequency of shaving) and others problematic (e.g. vaginal pain and itching, hot flushes, fatigue, subjective weakness). Another expected effect of pubertal progression is the relative changes in body composition that patients experience. Reports describe a decrease in lean body mass and increase in body fat percentage in both girls and boys [42], an effect that appears to be present only at the start of treatment and normalize thereafter [49, 50]. Furthermore, another research focus has been fertility outcomes in children with precocious puberty treated with GnRH agonists, with results being reassuring as to an intact gonadal function after discontinuation of treatment [51, 52]. However, for the transgender population although puberty suppression alone does not affect fertility outcomes, the addition of cross sex steroids certainly does interfere with reproductive potential (for a recent review on the topic see work by Rowlands and Amy, 2018 [53]).

The expanding use of GnRH agonists has been associated with a flourish of studies investigating adverse effects on bone health. Missing the opportunity for bone mineral accruement due to lack of sex steroids is always a concern when starting GnRH agonists. However, with eventual exposure to sex steroids (endogenous or exogenous) these skeletal effects should recover. Since treatment duration in transgender adolescents is longer, there is an increased concern for increased skeletal complications from puberty suppression in these youth. Studies on patients with precocious puberty have shown conflicting effects of GnRH on BMD, will follow-up studies indicating reversal of any adverse effects on BMD, once GnRH therapy is halted and puberty is allowed to progress [54–58]. Unfortunately, studies using transgender subjects are limited to-date. A 2015 study by Klink et al. showed deceleration of accruement of BMD during GnRH treatment, which had not completely reversed after 6 years of cross-sex steroids [59]. However, all subjects enrolled were either in late-pubertal or post-pubertal stage, which is not clinically comparable to transgender patients starting GnRH treatment right after reaching Tanner 2 pubertal stage. A more recent study showed that use of GnRH agonists decreased markers of bone turnover in transgender adolescents, with a reciprocal decrease in bone apparent mineral densities. This change was successfully reversed after two years of cross-sex steroid treatment [60].

4 Future research

With increasing social acceptance [61, 62] and younger ages of presentation seen in demographic studies of transgender youth, patients and families are driven to seek endocrine care in larger amounts and at younger ages [63]. Due to a relative gap in having easy access to a trained pediatric endocrinologist [64], most of these patients are now seen in dedicated pediatric tertiary centers [4]. This provides for a fruitful ground for clinical researchers to attempt to answer some of the emerging questions regarding pediatric endocrine transgender care, as it pertains to puberty suppression.

More studies are needed to delineate the effect of current transgender hormonal treatment protocols on the growing skeleton. A specific point of emphasis would be to include patients from younger ages so that we understand the effects not only in persons treated in adolescence but those that are now treated in childhood too. Typically, a patient with precocious puberty only requires GnRH agonist treatment for about 5–6 years until age 11–12 [65], whereas a transgender person might need to continue taking it until late adolescence with sex steroid exposure typically only after age 16 [5, 66]. Therefore, the populations used in central precocious puberty studies are not representative of the transgender populations. Future studies should focus on effects in bone mineral density and markers of bone turnover when transgender children are placed on treatment at Tanner stage 2. It is important to know how those effects differ with initiation and completion of the exogenous puberty at an older age compared to persons with normal puberty timing.

Another, yet unanswered, clinical question is the effect of puberty blockage on cognition. Only one case report thus far has commented on this topic [67], and more broad widespread studies are needed to ensure brain development during adolescence is not adversely effected in treated patients. One

omitted clinical question regards the use of a subcutaneous daily preparation of GnRH agonists [68] versus the more expensive intramuscular preparations or transdermal implants of GnRH agonists. The former have easier, painless administration as well as reduced cost, which might make them a superior choice for some families, if proven to be equally efficacious in suppressing puberty in transgender children.

As our experience with puberty suppression in transgender children broadens, one would hope that so will our knowledge regarding the best and safest ways to provide this aspect of endocrine transgender care. What we knew twenty years ago is different to what we know now, and that, in turn, will certainly will be different from what we will know in another twenty years from now. The future of pediatric endocrine transgender care is exciting and left to be seen.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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