What is the Role for Puberty Blockers in Gender Affirming Care for Youth

Phoenix Children’s Hospital - Gender Support Team
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MA is an 11 year old male assigned female at birth. He presents for medical consultation with his adoptive mother for evaluation of gender dysphoria. His mother reports that this is “all new to me” with MA reported to have been “quite the girl” until almost 2 years ago.

MA reports questions regarding gender identity in the last several years but not having the concept of transgender until later. He describes his “girly phase” as a result of wanting to fit in and not wanting to disappoint his family.

He expresses distress with breast development and dreads impending periods. His history is significant for symptoms of anxiety and depression.
I. Goals of Gonadotropin Releasing Hormone (GnRHa) Analogue Therapy in Gender Dysphoric (GD)/Gender-Incongruent Youth

II. How to assess puberty

III. When and how to initiate GnRHa therapy

IV. SE/Monitoring while on GnRHa therapy

V. Duration of treatment
Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

Wylie C. Hembree,1 Peggy T. Cohen-Kettenis,2 Louis Gooren,3 Sabine E. Hannema,4 Walter J. Meyer,5 M. Hassan Murad,6 Stephen M. Rosenthal,7 Joshua D. Safer,8 Vin Tangpricha,9 and Guy G. T’Sjoen10
Evaluation of Youth and Adults

1.4 We recommend against puberty blocking and gender affirming hormone treatment in prepubertal children with gender dysphoria/gender incongruence.

1.5 We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy...in both adolescents and adults.
2.1 We suggest that adolescents who meet diagnostic criteria for gender dysphoria/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development

- More time to explore options...
- Reversible...

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2.2 We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty.

2.3 We recommend that, where indicated, GnRHa are used to suppress pubertal hormones.
Criteria for GnRHa Therapy

• A qualified mental health professional has confirmed:
  • The persistence of gender dysphoria
  • Any coexisting problems that could compromise txt adherence have been addressed
  • The adolescent has sufficient mental capacity to estimate consequences of (partly) irreversible txt, and give informed consent

• And the adolescent
  • Has been informed of the (irreversible) effects and side effects of treatment (loss of fertility and fertility preservation)
  • Has given informed consent. and the parents/guardians have consented to treatment and are supportive

• And a pediatric endocrinologist/clinician experienced in pubertal assessment
  • Agrees with the indication for GnRHa therapy
  • Has confirmed that puberty has started in the adolescent (T2/G2)
  • Has confirmed that there are no medical contraindications to GnRHa therapy
Physiology Puberty: Gonadarche
Pubertal Milestones

- **Natal Females**
  - Thelarche
  - Adrenarche/Pubarche
  - Menarche

- **Natal Males**
  - Inc in Test Volume
  - Growth Spurt
  - Adrenarche/Pubarche

Mean Age of Pubertal Milestone (y)

<table>
<thead>
<tr>
<th></th>
<th>Testic Volume &gt;3ml</th>
<th>Thelarche</th>
<th>Adrenarche</th>
<th>Menarche</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Female</td>
<td>N/A</td>
<td>10</td>
<td>10.5</td>
<td>12.7</td>
</tr>
<tr>
<td>AA Female</td>
<td>N/A</td>
<td>8.9</td>
<td>8.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Males</td>
<td>11.5</td>
<td>N/A</td>
<td>12</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Tanner Stages
Tanner Stages

Genital Stages

Stage 1  Stage 2  Stage 3  Stage 4  Stage 5

Pubic hair stages

Stage 1  Stage 2  Stage 3  Stage 4  Stage 5
• **Rise in LH is usually the first sign of puberty**
  - Pediatric Assays ICA and MS/MS
    - Lower limit of detection of $\leq 0.1$ mIU/ml

• $LH \geq 0.3$ mIU/ml, $FSH > 3$ mIU/ml (natal males) and $> 4.2$ mIU/ml (natal females)

• Estradiol $> 5$ pg/ml, Testosterone $> 10$ ng/dL
  - Thelarche present when estradiol is $> 10$ pg/ml
  - Early puberty labs at 8AM
GnRHa - Mechanism of Action

- Continuous release of GnRH
  - Tachyphylaxis

- Initial progression of pubertal development

- Followed by quiessence of HPG axis
GnRHa - Leuprolide Acetate Depot Ped

Intramuscular Injection

Can be monthly
- <25kg 7.5mg Q4 weeks
- 25-37kg 11.25mg Q4 weeks
- >37.5kg 15mg Q4 weeks

Can be Q3 monthly
- 11.25mg Q3 monthly
- 30mg Q3 monthly

Can be Q6 months
- Triptodur (Triptorelin) IM 22mg
- Fensolvi SQ 45mg

Side effects
- Headache
- Sterile Abscess w/IM (5%)
- Soreness
- Anaphlyaxis

https://www.webmd.com/drugs/2/drug-156805/lupron-depot-ped-3-month-intramuscular/details
GnRHa – SQ Histrelin Implant

- **Implant**
  - Supprelin FDA in peds

- **Replacement yearly**

- **Data suggests that implant can suppress puberty 2 yrs or more**
  - *J Pediatrics.* 2013 Oct; *A single histrelin implant is effective for 2 years for treatment of central precocious puberty.*
  - Lewis, KA, Goldyn AK, West KW, Eugster EA.
GnRHα – Non FDA approved in pediatrics

- Vantas implant

- Eligard SQ Q1 mo, 3mo, 4mo, or 6mo

- Lupron Depo Q1 1mo, 3mo, 4mo, 6mo
GnRHa-Side Effects

▶ Not FDA approved for pubertal suppression in trans youth
  • Approved for central precocious puberty (CPP)

▶ Data regarding use of GnRHa therapy comes from txt of girls w/CPP
  • Normalization of BMD
  • No effects on fertility

▶ Decreased BMD-Unclear in trans youth
  • BMD can theoretically be improved with cross sex hormone txt
  • Transgender women and girls have lower baseline bone densities
    — Even on estradiol therapy, long-term studies suggest ongoing lower bone mass and cortical size
  • Transgender men have stable or improved bone density
  • Fracture risk unclear
GnRHa – Side Effects

- **Growth Deceleration**

- **Increase in fat mass and decrease in lean body mass percentage**
  - No change in BMI

- **Arterial HTN has been reported in girls txt with GnRHa for CPP**
  - BP monitoring before and during txt

- **Hot flashes, fatigue, and mood alteration**
  - No consensus on txt

- **Effect of GnRHa on brain development is unclear**
  - Hough et al. found in sheep there maybe a negative effect of GnRHa on spatial memory
GnRHa-Side Effects

 Risk of QT prolongation

 GnRHa therapy does have implications on fertility
  • Needs to be discussed w/patient and family
  • Could allow endogenous puberty to progress to help with sperm and oocyte preservation prior to starting cross sex hormones
  • Usually not psychologically acceptable....as progression of secondary sex characteristics inconsistent with affirmed gender is distressing
  • Lack of fertility preservation programs available
    • Utilizing resources that are tailored to pediatric cancer survivors...
### Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3–6 mo</td>
<td>Anthropometry: height, weight, sitting height, blood pressure, Tanner stages</td>
</tr>
<tr>
<td>Every 6–12 mo</td>
<td>Laboratory: LH, FSH, E2/T, 25OH vitamin D</td>
</tr>
<tr>
<td>Every 1–2 y</td>
<td>Bone density using DXA</td>
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<tr>
<td></td>
<td>Bone age on X-ray of the left hand (if clinically indicated)</td>
</tr>
</tbody>
</table>

J Clin Endocrinol Metab, November 2017, 102(11):3869–3903
At pubertal initiation doses of testosterone and estrogen

- no suppression of endogenous HPG axis

Trans males: once testosterone is ~100ng/dL usually there is suppression of endogenous puberty
  - GnRHa therapy can be discontinued

Trans females: endogenous production of testosterone may interfere with effectiveness of estrogen
  - Continuation of GnRHa is advised until gonadectomy
  - Alternative Therapies: Progestins, antiandrogens
  - GnRHa have higher efficacy, safety, and reversibility
On my exam MA had T3 breast development, and T3 pubic hair

Baseline labs showed low Vit D at 18 so this was repleted. His 8AM LH was 0.8 mIU/ml, FSH was 4.5 mIU/ml. Estradiol was 24 ng/dL. Bone age was ~12 yrs

Baseline DXA showed z scores of +1.2 at the LS and whole body

MA established with one of the therapist in our gender support program who was able to provide a letter of readiness for puberty suppression after a few months of weekly sessions

Started treatment with Lupron depo ped 30mg Q3 mo

Continues to follow w/his therapist as needed. No longer have anxiety and depression over pubertal progression
References


References


