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ORIGINAL ARTICLE

Effectiveness of Puberty Suppression with Gonadotropin-Releasing Hormone Agonists in Transgender Youth

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Abstract

Purpose: To analyze the effectiveness of gonadotropin-releasing hormone agonists (GnRHa) in suppressing the hypothalamic-pituitary gonadal (HPG) axis in transgender adolescents.

Methods: Retrospective review of electronic medical records of transgender youth and children with central precocious puberty (CPP) treated with GnRHa. Blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and/or estradiol at baseline and during treatment were compared between groups.

Results: Data from 30 transgender and 30 patients with CPP were analyzed. Transgender patients were older with a mean age of 13.0 ± 2.1 years versus 7.7 ± 2.3 years in the CPP group, $p < 0.001$. There were more patients assigned male at birth (AMAB) in the transgender group (56.7%) than males in the CPP group (30%), $p < 0.001$. The transgender group had more patients with advanced puberty with 56% of patients having a Tanner stage of IV–V, versus none in the CPP group, $p < 0.01$. GnRHa treatment resulted in LH, FSH, and testosterone levels that were similar in males with CPP versus transgender patients AMAB; suppression of LH and FSH levels was similar in females with CPP versus transgender patients assigned female at birth, but estradiol levels were higher in the latter (1.8 ± 1.8 pg/mL vs. 9.4 ± 9.7 pg/mL, respectively, $p < 0.001$). FSH levels were lower in the transgender group treated with histrelin (0.8 ± 0.8 mIU/mL vs. 1.9 ± 1.2 mIU/mL in the leuprolide group, $p = 0.004$).

Conclusions: GnRHa are effective in suppressing the HPG axis in transgender youth, similar to that observed in children with CPP.

Keywords: puberty suppression; transgender; GnRH agonists; adolescents

Introduction

Gonadotropin-releasing hormone agonists (GnRHa) inhibit the hypothalamic-pituitary-gonadal (HPG) axis through continuous stimulation of the GnRH receptor, decreasing the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRHa have been used extensively in children to suppress central precocious puberty (CPP) and are considered effective and generally safe in this patient population.[1–4] GnRHa are also used to suppress the HPG axis in adult males with prostate cancer[5] and in adult females with endometriosis[6] and breast cancer.[7]

There has been a recent increase in the use of GnRHa to suppress puberty in transgender children and adolescents with gender dysphoria,[8] the distress that can occur if one's gender identity differs from the sex assigned at birth. Suppressing puberty improves gender dysphoria and prevents the development of secondary sex characteristics.[9,10] Puberty suppression can therefore avoid the need for certain types of gender-affirming invasive procedures such as mastectomy, breast augmentation, tracheal shave or hair removal therapy. Moreover, some puberty-induced physical changes cannot be readily modified with surgery or hormone therapy such as a deep voice, tall height, facial and body skeletal features in transwomen, or short height in transmen after fusion of the epiphyseal plate.

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The Endocrine Society has released guidelines that support the use of GnRHa for children and adolescents with gender dysphoria, who meet specific criteria and have started central puberty.[11] Nevertheless, data are lacking on the effectiveness of puberty suppression using GnRHa in the transgender pediatric population.

The aim of this study is to analyze the effectiveness of GnRHa in suppressing the HPG axis in transgender adolescents.

Materials and Methods

This study was approved by the UT Southwestern IRB. We performed a retrospective review of electronic medical records of patients seen between January 2014 and June 2018 in the GENder, Education and Care Interdisciplinary Support (GENECIS) program, a transgender clinic for youth at Children's Health in Dallas, TX, as well as of patients seen for CPP in a pediatric endocrine clinic of the same hospital.

Patients met inclusion criteria if they had been treated with GnRHa for puberty suppression and had undergone measurement of blood levels of LH, FSH, (total) testosterone, and/or estradiol at baseline (unstimulated) and 2–12 months after starting treatment. Patients were excluded if they had a previous or concomitant history of receiving progesterone or progestin-based therapies, oral contraceptives, testosterone, estradiol, or spironolactone, or had congenital adrenal hyperplasia. Patients in the CPP group who met inclusion and did not meet exclusion criteria were randomly selected for comparison.

Blood specimens were analyzed at LabCorp, Quest Diagnostics, or Children's Health laboratory in Dallas, TX. LH and FSH were measured with immunoassay (IA) in all laboratories, total testosterone was measured with IA at LabCorp and with liquid chromatography/mass spectrometry (LC/MS) at Quest Diagnostics and Children's Health, and estradiol was measured with LC/MS in all laboratories.

Demographic and clinical data collected included the type of GnRHa used and Tanner stage at the onset of treatment. Tanner stage was reported based on breast development for females with CPP and transgender patients assigned female at birth (AFAB), and on testicular/genital stage for males with CPP and transgender patients assigned male at birth (AMAB). Two-tailed Student's unpaired tests were used for comparisons of continuous variables. Fisher's exact tests were used for comparison of categorical variables. Continuous variables were reported as mean ± SD.

Results

Thirty-six patients in the transgender group met inclusion criteria; six of those met exclusion criteria and were not included in the analysis. Thirty-one patients with CPP met inclusion criteria; one patient who met exclusion criteria was not included in the analysis.

The demographic and clinical characteristics at baseline are shown in Table 1. Transgender patients were older than CPP patients. There were more patients AMAB in the transgender group (56.7%) than males in the CPP group (30%). Transgender patients were more likely to be white (96%) and non-Hispanic (77%) than CPP patients (50% and 43%, respectively). The transgender group had more patients with advanced puberty with 56% of patients having a Tanner stage IV–V, versus none in the CPP group.

The type of GnRHa used, histrelin implant (Supprelin or Vantas) versus leuprolide injections, differed between groups. Vantas and Supprelin were more frequently used in the transgender group (66%), while leuprolide injections were more commonly used in the CPP group (63%), $p < 0.0001$.

Table 2 shows the levels of gonadotropins and sex hormones at baseline (unstimulated) and during puberty suppression therapy. Time between onset of puberty suppression and measurement of follow-up levels was similar in both groups.

Baseline FSH levels were higher in males with CPP versus AMAB transgender patients. Baseline estradiol levels were higher in AFAB transgender patients versus females with CPP. Follow-up LH, FSH, and testosterone levels were similar in males with CPP versus AMAB transgender patients. Follow-up LH and FSH levels were similar in females with CPP versus AFAB transgender patients, but estradiol levels were higher in the latter. However, the change in estradiol levels with treatment did not differ significantly between groups (45.5 ± 45.7 in AFAB transgender patients vs. 20.1 ± 25.6 in CPP patients, $p = 0.7$).

Table 3 shows the levels of gonadotropins and sex hormones by type of GnRHa used. Only seven patients in the transgender group and one patient in the CPP group used Vantas. Therefore, data for both Supprelin and Vantas were combined within the histrelin group for comparison of the CPP versus the transgender group. Histrelin (Vantas or Supprelin) and leuprolide were similarly efficacious at suppressing LH and FSH levels in the transgender group versus the CPP group, as well as testosterone levels in males with CPP versus AMAB transgender patients. Estradiol levels were higher

Table 1. Baseline Demographic and Clinical Characteristics

Patient characteristics	CPP		Transgender		p[a]
	Male $N=9$ (30%)	Female $N=21$ (70%)	AMAB $N=17$ (56.7%)	AFAB $N=13$ (43.3%)	$p=$NS
Age (years)	9.6 ± 1.0	6.3 ± 2.3	13.2 ± 2.3	12.7 ± 1.8	< 0.001
Ethnicity					
Non-Hispanic	5 (56%)	8 (38%)	13 (78%)	10 (77%)	< 0.01[b]
Hispanic	4 (44%)	13 (62%)	3 (19%)	3 (23%)	
Unknown	—	—	1 (2%)	—	
Race					
White or	6 (67%)	9 (42%)	16 (94%)	13 (100%)	< 0.001[c]
Caucasian	1 (11%)	4 (19%)	—	—	
Black or AA	1 (11%)	4 (19%)	—	—	
Hispanic					
American Indian or Alaska Native	—	1 (5%)	—	—	
Other	1 (11%)	2 (10%)	—	—	
Unknown	—	1 (5%)	1 (6%)	—	
Tanner stage					
II	5 (55%)	7 (33%)	5 (29%)	3 (23%)	< 0.001[d]
III	3 (33%)	11 (52%)	3 (18%)	1 (8%)	
IV	1 (12%)	3 (14%)	5 (29%)	4 (31%)	
V	—	—	4 (23%)	4 (31%)	
Not reported	—	—	—	1 (8%)	
GnRHa type					
Leuprolide 7.5 mg	—	5 (24%)	—	—	< 0.05[e]
Leuprolide 15 mg	2 (22%)	4 (19%)	2 (12%)	1 (8%)	
Leuprolide 30 mg	2 (22%)	6 (29%)	3 (18%)	4 (31%)	
Supprelin implant	5 (55%)	5 (24%)	8 (47%)	5 (38%)	
Vantas implant	—	1 (4%)	4 (23%)	3 (23%)	

[a]p-values for (total) transgender group versus (total) CPP group.
[b]Hispanic versus non-Hispanic.
[c]Comparison of White/Caucasian, Black/AA, and Hispanic.
[d]Comparison of tanner groups II, III, IV, and V.
[e]Use of leuprolide (all doses grouped together) versus histrelin implant (Supprelin and Vantas grouped together).
AA, African American; AFAB, assigned female at birth; AMAB, assigned male at birth; CPP, central precocious puberty; GnRHa, gonadotropin-releasing hormone agonists; NS, not significant.

in the AFAB transgender patients versus females with CPP, treated with both leuprolide and histrelin.

We compared the effect of the Supprelin ($n=13$) versus the Vantas ($n=7$) implant in the transgender group. Follow-up levels were similar in those treated with Supprelin versus Vantas: LH (0.4 ± 0.2 vs. 0.4 ± 0.3 mIU/mL, $p=$NS), FSH (1.0 ± 0.9 vs. 0.5 ± 0.3, $p=$NS), testosterone in those AMAB (8.5 ± 7.6 ng/dL vs. 8.5 ± 6.6 ng/dL, $p=$NS), and estradiol in those AFAB (4.1 ± 2.3 pg/mL vs. 7.0 ± 1.4 pg/ml, $p=$NS).

When comparing the effectiveness of histrelin versus leuprolide within the CPP and the transgender groups

Table 2. Gonadotropin and Sex Hormone Levels at Baseline and During Puberty Suppression Therapy

	Baseline			Follow-up[a]		
	CPP	Transgender	p	CPP	Transgender	p
Male/AMAB[b]						
LH (mIU/mL)	2.9 ± 1.6	1.8 ± 1.4	NS	0.4 ± 0.4	0.6 ± 0.8	NS
FSH (mIU/mL)	8.0 ± 9.1	2.9 ± 1.9	0.03	0.4 ± 0.2	0.5 ± 0.3	NS
Testosterone (ng/dL)	180.8 ± 112.7	282.3 ± 224.7	NS	6.4 ± 2.6	12.1 ± 14.7	NS
Female/AFAB[c]						
LH (mIU/mL)	2.4 ± 2.9	3.1 ± 2.9	NS	0.4 ± 0.4	0.3 ± 0.2	NS
FSH (mIU/mL	4.8 ± 3.1	3.8 ± 2.3	NS	1.6 ± 0.7	2.0 ± 1.1	NS
Estradiol (pg/mL)	22.1 ± 26.5	50.5 ± 46.9	0.02	1.8 ± 1.8	9.4 ± 9.7	0.001

[a]Time after onset of GnRH therapy: 5.2 ± 1.9 months in the CPP group and 5.9 ± 2.9 months in the transgender group, $p=$NS.
[b]Males with CPP and AMAB transgender patients.
[c]Females with CPP and AFAB transgender patients.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 3. Gonadotropin and Sex Hormone Levels by Type of Gonadotropin-Releasing Hormone Agonists

	Baseline			Follow-up[a]		
GnRHa	CPP	Transgender	*p*	CPP	Transgender	*p*
Leuprolide						
LH (mIU/mL)[b]	3.8 ± 3.9	2.7 ± 2.3	NS	0.5 ± 0.5	0.7 ± 1.0	NS
FSH (mIU/mL[b]	6.6 ± 5.6	4.4 ± 1.9	NS	1.5 ± 0.8	1.9 ± 1.2	NS
Testosterone (ng/dL)[c]	159.7 ± 58.2	415.2 ± 96.7	0.002	7.4 ± 2.4	17.0 ± 20.6	NS
Estradiol (pg/mL)[d]	25.0 ± 29.5	49.7 ± 43.3	NS	2.0 ± 2.1	13.8 ± 13.5	0.003
Histrelin						
LH (mIU/mL)[b]	2.1 ± 2.2	2.1 ± 2.3	NS	0.3 ± 0.2	0.3 ± 0.2	NS
FSH (mIU/mL)[b]	5.2 ± 6.4	2.7 ± 2.0	NS	1.0 ± 0.8	0.8 ± 0.8	NS
Testosterone (ng/dL)[c]	197.6 ± 148.4	221.9 ± 243.2	NS	5.7 ± 2.7	8.5 ± 7.5	NS
Estradiol (pg/mL)[d]	14.1 ± 11.9	47.6 ± 50.3	NS	1.3 ± 1.1	5.3 ± 2.6	0.006

[a]Time after onset of GnRH therapy: 5.2 ± 1.9 months in the CPP group and 5.9 ± 2.9 months in the transgender group, p = NS.
[b]Both genders grouped together.
[c]Males for the CPP group and assigned males at birth for the transgender group.
[d]Females for CPP group and assigned females at birth for the transgender group.

separately, there were no differences in the CPP group, but the histrelin implant resulted in lower FSH levels in transgender patients (0.7 ± 0.8 mIU/mL vs. 1.9 ± 1.2 mIU/mL in transgender patients treated with leuprolide, $p = 0.004$). However, FSH levels trended higher at baseline in transgender patients who received leuprolide (4.2 ± 1.9 mIU/mL vs. 2.7 ± 2.0 mIU/mL in the histrelin group, $p = 0.07$), and thus, the decrease in FSH levels with treatment was not different (2.3 ± 2.6 with leuprolide and 2.0 ± 1.8 with histrelin, p = NS). There were no statistical differences when comparing the suppression of LH, testosterone, and estradiol with leuprolide versus histrelin within the CPP or the transgender groups.

Discussion

The Endocrine Society recommends the use of GnRHa for puberty suppression in transgender youth who meet specific criteria, including the diagnosis of gender dysphoria and the presence of central puberty.[11]

While GnRHa have proven effective in the CPP population, it was necessary to study the effectiveness in transgender youth because of different biological characteristics as shown in this study: transgender patients are older, and their stage of puberty is more advanced. GnRHa have also been proven effective in the adult population for prostate and breast cancer, as well as endometriosis, but the doses used are lower than in CPP.[12,13]

To our knowledge, this is the first study to evaluate the effectiveness of GnRHa in suppressing the HPG axis in transgender children and adolescents. As comparison, we used a group of children with CPP as effectiveness in this population is well known.[1–4]

We found that transgender adolescents had similar HPG axis suppression in response to GnRHa as children with CPP, except for higher estradiol levels in transgender patients AFAB at follow-up. A possible explanation is that transgender patients were in a more advanced stage of puberty with higher estradiol levels at baseline. While statistically significant, it is unlikely that this difference in estradiol levels is clinically meaningful, given that the remaining levels are still within the female Tanner I range with histrelin, and in the early Tanner II range with leuprolide.

Our study has important limitations derived from the characteristics of retrospective studies. Different doses of leuprolide and histrelin were used (slightly lower in Vantas vs. Supprelin), and the number of patients was too small to compare the effectiveness of each dose. The small number of patients limited power to detect small differences in gonadotropins and sex steroids. Different laboratories were used, and although assays only differed for total testosterone, reference ranges were not identical and this could affect comparability of hormone levels. While it is unlikely that this affected the results of this study, there were significant ethnic and racial differences between groups.

In conclusion, this study shows that GnRHa are effective in suppressing the HPG axis in transgender youth. This finding has relevant clinical implications as GnRHa are recommended to suppress puberty in children and adolescents with gender dysphoria.[11]

Authors' Contributions

X.L. conceived the idea and participated in the design of the study, collected and analyzed the data, and wrote the article. J.D.M.-O. participated in the collection and

analysis of data and edited the article. P.W. participated in the analysis of data and edited the article.

Author Disclosure Statement

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Abbreviations Used

AFAB = assigned female at birth
AMAB = assigned male at birth
CPP = central precocious puberty
FSH = follicle-stimulating hormone
GnRHa = gonadotropin-releasing hormone agonists
HPG = hypothalamic-pituitary gonadal
IA = immunoassay
LC/MS = liquid chromatography/mass spectrometry
LH = luteinizing hormone
NS = not significant