

TRANSGENDER HEALTH

## Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents



Sebastian E. E. Schagen, MD,<sup>1,2</sup> Peggy T. Cohen-Kettenis, PhD,<sup>3</sup>  
Henriette A. Delemarre-van de Waal, MD, PhD,<sup>1,2,a</sup> and Sabine E. Hannema, MD, PhD<sup>2</sup>

### ABSTRACT

**Introduction:** Puberty suppression using gonadotropin-releasing hormone agonists (GnRHAs) is recommended by current guidelines as the treatment of choice for gender dysphoric adolescents. Although GnRHAs have long been used to treat precocious puberty, there are few data on the efficacy and safety in gender dysphoric adolescents. Therefore, the Endocrine Society guideline recommends frequent monitoring of gonadotropins, sex steroids, and renal and liver function.

**Aim:** To evaluate the efficacy and safety of GnRHa treatment to suppress puberty in gender dysphoric adolescents.

**Methods:** Forty-nine male-to-female and 67 female-to-male gender dysphoric adolescents treated with triptorelin were included in the analysis.

**Main Outcome Measures:** Physical examination, including assessment of Tanner stage, took place every 3 months and blood samples were drawn at 0, 3, and 6 months and then every 6 months. Body composition was evaluated using dual energy x-ray absorptiometry.

**Results:** GnRHa treatment caused a decrease in testicular volume in 43 of 49 male-to-female subjects. In one of four female-to-male subjects who presented at Tanner breast stage 2, breast development completely regressed. Gonadotropins and sex steroid levels were suppressed within 3 months. Treatment did not have to be adjusted because of insufficient suppression in any subject. No sustained abnormalities of liver enzymes or creatinine were encountered. Alkaline phosphatase decreased, probably related to a slower growth velocity, because height SD score decreased in boys and girls. Lean body mass percentage significantly decreased during the first year of treatment in girls and boys, whereas fat percentage significantly increased.

**Conclusion:** Triptorelin effectively suppresses puberty in gender dysphoric adolescents. These data suggest routine monitoring of gonadotropins, sex steroids, creatinine, and liver function is not necessary during treatment with triptorelin. Further studies should evaluate the extent to which changes in height SD score and body composition that occur during GnRHa treatment can be reversed during subsequent cross-sex hormone treatment.

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**Key Words:** Gender Dysphoria; Gonadotropin-Releasing Hormone Agonist; Puberty Suppression; Gonadotropins; Sex Steroids

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<sup>1</sup>Department of Pediatric Endocrinology, VU University Medical Centre, Amsterdam, the Netherlands;

<sup>2</sup>Department of Pediatrics, Leiden University Medical Centre, Leiden, the Netherlands;

<sup>3</sup>Department of Medical Psychology and Medical Social Work, VU University Medical Centre, Amsterdam, the Netherlands;

<sup>a</sup>Deceased 13 February 2014.

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### INTRODUCTION

Gender dysphoria is characterized by incongruence between the experienced gender and the sex assigned at birth. It was believed to be a rare phenomenon, but the number of individuals seeking advice and/or treatment at dedicated clinics is increasing.<sup>1</sup> Children can express a sense of belonging to the other sex at a very young age and might show gender role behavior typical of the experienced gender. However, studies have shown that in the children who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text*

*Revision* criteria for gender identity disorder, the gender dysphoria persisted into adolescence only in a minority.<sup>2</sup> If gender dysphoria persists or worsens at the onset of puberty, then it is very likely that it will persist into adulthood.<sup>2</sup>

The Endocrine Society has issued a clinical practice guideline on the endocrine treatment of gender dysphoric individuals.<sup>3</sup> For adolescents, pubertal development of the natal sex can be very distressing. Once irreversible characteristics of the natal sex have developed, such as breasts in natal girls and a low voice and outgrowth of the Adam's apple and jaw in natal boys, it becomes more difficult for the individual to live in the experienced gender. Therefore, treatment with gonadotropin-releasing hormone agonists (GnRHAs) to suppress puberty is recommended. This gives individuals time to carefully consider their wishes regarding gender-affirming treatment without the distress caused by the development of unwanted sex characteristics. From approximately 16 years of age, individuals can be treated with sex steroids to induce the sex characteristics consistent with the gender identity.<sup>3</sup>

Treatment with GnRHa has been shown to improve psychological well-being in several domains.<sup>4</sup> However, physical outcome has not been very well studied. The Endocrine Society guidelines describe that testicular volume decreases and slight development of sex characteristic regresses,<sup>3</sup> but little evidence is available to support these statements.<sup>5</sup> This makes it difficult to counsel individuals on what they can expect. In addition, it is recommended to measure gonadotropins and sex steroids every 3 months during treatment and monitor liver enzymes and renal function.<sup>3</sup> However, the necessity of these frequent measurements is uncertain. A consensus statement on the use of GnRHa in children states there is insufficient evidence for any specific short-term monitoring scheme.<sup>6</sup> GnRHAs have been used for many years for the treatment of children with precocious puberty and no side effects on liver or kidney function have been reported, but adolescents might respond differently.

## AIM

We set out to describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRHa treatment of gender dysphoric adolescents to evaluate the efficacy of this treatment. In addition, we report on the yield of monitoring liver enzymes and renal function and on changes in body composition.

## METHODS

### Subjects and Protocol

Gender dysphoric adolescents seen at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam Netherlands) from 1998 through 2009 were invited to participate in a study on brain development, brain functioning, growth, and metabolic aspects of their treatment. These adolescents were diagnosed as described in existing guidelines,<sup>3</sup>

were eligible for treatment fulfilling *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for gender identity disorder,<sup>7</sup> had lifelong extreme gender dysphoria, were psychologically stable, and were living in a supportive environment. The design of the study was observational and prospective. Treatment consisted of intramuscular injections of the GnRHa triptorelin 3.75 mg (Decapeptyl-CR, Ferring Pharmaceuticals, Copenhagen, Denmark), at 0, 2, and 4 weeks, followed by injections every 4 weeks. Individuals were seen at 3-month intervals. The duration of treatment with GnRHa alone depended on when the individual reached the age at which cross-sex hormone therapy could be added. Only individuals who had been treated for at least 3 months were included in this study.

Fifty-five male-to-female (MtF) and 73 female-to-male (FtM) adolescents started treatment according to this protocol. Twelve subjects were excluded from analysis because no baseline data were available ( $n = 4$ ), treatment duration was shorter than 3 months ( $n = 2$ ), or they were already being treated with medication that affects the hypothalamus-pituitary-gonadal axis at baseline (an antiandrogen,  $n = 1$ ; a GnRHa provided elsewhere,  $n = 2$ ; or a progestin,  $n = 3$ ). Data from 49 MtFs and 67 FtMs were analyzed. None of the subjects in this study discontinued the GnRHa treatment.

### Ethical Approval

Medical ethical approval was granted by the local medical ethics committee and informed consent was obtained from all participants and their parents or guardians. The study was placed on the International Standard Randomized Controlled Trial Number register and ascribed the registration number ISRCTN 81574253 (<http://www.controlled-trials.com/isrctn/>).

## MAIN OUTCOME MEASURES

### Physical Examination

Tanner stage was determined by the same examiners at each visit and based on breast development in FtMs and testicular volume and genital development in MtFs.<sup>8,9</sup> Testicular volume was determined using a Prader orchidometer. Weight and height were measured using an electronic scale and a wall-mounted stadiometer (SECA, Hanover, MD, USA), with weight measured to the nearest 0.1 kg and height to the nearest 0.1 cm. Height SD score (SDS) was calculated using Dutch reference data<sup>10</sup> and body mass index (BMI) SDS was calculated using reference data from Cole et al.<sup>11</sup>

### Laboratory Investigations

After 0, 3, and 6 months of treatment and every 6 months thereafter, blood was drawn for measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase,  $\gamma$ -glutamyl transferase, and creatinine. The

**Table 1.** Baseline characteristics and changes in anthropometric measurements and body composition during the first year of GnRH treatment\*

	MtF		<i>P</i> value	FtM		<i>P</i> value
	Start GnRH	1 y GnRH		Start GnRH	1 y GnRH	
Age (y), median (range)	13.6 (11.6–17.9)			14.2 (11.1–18.6)		NS
Tanner G and B stages, median (range)	4 (2–5)			4 (2–5)		NS
Menarche	N/A			49/65 (77%)		
Height (cm), mean (SD)	167.8 (7.5)	172.3 (6.5)	<.001	161.4 (8.4)	163.5 (7.9)	<.001
n	36	36		41	41	
Height SDS, mean (SD)	0.20 (1.0)	–0.04 (1.0)	<.001	–0.10 (1.1)	–0.25 (1.1)	<.001
n	36	36		41	41	
Weight (kg), mean (SD)	57.4 (11.1)	63.3 (11.9)	<.001	55.1 (14.7)	59.5 (14.4)	<.001
n	36	36		41	41	
BMI (kg/m <sup>2</sup> ), mean (SD)	20.3 (3.0)	21.2 (3.2)	<.001	21.0 (4.5)	22.1 (4.6)	<.001
n	36	36		41	41	
BMI SDS, mean (SD)	0.82 (1.1)	0.89 (1.2)	NS	0.68 (1.2)	0.84 (1.2)	.01
n	36	36		41	41	
Fat percentage (%), mean (SD)	22.4 (6.9)	26.8 (6.6)	<.001	25.0 (6.9)	29.5 (7.3)	<.001
n	26	26		27	27	
Lean body mass (%), mean (SD)	74.6 (6.4)	70.9 (7.3)	.001	71.5 (6.7)	67.7 (6.7)	<.001
n	26	26		27	27	
Testicular volume (ml), median (range)	13.5 (4–25)		<.001	8 (2.5–22.5)		N/A
n	33	33				
AP (U/L), mean (SD)	303 (109)	216 (79)	<.001	215 (101)	168 (58)	<.001
n	19	19		21	21	
Creatinine (μmol/L), mean (SD)	70 (12)	66 (13)	NS	73 (8)	68 (13)	.01
n	28	28		29	29	

AP = alkaline phosphatase; B stage = breast stage; BMI = body mass index; FtM = female-to-male; G stage = genital stage; GnRH = gonadotropin-releasing hormone agonist; MtF = male-to-female; N/A = not applicable; NS = not significant; SDS = SD score.

\*Baseline characteristics are shown for all included patients. Where data at the start of treatment are compared with data after 1 year of treatment, results are shown of individuals from whom data were available at the two time points.

following assays were used: an immunometric assay for LH and FSH (Delfia, PerkinElmer, Wallac Oy, Finland; lower limit of quantification = 0.3 U/L for LH and 0.5 U/L for FSH), a radioimmunoassay for estradiol (Diasorin, Saluggia, Italy; lower limit of quantitation = 18 pmol/L), and a radioimmunoassay for testosterone (Siemens Medical Solutions USA, Malvern, PA, USA; lower limit of quantification = 1 nmol/L). The laboratory participates in external quality control and meets International Organization for Standardization 15189 criteria.

### Dual-Energy X-Ray Absorptiometry

Fat mass, fat percentage, and lean body mass percentage were measured with dual-energy X-ray absorptiometry using a Hologic QDR 4500 scanner (Hologic Inc, Waltham, MA, USA).

### Statistical Analysis

The statistical package used was SPSS 22 (SPSS Inc, Chicago, IL, USA). Changes in various laboratory parameters between two time points in participants with complete data were compared using paired-samples *t*-test if normally distributed and Wilcoxon

signed rank test if not normally distributed. Correlations were analyzed using bivariate correlations. Results were considered statistically significant at a *P* value less than .05.

## RESULTS

### Anthropometry and Body Composition

Baseline characteristics are presented in Table 1. Height, weight, and BMI significantly increased during the first year of treatment in girls and boys. In MtFs, height SDS significantly decreased by  $0.23 \pm 0.23$  in the first year of treatment ( $n = 36$ ,  $P < .001$ ), by  $0.28 \pm 0.14$  in the second year ( $n = 21$ ,  $P < .001$ ), and did not change in the third year ( $n = 3$ ). BMI SDS did not significantly change in the first year and increased by  $0.13 \pm 0.21$  in the second year ( $n = 21$ ,  $P = .009$ ). In FtMs, height SDS decreased by  $0.15 \pm 0.23$  SDS in the first year ( $n = 41$ ,  $P < .001$ ), by  $0.13 \pm 0.24$  in the second year ( $n = 22$ ,  $P = .02$ ), and did not significantly change in the third year ( $n = 10$ ). BMI SDS increased by  $0.17 \pm 0.41$  in the first year ( $n = 41$ ,  $P = .01$ ) and did not significantly change

thereafter. The lean body mass percentage significantly decreased during the first year of treatment in MtFs and FtMs, whereas fat percentage significantly increased (Table 1). Absolute fat mass increased in MtFs and FtMs ( $P < .001$ ).

### Pubertal Development

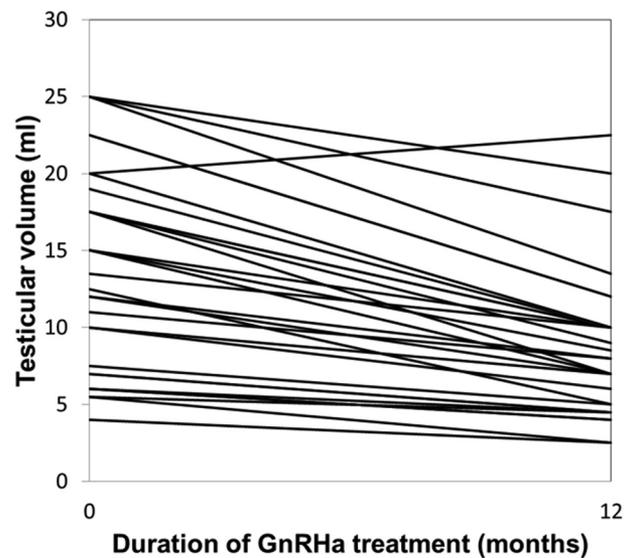
Many subjects were in late puberty (Tanner stages 4 and 5) at the time GnRHa treatment was started. Only four FtMs were at Tanner breast stage 2 at baseline and in one of these individuals breast development regressed completely to Tanner breast stage 1 after 6 months of treatment with GnRHa. In the other FtMs, some unstimulated tissue remained palpable. In the FtMs who had had menarche, menses ceased, often after a withdrawal bleed. Testicular volume decreased during GnRHa treatment in 43 of 49 MtFs. One of the individuals who did not show a decrease had not adhered to the therapy. Three others had been treated for less than 1 year. In one individual, mean testicular volume had increased slightly from 20 mL at baseline to 22.5 mL at 12 months but decreased again to 20 mL at the next measurements. In 33 individuals from whom testicular volume measurements were available at baseline and at 12 months, testicular volume decreased from  $13.9 \pm 6.5$  to  $8.6 \pm 4.7$  mL ( $P < .001$ ; Figure 1). The decrease was significantly correlated to the testicular volume at baseline ( $P < .001$ ). During the second year of treatment, testicular volume did not significantly change in 17 individuals (mean =  $8.2 \pm 4.4$  mL at 12 months and  $8.4 \pm 3.7$  mL at 24 months,  $P = .65$ ).

### Gonadotropin and Sex Steroid Levels

Gonadotropins decreased within the first 3 months of treatment and did not change thereafter (Table 2). In MtFs, testosterone decreased from a median of 9.1 nmol/L (range < 1.0–34) at baseline to lower than 1.0 nmol/L (<1.0–1.1) at 3 months; in FtMs, estradiol decreased from a median of 123 pmol/L (23–1136) to 29 pmol/L (<18–73). Estradiol levels after 3 months of treatment were not as low in some FtMs who were in Tanner breast stages 4 and 5 at the start of treatment compared with those who were in Tanner breast stages 2 and 3 at baseline (Figure 2). However, these slightly higher estradiol levels under GnRHa treatment were not associated with clinical signs of insufficient suppression such as progressive breast development or uterine bleeding. GnRHa treatment did not have to be adjusted because of insufficient suppression in any subject. Gonadotropins and testosterone were not suppressed in only one MtF after 6 months but this individual had not adhered to the therapy. After 3 months of treatment, estradiol also significantly decreased in MtFs ( $P < .001$ ). Sex steroid levels remained low thereafter.

### Creatinine Levels

In MtFs, no creatinine levels above the upper limit of normal (ULN) were detected during 1 year of treatment. In four FtMs, creatinine was just above the ULN ( $91\text{--}94 \mu\text{mol/L}$ , with ULN =  $90 \mu\text{mol/L}$ ; two at baseline, two during treatment) but no progressive increase was seen. In individuals from whom



**Figure 1.** Change in testicular volume during the first year of gonadotropin-releasing hormone agonist (GnRHa) treatment. A decrease in testicular volume was observed in 32 of 33 natal boys from whom data were available at the two time points.

creatinine levels were available at baseline and after 12 months of treatment, a significant decrease was seen in FtMs ( $73 \pm 8$  to  $68 \pm 13 \mu\text{mol/L}$ ,  $n = 29$ ,  $P = .01$ ) but not in MtFs ( $70 \pm 12$  to  $66 \pm 13 \mu\text{mol/L}$ ,  $n = 28$ ,  $P = .2$ ). There was no significant correlation between change in creatinine and change in lean body mass in either sex (data not shown).

### Liver Enzymes

$\gamma$ -Glutamyl transferase was not elevated in any subject. Mild elevations of AST and ALT above the reference range were fairly common at baseline (AST and ALT were elevated in 8/39 respectively 4/39 MtFs and 3/61 respectively 1/59 FtMs) but were not more prevalent during treatment than at baseline. Only one MtF and one FtM had AST and/or ALT levels more than twice the upper limit of normal after 3 months of treatment, but these levels subsequently decreased without any change to the treatment.  $\gamma$ -Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment.

In girls and boys, a significant decrease in alkaline phosphatase was observed during the first year of GnRHa treatment (Table 1). Individuals with a high alkaline phosphatase level at baseline showed the largest decrease. These were the individuals who were still growing as evident from the significant negative correlation between growth during the first year of treatment and the change in alkaline phosphatase (Spearman  $\rho = -0.624$ ,  $P < .001$ ; Figure 3).

### DISCUSSION

Although GnRHa treatment has become the treatment of choice in gender dysphoric adolescents, few data are available on the efficacy and safety of this treatment in this population.

**Table 2.** Changes in gonadotropins and sex steroid levels during the first year of GnRHa treatment\*

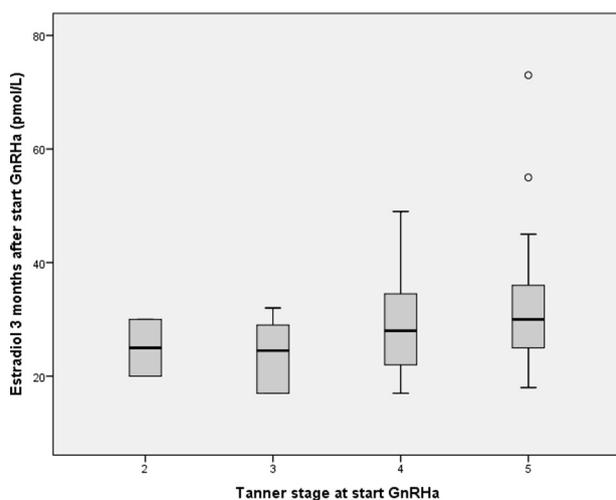
	Duration of GnRHa treatment (mo)			
	0	3	6	12
<b>MtF</b>				
LH (U/L)	1.7 (1.4, 49)	0.4 (0.4, 41)	0.4 (0.4, 44)	0.4 (0.3, 37)
FSH (U/L)	2.4 (1.4, 49)	<0.5 (0, 41)	<0.5 (0.1, 45)	<0.5 (0.1, 37)
T (nmol/L)	9.1 (8.7, 49)	<1.0 (0, 40)	<1.0 (0, 43)	<1.0 (0, 37)
E2 (pmol/L)	44 (35, 46)	25 (8, 37)	24 (7, 40)	26 (8, 34)
<b>FtM</b>				
LH (U/L)	3.0 (4.2, 64)	0.3 (0.3, 55)	0.4 (0.4, 58)	0.3 (0.3, 35)
FSH (U/L)	4.6 (2.1, 64)	1.3 (1.6, 55)	1.7 (1.4, 58)	1.7 (0.9, 35)
T (nmol/L)	<1.0 (0.4, 60)	<1.0 (0, 53)	<1.0 (0, 55)	<1.0 (0, 36)
E2 (pmol/L)	123 (118, 63)	29 (9, 53)	26 (12, 57)	30 (12, 37)

E2 = estradiol; FSH = follicle-stimulating hormone; FtM = female-to-male; GnRHA = gonadotropin-releasing hormone agonist; LH = luteinizing hormone; MtF = male-to-female; T = testosterone.

\*Data are presented as median (interquartile range for the number of measurements available).

Therefore, the Endocrine Society recommends rather extensive safety monitoring.<sup>3</sup> We set out to evaluate the extent to which (early) pubertal physical changes can be reversed, the need for monitoring of gonadotropins and sex steroid levels, and the need for screening of liver and renal function.

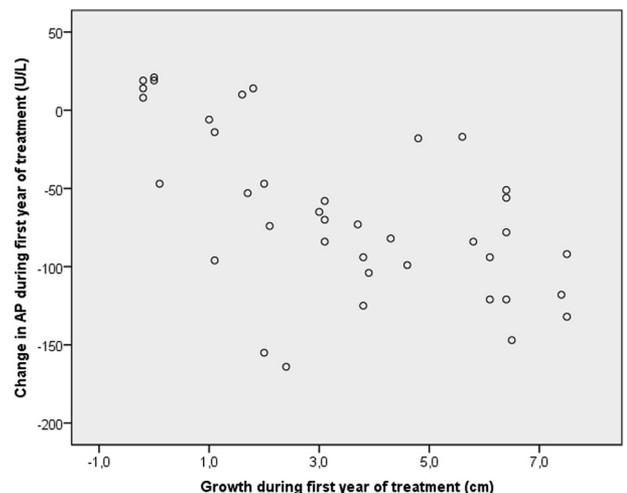
Regression of early sex characteristics is difficult to quantify. In natal girls, Tanner breast stage 2 development can be expected to regress to Tanner stage 1, because glandular breast tissue can atrophy in the absence of estradiol. Few individuals presented at this early pubertal stage, but only one of the four who did showed complete regression of breast development. However, unstimulated tissue that remains palpable behind the nipple on examination is of little clinical relevance. In practice, this is not experienced as the presence of breasts by the individual and is not visible.



**Figure 2.** Estradiol levels in female-to-male individuals after 3 months of gonadotropin-releasing hormone agonist (GnRHa) treatment according to Tanner breast stage at the start of treatment. In general, estradiol was well suppressed, although levels were slightly higher in some individuals who were at Tanner stage 4 or 5 at the start of treatment.

In natal boys, testicular volume decreased in 88% of adolescents. This is in accordance with previous studies that have reported a decrease in testicular volume in boys treated with GnRHa for precocious puberty.<sup>12,13</sup> In adults, testicular volume also has been shown to decrease by approximately 50% during treatment when gonadotropins are suppressed with a long-acting androgen or a long-acting androgen in combination with a GnRHa.<sup>14</sup> Why testicular volume did not change despite adequately suppressed gonadotropins in several individuals from our cohort is unclear, although the limited duration of GnRHa treatment could partly account for this finding in some of these individuals.

Gonadotropins and sex steroids decreased within 3 months in all individuals, after which levels remained low in all but one



**Figure 3.** Correlation between the change in alkaline phosphatase (AP) and growth velocity during the first year of gonadotropin-releasing hormone agonist treatment. Alkaline phosphatase decreased in those who were still growing and changed little in those who had completed growth as evident from the significant negative correlation between growth during the first year of treatment and the change in alkaline phosphatase (Spearman  $\rho = -0.624, P < .001$ ).

non-adherent individual. Therefore, it seems unnecessary to routinely monitor gonadotropins and sex steroids during treatment with triptorelin. Rather, these can be measured if there are clinical signs of inadequate suppression (ie, progressive breast development or increase of testicular volume).

In some FtMs who had (nearly) completed puberty before the start of treatment, estradiol levels did not decrease to levels as low as in those who started treatment in early puberty, but this was not associated with clinical signs of estrogen exposure such as uterine bleeding and treatment did not have to be adjusted. The FSH, LH, and estradiol levels we observed in natal girls were similar to or slightly lower than those found in girls treated with triptorelin because of central precocious puberty (CPP) or because of isolated growth hormone deficiency and early puberty.<sup>15,16</sup> In boys with CPP, median LH after 6 to 24 months of triptorelin treatment was 0.29 IU/L (range = 0.17–1.41), similar to what we observed and what has been reported in girls, but median FSH was lower than levels reported in girls with CPP (0.14 IU/L, range = 0.10–0.28).<sup>12</sup> Another small study reported undetectable FSH (<1.0 IU/L) in a boy with CPP on triptorelin, whereas FSH levels were not as well suppressed in four girls.<sup>17</sup> We also observed lower FSH levels during triptorelin treatment in natal boys compared with natal girls. Lower FSH levels also have been found in healthy boys compared with girls, prepubertally and during puberty, and in the basal state and in response to GnRH.<sup>18</sup> This might be due to sexually dimorphic development or programming of the hypothalamus-pituitary-gonadal axis, for example, by prenatal sex steroids.

Suppression of gonadotropins and estradiol by triptorelin was superior to that reported in gender dysphoric adolescents (natal girls) treated with the androgenic progestin lynestrenol.<sup>19</sup> Many adolescents reported metrorrhagia during lynestrenol treatment, especially during the first 6 months,<sup>19</sup> which was not observed during treatment with triptorelin.

None of the adolescents discontinued GnRHa treatment because of side effects. This is in agreement with the finding that GnRHa treatment is well tolerated by children and adolescents with CPP.<sup>6</sup> In a Canadian study, 1 of 27 individuals with gender dysphoria who were treated with GnRHa was reported to have stopped treatment owing to emotional lability.<sup>20</sup> Another developed sterile abscesses from leuprolide injections and therefore was switched to triptorelin, which was well tolerated<sup>20</sup>; this complication also has been observed in children treated for CPP but is very rare.<sup>6</sup> Although few adolescents seem to discontinue GnRHa treatment, side effects such as hot flushes are common, but these were not formally assessed in the present study.

We found small changes in BMI SDS in contrast to a previous study that did not report a change in BMI SDS in gender dysphoric adolescents treated with triptorelin.<sup>21</sup> From a combined analysis of several studies in children with CPP, it was concluded that long-term GnRHa treatment does not seem to cause an increase in BMI SDS.<sup>6</sup> We observed an increase in fat percentage and decrease in lean body mass percentage in boys

and girls. Because no controls were included, it is unclear to what extent the changes in body composition can be attributed to the treatment, but studies in adults are in agreement with our findings. Healthy premenopausal women showed a decrease in fat-free mass in response to treatment with GnRH analogues,<sup>22,23</sup> but no change in fat mass.<sup>23,24</sup> In healthy men, GnRH analogue treatment was found to induce an increase in body fat and a decrease in lean mass.<sup>25</sup> Further studies are needed to determine the extent to which changes in body composition during GnRH analogue treatment are reversed during treatment with cross-sex hormones. In children who had been treated with GnRH analogues for CPP or to delay puberty during growth hormone treatment, body composition at adult height was comparable to that of controls.<sup>26,27</sup>

We did not identify any renal or hepatic complications of the treatment, and previous studies on GnRHa treatment in children with precocious puberty did not find such adverse effects.<sup>6</sup> Therefore, it does not seem necessary to routinely monitor these parameters. Alkaline phosphatase decreased during GnRHa treatment. This is most likely due to a decrease of the bone fraction rather than the liver fraction of alkaline phosphatase, because none of the other liver enzymes showed similar changes. This decrease is probably related to a change in growth velocity and lower bone mineral accrual, which are known determinants of alkaline phosphatase levels,<sup>28</sup> because we observed a decrease in height SDS and GnRHa treatment has been shown to result in a decrease in bone mineral density z-scores.<sup>21</sup>

This study has some weaknesses. First, the number of adolescents who presented in early puberty was small, which made it difficult to assess whether early pubertal changes regress under GnRHa treatment and whether prolonged puberty suppression is safe. Now that adolescents are finding their way to gender clinics at younger ages, we should increase our knowledge of the efficacy and safety of this treatment in early pubertal subjects. Second, no control group was included, so it remains unclear how changes in, for example, body composition and alkaline phosphatase during GnRHa treatment in the gender dysphoric adolescents differ from changes that normally occur during the progression of puberty. Ideally, future studies would include age-matched control subjects. Third, the safety parameters assessed in the present study were limited. Effects on bone mineral density and on executive function have been reported, but further studies are necessary.<sup>21,29</sup> These should explore the effects of cross-sex hormone treatment in individuals who have been treated with GnRH analogues to assess outcomes such as adult height and body composition.

## CONCLUSIONS

We have shown that GnRHa treatment using triptorelin is effective in suppressing gonadotropins and sex steroids and results in a decrease in testicular volume and cessation of menstrual bleeding. Monitoring of creatinine and liver enzymes did not identify any pathology. Therefore, we propose that routinely

monitoring gonadotropins, sex steroid levels, renal function, and liver enzymes during GnRHa treatment using triptorelin is not necessary. Further studies will have to determine the extent to which changes in height SDS and body composition that were observed during GnRHa treatment can be reversed during subsequent cross-sex hormone treatment.

**Corresponding Author:** Sabine E. Hannema, Postbus 9600, 2300 RC Leiden, the Netherlands. Tel: +31-71-526-2824; fax: +31-71-524-8198; E-mail: [s.e.hannema@lumc.nl](mailto:s.e.hannema@lumc.nl)

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## STATEMENT OF AUTHORSHIP

### Category 1

#### (a) Conception and Design

Peggy T. Cohen-Kettenis; Henriette A. Delemarre-van de Waal

#### (b) Acquisition of Data

Sebastian E.E. Schagen; Henriette A. Delemarre-van de Waal

#### (c) Analysis and Interpretation of Data

Sebastian E.E. Schagen; Sabine E. Hannema

### Category 2

#### (a) Drafting the Article

Sabine E. Hannema

#### (b) Revising It for Intellectual Content

Sebastian E.E. Schagen; Peggy T. Cohen-Kettenis

### Category 3

#### (a) Final Approval of the Completed Article

Sebastian E.E. Schagen; Peggy T. Cohen-Kettenis; Sabine E. Hannema

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