

ORIGINAL RESEARCH

# Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria



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## ABSTRACT

**Introduction:** Gender-affirming hormone treatment is known to affect adrenal androgen levels in adult individuals with gender dysphoria (GD). This may be clinically relevant because the adrenal gland plays a critical role in many different metabolic processes.

**Aim:** This study aims to assess the effects of gonadotropin-releasing hormone analogs (GnRHa) treatment and gender-affirming hormone treatment on adrenal androgen levels in adolescents with GD.

**Methods:** In this prospective study, dehydroepiandrosterone-sulfate (DHEAS) and androstenedione values were measured every 6 months during 2 years of GnRHa treatment only, and 2 years of GnRHa combined with gender-affirming hormone treatment (estradiol or testosterone) in 73 transgirls and 54 transboys. To determine trends in adrenal androgen levels a linear mixed model was used to approximate androgen levels.

**Main Outcome Measures:** DHEAS and androstenedione levels were the main outcome measures.

**Results:** DHEAS levels rose in transboys during GnRHa treatment, which may represent the normal increase during adolescence. In transgirls no change in DHEAS levels during GnRHa treatment was found. Gender-affirming hormone treatment did not affect DHEAS levels in either sex. In transboys androstenedione levels decreased during the first year of GnRHa treatment, which may reflect reduced ovarian androstenedione synthesis, and rose during the first year of gender-affirming hormone treatment, possibly due to conversion of administered testosterone. In transgirls androstenedione levels did not change during either GnRHa or gender-affirming hormone treatment.

**Clinical Implications:** No deleterious effects of treatment on adrenal androgen levels were found during approximately 4 years of follow-up.

**Strengths & Limitations:** This is one of the largest cohort of adolescents with GD, treated using a uniform protocol, with standardized follow-up. The lack of a control group is a limitation.

**Conclusion:** The changes in androstenedione levels during GnRHa and gender-affirming hormone treatment in transboys may not be of adrenal origin. The absence of changes in androstenedione levels in transgirls or DHEAS levels in either sex during gender-affirming hormone treatment suggests that gender-affirming hormone treatment does not significantly affect adrenal androgen production. **Schagen SEE, Lustenhouwer P, Cohen-Kettenis PT, et al. Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. J Sex Med 2018;15:1357–1363.**

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**Key Words:** Gender Dysphoria; Dehydroepiandrosterone-Sulfate; Androstenedione; Testosterone; Estradiol; Gonadotropin-Releasing Hormone Analog

Received March 9, 2018. Accepted July 20, 2018.

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<https://doi.org/10.1016/j.jsxm.2018.07.017>

## INTRODUCTION

Gender dysphoria (GD) is the distress associated with an incongruence between the sex assigned at birth and the gender identity. The cause of this incongruence is presumed to involve a complex interaction among biological, social, and cultural factors.<sup>1</sup> Adolescents with a diagnosis of GD according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria who have entered puberty (Tanner stage  $\geq 2$ ) can be treated with gonadotropin-releasing hormone analogs (GnRHa) to suppress endogenous sex hormone production and prevent the development of unwanted sex characteristics.<sup>1</sup> Such treatment is recommended by the Endocrine Society and the World Professional Association for Transgender Health as standard of care.<sup>1,2</sup> If GD persists and the adolescent meets eligibility criteria in accordance with Endocrine Society guidelines, treatment with gender-affirming hormones can be started.<sup>1</sup> These include either estrogens, given to transfemales (individuals assigned male at birth with a female gender identity) or testosterone, given to transgender males (individuals assigned female at birth with a male gender identity). One follow-up study has shown that such treatment during adolescence, followed by gender-affirming surgery, results in good psychological outcome in young adults (at an average of 20.7 years).<sup>3</sup> However, limited data are available on the safety and side effects of this treatment and this remains an important concern.<sup>4,5</sup>

The adrenal gland produces various androgens, in addition to mineralocorticoids, glucocorticoids, and catecholamines. The most important adrenal androgens are dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), and androstenedione. After hydrolysis from DHEAS, DHEA is thought to exert its effects after conversion in peripheral tissues and the gonads to androstenedione, testosterone, dihydrotestosterone, and/or estradiol.<sup>6</sup> The adrenal androgens are involved in pubarche during childhood/adolescence. Their role in adult life is not fully understood but DHEA(S) is thought to have effects on insulin sensitivity, lipid metabolism, leptin production by adipocytes, body temperature regulation, and on the brain and the immune system.<sup>6</sup> Given this multitude of effects, it is important to evaluate adrenal androgen levels during hormonal treatment in adolescents with GD even though it is currently difficult to predict what the clinical impact is of changes in adrenal androgen levels on future health.

In adults, changes in serum levels of adrenal steroids have been observed during gender-affirming hormone treatment.<sup>7</sup> An increase of adrenal androgens was seen in transmen treated with testosterone. Adrenal androgen levels (DHEAS and androstenedione) decreased in transwomen treated with ethinyl-estradiol and the anti-androgen cyproterone acetate. In a more recent study, Mueller et al<sup>8</sup> have shown similar changes in middle-aged transwomen who received a combination of GnRHa and 17-beta estradiol.<sup>8</sup> The cause of these changes is not completely clear yet; both effects on the adrenal gland and on the testes have been proposed.<sup>8</sup> Normally adrenal androgen levels rise during

adolescence.<sup>9–11</sup> They reach a peak at age 20–30 years and decrease thereafter.<sup>9–12</sup> This suggests that adrenal synthesis and/or metabolism of androgens differs between adolescents and adults. Therefore, GnRHa and gender-affirming hormone treatment may have different effects in adolescents as compared to adults.

As part of a larger study initiated to investigate the efficacy and safety of GnRHa and gender-affirming hormone treatment in adolescents with GD, we aimed to assess the effects of these treatments on DHEAS and androstenedione serum levels. This should add to the scarce data available on the safety and side effects of this treatment in adolescents.

## METHODS

### Subjects

127 adolescents with GD (54 transgirls [assigned male at birth] and 73 transboys [assigned female at birth]) treated between 1998 and 2009 at the VU University Medical Center in Amsterdam were included in a prospective study on brain development, brain functioning, growth, and metabolic aspects in the clinical management of adolescents with GD. Adolescents were included if they fulfilled the criteria for gender identity disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* and the criteria for treatment according to the Endocrine Society.<sup>13</sup> There were no exclusion criteria.

### Treatment Protocol

Treatment consisted of intramuscular injections of the GnRHa triptorelin (3.75 mg) (Decapeptyl-CR; Ferry B.V., Hoofddorp, The Netherlands) 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 gender-affirming hormone therapy could be added (approximately 16 years). In transgirls gender-affirming hormone treatment consisted of daily oral doses of 17-beta estradiol, starting at 5  $\mu\text{g/kg/d}$ . Doses were increased by 5  $\mu\text{g/kg/d}$  every 6 months until the maintenance dose of 2 mg/d was reached. In transboys 25 mg/m<sup>2</sup> of testosterone esters (Sustanon; Aspen Pharma Trading Limited, Dublin, Ireland) were administered every 2 weeks through intramuscular injections. Doses were increased every 6 months by 25 mg/m<sup>2</sup> per 2 weeks until the maintenance dose of 125 mg per 2 weeks (or 250 mg per 4 weeks) was reached. If GnRHa treatment was started after the age of 16 years (and endogenous puberty had been completed), gender-affirming hormone treatment was usually added after 3 to 6 months and increased more rapidly. Transgirls were treated with 1 mg 17-beta estradiol daily for 6 months, followed by the maintenance dose of 2 mg; transboys were treated with 75 mg testosterone esters per 2 weeks for 6 months, followed by the maintenance dose of 125 mg per 2 weeks.

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