Chapter 10
Early Medical Intervention in Adolescents with Gender Dysphoria

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Abstract During the last 10 years, the Dutch protocol that comprises medical intervention in the management of gender dysphoria in adolescents has appeared to be safe and efficient. Using GnRH analogs, physiologic pubertal development is suppressed. From the age of 16 years, cross-sex steroids are added to the GnRH analog to induce the pubertal sex characteristics of the desired sex.

Side effects of the GnRH analog treatment are conceivable in the areas of growth, bone development, metabolism, and brain development. Up until now, however, we have not observed major side effects. On the contrary, with respect to growth, when medical intervention is started early in puberty, we are able to manipulate growth in a way that final adult height is more appropriate for the desired sex.

Currently, before the treatment is started to suppress puberty (with GnRH analogs) or to induce puberty (with cross-sex hormones), the treatment guidelines suggest to medical professionals that adolescents should have reached a certain pubertal stage, as well as a certain age. Because of the current positive outcomes, protocols may permit an earlier start to puberty suppression and induction of cross-sex secondary sex characteristics. This would result in a more typically timed physiologic pubertal development in adolescents with gender dysphoria.

10.1 Introduction

In the 1970s, treatment of gender identity disorders (GID) started with an experimental design in adults (Asscheman, Gooren, & Eklund, 1989). Female-to-male transsexuals (FtMs) were treated with androgens, while male-to-female

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transsexuals (MtFs) received cyproterone acetate to suppress androgen activity, combined with estrogens. The morbidity and mortality of this relatively young population was higher compared to a reference population (Asscheman et al., 1989). Over time, the management in adults has been improved and adjusted for individual patients (Gooren, 2011).

The supportive care for prepubertal children with GID is predominantly psychological. Since the late 1990s, the possibility of puberty suppression when GID persists during adolescence has generated a new but still controversial dimension to clinical management. Puberty suppression is considered a fully reversible medical intervention that can serve as a diagnostic aid in gender dysphoric adolescents. It provides the gender dysphoric adolescent with time and rest before a more definite decision is made on (partially) irreversible steps of gender reassignment (cross-sex hormones and surgeries). However, this early treatment of adolescents revealed concerns about potential risks, such as a poor physical and psychological outcome due to adverse effects of puberty suppression on bone and brain development, respectively. An important concern is whether an adolescent is capable of making such a major decision. The first gender dysphoric adolescents for whom puberty was suppressed were far in their pubertal development when treatment was applied using gonadotropin-releasing hormone (GnRH) analogs.

Case History

The first patient Peggy Cohen-Kettenis and myself treated was a 13-year-old girl in pubertal Tanner stage four (Cohen-Kettenis et al., 2011). Treatment consisted of a GnRH analog, followed by a combination with androgens. At the age of 20 and 22 years, she underwent reassignment surgery, and thereafter medication consisted of only androgens. During the follow-up at 22 years of age, he indicated he had no regrets about this treatment. He was functioning well psychologically, intellectually, and socially. There were no clinical signs of physical imbalance; metabolic and endocrine (male) parameters were in the normal reference range, as was bone density. He believed himself in good physical health.

This long-term follow-up of puberty suppression suggested that such a treatment can be a useful tool in the diagnosis and treatment of gender dysphoric adolescents.

A treatment protocol based on both aspects (diagnostics and treatment) was composed, which was included in the official guidelines of the American Endocrine Society and the European Society of Pediatric Endocrinology (Delemarre-Van de Waal & Cohen-Kettenis, 2006; Hembree et al., 2009).

Although this approach is increasingly accepted, the treatment of adolescents with GID is still under debate among professionals and policy makers. Therefore, we still need to collect data on the health outcome of adolescents treated for gender dysphoria.

10.2 Ethical Aspects of Clinical Management: Why Should We Treat Adolescents with Gender Dysphoria?

There are still many questions about whether or not the treatment of adolescents with GID is ethical. Aren't these youngsters too young to be fully cognizant of the consequences of their choices? Although the use of puberty suppressants is described in international guidelines, there is no worldwide consensus on the Endocrine Society Guidelines and the Standards of Care of the World Professional Association of Transgender Health (Coleman et al., 2012; Hembree et al., 2009). In the Netherlands, puberty suppression is part of the treatment protocol for gender dysphoric adolescents. In recent years, various countries in North America and Europe have adopted this model of care that is sometimes referred to by the country of its developers: "The Dutch approach" (Olson, Forbes, & Belzer, 2011; Spack et al., 2012; Zucker, 2010). However, in some countries, it is not the standard of care due to various ethical concerns, including fears about harm from the treatment. Concerns that are raised include the following: Can a reliable diagnosis of GID be made in children and adolescents? Is there psychopathology involved in the child with GID and his or her parents that obscures this diagnosis?

Suppression of puberty resulting in "freezing" puberty may help in the diagnostic phase by "buying time." In collaboration with both a medical and mental health professional, the adolescents may explore their gender identity without the distress of developing secondary sex characteristics. If the adolescents want to live permanently in the desired gender role as adults, they will be spared the torment of the "wrong" secondary sex characteristics.

With regard to side effects of the treatment, suppression of puberty will have its influence on height, bone development, and possibly on metabolism (for carbohydrates and lipids). The question is whether these side effects are always harmful; with respect to height, an early intervention in a male-to-female transsexual may result in a more acceptable "female" final height. Other aspects of debate are the loss of fertility in males in case of early treatment, as well as the influence on gender identity development and brain development. Finally, one may have concerns regarding the costs of treatment associated with GID. Before discussing these aspects, a more detailed description of the Dutch protocol will be given.

10.3 Treatment Protocol: The Dutch Experience

For prepubertal children, treatment includes psychological counseling. When GID persists into adolescence, suppression of puberty can be considered.

The first adolescents for whom puberty was suppressed were treated with progestins and modified sex steroids (cyproterone acetate). These drugs exert a negative feedback on the secretion of gonadotropins, resulting in lower gonadotropin

and sex steroid levels. In addition, most of these drugs have a direct negative effect on the activity of sex steroids as a blocker at the steroid receptor level. This suppression was often incomplete, resulting in a slow continued progression of pubertal development including skeletal maturation, although height velocity decreased (Lee, Thompson, Migeon, & Blizzard, 1975).

The availability of GnRH analogs in the 1980s gave the opportunity to suppress the gonadotropins more adequately. These analogs have prolonged binding at the GnRH receptor, resulting in desensitization and a complete block of gonadotropin release. A complete block of the endocrine and clinical pubertal development occurs. The GnRH analogs were originally developed in order to suppress gonadotropin secretion in central precocious puberty (Boepple et al., 1986). Thirty years of experience since its introduction revealed that this treatment is safe and, most importantly, very effective at suppressing puberty. Discontinuation of the analog showed a rapid recovery of the gonadotropin axis and, in girls, restoration of the menstrual cycle. At the moment, the main official indication to use GnRH analogs in children is central precocious puberty (Carel et al., 2009).

Because of its efficacy to suppress gonadotropin secretion, GnRH analogs are the optimal treatment option in the management of a pubertal girl or boy with GID. The first GID patients we treated were in the second half of puberty, and consequently the girls may have experienced menarche and boys may have already shown signs of masculinization, such as lowering of the voice. The GnRH analogs completely suppress gonadotropin and sex steroid levels; estradiol levels in girls are not detectable anymore, and testosterone levels in boys are below 1.0 nmol/L. Clinically, in girls, breast mass will become weak and diminish. A problem in boys is that masculinization, such as outgrowth of the cheeks and lowering of the voice, is not reversible. That means that although testicular volume decreased, the visible sex characteristics as result of androgen exposure remained.

Seeking the best way of treating children with GID, we started the GnRH analog in adolescents with some early pubertal development. For girls, this means that they are in Tanner stages 2–3, with budding of the nipple or slightly more volume of the breast and measurable estradiol levels. For boys, Tanner stage 3 is characterized by testicular volume of about 10 ml and measurable testosterone levels. The start of puberty is considered of diagnostic value, since most adolescents experience an aggravation of their distress resulting from gender dysphoria. They may not want to be confronted with their bodies, may not take showers anymore, and may refuse physical examinations.

GnRH analogs immediately halt pubertal progression. In addition to the effects on the sex characteristics, skeletal age is delayed and height growth continues in a prepubertal velocity (Delemarre-Van de Waal & Cohen-Kettenis, 2006). Follow-up measurements of the endocrine parameters revealed an adequate suppression of gonadotropins, while other endocrine systems remained in the normal range. Therefore, GnRH analogs appear to be an effective and safe treatment in order to stop endogenous pubertal development. An advantage of this intervention is that it is fully reversible; discontinuation will restore endogenous pubertal development.

Table 10.1 Treatment schedules to initiate pubertal development

Induction of female puberty with 17-beta estradiol, increasing the dose every 6 months
5 μg/kg/day
10 μg/kg/day
15 μg/kg/day
20 μg/kg/day
Adult dose = 2 mg per day
Induction of male puberty with testosterone esters increasing the dose every 6 months
25 mg/m^2/2 weeks im
50 mg/m^2/2 weeks im
75 mg/m^2/2 weeks im
100 mg/m^2/2 weeks im
Adult dose 250 mg per 3–4 weeks

The next step of treatment is to start cross-sex hormones. This treatment is partially reversible, meaning that the achieved changes in external sex characteristics will not disappear completely after discontinuation of the sex steroids. The age we start with cross-sex hormones is 16 years and is based on the fact that in the Netherlands (as in many European countries), a 16-year-old is a legal adult for medical decision making. Parental consent is not obligatory but is preferred, since the adolescent needs social support in this complex phase of life.

In the first step of treatment with GnRH analogs, we make the patient hypogonadotropic without gonadal sex steroids. To induce female sex characteristics in MtFs, estrogens are prescribed in an increasing dose as shown in Table 10.1. Breast development and female-appearing body shape will be initiated. When patients are on an adult dose, this will be continued for the rest their lives. Once a patient is older than 16 years of age, the levels of the dose can be adjusted. In FtMs, androgens induce virilization, including male body features such as a low voice, facial and body hair growth, and a more masculine body shape. Androgen treatment will also result in clitoral enlargement, although the final size will never reach the size of a normal penis. If still present, mild breast mass will become more atrophic and may even disappear. Also, in FtMs older than 16 years of age, the treatment schedule can be sped up.

10.4 Physical Aspects of Treatment of Adolescents with Gender Dysphoria

10.4.1 Growth

Suppression of puberty will delay height velocity and skeletal maturation. It appears that a delay in growth will remain and will result in catch-up growth at a later phase. The patient will continue to grow with prepubertal height velocity. The problem for

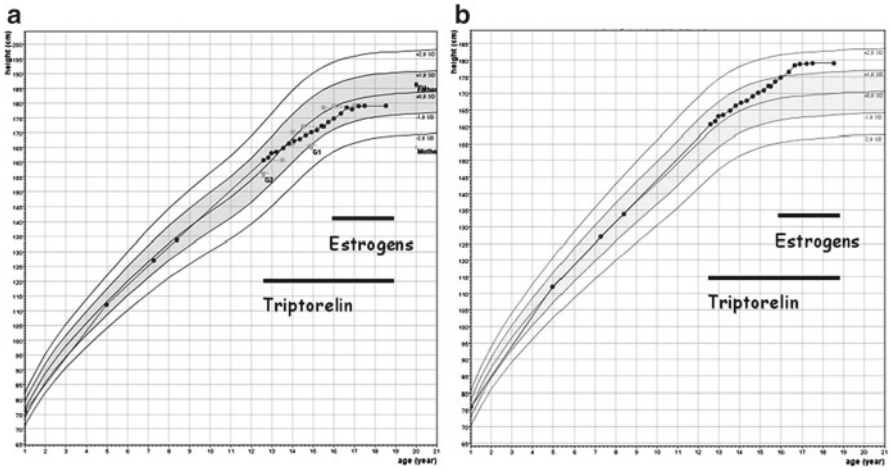

Fig. 10.1 Growth curve, depicted on a male (**a**) and female curve (**b**), respectively, of a MtF transsexual during treatment with GnRH analog and during combination treatment of GnRH analog (Triptorelin^{R}) with estrogens from the age of 16 years. Patient was in Tanner stage G2 at start of the treatment. Since testicular volume decreased to below 4 ml, pubertal stage regressed to G1. [This figure is reprinted from Delemarre-Van de Waal and Cohen-Kettenis (2006)]

MtFs is that their adult predicted height is relatively tall for females. The mean adult difference in height between males and females is 12 cm in the Dutch population. Therefore, the MtF will want to limit the final height. The experience in MtFs is that, after several years of suppression of puberty, the growth curve crosses the SD (standard deviation) curves downwards (see Fig. 10.1) (Delemarre-Van de Waal & Cohen-Kettenis, 2006). When estrogens are started, a small catch-up can be seen, followed by a decrease in height velocity. If (female) tall stature is expected, one can increase the estrogen dose in order to reduce final height.

The opposite is the case in FtMs, as Dutch females are on average 12 cm shorter than males. Suppression of puberty will stop the female pubertal growth spurt and a prepubertal height velocity will decrease height SD. Since female puberty on average starts 2 years earlier than male puberty, the FtMs need to be treated longer before androgens can be started at the age of 16 years. To increase height velocity, anabolic steroids can be used such as oxandrolone with a strong height velocity-stimulating effect and with a mild progressive effect on skeletal age. Our data show an increase in FtM's final height compared to predicted height when started with suppression of puberty.

In conclusion, medical intervention in gender dysphoric adolescents will influence height. However, this may be positive as MtFs may have a more appropriate female height and FtMs a more appropriate male height.

10.4.2 Bone Development

From the experience with suppression of puberty in girls with central precocious puberty (CPP), we know that bone mass can be lost. At start of treatment, girls with CPP have, in contrast to adolescents with GID, increased bone mass (for age) because of the exposure to sex steroids at a younger age. They are losing bone mass during treatment with GnRH analogs, but in the long term, bone mass is in the normal range (Poomthavorn, Suphasit, & Mahachoklertwattana, 2011). Adolescents with GID have, in principle, a normal bone mass for their age. GnRH analogs may intervene with the physiologic accretion of bone during puberty. Therefore, we examine the patients' bone development on a regular base. Data from about 120 patients showed that, at start of the treatment, all had a bone density in the normal range. Surprisingly, the MtFs had relatively lower normal values, which may be the result of a more sedentary way of life compared to the reference boys. During GnRH analog treatment, bone mass increased gradually in the young patients, while slightly decreasing in the relatively older adolescents. During cross-sex hormones, bone density appears to catch up comparably to the increase in physiologic puberty (Van Coeverden et al., 2002). The best results for bone mass at the end of the treatment protocol are seen among patients who started with suppression of puberty at a young age and thus in early puberty.

In conclusion, although in CPP a significant decrease of bone mass is seen during GnRH analog treatment, we observed, during the long-term treatment of adolescents with gender dysphoria, a continued increase of bone mass. During cross-sex hormones, a catch-up of bone accretion is seen comparable with the normal physiologic increase.

10.4.3 Metabolic Aspects

During physiologic puberty, body composition changes. Especially in girls, the amount of fat mass increases and therefore the body mass index (BMI) increases. Insulin sensitivity correlates inversely with BMI (Cook, Hoffman, Stene, & Hansen, 1993). Girls with CPP show an increase of BMI during suppression of their puberty with GnRH analogs (Aguiar et al., 2006). The question arises how BMI and insulin resistance would respond to treatment with GnRH analogs in healthy adolescents with gender dysphoria. During a period of 24 months of treatment with GnRH analogs, both biologic males' and females' BMI slightly increased about 6 %, while body fat mass increased more in biologic males than females. Surprisingly, insulin sensitivity did not decrease during this period, while in both sexes, insulin growth factor (IGF-1) and sex steroids decreased. The lack of a change in insulin sensitivity on the increase of BMI may be the result of the disappearance of sex steroids during this treatment (Wouters, Schagen, Cohen-Kettenis, & Delemarre-van de Waal, 2007).

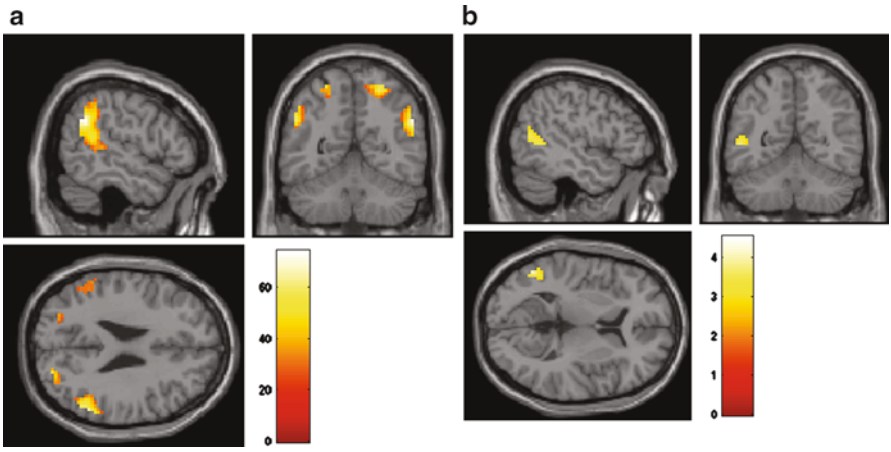

Fig. 10.2 (**a**) shows the average effect of the brain areas with increased activation during the mental rotation task. Main effects for the task are reported at $p<0.05$ family-wise error (FWE) corrected. The threshold for cluster size is set to 10 voxels. (**b**) shows increased activation in FtM adolescents as compared to MtF adolescents in the left temporal lobe during the mental rotation task. Group by task interactions are reported as $p<0.005$ uncorrected. The threshold for cluster size is set to 10 voxels. MRIs are performed before the start of any medical intervention

10.4.4 Brain Development

There are sex differences in brain anatomy. Significantly greater cortical thickness is observed in women compared to men, after correcting for individual differences in brain size, while no significant regional thickness increases are observed in males. Gender-specific findings support the idea of a dimorphic organization in male and female brains, which affects the architecture of the cortex (Luders et al., 2006). In addition, Zhou, Hofman, Gooren, and Swaab (1995) showed that the volume of the bed nucleus of the stria terminals (BSTc), the nucleus involved in sexual behavior, is larger in men than in women. In MtF transsexuals, they found a female-sized BSTc. The same research group also showed that men have twice as many somatostatin neurons in the BSTc as do women. In one FtM, the number of somatostatin neurons was similar to the normal male control group (Kruijver et al., 2000). These data support the hypothesis that there is a neurobiological basis of gender dysphoria.

In the Dutch adolescent gender identity clinic, we found that several neuropsychological tests concerning verbal performance, emotion, and mathematics were performed in accordance to the desired or experienced gender. For verbal fluency, MtFs produced more words than control boys and even more than FtMs and control girls (Soleman et al., 2013). Comparisons of brain activity in an fMRI design between control boys and girls showed more activation in the boys in the right Rolandic operculum, a small area adjacent to Broca's area. No significant differences were found comparing transsexual adolescents, although sub-threshold

activation was found in the right Rolandic operculum, indicating a trend-wise increase in activation from control girls, to FtMs, to MtFs, and to control boys (Schagen et al., submitted). For the mental rotation test, a higher performance as well as increased activation of the sulcus parietalis was found in control boys compared to girls, as well as in FtMs than in MtFs (see Fig. 10.2a, b).

In conclusion, there are increasing data available supporting the paradigm that gender dysphoria has a neurobiological basis. The origins, however, remain unknown, but (placental) steroids and growth factors may play a role.

10.5 Conclusions Regarding the Dutch Protocol

To date, the experience of more than 10 years with this protocol in the management of adolescents with gender dysphoria, as indicated above, has not revealed complications. The patients reported satisfaction with regard to suppression of puberty and reported no regrets after treatment. However, some patients consider the age of 16 too late for the start of cross-sex hormones. In addition, in young patients diagnosed to be gender dysphoric, we have to wait until the first signs of puberty appear.

The question arises whether in cases with a long-standing diagnosis of childhood gender dysphoria the treatment can be started at the onset of puberty based on skeletal age, endocrine evaluation, and the earliest signs of puberty (budding of the nipple in girls and testicular growth in boys).

Primum non nocere (Hippocratic Oath), "at least do no harm," may be applied to this group of patients in whom the diagnostic value of puberty in distinguishing between desisting or persisting gender dysphoria is deemed less relevant. In the future, starting medical treatment at the onset of puberty to suppress endogenous puberty while adding cross-sex hormones soon thereafter may be considered. Then the gender dysphoric patient can have a more physiologic pubertal development consistent with the typical timing of the experienced gender.

10.6 Future Perspectives

The Dutch experience on management of young transsexuals is very satisfactory for the patients, their parents, and their environment. However, adjustment of the interventions we use now may improve both physical and mental aspects. At the moment, earlier intervention is obstructed by the fact, among other things, that there is not any hard diagnostic tool to determine whether the patient has persisting gender dysphoria and is a good candidate for gender reassignment. Although it is doubtful that such a tool will become available, hopefully better indicators will be developed in the future.

On the other hand, the good results we have now with this protocol may give us the confidence that psychological assessment is the best diagnostic tool at the moment. Today we do not have any regrets in our young patient group. This may

result from being too strict in deciding who is eligible for puberty suppression and who is not, and thereby, we may miss patients that could benefit from treatment. Since the first step of suppression of puberty is completely reversible, we may recommend starting earlier, right at the onset of puberty, rather than waiting until pubertal Tanner stages 2–3. In addition, we may start with cross-sex hormones earlier so that we mimic a completely opposite desired pubertal development at an age that is comparable to the average age of "physiological" puberty and with a typical "physiologic" progression.

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