

Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects

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Abstract

Treatment outcome in transsexuals is expected to be more favourable when puberty is suppressed than when treatment is started after Tanner stage 4 or 5. In the Dutch protocol for the treatment of transsexual adolescents, candidates are considered eligible for the suppression of endogenous puberty when they fulfil the Diagnostic and Statistical Manual of Mental Disorders-IV-RT criteria for gender disorder, have suffered from lifelong extreme gender dysphoria, are psychologically stable and live in a supportive environment. Suppression of puberty should be considered as supporting the diagnostic procedure, but not as the ultimate treatment. If the patient, after extensive exploring of his/her sex reassignment (SR) wish, no longer pursues SR, pubertal suppression can be discontinued. Otherwise, cross-sex hormone treatment can be given at 16 years, if there are no contraindications. Treatment consists of a GnRH analogue (GnRHa) to suppress endogenous gonadal stimulation from B2-3 and G3-4, and prevents development of irreversible sex characteristics of the unwanted sex. From the age of 16 years, cross-sex steroid hormones are added to the GnRHa medication.

Preliminary findings suggest that a decrease in height velocity and bone maturation occurs. Body proportions, as measured by sitting height and sitting-height/height ratio, remains in the normal range. Total bone density remains in the same range during the years of puberty suppression, whereas it significantly increases on cross-sex steroid hormone treatment. GnRHa treatment appears to be an important contribution to the clinical management of gender identity disorder in transsexual adolescents.

European Journal of Endocrinology 155 S131–S137

Introduction

Transsexuals are applying for sex reassignment (SR) surgery at increasingly younger ages. Yet clinicians are usually reluctant to start the SR procedure before adulthood. They assume that adolescents are not able to make a sensible decision about something as drastic as SR. They fear that the risk of postoperative regrets will be high and the treatment will have unfavourable physical, psychological or social consequences. Post-operative regret or any other unfavourable result of SR naturally is of serious concern to clinicians. However, the decision of what age to start SR should be a balanced one. There are two main reasons to consider early treatment as appropriate.

One reason for early treatment is that an eventual delay or arrest in emotional, social or intellectual development can be warded off more successfully when the ultimate cause of this arrest has been taken care of. Suffering from gender dysphoria without being able to present socially in the desired social role, and/or to stop the development of secondary sex characteristics usually leads to problems in these areas. Adolescents find it hard to live with a secret. Often have difficulties in connecting socially and romantically with peers while still in the undesired gender role, or the physical developments create an anxiety that limits their capacities to concentrate on other issues.

A second reason to start SR early is that the physical treatment outcome following interventions in adulthood is far less satisfactory than when treatment is started at an age at which secondary sex characteristics have not yet been (fully) developed. Looking like a man (woman) when living as a woman (man) creates barriers that are not easy to overcome. This is obviously an enormous and lifelong disadvantage. Indeed, Ross

This paper was presented at the 4th Ferring Pharmaceuticals International Paediatric Endocrinology Symposium, Paris (2006). Ferring Pharmaceuticals has supported the publication of these proceedings.

and Need (1) found that postoperative psychopathology was primarily associated with factors that made it difficult for postoperative transsexuals to pass successfully to their new gender or that continued to remind them of their transsexualism. Furthermore, follow-up studies show that unfavourable postoperative outcome seems to be related to a late rather than an early start of the SR procedure (for a review, see (2)). Age at the time of assessment also emerged as a factor differentiating two groups of male-to-female transsexuals (MFs), one with and one without post-operative regrets (3).

The psychological problems of untreated adolescents and the impact of an unfavourable physical appearance significantly contributed to the decision of the Amsterdam Gender Clinic for Adolescents and Children to prescribe hormones before the age of 18 (legal adulthood). First, patients were considered eligible for a staged hormone treatment if they were (i) between 16 and 18 years, (ii) suffering from life-long gender dysphoria that had increased around puberty, (iii) functioning psychologically stable, and (iv) supported by their environment. For females, the staged approach consisted of treatment with progestagens to suppress menses for at least 3 months, followed by androgen treatment. For males, antiandrogens were given first, followed by oestrogens. The first retrospective and prospective studies among these transsexual adolescents, who were found eligible for treatment between 16 and 18 years, showed a significant postsurgery decrease in gender dysphoria, and an increase in body satisfaction. They were also functioning psychologically in the normal range, and did socially quite well (4, 5). They functioned psychologically better than transsexuals, who were treated in adulthood, and evaluated with partly the same instruments (6, 7). The policy implied that younger adolescents (between 12 and 16 years), who were referred for SR, had no other option than to wait for several years before they could be treated medically.

Since the experience of a full biological puberty may seriously interfere with healthy psychological functioning and well being, we have changed our protocol after the first follow-up studies on the 16–18-year olds (4, 5). Adolescents are now allowed to start puberty suppressing treatment with gonadotrophin-releasing hormone analogues (GnRHa) if they were older than 12 years of age and fulfil the same criteria as were used for the 16–18-year olds. They should also have reached Tanner stage 2 or 3 in combination with pubertal levels of sex hormones. The suppression of puberty using GnRHa is a reversible phase of treatment. This treatment is a very helpful diagnostic aid, as it allows the psychologist and the patient to discuss problems that possibly underlie the cross-gender identity or clarify potential gender confusion under less time pressure. It can be considered as 'buying time' to allow for an open exploration of the SR wish (8).

It is conceivable that lowering the age limit increases the incidence of 'false positives'. However, it most certainly results in high percentages of individuals who more easily

pass into the opposite gender role than when treatment commenced well after the development of secondary characteristics. This implies an improvement in the quality of life in these individuals, but may also result in a lower incidence of transsexuals with postoperative regrets or poor postoperative functioning. Clinically, it is known that some patients who were treated in adulthood regret SR because they have never been able to function inconspicuously in the opposite gender role. This holds especially for MFs, because beard growth and voice breaking give so many of them a never disappearing masculine appearance. But, since the number of 'false positives' should be kept as small as possible, the diagnostic procedure should be carried out with great care. Until now, no patients who started treatment before 18 years have regretted their choice for SR.

The Amsterdam Gender Clinic has developed the following protocol for the management of young applicants for SR and is currently evaluating this protocol in several studies.

Diagnostic procedure

The recommended procedure in the Standards of Care of the Harry Benjamin International Gender Dysphoria Association (HBI-GDA; now called World Professional Association of Transgender Health or WPATH) – a professional organization in the field – is to come to the SR decision in various steps (9). In the first phase, it is investigated whether an applicant fulfils Diagnostic and Statistic Manual of Mental Disorders-IV-RT criteria for gender identity disorder (GID). The next phase has three elements: a real-life experience (RLE) in the desired role, hormonal interventions (in order to suppress puberty and cross-sex hormone treatment) and finally, surgery to correct the genitals.

In the first diagnostic phase, information must be obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent's current functioning and functioning of the family. Standardized psychological assessment is a part of the procedure. The patient is always seen by two members of the gender team. If a child and adolescent psychologist makes the diagnosis, the child is also seen by a child and adolescent psychiatrist and *vice versa*. In order to prevent unrealistically high expectations with regard to their future lives, the adolescent has to be clearly informed about the possibilities and limitations of SR and other kinds of treatment. The way a patient responds to the reality of SR can be diagnostically informative. The decision to start medical intervention is always taken by the whole team (for a more detailed description of the diagnostic procedure, see (10)).

During the RLE phase, applicants have to live permanently in the role of the desired sex, if they were not already doing so. Before this is done, significant persons in the adolescents' life have to be informed about

the impending changes. The underlying idea of these requirements is that applicants should have had ample opportunity to appreciate *in vivo* the familial, interpersonal, educational, and legal consequences of the gender role change. In adolescents, who are referred at very young ages (around 12 years), the RLE usually starts when they are on GnRHa treatment only. However, at this stage the RLE is not a requirement. When, after the age of 16 years, the cross-sex hormone treatment is started, the RLE is required for obvious reasons.

Medical interventions

For adolescents, the guidelines of the Royal College of Psychiatrists (11), as well as the HBIGDA (or WPATH) Standards of Care, make a distinction between two stages of endocrine intervention: fully reversible interventions and partially reversible interventions. A fully reversible treatment can be achieved using GnRHa, while a partially reversible treatment consists of cross-sex hormone treatment (in addition to the GnRHa treatment, for adolescents (Fig. 1)).

Fully reversible interventions

When the development of secondary sex characteristics has begun, adolescents with extreme forms of GID and fulfilling the earlier mentioned additional criteria are eligible for GnRHa treatment in order to suppress the production of sex steroids. Psychological or psychiatric involvement, for a minimum period of six months before GnRHa treatment and continuing until surgery, is another requirement for endocrine intervention of adolescents. The objective of this involvement is that the treatment is thoughtfully and recurrently considered over time.

The GnRHa will discontinue progression of puberty by blocking the activity of the GnRH receptor at the pituitary level, which results in a decrease of gonadotrophin release. In turn, a decrease in the stimulation of gonads will lead to

low, prepubertal, levels of oestrogens in girls and androgens in boys. GnRHa treatment will lead to regression of the first stages of the already developed sex characteristics. In girls, the present breast tissue will become weak and may disappear completely. In boys, testicular volume will regress to a lower volume.

This protocol can also be applied to adolescents in later phases of pubertal development. In contrast to patients in early puberty, the various physical changes of pubertal development, such as a late stage of breast development in girls and lowering of the voice and facial hair in boys, will not regress completely, although any further progression will be stopped.

Partially reversible interventions

Adolescents eligible for cross-sex hormone therapy are 16 years of age or older. As in many European countries, in The Netherlands, 16-year olds are considered legal adults for medical decision-making. Although parental consent is not required, it is preferred, as adolescents need the support of their parents in this complex phase of their lives.

In addition to the GnRHa treatment, which makes the patient hypogonadotrophic, an ‘opposite sex puberty’ is induced by adding cross-sex hormones to the treatment. To induce female sex characteristics in MFs, oestrogens are prescribed in an increasing dose according to the schedule as presented in Table 1. Breast development and a female-appearing body shape will be initiated. When the patient is on an adult dose, this will be prescribed for the rest of their lives.

In female-to-male transsexuals (FMs), androgens are used in order to achieve 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 male penis. If still present, mild breast development will become more atrophic and may even disappear.

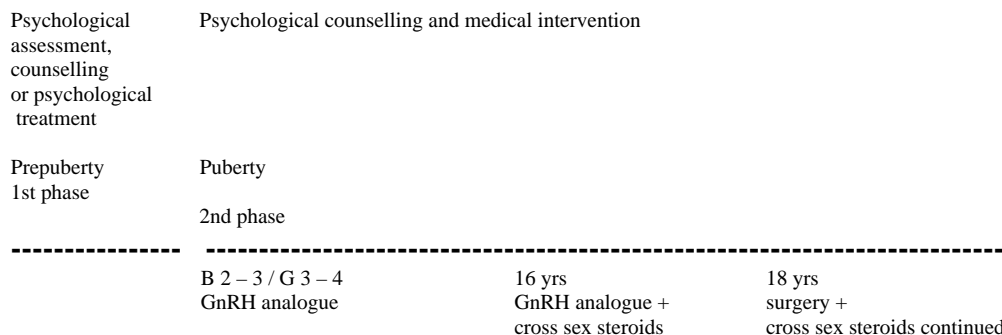


Figure 1 During the first phase, prepubertal children, who are referred for SR, will undergo a psychodiagnostic procedure to assess the gender identity disorder. If the gender identity problem persists into puberty, a second diagnostic protocol is followed. For eligible adolescents, the diagnostic phase can be extended (second phase) by suppressing puberty for several years. From the age of 16 years, cross-sex hormones can be added, and at an adult age of 18 years, the final step can be taken by correction of the genitals.

Table 1 Treatment schedules to initiate pubertal development.

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

Side effects of medical intervention with GnRH analogues and cross-sex hormones

In both girls and boys, after a short activation of the gonadal axes, GnRHs will bring the patients into a hypogonadotrophic state. In girls, withdrawal of oestrogens may induce a withdrawal bleeding. Cycling is disrupted. In early pubertal boys, the hypogonadotrophic state will block the development of fertility. In older-staged boys, fertility will regress. Therefore, in older boys, cryopreservation of semen should be discussed prior to the start of the treatment. As a result of the hypogonadal state, MFs can have complaints of fatigue and a decrease of body strength.

With respect to growth, the growth spurt will be hampered and fusion of the growth plates delayed. This phenomenon may give the opportunity to manipulate growth. Since females are about 12 cm shorter than males, we may intervene with growth-stimulating treatment in order to adjust the female height to an acceptable male height. In contrast, the blocking of the pubertal growth spurt in males is not a problem. During the treatment with oestrogens, the epiphyses will close progressively resulting in what would be a compromised final height for a non-transsexual male, but a quite acceptable height for MF.

During puberty, bone density shows a progressive accretion of bone, which is related to the exposure to sex hormones (12). Peak bone mass will be achieved at the age of 25–30 years. The question arises whether patients participating in this protocol may achieve a normal development of bone density, or will end with a decreased bone density, which is associated with a high risk of osteoporosis.

During physiologic puberty, carbohydrate and fat metabolisms change. Temporary insulin resistance occurs and an increase in fat mass is seen in pubertal girls. We do not know what the effects of GnRH treatment alone, or in combination with cross-sex hormones, are on these metabolic aspects.

Surgery (irreversible interventions)

Surgery is not carried out prior to adulthood (18 years of age). The Standards of Care emphasize that the 'threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention'. If the RLE supported by the cross-sex hormones has not resulted in a satisfactory social role change, if the patient is not satisfied with, or is ambivalent about, the hormonal effects or surgery, the applicant is not referred for surgery.

In MFs, female-looking external genitals are created by means of vaginoplasty, clitoroplasty and labiaplasty. In cases of insufficient responsiveness of breast tissue to oestrogen therapy administered for long enough, breast enlargement may also be performed. After surgery, intercourse is possible. Arousal and orgasm are also reported postsurgically, though the percentages differ between studies (13, 14).

In FMs, a mastectomy is often performed as the first surgery to successfully pass into the desired role. When skin needs to be removed, this will result in fairly visible scar tissue. Considering the still continuing improvements in the field of phalloplasty, some FMs do not want to undergo genital surgery until they have a clear reason for it. They may then choose to have a neoscrotum with a testis prosthesis with or without a metoidioplasty (this technique transforms the hypertrophic clitoris into a microphallus) or a phalloplasty. Other genital procedures include the removal of the uterus and ovaries. Whether FMs can have sexual intercourse using their neopenis depends on the technique and quality of the phalloplasty. Although some patients, who had a metoidioplasty, report that they are able to have intercourse, the hypertrophic clitoris usually is too small for coitus. In most cases, the capacity of sexual arousal and orgasm remains intact.

When the gonads of the patient are surgically removed, the patient can discontinue the GnRH treatment, but will continue the cross-sex hormone treatment.

Legal consequences

In many countries that derive their law from Napoleon's Civil Code of 1804, the birth certificate is the source for all other personal documents. Therefore, it is essential to change the sex in this document to endow a person with the full rights of his/her new gender. Since the ruling of the European Court of Human Rights (ECHR), in 2002, in the case of *Goodwin vs The United Kingdom*, all 46-member states of the ECHR do now fully accept a legal sex change. In the Netherlands, a change of birth certificate is only possible after the patient has been gonadectomized.

Follow-up protocol

In order to investigate the efficacy and safety of GnRHa treatment in adolescents with gender dysphoria, a follow-up protocol has been designed.

During the protocol the following aspects are investigated:

The patients are seen every 3 months by their psychologist or psychiatrist.

Laboratory measurements include levels of gonadotrophins and sex hormones, metabolic parameters such as fasting glucose, insulin, cholesterol, high-density lipoprotein and low-density lipoprotein levels. In addition, safety parameters, such as renal and liver functions, are estimated.

Growth Anthropometric measurements are performed including height, weight, sitting height, hip and waist circumferences and Tanner pubertal stages. Yearly, a skeletal age is estimated using an X-ray of the left hand.

Bone density Just prior to start of the treatment with either GnRHa or the addition of cross-sex hormones a bone density measurement using dual-energy X-ray absorptiometry is performed. The locations of measurement are the non-dominant hip and the lumbar spine as well as the whole body.

First experiences with the protocol

At present, 54 patients are being treated according to this protocol, 30 of whom are FMs. The GnRHa triptorelin (TRP) is administered in a dose of 3.75 mg every 4 weeks intramuscularly or subcutaneously. At the introduction of the treatment, an extra dose is given at 2 weeks.

Preliminary results of the first 21 patients (11 FMs, 10 MFs), treated for 2 years or longer, are as follows:

With respect to the gonadal axis TRP treatment resulted in an adequate suppression of the pituitary gonadal axis, with low gonadotrophin levels and suppressed prepubertal values for oestradiol in FMs and testosterone in MFs. There was no progression of the pubertal stage. In boys, testicular volume decreased. In girls, when treatment was started in the late pubertal stages B4 and B5, frequent hot flushes occurred, which decreased in frequency with time. When cross-sex hormones were added, FMs started to virilize with lowering of the voice, clitoral enlargement and growth of facial and body hair. In MFs, oestrogen treatment induced breast development.

With respect to growth Height SDS in patients with still-growth potential (bone age in girls < 13 years and in boys < 15 years) showed a significant decrease, while sitting-height:height ratio did not change. Figure 2 shows the growth curve in an MF patient. In general, during TRP, slowing down of height velocity is observed. Oestrogens did not elicit a clear growth spurt, while substitution with androgen did (Fig. 3).

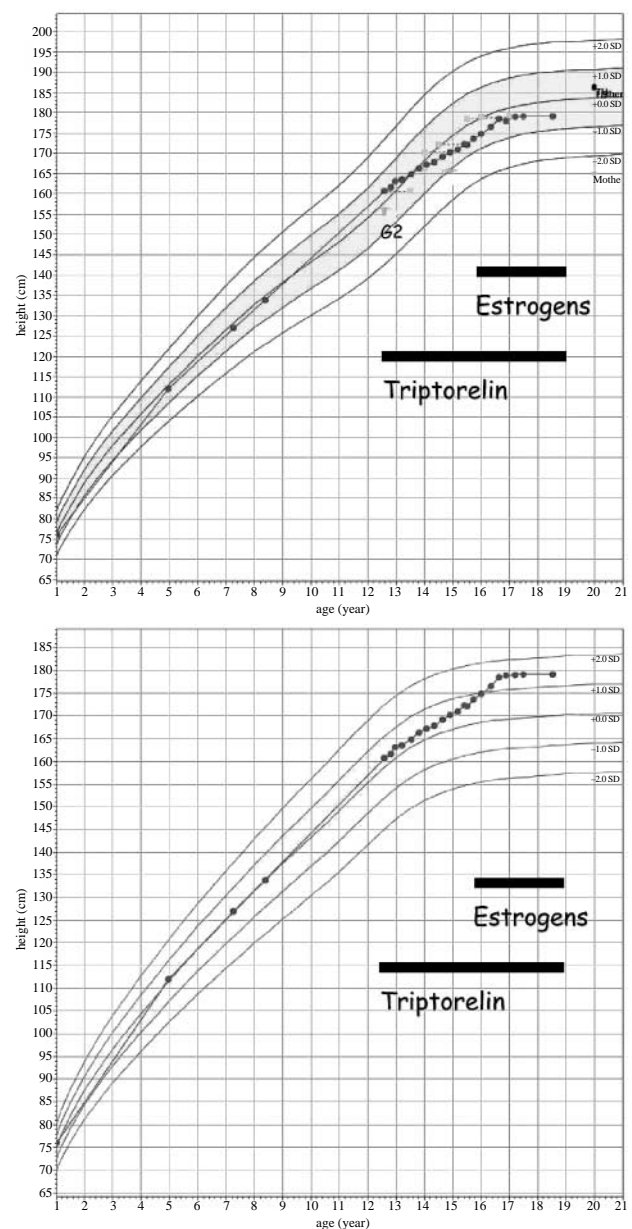


Figure 2 Growth curve (depicted on a male and female curve respectively) of MF during treatment with GnRH analogue (GnRHa) and combination treatment of GnRHa with cross-sex hormones from the age of 16 years. Patient was in stage G2 at the start of the treatment. Since testicular volume decreased to below 4 ml, pubertal stage regressed to G1.

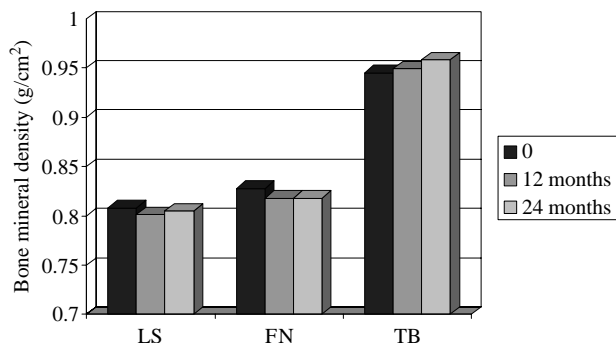


Figure 3 Bone mineral density of the lumbar spine (LS), femoral neck (FS) and total body (TB) in nine transsexual adolescents during a period of 24 months of treatment with a GnRH analogue (GnRHa), measured just prior to the start of the GnRHa treatment (0) and after 12 and 24 months. There were no significant differences.

With respect to bone density During GnRHa treatment, bone density remained in the same range. There were no significant changes in bone densities at three locations: lumbar spine, non-dominant hip and total body, during TRP treatment. However, when calculated as a Z-score, there appears to be a significant decrease during this period. During cross-sex hormone treatment, bone density increased significantly in both MFs and FMs, which is associated with an increase in the bone density Z-score. Figure 4 shows the data of bone density in an MF patient during 2 years of TRP treatment, followed by 2 years of combination therapy with cross-sex hormones.

With respect to body composition During the first year of TRP treatment, the percentage of fat mass increased significantly, but remained at the same level

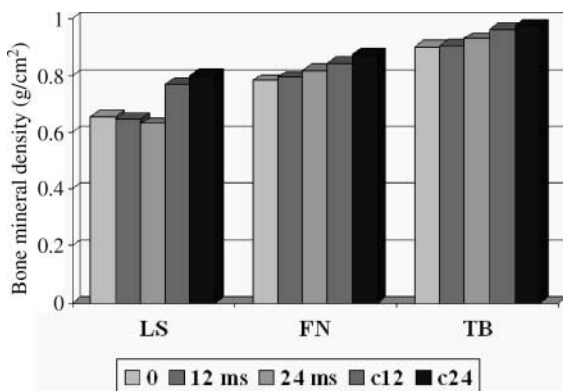


Figure 4 Bone mineral density in a FM individual at the lumbar spine (LS), femoral neck (FN) and total body (TB). The left most bar indicates bone density at the start of treatment with the GnRH analogue (GnRHa). The following two bars to the right indicate bone density at 12 and 24 months on the GnRHa. Oestrogen therapy to induce female puberty starts at 24 months. The two bars on the right side show bone densities in combination treatment of the GnRHa and oestrogens.

thereafter. Lean body mass showed a contrary effect, i.e. a significant decrease during the first year of treatment followed by stabilization at the same level.

Carbohydrate and lipid metabolism did not show any change during treatment either with TRP alone or in combination with cross-sex hormones.

In general, patients repeatedly reported that they are satisfied with the suppression of their pubertal development. This is confirmed in the reports of their parents.

Discussion

The present protocol, developed to ameliorate treatment outcome in adolescent patients with an early onset of GID, appears to be a suitable way to treat such patients. It seems possible to select patients who will profit from early interventions, starting at 12 years with GnRHa and followed at 16 years by cross-sex hormone treatment, provided that the diagnostic procedure is carried out with great care and by an experienced team.

Careful diagnosis should focus on the assessment of the GID as well as potential risk factors (e.g. severe co-morbidity). If any risk factors are present, these should be addressed first, before any medical intervention takes place. Since the diagnostic procedure is lengthy, there is ample time for patient, the family and the psychologist or psychiatrist to make the final decision. Making a balanced decision on SR is far more difficult for adolescents, who are denied medical treatment (GnRHa included), because much of their energy will be absorbed by obtaining treatment rather than exploring in an open way whether SR actually is the treatment of choice for their gender problem. By starting with GnRHa their motivation for such exploration enhances and no irreversible changes have taken place if, as a result of the psychotherapeutic interventions, they would decide that SR is not what they need. However, until now, none of the patients who were selected for pubertal suppression has decided to stop taking GnRHa. On the contrary, they are usually very satisfied with the fact that the secondary sex characteristics of their biological sex did not develop further.

Side effects of pubertal suppression result from the physiological developments occurring during this period. The normal pubertal growth spurt will not continue, resulting in a delay of growth. In girls, we should therefore try to overcome the 12 cm difference that exists between non-patient boys and girls. In the period of suppression, growth-stimulating medication can be offered in order to increase the height velocity. Androgens, which will be introduced in increasing doses from the age of 16 years, may elicit a 'puberty growth spurt' when skeletal maturation is retarded. Boys, who are taller than girls, will also experience growth retardation during GnRHa treatment. Since oestrogen treatment has a growth-inhibiting effect

shortly after the start of treatment (15), oestrogen medication to initiate female puberty may not be associated with a pubertal growth spurt and therefore may result in a more appropriate 'female' final height.

Since puberty is an important phase for the increase of bone density, which lasts until peak bone mass, suppression of puberty may interfere with a normal bone mass increase. The first clinical data suggest that bone mineral density remains at the same level during treatment, which indicates a decrease in Z-score when compared with reference values. However, when, at the age of 16 years, suppression of puberty is combined with cross-sex hormone treatment, a catch-up for bone accretion is observed, resulting in a decrease and normalization of the bone mineral density Z-score. This medical intervention, therefore, does not seem to harm bone development in the short term, but long-term data on peak bone mass should be assessed before a final conclusion can be drawn.

With respect to metabolic parameters, the only significant changes are an increase in fat mass accompanied by a decrease of lean body mass. These changes occurred only during the first year of suppression of puberty. Thereafter, body composition remained at the same level. During treatment with cross-sex hormones, the percentages return to the pretreatment values. The ultimate effect of this manipulation on pubertal development should be investigated in a long-term follow-up.

During puberty, developmental processes also take place in the brain. In the adult brain, a number of sex differences have been reported. For example, the amount of grey matter is higher in adult females than males in the gyrus cingulatus, the median frontal area and the lobus paracentralis in particular (16). It is not clear yet how pubertal suppression will influence brain development. From our experience with adolescents, who have been taking GnRH α and are now adults, no gross effects on their functioning are detectable. However, a study on brain development of adolescent transsexuals, who have used GnRH α , will be carried out to detect eventual subtle functional and structural effects.

Acknowledgements

The authors are very grateful to Ferring Pharmaceuticals for the financial support of studies on the treatment of adolescents with gender identity disorders.

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Received 12 May 2006

Accepted 20 June 2006