Clinical Commissioning Policy Proposition:

Prescribing of Cross-Sex Hormones as part of the Gender Identity Development Service for Children and Adolescents

Reference: NHS England E03X16/01

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Plain Language Summary

Gender dysphoria is a condition where a person, in this case, a child or adolescent, experiences discomfort or distress because there is a mismatch between their biological sex and their gender identity. Biological sex is assigned at birth, depending on the appearance of the genitals. Gender identity is the gender that a person identifies with or feels themselves to be.

This identity may change over time, particularly during adolescence, or it may be persistent. Treatment for gender dysphoria aims to help reduce or remove the distressing feelings of a mismatch between biological sex and gender identity.

Treatments for gender dysphoria include psychological therapies, hormone blockers to alleviate distress associated with pubertal development, cross sex hormones and sex alignment surgery.

In the UK, standard protocols allow for the use of cross sex hormones, after careful assessment, from a person's 16th birthday, and these follow a gradual introduction regimen. Some experts have suggested that cross sex hormones could be used from the 15th birthday.

NHS England has reviewed the available evidence and concluded that:

- treatment from the 15th birthday will be not routinely commissioned in view of the limited available evidence on comparative effects and harms of cross sex hormones at the 15th birthday, as compared to initiating cross sex hormones at the 16th birthday or older;
- changes in the current protocol should only be considered in the context of a research study for young people – the scope of which is yet to be agreed.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission cross sex hormones in the treatment of gender dysphoria in an adolescent before their 16th birthday.

For the purpose of consultation, NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether or not cross sex hormones in the treatment of adolescents with gender dysphoria before their 16th birthday will be routinely commissioned, is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

In the UK and most other European countries, the treatment options for gender dysphoria in adolescents, following an initial psychological assessment and where hormone therapy is considered appropriate, include:

- hormone blockers, which are gonadotropin-releasing hormone analogues and suppress the onset of puberty. This decision is based on the patient's clinical presentation of gender dysphoria, psychological assessment and Tanner staging. (The Tanner scale (also known as the Tanner stages) is a scale of physical development in children, adolescents and adults - see https://www.google.co.uk/?gws_rd=ssl#q=tanner+stages)
- for some patients, this could be followed by the partially reversible use of cross sex hormones at or after 16th birthday for those who have persistent gender dysphoria and wish to continue with gender reassignment.
- some patients may then move to the final step of irreversible sex alignment surgery a few years later, typically at an age greater than 18 years, which is part of the service offering of the adult service.

Some clinical experts have advised that given the early onset of puberty in some cases and the presence of long standing and persistent gender dysphoria, there may be just cause for considering earlier initiation of cross sex therapy in selective cases (i.e. before the person's 16th birthday).

3. Definitions

Cross sex hormones: is where a patient takes the hormones of the preferred gender: for example:

- a trans man (female to male) will take testosterone, which is a masculinising hormone
- a trans woman (male to female) will take oestrogen, which is a feminising hormone

Gender dysphoria: Gender dysphoria is a condition where a person experiences discomfort or distress because there is a mismatch between their biological sex and gender identity.

Hormone blockers: gonadotrophin releasing hormone analogues are synthetic (man-made) hormones that suppress the hormones naturally produced by the body and in doing so, suppress puberty. The effects of treatment with hormone blockers are considered to be fully reversible.

4. Aim and objectives

This policy proposition considered evidence on the use of cross sex hormones in the treatment of adolescents with persistent gender dysphoria after their 15th birthday.

The objectives were to answer the following questions:

1. Given that the use of cross sex hormone treatment is established for the management of gender dysphoria after the 16th birthday, what are the ethical and developmental effects and harms (to include consent, outcome of gender dysphoria and the developing brain) of cross sex hormone therapy for adolescents after their 15th birthday with persistent gender dysphoria?

2. Are the effects and harms of cross sex hormone therapy for adolescents after their 15th birthday with persistent gender dysphoria different for biologically male and biologically female patients?

3. Are the effects and harms of cross sex hormone therapy for adolescents after their 15th birthday with persistent gender dysphoria different for patients in whom irreversible physical changes have already occurred after onset of puberty?

4. How does length of time on the analogue blocker prior to treatment with cross sex hormones relate to different presentations of gender dysphoria (early/late presentations)?

5. Epidemiology and needs assessment

The true incidence and prevalence of gender dysphoria in adolescence is very difficult to ascertain. Of pre pubertal children who present with the features of a gender dysphoria, the dysphoria only persists in 10 to 20% throughout childhood, adolescence and into adulthood, with or without any therapeutic intervention (Di Ceglie 2010). This adds to the difficulty of assessing the number likely to be considered for cross sex hormones.

Based on data from the national gender identity development service, the likely target population for this policy (i.e. adolescents aged over 15 but under 16 with gender dysphoria in whom cross sex hormones might be considered as a therapeutic option) is likely to be very small relative to the total number of referrals to the service.

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Cross sex hormones treatment is established for the management of gender dysphoria after the 16th birthday. A review was undertaken to identify the current evidence on use of cross sex hormone therapy for adolescents with persistent gender dysphoria after their 15th birthday. The systematic literature search identified 54 studies. Many of these were expert commentaries. Fourteen studies met the review criteria and were appraised in detail. The questions considered were:

1. What are the ethical and developmental effects and harms (including consent, outcome of gender dysphoria and the developing brain) of cross sex hormone (CSH) therapy for adolescents after their 15th birthday with persistent gender dysphoria?

Given that there is a general protocol of only using cross sex hormones at or beyond the age of 16 years, the review found limited available evidence on comparative effects and harms of initiating cross sex hormones at the 15th birthday, compared to initiating these at the 16th birthday or older. Some studies have included a few cases of younger patients (less than 16 years) beginning cross sex hormones, but this subgroup was not separately analysed. The body of available evidence comprises case series and both cross-sectional and cohort studies of patients treated in tertiary centres in the Netherlands, the United States and Canada.

Khatchadourian et al. (2014) retrospectively examined the treatment of gender

dysphoric adolescents in Vancouver, Canada. Federal legislation permits consent to treatment below the age of 16, so this case series had less constraints on the age at which cross sex hormones is begun. However, the median age at start of cross sex hormones for natal males was 17.9 years with a range of 13.3 to 22.3 years and for natal females 17.3 years with range of 13.7 to 19.8 years. No subgroup analysis was undertaken to compare those starting cross sex hormones before and after the 16th birthday. Of the 84 patients who initiated hormone blockers, 63 proceeded to receive cross sex hormones (87% of total natal females and 65% of natal males in the study). Cross sex hormones were generally well tolerated in natal males, although twelve of the 39 natal female patients had minor complications from female cross sex hormones: seven developed severe acne, one developed androgenic alopecia, three had mild dyslipidaemia and one had mood swings. Three of these patients stopped cross sex hormones, two because of concomitant psychiatric comorbidities and one because of distress due to androgenic alopecia. The authors did not analyse any factors that could be potentially linked with these side effects, including age.

Despite the Dutch protocol of cross sex hormone being started from 16 years of age, the mean age of initiation of cross sex hormones in Dutch studies is 16.4 to 16.7 years, with the lowest age ranging between 13.9 to 14.9 years (de Vries et al., 2011, 2014; Klink et al., 2015).

Staphorsius et al. (2015) in a large case control study of 84 adolescent patients (13-17 years) demonstrated that hormone blockers did not adversely impact executive function. The Tower of London performance scores (reaction times and accuracy) for hormone blocker treated patients did not differ significantly from the untreated sub group. Functional magnetic resonance imaging (MRI), region-of-interest analyses showed that hormone blocker treated adolescents showed sex differences in neural activation similar to their natal sex control groups. In contrast, untreated adolescents with gender dysphoria did not show significant sex differences in task load-related activation.

Klink et al. (2015), in a case series of 34 patients in Netherlands reported recovery in bone mineral density scores from treatment with hormone blockers during cross sex hormone treatment for both natal males and natal females, although the Z score at age 22 years remained lower than at start of the treatment (0.2 at start to -0.3 at 22 years). An earlier Dutch study (Delemarre-van de Waal et al., 2006) had reported concurring results in 54 patients with significant increase in bone mineral density during cross sex hormone treatment. Neither study followed patients long enough to confirm whether peak bone mass was delayed or permanently reduced.

Delemarre-van de Waal et al. (2006) reported significant decrease in growth potential under GnRH therapy. Once cross sex hormones were started, there was a clear growth spurt with androgen therapy, but not with oestrogen. Many factors (including a differing dose-response relationship depending on the hormone

regime, age and/or Tanner stage at suppression, and delayed growth response with oestrogen outside the study window) could explain this difference in growth potential and bone mass recovery. However, these potential confounders were not addressed in the studies.

The impact on the psychological functioning and well-being of the adolescent throughout the gender dysphoria treatment remains a key issue, especially given the high prevalence of psychiatric comorbidity.

Studies report that 22% to 44% of adolescents with gender dysphoria have significant psychiatric comorbidities including depression and anxiety (de Vries et al., 2011; Spack et al., 2012). De Vries et al. (2014) examined changes in psychological functioning throughout the treatment span. The study reported on the psychological functioning, subjective and objective well-being of 55 adolescents (age at start of cross sex hormones, mean 16.7, range 13.9 to 19.0) before administration of hormone blockers, before cross sex hormones and one year after cross sex hormones, with a total mean follow-up of seven years per patient. Global functioning in the subjects improved after hormone blockers and continued to improve after cross sex hormone initiation. Satisfaction with body image and levels of gender dysphoria were unchanged with hormone blockers, but decreased after starting cross sex hormones. Depression levels decreased after starting hormone blockers, but partially increased after starting cross sex hormones and prior to sex realignment, with natal females demonstrating higher levels of depression. Anxiety levels appeared to increase after starting cross sex hormones but anger levels decreased.

Clearly such studies have potential biases coming from many other factors impacting psychological wellbeing in the period of time before, during and after puberty. Limitations of the study included its single-arm study design and the potential confounding of age and other social and developmental factors which may directly or indirectly impact psychological functioning especially during teenage years.

Ethical review

Abel et al. (2014) considered the key ethical principles affecting decisions about early prescribing of cross sex hormones. The principle of non-maleficence ("first, do no harm") offers the strongest ethical argument against early cross sex hormone therapy because the long-term effects of this are not well known and it has potential for sterility. Hormone blockers, by contrast, have largely been considered free of long-term harm based on generations of follow-up studies with the large population of individuals prescribed such drugs for precocious puberty.

Beneficence (i.e. the obligation of physicians to help their patients) is another key principle in considering early cross sex hormone therapy as only a subset of patients on hormone blockers decide to proceed to cross sex hormones. While

delaying hormone therapy may conform to the principle of non-maleficence for this group, the significant prevalence of desistence (stopping treatment) and the inability to predict which patients will persist with treatment, detracts from the argument for beneficence.

Given the possibility of desistence, physicians must consider the unlikely situation where cross sex hormone therapy renders permanent harm in a desisting child. Helping an adolescent to appreciate the seriousness of infertility is an important ethical obligation and one complicated by the fact that the adolescent's developing brain is generally more limited than the adult brain in its ability to weigh long term consequences (Abel et al., 2014). The task becomes more complex given the prevalence of autism (Kaltiala-Heno et al., 2015) and psychiatric comorbidities as high as 22% to 44% amongst gender dysphoric adolescents (de Vries et al., 2011; Spack et al., 2012).

2. Are the effects and harms of cross-sex hormone therapy for adolescents after their 15th birthday with persistent gender dysphoria different for biologically male and biologically female patients?

The effect of cross sex hormones is expected to be different in natal male and female subjects. Evidence is not available regarding any difference on response to cross sex hormones specifically below the age of 16. In the available evidence, with respect to reversing some of the effects of gonadal suppression, Klink et al. 2014 report minimal difference in response to cross sex hormones in biologically female and biologically male patients in improving bone density.

For biological females, lumbar spine area bone mineral density (LS aBMD) scores were below the population mean at the start of the treatment and in natal males LS aBMD score was normal at the start of the treatment but decreased during hormone blocker therapy. During cross sex hormone therapy, LS aBMD improved for both groups. However the z score at age 22 years remained lower than that at start of the treatment.

A cross-sectional survey on psychological comorbidities on 105 gender dysphoria patients in the Netherlands (de Vries et al. 2011) found that natal males had higher rates of social phobia and mood disorders. In contrast, in two potentially overlapping case series by the same lead author (de Vries et al., 2011, 2015), biologically male subjects were reported to have significantly lower level of gender dysphoria, anger, anxiety, depression and higher levels of body image satisfaction, global functioning, than biological female subjects. Both genders showed improvement in symptoms with cross sex hormones.

3. Are the effects and harms of cross sex hormone therapy for

adolescents after their 15th birthday with persistent gender dysphoria different for patients in whom irreversible physical changes have already occurred after onset of puberty?

There was no relevant evidence available in this review. Rosenthal et al. (2014) expressed the opinion that transgender youth who are at Tanner stage 4 to 5 but less than 14 years of age, should only be considered for pubertal suppression but not for cross sex hormones before 16 years of age given the lack of supportive outcome data. Authors also recommended not using hormone blockers below 12 years of age given the lack of safety data in these age groups.

4. How does length of time on the analogue blocker prior to treatment with cross-sex hormones relate to different presentations of gender dysphoria (early/late presentations)?

The length of time on hormone blockers varied amongst different studies reviewed. There was no direct information on the impact of length of time on gender dysphoria presentation. One study, de Vries et al. (2011) assessed patients at the start of puberty suppression and again two years later at the start of cross sex hormones and found no change in levels of gender dysphoria or body image satisfaction but statistically significant improvement in depression and global functioning for most patients. Prevalence of other behavioural presentations such as anger, anxiety remained unchanged.

There was no evidence available to answer the question regarding effects and harms of reducing the time on the hormone blocker alone to six months, rather than the current year, prior to decisions about whether or not to proceed to cross sex hormones, especially for adolescents who started the hormone blocker after secondary sex characteristics had developed and reach their 15th or 16th birthday before a year on the blocker and for late presenting adolescents age 16 years and over.

Conclusion

In conclusion, given the current accepted practice in most countries of offering cross sex hormones at 16 years of age or greater, there is insufficient evidence available on the effects and harms of cross sex hormones at a younger age to warrant a change to the current protocol.

Further research is required to study the benefits, harms and ethical concerns surrounding use of cross sex hormones in specific groups of younger people who have been clinically established as most likely to persist and function in preferred gender, such as those who started hormone blockers in the early stages of puberty and to fully understand and consent to the impacts of these, including partial irreversibility of cross sex hormone therapy.

The service provider proposes to undertake this research following the formal NHS ethical approval process - which would mirror the process followed in 2011 for offering the hormone blocker in the early stages of puberty. The service provider proposes to undertake the cross sex hormone research trial with its Dutch counterpart.

7. Documents which have informed this policy proposition

Not applicable

8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by July 2016).

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Version Control Sheet

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