NHS England

Evidence Review:

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

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1. Introduction

In the UK and most other European countries gender dysphoria in adolescents is usually treated, following an initial psychological assessment, by firstly using Gonadotropin-releasing hormone analogue (GnRHa) to suppress the onset of puberty. This is a decision based on the patient's clinical presentation of gender dysphoria, psychological assessment and tanner staging. This could be followed by the partially reversible use of cross sex hormones (CSH) at or after 16th birthday for those who wish to continue with gender reassignment. Some patients may move to the final step of irreversible gender reassignment surgery (GRS) a few years later, typically at an age greater than 18 years. Some clinical experts have advised that given the early onset of puberty in some cases and increasingly younger presentation of gender dysphoria, there may be consideration for earlier initiation of cross sex therapy in selective cases.

2. Summary of results

Cross-sex hormone treatment is established for the management of gender dysphoria after the 16th birthday. This review was undertaken to identify the current evidence on use of cross-sex hormone therapy for adolescents after their 15th birthday with persistent gender dysphoria. The systematic literature search identified 54 studies, a significant number of these were expert commentaries. In addition, recommendations were received from clinical experts regarding relevant studies, most of which were captured in the systematic search. 14 studies met the review criteria and were appraised in detail. The summary findings of the review are as follows:

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 CSH at or beyond the age of 16 years, this review found very limited available evidence on comparative effects and harms of initiating CSH at 15th birthday, compared to initiating CSH at 16th birthday or older. Some studies have included a few cases of younger patients (<16 years) beginning CSH, but this subgroup has not been separately analysed. The body of available evidence comprises case series and both cross sectional and cohort studies of patients treated in tertiary centres in Netherlands, United States and Canada.

Complications

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 CSH is begun. However, the median age at start of CSH for natal males was 17.9 years with a range of 13.3-22.3 years and for natal females 17.3 years with range of 13.7 - 19.8 years. No subgroup analysis was undertaken to compare those starting CSH before and after 16th birthday. Of the 84 patients who initiated GnRHa, 63 proceeded to receive CSH (87% of total natal females and 65% of natal males in the study). CSH was generally well tolerated in natal males. Twelve of the 39 natal female patients had minor complications from female CSH. Seven developed severe acne, one developed androgenic alopecia, three had mild dyslipidaemia and one had mood swings. Three of these patients stopped CSH, two because of concomitant psychiatric comorbidities and one because of distress due to androgenic alopecia. 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 CSH initiation in Dutch studies has been 16.4-16.7 years with lowest age ranging between 13.9 to 14.9 years (de Vries et al., 2011, 2014; Klink et al., 2015).

Bone Mineral Density

Klink et al. (2015), in a case series of 34 patients in Netherlands reported recovery in bone mineral density scores from GnRHa treatment during CSH 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 CSH treatment. Neither study followed patients long enough to confirm whether peak bone mass was delayed or permanently reduced.

Growth potential

Delemarre-van de Waal et al. (2006) reported significant decrease in growth potential under GnRH therapy. Once CSH was 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.

Psychological functioning

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 22%-44% adolescents with gender dysphoria having 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 CSH, mean 16.7, range 13.9-19.0) before administration of GnRHa, before CSH and one year after CSH, with a total mean follow-up of 7 years per patient. Global functioning in the subjects improved after GnRHa and continued to improve after CSH initiation. Satisfaction with body image and levels of gender dysphoria were unchanged with GnRHa but decreased after starting CSH. Depression levels decreased after starting GnRHa, but partially increased after starting CSH and prior to sex realignment with natal females demonstrated higher levels of depression. Anxiety levels appeared to increase after starting CSH but anger levels decreased. Clearly such studies have potential biases coming from many other factors impacting psychological wellbeing, 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.

Executive functioning

Staphorsius et al. (2015) in a large case control study of 84 adolescent patients (13-17 years) demonstrated that GnRHa did not adversely impact executive functions. The Tower of London performance scores (reaction times and accuracy) for GnRHa treated patients did not differ significantly from untreated sub group. On functional MRI, region-of-interest (ROI) analyses showed that GnRHa 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.

Ethics

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

Beneficence ethical principle (i.e. obligation of physicians to help their patients) is another key principle in considering early CSH therapy. A subset of patients on GnRHa decide to proceed to CSH. 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.

This ethical review also highlighted that given the possibility of desistence, physicians must consider the not

unlikely situation where CSH therapy renders permanent harms in a desisting child, helping an adolescent 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%-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?

CSH effect is expected to be different in natal male and female subjects. Evidence is not available regarding any difference on response of CSH specifically below age 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 CSH 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 GnRHa therapy. During CSH, 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 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 CSH.

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 on the effects and harms of cross-sex hormone therapy after the 15th birthday in patients with persistent gender dysphoria in whom irreversible physical changes have already occurred after onset of puberty. Rosenthal et al. (2014) noted that occasionally, some gender-dysphoric youths first come to medical attention when they are Tanner 4/5, but <14 years of age. Such individuals would be candidates for pubertal blockers, but without supportive outcome data, not currently candidates for cross-sex hormone use under most circumstances. Authors also recommend not using GnRH 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 GnRHa blocker 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 CSH 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 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 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.

In conclusion, given the currently accepted practice in most countries of offering cross sex hormones at age > 16 years, there is insufficient evidence available on effects and harms of cross sex hormones at a younger age to inform any change in 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 such as those who started GnRHa in the early stages of puberty, fully understand and consent to the impact including partial irreversibility of

cross-sex therapy and who have been clinically established as most likely to persist and function in preferred gender.

3. Research 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)?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complicat-ions noted	Benefits noted	Comments
4	Other	Varied	GnRH and cross sex hormones (CSH)	Safety of the intervention	Diagnostic and therapeutic strategies for transgenderism in youth/adolescents	Authors note that for transgender youth who at tanner stage 4/5 but <14 years of age, should only be considered for pubertal suppression but should not be considered for CSH before 16 years of age given the lack of supportive outcome data. Authors noted lack of supportive data on use of GnRH <12 years of age.	-	-	Rosenthal, Stephen M.. Approach to the patient: transgender youth: endocrine considerations. J. Clin. Endocrinol. Metab.. 2014.	-	-	This is a non systematic review of selected evidence for treatment of transgender youth. The key studies quoted are included in the evidence review.
3	Case series	101 patients, 2 received GnRH	2 patients received GnRH, all expressed a desire to receive CSH	Other	Gender demographics; Psychological parameters	Age, realised gender difference: MtF 8.42 FtM 8.17 range(2-22) Age, living as asserted gender: MtF 16.57 FtM 16.59 range(2-23) Utrecht Gender Dysphoria Scale (23-60): MtF 50.06 FtM 55.86 Mild depression (14-19): MtF 11% FtM 21% Moderate depression (BID 20-28): MtF 11% FtM 7% Severe to extreme (BID 29-63): MtF 13% FtM 9% Attempted suicide: MtF: 27% FtM: 33%, total (30%)	Sexual orientation	Attracted to same natal sex: FtM 57% MtF 60% Attracted to opposite natal sex: FtM 2% MtF 12.8% Attracted to both: FtM 11% MtF 13% Unsure: FtM 4% MtF 2%	Olson, Johanna; Schrager, Sheree M.; Belzer, Marvin; Simons, Lisa K.; Clark, Leslie F.. Baseline Physiologic and Psychosocial Characteristics of Transgender Youth Seeking Care for Gender Dysphoria. J Adolesc Health. 2015.	-	-	This case series presents the demographic data on gender dysphoric adolescents in California. Note this study does not present results on the impact of CSH and so is of only indirect relevance to PICO questions. Young age of realisation of gender difference mean 8 years, (range 2-22 years) is notable. Similar levels of depression between MtF and FtM, with high attempted suicide rates (30%).

3	Case series	97 consec-utive patients, 39 received CSH, 11 received GnRH	Considerable variation. 39 received CSH and 11 received GnRH. Precise treatment strategies not detailed.	Other	1.Mean age at presentation. 2. Prevalence of psychiatric diagnosis in gender dysmorphic children and adoloscents	1. Mean age at presentation: Age of presentation was 14.8 ± 3.4 years (mean ± SD) without sex difference (p = 0.11). Tanner stage at presentation was 4.1 ± 1.4 for genotypic female patients and 3.6 ± 1.5 for genotypic male patients (p = 0.02). Age at start of medical treatment was 15.6 ± 2.8 years. 2. Prevalence of significant psychiatric disorder in 43/97patients (44.3%), of which depression: 25/43 (58.1%). History of self mutilation: 20/97 (20.6%). History of suicide attempts: 9/97 (9.3%).	Sexual orientation	Attracted to same natal sex: FtM 62.9% MtF 55% Attracted to opposite natal sex: FtM 17.1% MtF 20.0% Attracted to both: FtM 8.6% MtF 10.0% Unsure: FtM 11.4% MtF 15.0%	Spack, Norman P.; Edwards-Leeper, Laura; Feldman, Henry A.; Leibowitz, Scott; Mandel, Francie; Diamond, David A.; Vance, Stanley R.. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012.	-	-	Although this case series aims at presenting demographic data on psychiatric co-morbidity in gender dysphoric adolescents in USA. However given that this is a subset of patients presenting at a single institution, albeit consecutive and large, it is unlikely to be a true respresentative of national norms. Hence, difficult to establish the true prevalence of the condition in USA on the basis of a single study. A key reason for wide variety of different combinations of GnRH and CSH reported in the study was a lack of standardised strategy for treating gender dysphoria in the US between 1998 and 2006.
3	Case series	84 patients, 63 received CSH	GnRH, followed by CSH, for some but not all patients. 84 total patients, 63 received CSH and 27 GnRH. Considerable variation in precise treatment.	Safety of the intervention	1. Prevalence of MtF and FtM, proceeding to CSH 2. Psychiatric comorbidity	1. 39/45 (87%) FtM patients received CSH, while 24/37 (65%) MtF (p<0.02). For MtF, Median age of presentation was FtM 16.9 years (range 11.4 - 19.8 years) and MtF16.6 years (range 12.3 - 22.5 years). Median age for initiation of CSHand for FtM 17.3 (range 13.7 - 19.8) and for MtF was 17.9 years (range 13.3 - 22.3). 2. Mood disorders: 35% FtM (n=45) vs 19% MtF (n=37), p=0.01. Anxiety disorder: 24% FtM (n=45) vs 11% MtF (n=37), p=0.02. Other disorders no significant difference.	Complicatio ns	12/39 FtM patients had minor complications from CSH. Seven developed severe acne, 1 developed androgenic alopecia, 3 had mild dyslipidaemia and 1 had mood swings. 3 patients of 63 stopped CSH (all FtM). 2 stopped because of concomitant psychiatric comorbidities and 1 because of distress due to androgenic alopecia.	Khatchadourian, Karine; Amed, Shazhan; Metzger, Daniel L.. Clinical management of youth with gender dysphoria in Vancouver. J. Pediatr.. 2014.	-	-	This case study retrospectively examines the treatment of gender dysphoric adolescents in Canada. Under the British Columbia Infants Act, any child of any age can consent to a medical treatment, provided the child can demonstrate an understanding of the risks and benefits. Hence this case series has less constraints on the age at which CSH is begun. Median age of presentation was older than in (Hewitt et al., 2012). No subgroup analysis was undertaken to compare those starting CSH before and after 16.

3	Cross-sectional	105 patients	N/A	Other	Prevalence of mental disorders measured using the diagnostic interview schedule for children	Most gender dysphoric youth (68%) had no concurrent comorbid psychiatric diagnosis. There was statistically significant differences between rates for natal males and females. In particular, natal males had higher rates of social phobia, any mood disorder and two or more disorders. % of natal males and natal females with one or more disorder (21% vs 13% p=0.08). % natal males and females had two or more disorders (22% vs 8% p=0.03). % natal males and females had social phobia (15% vs 4% p=0.049) and any mood diagnosis (21% vs 4%, p=0.008).	Difference in prevalence of mental disorders between patients deemed eligible for GnRH treatment or delayed eligible.	There was no statistically significant difference in prevalence of psychological comorbidities between with immediate and delayed puberty suppression therapy from time of diagnosis of psychiatric comorbidity in prevalence of disorders.	de Vries, Annelou L. C.; Doreleijers, Theo A. H.; Steensma, Thomas D.; Cohen-Kettenis, Peggy T.. Psychiatric comorbidity in gender dysphoric adolescents. J Child Psychol Psychiatry. 2011.	-	-	This a cross sectional study aimed at examining the levels of psychiatric comorbidity in adolescents with gender dysphoria. The prevalence rates are based on the children presenting at the clinic, hence potential for selection bias.
3	Case series	70 patients	GnRH, followed by CSH	Clinical effectiveness of the intervention	Level of gender dysphoria, body image satisfaction and psychological functioning of patients before the administration of GnRH and before the start of CSH (t0: start of GnRH, t1: start of CSH). Beck depression inventory (BDI), (0-9: minimal depression, 30-63: severe depression). Utrecht Gender Dysphoria Scale (UGDS) based on 12 items with 1-5 range. I.e. score 12-60, 60 indicating 'a continuous desire to be treated a man/women'. Child behaviour checklist (CBCL) >63 considered in clinical range.	Approximately 2 years of GnRH and no CSH - there was a statistically significant improvement in depression and global functioning. - there was no statistically significant change in anger, anxiety, levels of dysphoria and body image satisfaction. Gender dysphoria and body satisfaction did not change between T0 and T1. While changes over time were equal for both sexes, compared with natal males, natal females were older when they started puberty suppression and showed higher level of dysphoria and higher anger, anxiety, depression and lower levels of body image satisfaction, global functioning than natal males at both T0 and T1. No adolescent withdrew from puberty suppression, and all started cross-sex hormone treatment. Data: CBCL: MtF: t0: 59.42(11.78); t1:50.38(10.57); FtM: t0:61.73(13.60) t1:57.73(10.82) BDI: MtF: t0: 5.71(4.31); t1:3.50(4.58); FtM: t0:10.34(8.24) t1:6.09(7.93) UGDS: MtF: t0: 47.95(9.70); t1:49.67(9.47); FtM: t0:56.57(3.89) t1:56.62(4.00)	-		de Vries, Annelou L. C.; Steensma, Thomas D.; Doreleijers, Theo A. H.; Cohen-Kettenis, Peggy T.. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med. 2011.	-	-	The study reports on adolescents who began GnRH between the age of 11.3-18.3 and who started CSH at 13.9-19.2 (mean 16.6). CSH was started when the adolescents have reached at least Tanner stage 2-3 and were deemed eligible after psychological testing. The results are in good agreement with (de Vries et al., 2015), although it is also possible that the patients overlap between the two studies. This is not clarified in 2015 study. In addition to the inherent limitations of a single arm case series , the study suffers from a potentially significant confounding due to normative biological changes in psychological functioning in teenage years (12 to 16), when many other socio-environmental factors can be relevant.

3	Case series	34 patients, 15 trans-women, 19 transmen	GnRH, followed by CSH	Safety of the intervention	Area Bone Mineral Density (aBMD, g/cm2), and volumetric (apparent) BMD (BMAD) and Z scores comparing BMD to national average for natal sex, age and ethnicity at 22 years	In transwomen, (lumbar spine) LS aBMD scores were below the population mean at the start of the treatment. The scores did not change during GnRHa therapy. During CSH LS aBMD improved but the z score at age 22 years was still significantly lower than that at start of the treatment (-0.8 at start to -1.4 at 22 years) . In transmen, LS aBMD score was normal at the start of the treatment but decreased during GnRHa therapy. During CSH LS aBMD improved but 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). Hence the conclusion that attainment of peak bone mass has been delayed or peak bone mass itself is reduced during treatment for gender dysphoria.	-	-	Klink, Daniel; Caris, Martine; Heijboer, Annemieke; van Trotsenburg, Michael; Rotteveel, Joost. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J. Clin. Endocrinol. Metab.. 2015.	-	-	This case study examines the bone mass density of adolescents being treated with GnRHa and CSH. Some of the patients started CSH below 16, but the mean was 16.5 years. There was no subgroup analysis for those who started CSH <16 years of age. Given the limitations of the study design and the fact that most patients were late pubertal at the start and the duration of GnRHa was relatively short, the impact of GnRHa on bone loss needs to be interpreted with caution. Authors also note that the CSH regime was relatively low in initial stages which might impact BMD recovery. Since the follow-up was stopped at 22 years of age, it is not known if the patients were able to recover bone mass at a later stage.

3	Case series	55 trans-genders, 22 trans-women and 33 transmen	Began GnRH (mean age 13.6), began CSH (mean age 16.7), had gender reassignment surgery (mean age 20.7)	Clinical effectiveness of the intervention	Questionnaires to assess the level of gender dysphoria, body image satisfaction and psychological functioning at three stages, before the use of GnRH (t0), before the use of CSH (t1) and 1 year after Gender reassignment surgery GRS (t2). Measures used Utrecht Gender Dysphoria Scale (UGDS) based on 12 items with 1-5 range. I.e. score 12-60, 60 indicating 'a continuous desire to be treated a man/women'. Body image scale (BIS) range 1-5, higher scales indicate more dissatisfaction.	Patients followed 'Dutch protocol' in which puberty suppression is begun at Tanner stage 2-3, with GnRH. Eligible for GnRH, CSH and gender reassignment surgery (GRS) at 12, 16 and 18, following psychological assessment. The age range for patients beginning CSH was 13.9-19 years. Key findings are: -Global functioning improved between t0 and t1 and between t1 and t2. -Depression levels decreased between t0 and t1, but partially increased between t1 and t2. FtM demonstrated higher levels of depression than MtF. -Anxiety levels were unchanged between t0 and t1, but increased between t1 and t2. -Anger levels (STAI) were unchanged between t0 and t1, but decreased between t1 and t2. -The satisfaction with body image increased between t0 and t1 and between t1 and t2. -Levels of gender dysphoria (UGDS) were unchanged between t0 and t1, but decreased between t1 and t2. FtM demonstrated higher levels of gender dysphoria than MtF. P values only computed between t0 and t2, so it is challenging to assess if changes between t0 and t1 and between t1 and t2 are statistically significant. DATA Global functioning (CGAS): MtF: t0: 74.33, t1: 78.20 and t2: 82.40 FtM: t0: 67.65, t1: 70.65 and t2: 76.29 Depression (BDI): MtF: t0: 4.73, t1: 2.25 and t2: 3.38 FtM: t0:10.09, t1:5.05 and t2: 6.95 Anxiety (STAI): MtF: t0: 31.87, t1: 31.71 and t2: 35.83 FtM: t0:44.41, t1:41.59 and t2: 39.20 Anger (TPI): MtF: t0: 14.17, t1: 14.00 and t2: 5.58 FtM: t0: 19.55, t1: 19.25 and t2: 16.56 UGDS: MtF: t0: 47.07, t1: 48.95, t2:17.27 FtM: t0: 56.74, t1: 57.11, t2:15.08 BIS (primary sex characteristics): MtF: t0: 4.03, t1: 3.82, t2:2.07 FtM: t0: 4.18, t1: 4.13, t2:2.89 BIS (secondary sex characteristics): MtF: t0: 2.63, t1: 2.34, t2:1.93 FtM: t0: 2.80, t1: 3.18, t2:2.48	-	-	de Vries, Annelou L. C.; McGuire, Jenifer K.; Steensma, Thomas D.; Wagenaar, Eva C. F.; Doreleijers, Theo A. H.; Cohen-Kettenis, Peggy T.. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics. 2014.	-	-	Other than the limitations of a single arm case series, the study results could be impacted by significant responder and reporting bias given that the outcome is largely based on self-reported questionnaires. Potential significant confounders impacting psychological well-being, before during and after puberty have not been addressed.

3	Case series	54 patients	Triptorelin GnRHa, followed by CSH	Safety of the intervention	Bone Mineral Density Changes with respect to gonadal axis. Changes with respect to growth.		-	-	Delemarre-van de Waal, Henriette A., and Peggy T. Cohen-Kettenis. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects.. 0. 2006.	-	-	This case series outlines and offers the initial results on the use of the `Dutch strategy' for treating gender dysphoric adolescents. Limitations as per previously listed.
3	Cohort	247, 150 MtF (60.7%) and 97 FtM (39.3%)	Cross sex hormones	Safety of the intervention	Changes in cardiovascular profile	Increase in weight and BMI during follow-up without increase in proportion of obese individuals in both MtF and FtM groups. Mean systolic and diastolic blood pressure increased in Mtf but remained within normal range. No significant differences in lipid profile in MtF group. Changes were observed in FtM group with a significant increase in total cholesterol, triglyceride and LDL cholesterol and a decrease in HDL cholesterol; yet clinical relevance is uncertain as all parameters remained within normal range.	None	None	Quirós, Carmen; Patrascioiu, Ioana; Mora, Mireia; Aranda, Gloria Beatriz; Hanzu, Felicia Alexandra; Gómez-Gil, Esther; Godás, Teresa; Halperin, Irene. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinol Nutr. 2015.	Refer outcomes	Refer outcomes	The study has significant confounders such as diet, family history, age and exercise etc. which have not been adjusted for in the analysis. In addition, nearly half of the patients started treatment prior to the 2 years period whose chi will impact the time to effect estimation.

0	Other	Not applicable	GnRha and cross sex hormones	Other	Ethical principles behind CSH therapy	Non-maleficence ethical principle i.e. “first, do no harm offers the strongest ethical argument against early cross-sex hormone treatment because the long-term effects of this therapy are not well known and it has the known side effect of rendering most patients sterile. A much smaller subset of patients on GnRHa decide to proceed to CSH (persisters). GnRHa, by contrast, has largely been considered free of long-term harm based on many generations of follow-up studies with the large population of individuals prescribed such drugs for precocious puberty. For earlier access to cross-sex hormone therapies for adolescents, additional research in understanding which factors can predict gender dysphoria persistence could significantly mitigate some of these ethical concerns. Beneficence ethical principle i.e. obligation of physicians to help their patients. While delaying hormone therapy may conform with the principle of non-maleficence, it does not support beneficence if one assumes that a child’s desire to have his or her outward gender conform to his or her self-perceived gender is a valid good. A finding of a high prevalence of desistence detracts from the argument for beneficence. Given the possibility of desistence, physicians must consider the not unlikely situation where CSH therapy renders permanent harms in a desisting child, helping an adolescent 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.	Not applicable	Not applicable	Abel, Brendan S.. Hormone treatment of children and adolescents with gender dysphoria: an ethical analysis. Hastings Cent Rep. 2014.	Not applicable	Not applicable	This is an ethics review, hence the evidence was not graded. The review acknowledged that transgender youth have high rates of self-harm and suicide but does not take that into account in the ethical analysis.

2+	Case-control	84 (40 cases with 22 FtM and 18 MtF and 24 girls (F) and 21 boys (M) controls)	Tower of London (ToL) performance and brain activation patterns (using functional magnetic resonance imaging (fMRI).	0	Executive function (ToL)	No significant effect of GnRHa on ToL performance scores (reaction times and accuracy) when comparing GnRHa treated MtFs with untreated MtFs or when comparing GnRHa treated FtMs with untreated FtMs. However, the GnRHa MtFs had significantly lower accuracy scores than the control groups and the untreated FtMs. Authors conclude that GnRHa treatment had no effect on ToL performance in adolescents with GD. Low accuracy scores in GnRHa MtFs may partly reflect their low IQ scores or just a chance finding due to the small size of this subgroup (n = 8). No sex differences in performance were found in the control groups.	Sex-atypical brain activations during ToL performance on fMRI	Region-of-interest (ROI) analyses showed significantly greater activation in control boys than control girls during high task load ToL items in the bilateral presumes and a trend ($p < 0.1$) for greater activation in the right DLPFC. In contrast, untreated adolescents with GD did not show significant sex differences in task load-related activation and had intermediate activation levels compared to the two control groups. GnRHa treated adolescents with GD showed sex differences in neural activation similar to their natal sex control groups. Furthermore, activation in the other ROIs (left DLPFC and bilateral RLPFC) was also significantly greater in GnRHa treated MtFs compared to GnRHa treated FtMs. Authors conclude that pubertal hormones may induce sex-atypical brain activations during EF in adolescents with GD.	Staphorsius, Annemieke S.; Kreukels, Baudewijntje P. C.; Cohen-Kettenis, Peggy T.; Veltman, Dick J.; Burke, Sarah M.; Schagen, Sebastian E. E.; Wouters, Femke M.; Delemarre-van de Waal, Henriëtte A.; Bakker, Julie. Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. Psychoneuroendocrinology. 2015.	Not applicable	Not applicable	The study aimed to identify whether puberty suppression affected brain development and executive function. The key limitation is the small size of subgroups which is likely to introduce variability and selection bias. This is confirmed by the fact that a key finding in the study of low accuracy scores in GnRHa MtF had to be disregarded due to small size (n=8) of this subgroup.

0	Case series	47 (41 FtM, 6 MtF)	-	0	Epidemiology of GD in Finland	The number of referrals exceeded expectations in light of epidemiological knowledge. Natal girls were markedly overrepresented among applicants. Severe psychopathology preceding onset of gender dysphoria was common. Autism spectrum problems were very common. Of the applicants, 32% (14/47) reported having started to consciously question their gender before age 12, 62% (30/47) at 12 or later, and three applicants (6%) could not define this. Most commonly (one in five) these concerns had started at age 14.Of those who felt sure about their cross-gender identity, 15% (5/34) recalled reaching the conclusion before age 12, 79% (27/34) at 12 or later, and two (6%) could not define at what age they had reached the conclusion.	-	-	Kaltiala-Heino, Riittakerttu; Sumia, Maria; Työläjärvi, Marja; Lindberg, Nina. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. Child Adolesc Psychiatry Ment Health. 2015.	-	-	Epidemiological findings from a tertiary national centre.
3	Cohort	127 adolescents (79 boys, 48 girls), who were referred for GD in childhood (<12 years of age) and followed up in adolescence.	Not applicable	Other	Predictors of Persistence	Key predictors of persistence were age at intake, social role transition, and both cognitive and affective responses to the Gender Identity Interview for Children (GIIC).Cognitive responses to the GIIC were the strongest predictor with the persisters reporting higher intensities of GD, more body dissatisfaction, and higher reports of a same-sex sexual orientation compared to the desisters. Chance of persisting was greater in natal girls with GD than in boys. Psychological functioning and the quality of peer relations did not predict the persistence of GD.	-	-	Steensma, Thomas D.; McGuire, Jenifer K.; Kreukels, Baudewijntje P. C.; Beekman, Anneke J.; Cohen-Kettenis, Peggy T.. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013.	Not applicable	Not applicable	This cross sectional study which provides useful insight into potential predictions for patients who might proceed from GnRHa to CSH.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	gender dysphoria OR gender identity disorder
Updated search terms - Intervention	cross sex hormone OR cross sex hormones OR cross-sex hormone OR cross-sex hormones
Updated search terms - Comparator	Psychological therapies OR Continuation of GnRH alone until after the 16th birthday
Updated search terms - Outcome	ethics OR developmental OR morbidity OR self-harm OR psychosocial outcomes OR quality of life OR reduction of gender dysphoria OR engagement/disengagement from society OR normal developmental processes OR peer relationships OR adverse events OR impact on fertility OR development of the brain OR persistence rates of gender dysphoria OR desistence rates of gender dysphoria

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	None
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None