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Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review

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ABSTRACT

Background Clinical guidelines outline the use of hormones for masculinisation/feminisation in adolescents experiencing gender dysphoria or incongruence. Robust evidence concerning risks and benefits is lacking. There is a need to aggregate evidence as research becomes available.

Aim Identify and synthesise studies assessing the outcomes of hormones for masculinisation/feminisation in adolescents experiencing gender dysphoria/incongruence.

Methods Systematic review and narrative synthesis. Database searches (MEDLINE, Embase, CINAHL, PsycINFO, Web of Science) were performed in April 2022, with results assessed independently by two reviewers. An adapted version of the Newcastle-Ottawa Scale for Cohort Studies was used to assess study quality. Moderate- and high-quality studies were synthesised.

Results 12 cohort, 9 cross-sectional and 32 pre–post studies were included (n=53). One cohort study was high-quality. Other studies were moderate (n=33) and low-quality (n=19). Synthesis of high and moderate-quality studies showed consistent evidence demonstrating induction of puberty, although with varying feminising/masculinising effects. There was limited evidence regarding gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, and fertility. Evidence from mainly pre–post studies with 12-month follow-up showed improvements in psychological outcomes. Inconsistent results were observed for height/growth, bone health and cardiometabolic effects. Most studies included adolescents who received puberty suppression, making it difficult to determine the effects of hormones alone.

Conclusions There is a lack of high-quality research assessing the use of hormones in adolescents experiencing gender dysphoria/incongruence. Moderate-quality evidence suggests mental health may be improved during treatment, but robust study is still required. For other outcomes, no conclusions can be drawn. More recent studies published since April 2022 until January 2024 also support the conclusions of this review.

PROSPERO registration number: CRD42021289659.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Increasing numbers of children and adolescents experiencing gender dysphoria/incongruence are being referred to specialist gender services.
⇒ National and international guidelines outline the use of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence.
⇒ Several systematic reviews report a limited evidence base for initiating these treatments during adolescence, and uncertainty about benefits, risks and long-term effects.

WHAT THIS STUDY ADDS

⇒ There is a lack of high-quality research assessing the outcomes of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence.
⇒ There is limited or inconsistent evidence regarding gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, fertility, height/growth, bone health and cardiometabolic effects.
⇒ There is moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ There is a lack of high-quality evidence to support the initiation of hormones for masculinisation or feminisation in adolescents experiencing gender dysphoria/incongruence. Agreement on core outcomes and high-quality research are needed.

INTRODUCTION

Over the last 10-15 years, there has been a rise in the number of children and adolescents being referred to specialist paediatric gender services.[1 2] Clinical guidelines for managing gender dysphoria/incongruence recommend assessment and psychosocial care to alleviate gender-related distress and any co-occurring difficulties. For pubertal adolescents, medications to suppress puberty in early to mid-adolescence followed by hormones that induce feminisation/masculinisation are outlined in what is described as a staged model of care. These interventions, often referred to as cross-sex hormones or gender-affirming hormones, comprise testosterone for birth-registered females and oestrogen for birth-registered males, which is sometimes given in combination with gonadotropin-releasing hormone analogues (GnRH-a), progestins, or other medications with anti-androgenic properties.[3 4]

In early treatment protocols and clinical guidelines, treatments for feminisation/masculinisation were offered from age 16, and mainly in adulthood.[5 6] Over the last decade, guidelines have broadened these criteria, for example, removing minimum age[4 7 8] and making changes to the requirement of a diagnosis of gender dysphoria (Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5), being replaced by gender incongruence (International Classification of Diseases 11th revision, ICD-11).[3] In a study of 1766 children and adolescents receiving care at a national gender service in the Netherlands (1997–2018), 202 birth-registered males and 454 birth-registered females received hormones at a median age of 16.0 (IQR 15.5–17.1) and 16.7 (16.0–17.5), respectively.[9] In the UK, the mean age of consent for treatment was 17.3 (SD 0.1).[10]

Robust evidence concerning the risks and benefits of initiating hormones during adolescence is lacking. Several systematic reviews have found mainly low-quality or limited evidence.[11–20] Due to the proliferation of research in this area, there is a need to update systematic reviews as evidence becomes available. This systematic review aims to synthesise evidence published up to April 2022 that reports outcomes of feminising/masculinising hormones in adolescents experiencing gender dysphoria/incongruence.

METHODS

The review forms part of a linked series examining the epidemiology, care pathways, outcomes and experiences of children and adolescents experiencing gender dysphoria/incongruence and is reported according to Preferred Reporting Items for Systematic review and Meta-Analysis guidelines.[21] The protocol was registered on PROSPERO (CRD42021289659).[22]

Search strategy

A single search strategy was used to identify studies comprising two combined concepts: 'children', which included all terms for children and adolescents; and 'gender dysphoria', which included associated terms such as gender-related distress and gender incongruence, and gender identity terms including transgender, gender diverse and non-binary.

MEDLINE (online supplemental table S1), Embase and PsycINFO through OVID, CINAHL Complete through EBSCO and Web of Science (Social Science Citation Index) were searched (13–23 May 2021; updated 27 April 2022).

Reference lists of included studies and relevant systematic reviews were assessed.[11–20]

Inclusion criteria

The review included published research that reported outcomes of hormones used for masculinisation/feminisation in adolescents experiencing gender dysphoria/incongruence (table 1).

Selection process

Results of all searches were uploaded to Covidence[23] and screened independently by two reviewers. Full texts of potentially relevant articles were reviewed against inclusion criteria by two reviewers independently. Disagreements were resolved through discussion or by a third reviewer.

Table 1 Inclusion and exclusion criteria

Population	Children and/or adolescents aged 0–18 experiencing gender dysphoria, gender incongruence or referral to a gender identity service. Studies of adults or a mixed population of adolescents and adults where treatment was initiated in adolescence (<18).
Intervention	Masculinising or feminising hormone treatments.
Comparator	Any or none.
Outcomes	Pubertal development, side effects, gender dysphoria or other gender-related outcomes, psychological health, physical health, psychosocial outcomes, cognitive outcomes, fertility.
Study design	Clinical trials, cohort studies, case–control studies, cross-sectional studies, pre–post single-group design studies or service evaluations that provided treatment outcome data. Case studies and case series were excluded.
Publication	Studies published in the English language in a peer-reviewed journal. Conference abstracts were excluded.

Data extraction

Data on study characteristics, methods and outcomes were extracted into pre-piloted data extraction templates by one reviewer and second-checked by another.

Study quality

Critical appraisal was undertaken by two reviewers independently, with consensus reached through discussion or involvement of a third reviewer.

Quality was assessed using a modified version (online supplemental file 1) of the Newcastle-Ottawa Scale for cohort studies, a validated scale of eight items covering three domains: selection, comparability and outcome.[24] Scale modification included not scoring certain question(s) for cross-sectional or single-group designs, or particular outcomes; specification of key confounders to assess comparability of cohorts; guidance regarding sufficiency of follow-up; and use of numerical scores for items and overall (maximum score 9 for cohorts, 8 for pre–post and cross-sectional studies with a comparator). Total scores are presented as percentages to account for different total scores (≤50% low, >50–75% moderate, >75% high quality).

Synthesis

Narrative synthesis methods were used because of heterogeneity in study design, intervention, comparator, outcome and measurement. Low-quality studies were excluded from the synthesis due to the high risk of bias. For studies that reported outcomes for both puberty suppression and hormones, only the findings relating to hormones were synthesised.

Outcomes were grouped into distinct and clinically meaningful categories for synthesis, based on what had been measured across the studies in addition to the a priori categories informing the review. Care was taken to differentiate between different study designs, comparators and interventions. Where possible, potential differences by birth-registered sex, and treatment duration/initiation were examined.

RESULTS

Database searches yielded 28 147 records, 3181 of which were identified as potentially relevant for the linked systematic reviews, and full texts reviewed. From these, 53 studies met the inclusion criteria for this review (figure 1).

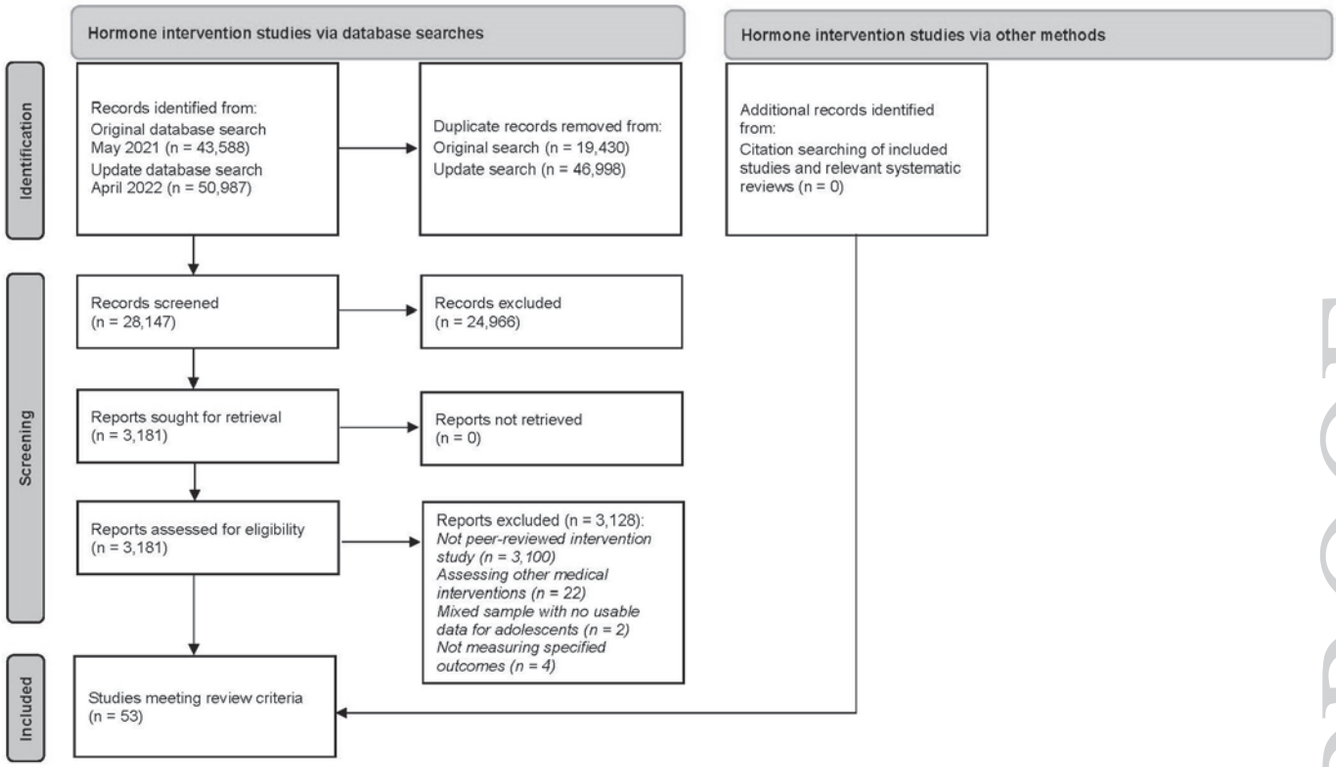

Figure 1 Study flow diagram.

Study characteristics

Studies were published from 2006 to 2022 (with 60% from 2020 to 2022 (n=32)), and conducted in the Netherlands (n=17),[25–41] US (n=24),[42–65] Israel (n=3),[66–68] Belgium (n=2),[69 70] Canada (n=2)[71 72] and one in Brazil,[73] Finland,[74] Germany,[75] Spain[76] and the UK[77] (online supplemental table S2).

Of the 53 studies, 12 were cohorts comparing adolescents experiencing gender dysphoria/incongruence receiving hormones with a comparator,[34 37–39 42 43 46 49 54 64 75 76] 9 cross-sectional with comparator[25 45 50 51 57 60 65 73 77] and 32 pre–post designs.[26–33 35 36 40 41 44 47 48 52 53 55 56 58 59 61–63 66–72 74] Over half of the studies (n=30) used retrospective chart review.

All but five studies recruited adolescents experiencing gender dysphoria/incongruence from specialist gender or endocrinology services: 46 from single clinics (in Belgium, Israel, Netherlands and the UK these were large regional/national services), and 2 from multiple US clinics. Of the remaining five, four were US studies (national survey recruiting via community settings,[65] clinical and community settings,[45] social media platforms,[50] US Military Healthcare Data Repository[47]). The final study from Brazil recruited via Facebook.[73]

Overall, the studies included 40 906 participants, of which 22 192 were adolescents experiencing gender dysphoria/incongruence (8164 received hormone treatments and 14 028 did not), and 18 714 comparators. Comparator groups included adolescents who had either not received hormones or received it in adulthood[34 39 42 43 45 46 49–51 65 73 75 78]; adolescents not experiencing gender dysphoria/incongruence[37 38 57 60 64 76]; both comparators[25]; or studies comparing those receiving hormones alone with those receiving it in combination with GnRH-a/progestins/anti-androgens.[54]

The most frequently reported outcomes were physical health outcomes (n=29) and puberty development (n=25) (figure 2, online supplemental table S3). Side effects, bone health and fertility were measured in six, five and one study, respectively. Psychological health was measured in 15 studies, psychosocial in 7 and cognitive/neurodevelopmental outcomes in 4. Gender-related outcomes and body image were each measured in three studies.

Study quality

One cohort study measuring side effects only was rated as high-quality,[54] 33 were moderate[25 30–41 45 47 48 50–53 55 56 59–63 66 67 69 70 74 76] and 19 low.[26–29 42–44 46 49 57 58 64 65 68 71–73 75 77] Of the 12 cohort studies, (the only studies to include a comparator group and assess outcomes over time), 6 were rated as high or moderate quality (figure 2, online supplemental table S4).[34 37–39 54 76]

In most studies, there were concerns about the representativeness of the population due to single-site recruitment, selective inclusion and/or poor reporting of the eligible population. In the 21 studies including a comparator, most did not report or control for key differences between groups, and only 6 used matched controls.[25 37 38 60 64 76] Most studies presented results separately by birth-registered sex or controlled for this, but few controlled for age, Tanner stage or co-interventions.

Overall, studies used appropriate methods to ascertain exposure and assess outcomes. Follow-up was adequate in 22 studies, with others not reporting clear information, or follow-up varying between participants or not linked to treatment initiation. Missing data at follow-up/analysis or poor reporting of this affected many studies.

Three studies did not report separate outcomes for adolescents receiving puberty suppression or hormones (one was moderate quality and excluded from synthesis).[47 73 77] One moderate-quality study assessing the amplitude of click-evoked otoacoustic emissions was excluded from the synthesis due to not being clinically relevant.[25]

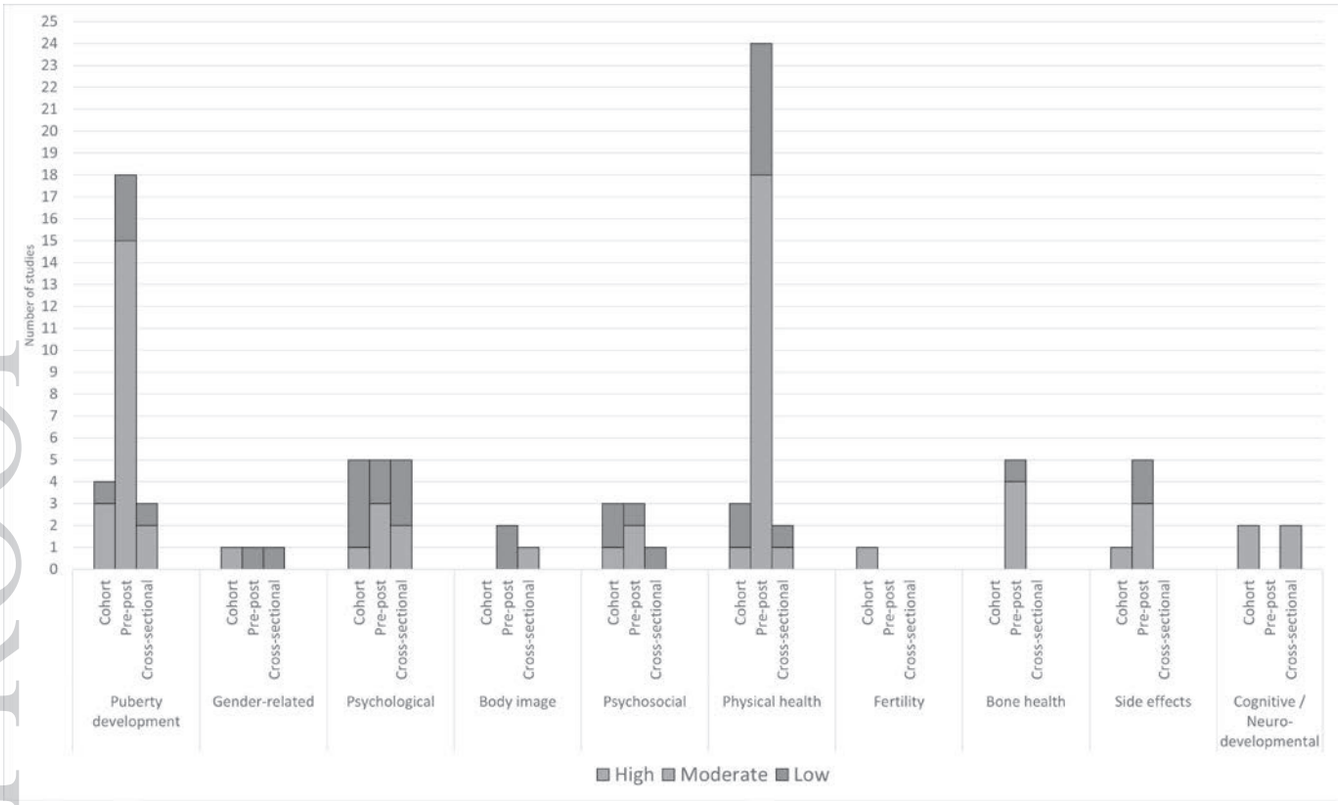

Figure 2 Outcome categories by study quality and design.

Synthesis of outcomes

Gender dysphoria and body satisfaction

One cohort study measured gender dysphoria pre–post, and reported a reduction in dysphoria with no participants in clinical range at follow-up.[76] One cross-sectional study measured body satisfaction in birth-registered females and reported lower dissatisfaction in those receiving hormone treatment compared with those who had not[51] (online supplemental table S5).

Psychological health

Five studies (one cohort,[76] two pre–post[48 74] and two cross-sectional[50 51]) measured psychological health. In four studies, participants had received hormones for ~12 months at follow-up. One cross-sectional study did not report treatment duration.[50] Reported outcomes were depression (n=4), anxiety (n=3), suicide and/or self-harm (n=4), need for specialist-level psychiatric treatment for different mental health difficulties (n=1) and internalising and externalising symptoms (n=1) (online supplemental table S5).

Studies found a reduction in depression and anxiety at follow-up (cohort[76]) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional[51]), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort[76]). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.[74] A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.[50]

A pre–post study found no changes in treatment need for conduct problems, psychotic symptoms/psychosis, substance abuse, autism spectrum condition, attention-deficit hyperactivity disorder or eating disorders,[74] but two pre–post studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm.[48 74] Two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones,[50] and in birth-registered females there was no difference between groups.[51]

One cohort study reported a significant decrease in total psychological difficulties and scores for hyperactivity, emotional and conduct problems, with fewer participants in borderline and abnormal ranges at follow-up.[76] Compared with adolescents not experiencing gender dysphoria/incongruence, psychological difficulties were higher at baseline but similar at follow-up.

Psychosocial functioning

A cohort study reported no change in family functioning or peer problems but more peer problems when compared with adolescents not experiencing gender dysphoria/incongruence.[76] A small improvement was reported in prosocial skills. A pre–post study measured peer relations, living arrangements, school/work participation, romantic involvement and competence in managing everyday matters, with the only changes being a decrease in participants living with parents/guardians at follow-up and a small decrease in normative peer relationships.[74] A pre–post study reported an increase in well-being after receipt of hormones[48] (online supplemental table S5).

Cognitive outcomes

Two cohort studies of birth-registered females assessed whether exogenous testosterone-induced changes reflect sex-based differences in brain activity. One study measured visuospatial working memory, and found no difference in performance between those treated and female and male controls not experiencing gender

dysphoria/incongruence, but did observe stronger frontal and parietal activation at follow-up in male controls and those treated.[38] The second study measured amygdala activation, observing slightly more rightward lateralisation following treatment, and similar lateralisation in those treated compared with female and male controls who did not change.[37]

Amygdala activation was also assessed in a cross-sectional study of birth-registered females, finding greater activation and increased connectivity between the amygdala and prefrontal cortex in those receiving hormones compared with those who had not.[51]

A cross-sectional study found those receiving hormones had better executive functioning, cognitive flexibility and working memory compared with a group not receiving hormones[45] (online supplemental table S5).

Physical health outcomes

Bone health

Four pre–post studies[30 32 33 36] measured bone health. Two reported an increase at follow-up in absolute measures of bone density and SD scores[32 33] (one included birth-registered females only[33]), and two reported no change in these and/or bone biomarkers, although these included small samples[30 36] (online supplemental table S6).

Cardiometabolic health

Body mass index (BMI) and/or a standardised measure (BMI SD/z score or percentile) was reported in 16 studies (1 cohort,[34] 14 pre–post[30 33 35 40 53 55 56 61–63 66 67 69 70] and 1 cross-sectional[60]), showing no change overall but some inconsistencies (online supplemental table S6).

For birth-registered males, one study reported an increase in SD score,[30] one a decrease[40] and two no change.[66 70] All reported no clinically significant change in BMI.[30 40 66 70] Four studies only reported BMI: three found no change[53 56 62] and one reported an increase for participants starting GnRH-a in early puberty prior to initiating hormones.[35]

For birth-registered females, two studies reported an increase in SD score[30 69] and four no change.[33 55 63 67] All but one of these, which found an increase in BMI as well as SD score,[69] reported no change in BMI.[33 55 63 67] Five studies only reported BMI: four found no change,[53 56 61 62] and one an increase in the early puberty group.[35]

A cross-sectional study of both sexes found no difference in BMI percentile between those receiving hormones compared with controls,[60] and a single cohort study found those who started hormones earlier had a lower BMI (although not clinically significant) than those who started treatment later.[34]

Seven pre–post studies assessed cholesterol markers: three reported a decrease in high-density lipoprotein (HDL),[33 53 55] one an increase[62 70] and three no change.[61 69 70] A cross-sectional study found that birth-registered females receiving hormones had lower HDL than controls, whereas birth-registered males had higher HDL than controls.[60]

Eight pre–post studies measured blood pressure[33 40 53 61 62 66 67] and one hypertension,[55] all reported no clinically significant change. One cross-sectional study found similar blood pressure in adolescents receiving hormones compared with adolescents not experiencing gender dysphoria/incongruence.[60]

Six studies measured HbA1c (glycated haemoglobin),[33 40 53 60 69 70] four glucose levels,[60 62 69 70] three fasting insulin[60 69 70] and two homeostatic model assessment (HOMA) index.[60 69] One cross-sectional study reported differences between birth-registered males and controls in the inverse of fasting insulin (lower) and HOMA insulin resistance (higher) compared with controls.[60] No changes were reported by other studies.

Other parameters

Twelve studies assessed other physiological parameters obtained from blood tests (11 pre–post[31 33 40 41 53 55 56 61 62 69 70] and one cross-sectional[60]; (online supplemental table S6)): dehydroepiandrosterone sulfate (n=3), androstenedione (n=2), creatinine (n=6), estimated glomerular filtration rate (n=1), prolactin (n=5), alanine transaminase (n=8), aspartate transaminase (n=8), g-glutamyl transferase (n=1), haematocrit (n=7), serum urea nitrogen (n=1), haemoglobin (n=7), potassium (n=1), vitamin D (n=1), thyroid stimulating hormone (n=3), free thyroxin (n=3), anti-Müllerian hormone (n=1), alkaline phosphatase (n=2), sex hormone binding globulin (n=4), free androgen index (n=1) and urea (n=1). For most outcomes there were no changes pre–post or differences between groups; where there were changes results were inconsistent.

One pre–post study found no occurrence of thrombosis after masculinising/feminising hormones.[59]

Pubertal development

Hormone levels

Fifteen studies measured hormone levels (2 cohort,[37 38] 12 pre–post[33 35 40 53 55 59 61 62 66 67 69 70] and 1 cross-sectional[60]), 7 studies in birth-registered females,[33 37 38 55 61 67 69] 3 in birth-registered males[40 66 70] and 5 both (online supplemental table 7).[35 53 59 60 62]

All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males, respectively.[33 35 40 53 55 59 61 62 66 67 69 70] Three studies (two cohort and one cross-sectional) found testosterone levels in birth-registered females receiving hormones were higher than female controls but lower than male controls.[37 38 60] The cross-sectional study reported similar oestradiol levels in birth-registered males receiving hormones and female controls, and higher levels compared with male controls.[60] Luteinising and follicle-stimulating hormones remained constant or decreased slightly.[33 40 60 66 67 69 70]

In birth-registered females, three studies reported increases in oestradiol,[33 35 67] two no change[53 69] and three reported decreases[55 61 62] (with varying follow-up across studies). In birth-registered males, one study reported no change in testosterone,[66] four a decrease[35 53 62 70] and one observed higher testosterone levels compared with female but lower compared with male controls.[60]

Induced pubertal progression

Four pre–post studies with at least 12 months follow-up measured pubertal development,[33 36 40 70] and three Tanner breast stage (online supplemental table 7).[36 40 70] Two observed an increase in breast volume in birth-registered males after hormones,[40 70] although objectively breast volume was small,[70] and another reported no change in breast volume in birth-registered females.[36] One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up.[33] Another reported no change in Tanner genital stage in birth-registered males,[36] and no change in Tanner pubic hair stage for both.[36]

Menstrual suppression

Three pre–post studies reported suppression in most participants (online supplemental table 7): 85% cessation after 6 months,[61] 80% no breakthrough bleeding at 12 months[52] and nearly all reported suppression on 200 mg of subcutaneous testosterone, although just over half reported suppression on 140 mg (median follow-up 1.9 years).[55]

Height/growth

One cohort[34] and six pre–post studies[30 33 35 36 40 70] reported height and/or height SD score, showing mixed results (online supplementary material S7).

For birth-registered males, two studies reported an increase in height SD score[30 70] and one no change.[40] Three studies reported an increase in absolute height.[30 36 40] An increase was observed in height SD when using affirmed-gender references.[40]

For birth-registered females, two studies reported no change in height SD score,[30 33] and three reported an increase in absolute height.[30 33 36]

One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later. There was no difference for birth-registered males.[34] All participants in the study had first received puberty suppression. A second study found that for both sexes, the average height at follow-up was higher in those who started hormone treatment earlier.[35]

Body composition/shape

Birth-registered females receiving testosterone had lower body fat percentage and fat mass, and higher lean tissue percentage and lean mass than female controls not experiencing gender dysphoria/incongruence, and the converse compared with males controls.[60] Higher body fat percentage and fat mass and lower lean tissue percentage were seen for birth-registered males compared with male controls, and the converse compared with females controls (online supplemental table 7).

A pre–post study in birth-registered males reported no change in fat mass after 2 years of treatment, but at 3 years it was higher compared with baseline (online supplemental table 7). Both fat percentage and lean body mass percentage remained the same.[40] The same study reported a decrease in absolute and SD score for waist–hip ratio (compared with reference data for males and females), a decrease in SD score but no absolute change in waist circumference, and no change in SD score but an absolute increase in hip circumference.[40]

Bone age and geometry

Two pre–post studies measured bone age and reported an increase after treatment (online supplementary material S7).[36 40] In birth-registered males who started GnRH-a in mid-puberty or late-puberty prior to initiating hormones, there was an increase in subperiosteal width and endocortical diameter, but not in those who started this treatment in early puberty.[35] For birth-registered females, there was no evidence of change.

Fertility

One cohort study measured fertility in birth-registered males by comparing orchiectomy specimens of those who started hormone treatment at Tanner stage 2/3, 4/5 or in adulthood, with all adolescents first receiving puberty suppression (online supplemantary table S6).[39] Mature spermatozoa were only encountered in those who started this treatment at Tanner stage 4 or higher. Immature germ cells were present in all those treated in early puberty. Duration of hormone treatment did not influence study outcomes.

Side effects

Four studies reported side effects (one cohort[54] and three pre–post[55 69 70]). Three studies of birth-registered females reported an increase in acne at follow-up.[54 55 69] One study also reported mood changes, elevated red blood markers and increased appetite as common, with headaches, hot flashes, fatigue and hair loss less commonly reported.[54] One study reported a slight increase in metrorrhagia after adding testosterone following <6 months of lynestrenol.[69]

Breast tenderness was commonly reported in two studies of birth-registered males,[54 70] with less common reports of increased liver enzymes and oestradiol levels above the normal limit,[54 70] and mood swings and increased appetite frequently reported.[70] The cohort study reported similar side effect profiles in those receiving GnRH-a concurrently with hormones and those receiving hormones alone.[54]

DISCUSSION

This systematic review identified 53 studies reporting outcomes for feminising/masculinising hormones for adolescents experiencing gender dysphoria/incongruence. Only 6 of the 12 cohort studies were rated as high or moderate quality.[34 37–39 54 76]

There was evidence from multiple studies that exogenous hormones increase hormone levels and to varying degrees induce pubertal development, with potential differences depending on birth-registered sex and timing of treatment. Inconsistent results were found for height/growth, bone health and cardiometabolic health. There was insufficient evidence regarding changes to gender dysphoria, body satisfaction, psychosocial and cognitive outcomes, or fertility (no study assessed fertility in birth-registered females). These findings add to other systematic reviews in concluding there is insufficient and/or inconsistent evidence about the risks and benefits of hormone interventions in this population.[11–20]

Regarding psychological health, evidence from mainly pre–post studies suggests hormones are associated with improvements in depression, anxiety and other mental health difficulties after 12 months of treatment, although there were inconsistencies regarding suicidality and/or self-harm, with three of four studies reporting an improvement and one no change. Concerns about study representativeness and comparability of control groups (where used) mean these findings must be interpreted with caution. Well-designed robust studies that control for key confounding factors with longer-term follow-up are needed.

Over half of the studies reported the effects of both puberty suppression and hormones. In adolescents, GnRH-a often continues during hormone treatment.[9] For adolescents who do not first receive puberty suppression, GnRH-a or another anti-androgenic treatment may be offered at the initiation of hormones although the reasons for this are unclear.[79] Although recent studies suggest most adolescents who proceed with hormones will receive puberty suppression before this,[9 10 80] research that robustly compares outcomes for adolescents on this treatment pathway versus receiving hormones alone is needed, especially given recent studies suggesting the effect on secondary sex characteristics and fertility may be different.[34 39]

Agreement about core aims and outcomes for hormone interventions for adolescents would facilitate future aggregation of evidence. Included studies assessed multiple different outcomes across various domains. The rationale for cognitive outcomes

varied, with some studies primarily focusing on sex-based differences presumed from wider research.[81] Few studies examined whether hormones influence cognitive development in adolescence, which is identified as a key area of uncertainty.

Clinicians should ensure that adolescents considering hormone interventions are fully informed about the potential risks and benefits including side-effects, and the lack of high-quality evidence regarding these. In response to their own evidence review, the Swedish National Board of Health and Welfare now recommends that hormone treatments should only be provided under a research framework, a key aim for which is to develop a stronger evidence base.[82] As they point out, this approach is common practice in other clinical specialties, where to receive treatments for which the benefits and risks are uncertain, patients must take part in research.

Strengths and limitations

Strengths include a published protocol with robust search strategies, and comprehensive synthesis of high-quality and moderate-quality studies. Poor study reporting may have resulted in moderate-quality studies being rated as low-quality and excluded from the synthesis. As searches were conducted to April 2022 this review does not include more recently published studies. However, this review draws similar conclusions to other reviews despite including numerous additional studies. Of other studies published since April 2022 until January 2024, very few used a cohort design or an appropriate comparator and were of similar low-quality to moderate-quality. Of those likely to contribute new data to the synthesis, five focused on bone health and growth,[83–87] one on cardiometabolic risk[88] and two assessed psychological health,[89 90] one of which also assessed life satisfaction and congruence with gender identity and appearance,[89] and the other additionally assessed body image and sex-typed brain activity.[90]

All three studies assessing bone health examined changes over time for participants treated with GnRH-a followed by hormones and found, overall, that after hormone treatment, bone mineral density scores were in line with expected maturation, despite a deceleration during GnRH-a treatment.[83 86 87] Two of these studies also found that height growth was not affected following hormone treatment,[84 87] and this was found in a third study as well.[85] The increasing number of studies assessing bone health and height growth potentially indicate that following hormone treatment, bone health is in line with expected maturation and height growth is not affected. However, there remains uncertainty about these outcomes due to the lack of high-quality studies that use a longitudinal design and appropriate comparator with longer-term follow-up.

A single new study assessed changes in body composition.[83] It found an increase in lean body mass z-scores and a decrease in fat mass z-scores during the first year of treatment in birth-registered females, which remained stable over 3 years of treatment. For birth-registered males, there was a slight decrease in lean mass z-scores in the first year which remained stable over time, but little change in fat mass z-scores. This study adds to the limited evidence base for body composition, but no conclusions can be drawn due to the inconsistency in results across studies.

One study examined whether receipt of hormone interventions was associated with cardiometabolic-related diagnoses and found that certain diagnoses were more likely in birth-registered females receiving testosterone, suggesting that cardiometabolic health may be compromised in this group.[88] However, it is the only study that has examined diagnoses rather than cardiometabolic markers, and it used a cross-sectional design, therefore no conclusions can be drawn about these outcomes.

Two studies measured psychological health.[89 90] They both found lower levels of anxiety and depression for birth-registered females, in one study during 2 years after hormone initiation,[89] and in the other when compared with those not receiving hormones,[90] which also found lower levels of suicidality in those receiving hormones but no difference for internalising symptoms.[90] Overall, no differences for birth-registered males were observed for the same outcomes in both studies, although one study found that for both sexes, taking hormones for longer durations was associated with fewer depression and suicidality symptoms, with a stronger association between longer duration and lower suicidality in birth-registered males.[90] These studies add to the moderate-quality evidence that hormone treatment may improve psychological health, although robust research with long-term follow-up is still needed.

A single study assessing outcomes during the 2 years after hormone initiation found that scores for gender congruence and life satisfaction increased, but there were differences by birth-registered sex and timing of hormone initiation.[89] Lastly, a single cross-sectional study explored body image and sex-typed brain activity.[90] It found body image satisfaction was higher in those receiving hormones compared with those not receiving hormones and those taking hormones for longer durations. In terms of sex-typed brain activity, analysis of amygdala-vmPFC (ventromedial prefrontal cortex) coupling found greater coupling in those receiving hormones. However, as there is still limited evidence about the effect of hormones on gender-related, psychosocial and cognitive outcomes, no further conclusions can be drawn.

CONCLUSIONS

There is a lack of high-quality research assessing the outcomes of hormone interventions in adolescents experiencing gender dysphoria/incongruence, and few studies that undertake long-term follow-up. No conclusions can be drawn about the effect on gender-related outcomes, body satisfaction, psychosocial health, cognitive development or fertility. Uncertainty remains about the outcomes for height/growth, cardiometabolic and bone health. There is suggestive evidence from mainly pre–post studies that hormone treatment may improve psychological health although robust research with long-term follow-up is needed.

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