



Psychosocial challenges and hormonal treatment in gender diverse children and adolescents. A narrative review

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Abstract

Gender dysphoria (GD) in children and adolescents is a condition that is characterized by an incongruence between the assigned and experienced gender. Despite the diversity in clinical presentation, literature demonstrates that GD might lead to poor mental health and high rates of co-occurring psychopathology. Due to the overlap of physical aspects as well as psychological needs in these children, a multidisciplinary approach is highly desirable. The aim of this narrative review is to give an overview of recent literature on several topics relevant in this domain. Guidelines on psychological counseling and hormonal treatment are given and challenging topics subject to controversy are explained. Furthermore, attention is drawn to the risks and protective factors in psychological functioning, including the growing evidence of a frequent co-occurrence with Autism Spectrum Disorder. Finally the psycho-sexual development in these children, the impact on fertility and fertility preservation are discussed.

Introduction

For most children, gender role expressions, behavioral interests and preferences are largely in congruence with their experience of being male or female. In contrast with gender diverse children and adolescents, an incongruence between experienced gender and assigned gender can occur and is often then the origin of significant distress or gender dysphoria (GD). However, the clinical expression and psychological functioning of these children may be highly variable. International literature demonstrates convincingly that GD on the clinical spectrum in this population can lead to poor mental health and high rates of co-occurring psychopathology [1]. In the line of these observations, gender diverse children and adolescents, with or without a clear GD, and their families are often in need of clinical attention, counseling and treatment [2].

Although there has been many opposition against labeling gender diversity in diagnostic classification systems, today, GD is included in the current edition of the ‘*Diagnostic and Statistical Manual of Mental Disorders (DSM 5)*’ [2]. Especially in prepubescent children, the use of this classification system as such, is discussed. Opponents clearly mark the impact of stigmatization of having a mental disorder while medical interventions are still not considered. Revising the 10th version of the International Classification of Diseases and Related Health Problems (ICD-10) by the World Health Organization (WHO) in 2017, a reconceptualization of the definition and positioning of Gender Incongruence of Childhood (GIC) was included. Beek et al. collected the views of transgender individuals and professionals regarding the utility and the retention of the diagnosis [3]. The study suggests that, although in an ideal world a diagnosis is not welcomed, several participants felt the diagnosis should not be removed, likely due to concerns about restricting access to reimbursed health care. The choice for positioning of a diagnosis of GIC within the ICD-11 finally was a chapter dealing with symptoms and/or disorders regarding sexual and gender health [3]. According to the DSM-5, a diagnosis of GD in childhood can be made if gender incongruence is experienced for at least 6 months, as presented by six out of eight criteria. One dominant criterion must be ‘the feeling of a strong, insistent desire to be of another gender’. Two more criteria focus on anatomic

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Fig. 1 DSM-5 criteria gender dysphoria in childhood [2]. Classification of the GD criteria according to the DSM-5. DSM Diagnostic and Statistical Manual of Mental Disorders, GD gender dysphoria.

Gender Dysphoria in Children: DSM-5 Criteria	302.6
A. A Marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 month’s duration, as manifested by at least six of the following (one of which must be Criterion A1):	
1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one’s assigned gender).	
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.	
3. A strong preference for cross-gender roles in make-believe play or fantasy play.	
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.	
5. A strong preference for playmates of the other gender.	
6. In boys (assigned gender), a strong rejection of typically masculine toys, games and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games and activities.	
7. A strong dislike of one’s sexual anatomy.	
8. A strong desire for the primary and/or secondary sex characteristics that match one’s experienced gender.	
B. The condition is associated with clinically significant distress or impairment in social, school or other important areas of functioning.	

dysphoria: a dislike of one’s sexual anatomy as such and the desire for primary/secondary sex characteristics of the experienced gender. Other criteria refer to the preference of gender roles, dressing in the preferred gender and rejection of the typical gender congruent interests. The condition must be associated with significant distress or impairment in important areas of functioning (Fig. 1).

One of the main questions which seems difficult to answer is the prevalence of childhood GD. Valid information is scarce. Earlier in the Netherlands, the Child Behavior Checklist (CBCL) was used (item 5: ‘Behaves like the opposite sex’ and item 10: ‘Wishes to be of the opposite sex’) to estimate the prevalence of gender diversity in children. The questionnaire was completed by the parents. The 5th item scored for boys versus girls 2.6% versus 5.0%, the 10th 1.4 versus 2.6%. These data should be interpreted carefully. Not only are they the result of a parent’s opinion who completed the questionnaire, which might differ from the child’s feelings; also, a sociological shift in knowledge, acceptance and recognition today may have an important impact on the replication of these items.

Another possible bias in prevalence studies, usually published by expertise centers, is the fact that only GD children and adolescents who are seeking for help in these centers are counted. We do not have a real insight in the number of young people in the general population who struggle with their gender identity and/or feel distressed about it. Neither do we know how many of them finally

seek out for help, how many do not but want to and how many do not feel the need to.

Limited epidemiological data on the sex ratio exist. Steensma et al. reported on two different clinics (Amsterdam 1988–2016, Toronto; 1975–2015) and demonstrated that in both clinics, the sex ratio significantly favored assigned male at birth over assigned female at birth (Amsterdam 1,25:1; Toronto 4,33:1) with higher rates in Toronto for ages 9–12 years [4]. Clearly, by age 9–12 years, in Amsterdam, the number of birth assigned female was higher than birth assigned but not significant. Between the years 2006 to 2013, a certain shift in this sex ratio occurred in favoring birth assigned female; this was less pronounced in the Toronto clinic but still statistically significant [5]. In both clinics, children birth assigned male were referred at a significant younger age. Another study on the sex ratio in the United Kingdom demonstrated a significant higher number of birth assigned male (from 2000–2017) and not unlike the Amsterdam/Toronto results, a significant decrease was seen in the percentage of referred birth assigned male for the years 2007–2017 compared to the years 2000–2006. As expected, they were also referred at a younger age [6]. A clear scientific explanation for this shift is still lacking. We can assume that the sex difference and/or alteration in the age probably reflect greater parental concerns about gender nonconforming behavior in sons compared to daughters. The observation of increasing referrals of adolescents birth assigned female is not clear, but might

be explained by an earlier puberty onset in this group. Perhaps for GD adolescents assigned female, their 'coming out' is facilitated by less social stigmata and may result in an earlier search for counseling and/or medical treatment.

Psychological counseling and treatment of children with GD

The care for children and adolescents with gender incongruence has been changing rapidly over the past years. There is not only the growing number of specialized gender clinics [7–9]. Gender management clinics have emerged to assess, support and provide treatment for transgender adolescents across Europe and North America [10–14]. On a general basis, agreement exists on the need to diminish the distress of gender incongruent children by focusing on psychological difficulties, optimizing adjustment and well-being of the child and the family [15, 16]. The American Academy of Child & Adolescent Psychiatry has clearly stated that psychological treatment aiming to change gender nonconforming behavior is against good clinical practice [17]. However, when it comes to the prepubescent child, the best clinical practice remains often debated among professionals. We will come back on this topic later.

Despite the positive evolution, there still is a mismatch between provider education and expectations. Only a minority of the medical schools offer transgender-specific care [18]. In the next part, we will highlight 1/the guidelines regarding gender affirming treatment, but also 2/shed a light on the persisting challenges such as the social transition in young children and in addition 3/the related factors for persistence of GD.

Guidelines

The World Professional Association for Transgender Health (WPATH) first published Standards of Care for the health of gender non-conforming people in 1980 with its 7th edition in 2012 and is revising at this moment [16]. The American Psychological Association published in 2015 'Guidelines for psychological practice with transgender and gender nonconforming people'. These guidelines are recommendations for psychologists to assist with 'cultural competent, developmentally appropriate and trans-affirmative psychological practice' [19]. On the medical treatment side, the Endocrine Society (ES) recently (2017) issued clinical practice guidelines for the treatment of transgender persons, including pubertal suppression and cross-sex hormone therapy in adolescents [20]. The WPATH Standards of Care requires adolescents meet eligibility criteria before proceeding with hormone treatments. Medical interventions can be initiated after a referral

from a qualified mental health professional. The ES formulated on his turn recommendations more specifically that children and adolescents with GD should be seen by a professional with training in child and adolescent developmental psychology. The mental health care professional [1] determines whether the individual fulfills DSM-5 criteria for gender dysphoria [2]; informs the individual and parents of sex reassignment and other treatments and [3] assess for potential psychopathology. An important obstacle is the lack of mental health care professionals with expertise in this area, which often results in long waiting lists, poor access to health care systems and insurance coverage issues.

Gender affirming treatment should be mitigate mental health disparities and improve outcomes. Outcome studies in children and adolescents are rather scarce. The Dutch group who were pioneers in this area of care, described results on subjective and objective well-being in adolescents who received puberty suppression and were treated by a multidisciplinary team. Significantly improvement was seen on GD and body satisfaction after treatment with cross-sex hormones and surgery, but persisted through puberty suppression. Objective well-being in adolescents after treatment with cross-sex hormone and surgery was similar compared to the general Dutch population, however, adolescents who demonstrated higher scores on this measurements were more likely to live with parents, studying or pursuing a higher education [21]. This suggests that other factors such as social integration and acceptance by family and peers influence the psychological outcome of well-being. In the same study, positive effects on feelings of anger, anxiety were seen only in participants assigned female at birth. Over time, in global functioning, clinical scores were improved in both groups birth assigned female and male.

Psychological counseling in prepubescent children and the question of persisting-desisting GD

Counseling of young children with gender variant behavior and/or gender dysphoria remains an area of debate. In general, three approaches are to be distinguished. The first position refers to a reparative therapy. It is clear that in the past, these therapies failed and are, according to WPATH, designated as unethical [16]. The second approach is often referred to as 'watchful waiting'. Counseling implies support in dealing with 'uncertainty' and in providing psycho-education. In practice, the child and parents are encouraged to find a balance between accepting and a supportive attitude towards the GD, while at the same time the counseling should protect the child against any negative reactions and should remain realistic or unsure about the GD feelings in the future [22]. The third approach is the one that helps the child to build a positive self-identity and gender resilience

by affirming the child's wished gender. The rationale for supporting social transition before puberty is that these children can revert to their originally assigned gender if necessary. Critics mention that this argument cannot be decisive because to revert again might be difficult for the child, who has to make a social transition for another time. Steensma et al illustrated this in his paper on persisting and desisting GD [23]. Other critics point out that perhaps the social transition might increase the likelihood of the persistence, but scientific relevance for this is lacking.

Today this actual debate is flourishing and fundamental questions, we can poorly answer, arise: what do we know about gender identity as a developmental 'task' in humans? How fluid is such an identity? Who will persist in their desired gender, who will not? In a study of 53 adolescents in the Netherlands, this persisting or desisting of GD was evaluated [23]. It was clear that adolescents who experienced increased GD in early puberty stage (10–13 years) were unlikely to cease the transgender process. Also, children who persist may have more severe symptoms of GD in childhood. However, the uncertainty of future persistence, coupled with the reasoning that perhaps early social transition can lead to difficulties to reverse or even to persistence, has led to controversy regarding the appropriate counseling and mental health treatment strategies for prepubescent children with GD. In contrast, worsening of the GD beyond puberty is generally accepted as a diagnostic tool for clinicians and might be an important criterion for medical intervention [16]. Empirical answers how to counsel young prepubescent children and their families are not available. Balanced and informed care with shared decision making combined with respect for any particularity is probably the best way. Professionals together with the child and family should make a decision on which steps they agree and which particular choices are necessary to make. Psychological distress, global functioning of the child will have an important weight in this decision.

Hormonal treatment: puberty suppression and cross-sex hormone therapy

Puberty is the life stage in which developmental changes appear. Secondary sex characteristics gradually emerge together with brain development. Pulsatile gonadotropin release (GnRH) in the hypothalamus, results in the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH), consequently followed by cell maturation and testicular enlargement in males and the growth of ovarian follicles in females. Clinically, the onset of puberty can be assessed by the development of testicular enlargement in boys and breast budding in girls (Tanner stage 2). Children who experience GD, worsening in this developmental puberty stage, are eligible for medical treatment.

As mentioned earlier, the WPATH Standards of Care as well as the ES clinical practice guidelines recommend both the diagnosis of GD to be made by a mental health professional with expertise in gender identity prior to considering a hormonal intervention [16, 20]. Primary goals of the medical interventions include: (1) prevention of the development of the inconvenient biological secondary sex characteristics and (2) promotion of the development of desired secondary sex characteristics of the affirmed gender. An additional aim is to ameliorate psychological problems (anxiety, depression) so that they become less pronounced, together with the aim to enhance ability to 'pass' as the affirmed gender.

Hormonal interventions include puberty suppression using GnRH agonists and cross-sex hormone therapy (Fig. 2).

Puberty suppression therapy starting at Tanner 2 stage was first developed by the pioneer center in Amsterdam [24, 25]. The rationale for using GnRH analogs to suppress puberty is clear: it allows the child and family to have more time to further explore the gender identity without the fear that irreversible sex characteristics will appear and have a potential esthetical impact in the case a transition is preferred. Starting puberty suppression prior to Tanner stage 2 is not recommended by the guidelines because persistence of GD during early puberty is an important factor in the persistence of GD in later adolescence and should be used as a diagnostic tool [16, 20].

GnRH analogs are being used in children with precocious puberty for more than 25 years and are considered to be safe and reversible [26]. In GD children, they are usually started with the intent to treat with cross-sex hormones later on in life. Importantly, the child who has started with a GnRH analog and continues with cross-sex hormone therapy will never have spermatogenesis nor menarche. Therefore, patients and families should be informed repeatedly on this and have to outweigh the risk and/or benefits of this treatment. Unfortunately, GnRH agonists are often subject to availability problems. Moreover, the cost is high and reimbursement depends on local insurance rules. Alternatively, in older children with an evolving puberty (Tanner stage 3–4) other medications as progestins and antiandrogens can reduce the production of sex hormones or inhibit their actions. They are cheap and in the case of unavailability of GnRH analogs, welcomed, even when their suppressive actions are incomplete [5, 27]. Tack et al. demonstrated that pro-androgenic and anti-androgenic progestins induce body composition changes in line with the desired appearance within 1 year of treatment [28]. Progestins can be useful in adolescents assigned female who started menstruating and have completed breast development but are too young or still in process considering starting with testosterone. Antiandrogens can be used in

Fig. 2 Hormonal treatment in children/adolescents with confirmed GD. Left: age and/or Tanner Stage at which treatment is recommended and applied at the pediatric gender clinic in Ghent. Right: hormonal treatment options. GD gender dysphoria, GnRH gonadotropin-releasing hormone.

Hormonal treatment for children/adolescents with confirmed GD	
Tanner Stage I:	No hormonal treatment (psychological counseling only)
Tanner Stage II:	1/ Pubertal Suppression Therapy: GnRH analogues +
Shared decision making on the age for starting Gender-Affirming Hormone. No strict recommendations. Ghent University Hospital: after minimum 1 year of counseling and from age 15.	2/ Gender-Affirming Hormone Treatment: Testosterone (assigned females) or Estrogen (assigned males)
Tanner Stage III or IV:	1/ GnRH analogues or Progestins (assigned females) or Antiandrogens (assigned males) +
Shared decision making on the age for starting Gender-Affirming Hormone. No strict recommendations. Ghent University Hospital: after minimum 1 year of counseling and from age 16.	2/ Gender-Affirming Hormone Treatment: Testosterone (assigned females) or Estrogen (assigned males)

adolescents assigned male (Tanner 3-4) when they are worried about body and facial hair grow. The medication does not cause regression of the hair follicles, but implies often less need to shave and consequently includes better esthetic results for electrolysis therapy later on. Also, a significant reduction of spontaneous erections is often experienced as a relief.

The WPATH Standards of Care do not specify the age at which cross-sex gender affirming hormones can be administered. The ES advises to start ‘around 16 years’. The main goals are to improve general well-being and quality of life as well as to enhance the ability for adolescents to present in their experienced gender in society. In our experience, 16 years of age can be an unnecessary long time especially when gender identity is stable over time (e.g., in children with puberty suppression counseling for various years). Age 15 is than applied, other centers will even start at age 14 [10, 11]. Attention to parental consent and fertility counseling must be taken seriously and proportional. Again, a multi-interdisciplinary shared decision making is probably the best clinical practice in this.

GnRH analogs as well as pro-androgenic and anti-androgenic progestins can be continued during treatment with cross-sex hormones until gonadectomy is performed, or, in adolescents assigned female, until masculinizing chest

surgery, at which point monotherapy with testosterone should be suffice to prevent menstruation.

In general, long term effects of hormonal treatment on body systems and organs in children and adolescents are sparsely studied. Few research data focused on metabolic parameters and the impact of testosterone on ovarian tissue. More recently, attention was also put on the effect of hormonal therapy on the brain, an organ abundant with androgen and estrogen receptors.

The impact of estrogen therapy in trans gender male adolescents and young adults on psychological functioning and general quality of life are not conclusive to be negative. The study done by de Vries et al. in which the outcome was investigated in a follow up study with participants who received puberty suppression, showed stable or slightly more symptomatology on the measures of anger and anxiety, but improved on the total T scores of the Child behavior checklist or Adult behavior checklist (CBCL/ABCL) [21].

In transgender children, the intake of GnRH analogs might include a risk of a reduction in bone mineral density z-score during treatment. Also, bone health, especially at the lumbar spine, was found to be severely affected by androgen suppressive therapy [28]. However, scarce evidence suggested bone density accrual might improve after starting treatment with cross-sex hormones [25, 29].

Another important issue regarding the use of GnRH analogs is the underdevelopment of the penis, which might compromise future vaginoplasty [9].

The brain is clearly influenced by endogenous levels of sex hormones which can be observed during puberty and the menstrual cycle e.g. [30]. Adult brain studies in trans persons before and after several months of hormone treatment showed that estrogen plus anti-androgen treatment (in assigned male) is associated with a decrease in volume towards 'female proportions'; the ventricles were seen to increase in volume [31]. Moreover, testosterone treatment (in assigned female) resulted in increased total brain and hypothalamus volumes. Identical results were found by Zubiaurre-Elorza et al. [32]. These changes were suggested to be caused by the anabolic effects of testosterone, while the opposite decrease and expansion of the ventricles might be due to the suppression of normal anabolic effects of testosterone by the anti-androgens and the deleterious effects of estradiol [32]. Testosterone treatment also was demonstrated to effect white matter microstructure [33]. Information about the impact of GnRH analogs (suppressing puberty) on specific brain structures in prepubescent children is not available.

Cross sex hormone therapy was shown to be safe regarding metabolic and cardiovascular parameters on the short-term [34]. Data from adolescents between 14 and 25 years were collected in 4 clinics in the US. Recorded blood pressure, BMI, testosterone, estradiol, prolactin, lipids, electrolytes, liver function test, hemoglobin/hematocrit and hemoglobin A1c were reviewed. Data were collected until 6 months of cross sex hormone therapy and supported the short-term safety of this treatment in GD adolescents. A review of cross sex hormone therapy in adults, also mentioned an insufficient follow-up duration to make clear conclusions of cardio-metabolic effects from cross sex hormone therapy. Most data are retrospective but are comforting. However, in (older, >40 years) transgender women, transdermal patches or gel (or parenteral estrogen injections if available) may be safer with regard to triglycerides and clotting risk than oral oestradiol by passing hepatic metabolism, but randomized controlled trials comparing these formulae are not available. Smoking and the use of synthetic etinyl oestradiol (which is no longer used) on the contrary, were risk factors [35, 36].

In the past century, investigators reported that the androgen-exposed ovaries of transgender males showed polycystic ovary (PCO) syndrome-like features, that is: a thickened ovarian cortex and marked collagenization, with a greater number of cystic (atretic) follicles in the ovarian stroma. Recent studies replicated these findings in drug naive transgender male persons without PCO and found, to some extent, similar results after testosterone administration [37, 38]. A novel technique, texture profile analysis of the

ovarian cortex of transgender males, was compared with the ovarian cortex of oncological patients and concluded that the superficial part of cortex appeared to be significantly stiffer in the trans group [39]. It is clear that long term follow up and more research is necessary to comprehend the complete impact of cross sex hormone therapy in trans people.

Psychological well-being and co-existing problems in children and adolescents with GD

Children with GD are considered to be a more vulnerable group regarding psychological problems and generally report higher rates of mental health difficulties. The occurrence of behavioral and emotional problems in this group has been measured in several studies [40–44]. The absolute scores on questionnaires or answers on diagnostic interviews are interesting, but unfortunately most of them do not include a control population.

However, in Canada, a large well-designed randomized case control study was performed in which 923 transgender youth were recruited and asked about different aspects concerning their mental health: emotional distress, suicidality, self-harm and general mental health [45]. The results were striking: mental health disparities were significantly higher for transgender youth, compared with the general population-based estimates. Transgender youth between 14 and 18-years old had five times the risk of suicidal thoughts and 79.2% reported self-harming in the past year. Remarkably is the finding that non-binary youth consistently reported even worse mental health on average than trans adolescents. Another American retrospective observational cohort study, compared 180 transgender youth (aged 12–29) to a cisgender control group. Compared to cisgender matched controls, transgender participants had a two- to three-fold increased risk of depression, anxiety disorder, suicidal ideation, suicide attempt, self-harm without lethal intent, and both inpatient and outpatient mental health treatment [46].

The question how these findings of being at high risk to report mental health difficulties in GD youth can be understood, was answered by other studies showing that the effect is largely mediated through social (in)tolerance toward gender variant, gender non-congruent behavior and identity [47–50]. De Vries et al. concluded that the 'Peer Relations Scale' was the strongest predictor of both the CBCL and YSR 'Total Problem Score'. Other variables with a positive correlation were a lower IQ and a lower socioeconomic background [51].

A cross-international comparison study examining psychological functioning in gender diverse adolescents across

Europe was published in 2018 [52]. All adolescents aged 12–18 who were referred to one of the four European specialist gender clinics (Amsterdam, Ghent, Zurich and London) were included. Data from the CBCL and the YSR were analyzed. A similar pattern was found across the different clinics. A notable finding was that birth assigned girls reported more total problems and externalizing problems in the clinical range than the birth assigned boys. In the previous discussed study, birth assigned girls also reported a significantly higher externalizing problem score (although not in the clinical range) [51]. The hypothesis of a general pattern of an “inversion” of internalizing vs. externalizing problems in relation to the sex-typical pattern of more internalizing problems in girls and more externalizing problems in boys thus seems plausible, but further research is needed. Not unlike the previous findings of De Vries et al., a positive correlation between the Peer Relation Scale and both the CBCL and YSR was found here [51]. Across the four clinics, the highest prevalence of problem scores was found in the UK, the least problems were reported by the Dutch adolescents. Most likely, these differences can be explained by a difference in tolerance and acceptance of gender variance in the Dutch culture on the one hand and differences in the availability of GnRH treatment in the UK on the other hand until 2011.

The co-occurrence of GD and Autism

There is growing evidence concerning co-occurrence and/or overlap between GD and Autism Spectrum Disorder (ASD). The DSM-5 core criteria for an ASD diagnosis include significant impairments in social communication and interaction and restricted, repetitive patterns of behaviors, specific interests or activities. Most studies in this area examine the presence of ASD in GD populations [10, 53, 54]. The converse approach, investigating GD symptoms within an ASD population has also been used [55–57].

In a recent Dutch study, a sample of 542 children and adolescents with GD were investigated and compared to two groups from a normative study: 196 children and adolescents with ASD and 2507 TD (Typical Developing) children and adolescents. The Children’s Social Behavior Questionnaire (CSBQ) was used to investigate symptoms of ASD and was completed by parents or caregivers. On average, the scores of the children and adolescents with GD were all in between the scores of TD children and adolescents and those diagnosed with ASD. There was no main effect of assigned gender at birth nor a group by gender interaction effect [58].

In a second, international study, the association between gender variance (GV) and ASD was explored in a group of 2245 children between the age of 6 and 12 years of

age [59]. In an online questionnaire parents were asked if their children had received a developmental/mental health diagnosis from a healthcare professional and were asked to complete both the Gender Identity Questionnaire for Children (GIQC) and the CSBQ. A positive association between characteristics of ASD and GV in this nonclinical sample was found. This indicates that the association exists beyond the clinical domain. Furthermore, children with ASD showed significantly higher level of parent-reported GV compared to the reference group of children without reported clinical diagnosis [59]. This finding is thus in line with the previous mentioned study [58].

These studies confirm the bidirectional assumption that, not only children and adolescents with GD show more symptoms of ASD, but also that children with ASD show a higher level of reported GV in comparison to children without a reported diagnosis. However, concerns were expressed by some authors, about the specificity of using screening instruments to search for ASD symptoms instead of a confirmed ASD diagnosis on the one hand and search for GV symptoms rather than the real gender identity or confirmed GD on the other hand [60]. Even more, they critically state that sound underlying evidence for a GD-ASD link is currently still lacking. This publication led to a heated debate between several authors in this search field. Even when holding stigma and sexual minority stress into account as possible explanations for social difficulties individuals with GD, elevations on all of the subdomains of ASD were found, van der Miesen et al. responded [61]. Strang et al. at their turn, reacted by referring to 7 studies where clinical ASD diagnosis rates were 4,1 to 17,5 times more common than in the general population and stated that these findings are directly contradicting the argument that the reported over-occurrence of ASD in gender-diverse individuals is due to nonspecific ASD measures [62].

Several suggestions on how to understand the link between GD and ASD have been formulated but remain hypothetical [53, 63, 64]. As for now, causal relations between the two conditions cannot be withheld at this moment and further research is recommended.

Because of the fact that the co-occurrence of GD and ASD in adolescents is often complex and includes significant diagnostic and treatment challenges, specific guidelines for the assessment and care are needed. Initial guidelines were published and are provided in Fig. 3 [65]. The importance of screening for ASD among gender referrals and the importance of screening for gender issues among ASD referrals was one of the main recommendations. There is also a clear statement that the diagnosis of ASD should not exclude an adolescent from also receiving a GD diagnosis and, when indicated, appropriate GD treatment.

Fig. 3 Initial guidelines for co-occurring ASD and GD in adolescents [65]. Summary of the guidelines for assessment and treatment of GD in ASD adolescents formulated by Strang et al. [65]. GD gender dysphoria, ASD Autism spectrum disorder.

Initial Guidelines for Co-Occurring ASD and GD in Adolescents	
A. Assessment:	
-	When assessing for co-occurring ASD and GD, gender specialists and autism specialists should collaborate to be part of the assessment when there is no available clinician skilled in both specialities. A more extended diagnostic period may be needed, due to the complexity of diagnosis.
-	Gender referrals should be screened for ASD. (+ If ASD is suspected and the screening clinician is not an ASD specialist, the patient should be referred to an ASD specialist for ASD diagnosis)
-	Youth with ASD should also be screened for gender issues. (+ If gender concerns are noted, a referral should be made to an appropriate gender specialist for assessment and support).
-	The diagnosis of ASD should not exclude an adolescent from also receiving a GD diagnosis and, when indicated, appropriate GD-related treatment. (Note: Diagnosing ASD can be complex in gender nonconforming youth because they might appear socially awkward or withdrawn due to their history. Also, diagnosing GD can be complex in adolescents with ASD due to ASD-related weaknesses in communication, self-awareness, and executive function)
B. Treatment:	
-	Treatments must address both diagnoses (GD and ASD) concurrently and evaluate the gender-related needs as therapy progresses.
-	Adolescents and their parents often require psycho-education about the nature of ASD and Gender identification, with a focus on how GD presentation may be different in individuals with ASD.
-	To the extent possible, the assessment/intervention sequence should be outlined in a straightforward and visual manner for the adolescent with ASD.
-	It is critical to develop a plan to maximize a patient's motivation and ability to participate consistently in the treatment process. (Because some adolescent with the co-occurrence struggle with treatment compliance).
-	Adolescents who are clearly in an exploratory phase of gender should be encouraged to explore their gender identity over time before being considered for any potentially irreversible gender-related treatments. (+ Provide psycho-education about how gender for some people can be fluid.)
-	An ASD diagnosis should not exclude the potential for medical GD treatments. More caution may need to be taken in this population when deciding on medical treatments that may have irreversible effects given the presence of ASD-related deficits in future thinking and planning.

Fertility and psychosexual development in adolescents with GD

People with GD who are treated, either medically or surgically, are at risk for infertility [37, 66, 67]. Information should be provided early in the transition process which effects of treatment can be expected. Information about fertility preservation (FP) should be available. Additionally, it is interesting to understand how children and adolescents with GD judge fertility issues.

Pubertal suppression with GnRH analogs is reversible, but it does pause the maturation of germ cells, and this could affect fertility potential [68–70]. The long-term effects of gender affirming hormone therapy with testosterone on future fertility are unknown. Literature does not provide uniform results. Polycystic ovarian morphology was found whereas preservation of normal cortical follicle distribution was documented as well [71, 72]. The same conflicting results apply for estrogen therapy [73, 74]. The WPATH recommends counseling regarding fertility and

reproductive options before initiating hormonal treatment [16]. Cryopreservation of oocytes or embryos for adolescents assigned female or cryopreservation of sperm or embryos for those assigned male can be applied. For pre-pubescent children and adolescents who opt for FP before initiating hormonal therapy, the option of ovarian tissue or testicular tissue cryopreservation is still experimental [68, 75, 76].

Two different studies looked at the utilization rates of FP in transgender adolescents [77, 78]. In both studies, the authors concluded that these rates were low. Chen et al. reported 13 out of 105 transgender adolescents who were seen in formal consultation of FP before initiating hormone treatment. Five completed the FP process (four sperm and one oocyte cryopreservation) [77]. Nahata et al. reported only 2 out of 72 patients having attempted fertility preservation [78]. In adult studies, 51% of the birth assigned male say that they would have considered sperm banking if it had been offered, and 37.5% of the birth assigned female would have considered freezing germ cells [79, 80]. This discrepancy does raise questions as how many transgender youth change their perspectives about FP later in life and which barriers exist for using FP: invasiveness and/or costs of the procedures, a sense of urgency to move forward with the medical transition [77, 78]? Further research to examine the reproductive desires and attitudes regarding fertility preservations is needed. The “Transgender Youth Fertility Attitudes Questionnaire” was recently developed by Strang et al. [81]. The study builds on existent approaches and measures developed to assess fertility attitudes in youth with cancer and their parents [82–84]. In a pilot trial, more than 50% of the trans adolescents indicated the wish to have children, 24% expressed the desire to have their own biological child. Many wondered or did not know if their feelings about having a biological child might change in the future.

Little is known about the sexual development process in youth with GD. A study in the Netherlands was conducted to evaluate sexual and romantic experiences in adolescents with GD compared with a matched cisgender control group [85]. In the GD group gender differences were not observed for falling in love and romantic relationships, but adolescents assigned female at birth were more experienced in the areas of sexual fantasies, french kissing and petting while undressed. Adolescents birth assigned male however were more experienced in sexual intercourse. With respect to self-defining their sexual orientation, 27% of the participants assigned male and 44% of the assigned female reported defining themselves as heterosexual whereas 50% of the assigned male group and 43% of the assigned female group describe themselves as undecided. Compared with the control group, adolescents with GD had less sexual experience, 44% chose

“being ashamed of my own body” as a reason not to have intercourse. Of the sexually active transgender adolescents, 50% reported not involving their genitals. These results doubtless underline the importance of appropriate sexual counseling for this young people.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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