Gender Dysphoria in Young People: A Model of Chronic Stress

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Key Messages

- Gender dysphoria (GD) has similarities to other examples of chronic stress, with some evidence of both a psychological and biological stress response, but this has yet to be fully evaluated in longitudinal studies of young people with GD.
- GD, as a chronic stressor, may in part be responsible for reported poorer physical and mental health outcomes in young people.
- Uncertainties remain on the benefit of treatment in young people with GD, highlighting the need for specific measures of GD and stress to be used in both clinical monitoring and future research.

Keywords

Gender dysphoria · Chronic stress · Psychological stress response · Biological stress response · Gonadotrophin-releasing hormone analogue

Abstract

Background: Gender dysphoria (GD) refers to the distress that may accompany gender incongruence, often heightened at the onset of puberty, with the development of secondary sex characteristics. Children and adolescents may be especially vulnerable to severe stressors, including GD, with potentially irreversible effects if these exposures occur during critical periods of development and brain maturation.

Summary: We describe the evidence for GD as a chronic stressor, drawing parallels to other established models of stress, activating both innate psychological and biological stress responses. As well as being an inherently distressing experience, a person who experiences GD may also experi-

ence minority stress. Minority stress has been demonstrated in young people who experience GD with higher rates of social rejection and internalized stigma and shame. The biological stress response in young people with GD is illustrated through the activation of the hypothalamic-pituitary-adrenal axis, autonomic nervous system, and pro-inflammatory response. The number of young people who report experiencing GD has increased exponentially worldwide in the past decade, demanding a change in the clinic infrastructure. Paediatric endocrinologists and specialists in mental health work together to both support psychosocial well-being and offer individualized treatment to align the phenotype with gender identity with the aim of alleviating the distress of GD. Medical interventions may include puberty suppression and gender-affirming hormones. Ongoing monitoring is required prior to initiation and during treatment to ensure that the goals of treatment are being achieved.

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Introduction

Gender identity relates to an individual's innate sense of their own gender, whether male, female, or along a spectrum between male and female, which may or may not correspond to the sex assigned at birth. Gender incongruence is characterized by a marked and persistent conflict between an individual's gender identity and assigned sex, which often leads to a desire to transition, in order to live and be accepted as a person of the experienced gender [1]. Gender dysphoria (GD) is a clinical term which refers to the distress that may accompany gender incongruence [2]. GD is often heightened at the onset of puberty, with the development of secondary sex characteristics, and can be so debilitating as to hinder normal psychosocial development and activities of daily living, often resulting in depression and suicidal ideation [3].

Traditional depictions of the gendered roles of men and women in society remain common. However, in many Western societies, there has been an increasing acceptance and understanding of variance in both gender and sexuality with a progressive shift away from a binary view of gender and sexuality towards one based on a continuum or fluidity [4]. The prevalence of GD, according to published reports, ranges between 0.6% and 2.7%, depending on the selection and age of the study cohort and method of investigation [5]. Presentations in young people with GD, both for psychological and medical interventions, have increased exponentially worldwide in the past decade [6–8]. In addition to the overall rise in numbers of young people seeking help because of GD, we have witnessed a shift in the presentation towards birth-assigned females, the majority of whom are post-pubertal and in whom there is an increased prevalence of mental health problems such as anxiety, low mood, and depression [8]. Comorbidity studies in children and adolescents with GD have found a disproportionate number of young people with mental health problems, as well as a higher prevalence of autistic spectrum disorder than might be expected in the general population [8–10].

Several explanations have been proposed for the increase in referrals to gender identity clinics for young people, including changes in help-seeking attitudes, raised public awareness and increased media presentation of LGBT issues, the Internet as a source of information, LGBT support groups, campaigns for transgender rights, reduced discrimination, greater awareness of GD among healthcare professionals, and advances in understanding of the aetiology of GD [11]. The exponential in-

crease in referrals can be alternately explained by a greater ease of access of those young people seeking help for GD as more dedicated services are established, rather than adolescents being referred to gender identity services with lower intensities of GD or with more psychological difficulties [7]. In this review, we describe GD as a chronic stressor, the psychological and medical interventions practised, and the evidence that supports interventions mitigating stress of GD.

GD and Psychological Stress in Childhood and Adolescence

GD is a complex paradigm of chronic stress that can impact health throughout the lifespan (shown in Fig. 1). GD, by definition, involves the experience of distress or a negative effect to varying degrees of intensity, depending on the extent of the dysphoria. The experience of a chronic negative effect during childhood and adolescence is a psychologically stressful experience which activates the physiological stress response and is associated with negative physical and mental health outcomes later in life [12]. Children and adolescents may be especially vulnerable to severe stressors, including GD, with potentially irreversible effects if these exposures occur during critical periods of development and brain maturation.

As well as being an inherently distressing experience, GD can also be characterized as a form of minority stress [13]. The minority stress model posits that members of minority groups are subject to increased stressful experiences, on top of the general life stressors that individuals can expect to experience over the life course [14]. Children and adolescents with gender incongruence (many, but not all of whom will experience GD) are more likely to experience stressful external events than the general population, including discrimination, exclusion, and victimization [15]. Gender-diverse youths are more likely to experience bullying, harassment, and feelings of being unsafe at school [16–18]. The culmination of these negative experiences may, in turn, lead to outcomes that add further stress, such as school non-attendance and educational non-attainment [19, 20].

The negative experiences that contribute to minority stress involve social rejection, which has suggested similar neural correlates to physical pain [21] and is linked to the physiological stress response [22]. Adolescence is a period where group membership and social acceptance is regarded with greater importance [23, 24]. Therefore, the impact of minority stress is likely heightened in adolescents with

Fig. 1. A proposed model of chronic stress in GD and factors which may strengthen and mitigate against activation of the biological and psychological stress response. GD, gender dysphoria.

GD, who may already be hypersensitive to peer rejection. In support of this, there is evidence that the onset of GD during adolescence results in poorer educational attainment than during childhood or the adulthood onset.

Minority stress also involves internal stressors. These include the development of an expectation that external stressful experiences such as discrimination by others may occur. Therefore, as well as experiencing the stress associated with direct adverse experiences, a young person may also experience stress in the absence of these events, through the expectation that rejection will occur (internalized from previous experiences or through hearing of the experience of others). The expectation of negative evaluation and perception of “social evaluative threat” has been found to trigger the biological and psychological stress response as much as the direct experience of stressful events [25, 26]. In social situations, a young person with GD may constantly scan their environment for signs of threat, such as discrimination, aggression, or social rejection. This results in a chronic activation of the psychological and biological threat and stress systems.

Internalized stigma, where a young person internalizes society’s negative attributions and beliefs regarding young people with GD, can be a further possible contrib-

utor of stress. GD involves negative feelings and cognitions about one’s body. Internalized stigma and negative body image result in feelings of shame [27]. Shame is associated with a strong emotional and biological stress response in adults and children as young as 4 years [28, 29]. This internalized stigma often results in unhelpful behaviours that can perpetuate negative beliefs and fears of social evaluative threat. For example, a young person may hide or conceal their identity to avoid expected rejection. Identity concealment, across other minority groups, has been shown to cause significant distress and leads to a lower quality of life [30–32].

Reported physical activity levels and participation in sports are low in adolescents with GD despite citing their physical health as an area of high importance. Body image-related shame, internalized stigma, and fear of rejection in relation to wearing revealing sports clothing and use of changing rooms, as well as a negative self-evaluation when comparing themselves to others of their age and adopted gender are all reported as key barriers to participation in sport amongst adolescents receiving treatment for GD [33]. Barriers to participation in this cohort provide an exemplar of the impact of minority stress encountered in GD.

The Impact of GD on Mental Health and Quality of Life

GD is associated with poor mental health and quality-of-life outcomes. More than one third of those attending specialist clinics have a diagnosis of a mental health disorder [8]. GD has a negative impact on quality-of-life measures in adolescent and adult transgender populations when compared with cisgender populations [34, 35].

Being transgender in adolescence is associated with high rates of internalizing symptoms, depression, anxiety, self-harming behaviour, and suicidality and lower levels of psychosocial functioning [10, 36, 37]. Gender-diverse adolescents with high levels of internalized stigma are significantly more likely to meet the diagnostic criteria for major depressive disorder and generalized anxiety, whilst those with high levels of gender incongruence are more likely to meet diagnostic criteria for major depressive disorder [38].

The association between mental health and GD in children and younger adolescents is less clear. Transgender children (3–12 years) who had socially transitioned were found to have similar depression scores to a control group and population averages [39]. Similarly, transgender adolescents (9–14 years) who had socially transitioned did not have higher levels of depression but had marginally higher levels of anxiety than those in the control group or population norms [40]. This might suggest that a social transition in childhood results in better mental health outcomes, perhaps due to these individuals having the opportunity to live in and adapt to their desired gender prior to puberty and adolescence (i.e., prior to the development of secondary sex characteristics and prior to a period of social rejection sensitivity). However, the lack of long-term follow-up and control group comparison to these children limit the generalizability of these findings.

GD and the Biological Stress Response

Stress is a physiological state in which the normal homeostasis of an individual is threatened [41]. The stressor can be either physical or emotional [42]. Developmental stage, timing and duration, magnitude of the stressor, the presence of concurrent adverse or protective factors, and genetics may influence both vulnerability and resilience to stress. Developmental stages, including prenatal, infancy, childhood, and adolescence, are all considered as periods of increased vulnerability to stress, meaning that stress may have a greater impact in early years of life [43–

45]. Stereotypical innate responses to acute stress have evolved to restore the equilibrium of normal homeostasis through adoption of physical and behavioural changes in an individual, in which the overall aim is to ensure survival. If a stressor becomes chronic, then, these same adaptive responses may either fail to restore the normal equilibrium or become maladaptive.

In acute stress, there are time-limited changes in both the central nervous system and peripheral nervous system, which facilitate the “fight, flight, or freeze” response. The principal effectors are the glucocorticoids, controlled by the hypothalamic-pituitary-adrenal (HPA) axis of the central nervous system, and the catecholamines, norepinephrine and epinephrine of the peripheral nervous system [46]. The targets of the HPA axis include areas of the brain controlling executive function, fear/anger, and reward systems in addition to the wake-sleep centres. Activation of the HPA axis results in increased glucocorticoid production which in turn plays an important role in mobilizing energy through promoting gluconeogenesis, lipolysis, and protein catabolism [47]. Time-limited targets, with aims of improving survival and conserving energy, include suppression of the growth hormone (GH) insulin-like growth factor 1 (IGF1) and hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes such that stress is at the same time anti-growth, anti-reproductive, and catabolic. These targets in the acute response have the aim of achieving survival however would be maladaptive if the acute stressor was to become chronic.

In chronic stress, there is a decoupling of the feedback loop which controls activity of the HPA axis with resulting chronic elevation of cortisol. Inappropriately high basal cortisol has suppressive effects on both the GH-IGF1 and hypothalamic-pituitary-gonadal axis, culminating in abnormal growth and entry to and progress through puberty during childhood and adolescence. The behavioural consequences of chronic stress can include anxiety, anorexia, hyperphagia, and sleep disturbance [47]. In addition to the dysregulation of the HPA axis, there is a dysregulation of the immune response, evidenced by a shift towards pro-inflammatory cytokines and elevation in C-reactive protein (CRP), in response to chronic activation of stress [48]. Physical and psychological stresses and negative emotions of depression and anxiety have all been shown to account for stimulation in an acute phase response through an increase in one of the key regulatory cytokines, IL-6. IL-6 in turn is an important inducer of CRP in the liver. IL-6 and CRP in combination have negative consequences in the development of cardiovascular disease [48]. The somatic consequences of chronic stress

Table 1. Summary of studies investigating the use of biomarkers of stress, CRP, and cortisol, in young people with GD

Authors	Subjects	Mean age (SD) or range, years	Stress biomarker	Psychological scale	Results
Colizzi et al. [56]	45 transwomen 25 transmen	Transwomen: 29.3 (9.9) Transmen: 26.8 (8.09)	Morning plasma Cortisol	Cohen's Perceived Stress Scale Adult Attachment Interview	Adults with GD, prior to treatment with cross-hormone therapy, had higher cortisol levels on waking, higher perceived stress, and more attachment insecurity than in normative sample data Insecure attachment was associated with higher morning cortisol and perceived stress in untreated GD Cross-hormone therapy resulted in normalizing of morning cortisol and perceived stress such that these were not different from controls
DuBois [55]	65 transmen on testosterone	31.8 (9.1)	CRP measured on dried blood spots Nocturnal ABPM	In-person semi-structured interviews Cohen's Perceived Stress Scale	Transition-specific stress measures were associated with diminished nocturnal decline in ABPM and elevated levels of CRP
DuBois et al. [54]	65 transmen on testosterone	31.8 (9.1)	Salivary cortisol measured at 4 time points in 3 consecutive days	In-person semi-structured interviews Cohen's Perceived Stress Scale	Stigma-based, transition-related stressors were identified and associated with diurnal cortisol levels. Experiencing high/frequent stress related to these stressors is associated with amplified diurnal cortisol production throughout the day
Wallien et al. [58]	25 children with GD and 25 matched controls	7–12	Salivary cortisol (measured 1–4 p.m.) Heart rate and skin conductance measured continuously during the test	Child Behaviour Check List with repeated measures under non-stressful and stressful conditions	Children with GD did not differ from matched controls with respect to the HPA axis or ANS when exposed to stress Children with GD had a tonically elevated skin conduction level during stressful and non-stressful conditions compared to matched controls
McQuillan et al. [59]	12 transwomen 38 transmen	16 (1.9)	CRP measured on dried blood sample	GMSR tool	No significant differences in CRP were found associated with individual components (gender supports or stressors) of the GMSR. A composite score of 6 GMSR scales did suggest an association between greater stress and less support with inflammation
Ristori et al. [57]	160 transwomen 141 transmen	30.0 (10.0)	Plasma cortisol		In transmen, sexual distress was associated positively with plasma cortisol levels. The introduction of cross-hormone therapy led to a reduction in sexual distress in both transmen and transwomen

SD, standard deviation; GD, gender dysphoria; CRP, C-reactive protein; ABPM, ambulatory blood pressure monitoring; HPA, hypothalamic-pituitary-adrenal axis; ANS, autonomic nervous system; GMSR, gender minority stress and resilience.

include growth suppression, hypogonadism, hypertension, and visceral-fat accumulation. There are long-term increased risks of osteoporosis, cardiovascular disease, obesity, and metabolic syndrome [47, 49–51].

Being transgender is associated with poorer physical health outcomes [52]. Chronic activation of the physiological stress response is therefore a potential factor underlying the link between GD and poor physical health [53]. Studies on transgender adults suggest a positive association between minority stressors and biomarkers of the biological stress response: elevated CRP and elevated morning cortisol levels [54, 55] (Table 1). Individuals with GD have a higher cortisol awakening response, higher perceived stress, and more attachment insecurity relative to a control population prior to the initiation of gender-affirming hormone treatment [56]. Following treatment with gender-affirming hormone therapy, there is a significant reduction in sexual distress in both transwomen and transmen [57]. In addition, the cortisol awakening response, following cross-hormone therapy, was significantly lower and fell to within the normal range of a control population [54].

In children with GD, biomarkers of the biological stress response, CRP and morning cortisol levels, and the autonomic nervous system (heart rate and skin conductance) have been studied (Table 1). A stressful social task resulted in an attenuated psychological stress response in children with GD, in terms of an increased negative effect and decreased feelings of control. However, children with GD did not show an elevated physiological stress response [58]. In contrast, higher CRP levels, in young people with GD, were associated with a higher composite score of gender-based stressors and lower gender-based support [59]. The conflicting findings across studies in this area may be due to the use of different biomarkers and different measures of stress (i.e., minority stress vs. general social stress). Whilst more research is needed, the existing research does tentatively suggest an association between the minority stress associated with GD and activation of the physiological stress response.

There are, in existence, models of stress including exercise, anorexia nervosa, and post-traumatic stress disorder which have been more extensively researched [60–62]. The impact of each of these stressors has been studied in relation to their effects on hormonal axes (including HPA, GH-IGF1, hypothalamus-pituitary-gonadal, and hypothalamus-pituitary-thyroid) and the target organ effects. We might assume that a similar model for chronic stress could exist for GD; however, there are no studies yet to allow GD to be defined as a stressor in a similar way.

The impact of GD on the HPA axis, as a potential stressor, is limited to few studies describing differences in measured cortisol. The impact of GD has not been studied in relation to other hormone axes.

Clinical Management of Young People with GD

Several resilience factors mitigate the impact of GD-associated stress in children and adolescents. Having the freedom to live in one's preferred gender, positive relationships with parents and peers, and increased feelings of school belongingness have all been found to lessen associations with poor mental health [63]. Interventions offered to children and adolescents, psychological and medical, aim to both strengthen resilience factors and reduce the distress associated with GD.

Multidisciplinary Approach and Clinic Environment

The development of multidisciplinary clinical models of care, co-locating specialists of paediatric endocrinology and mental health professionals in GD to deliver integrated care, has evolved due to the increasing complexity of patient presentations and to facilitate treatment decision-making [8]. Young people attending the clinic meet with both specialists in clinical psychology and paediatric endocrinology have monitoring investigations and receive treatment in 1 visit. The 2 main outcomes of the multidisciplinary team (MDT), for the individual, are to support psychosocial well-being and align the phenotype with their gender identity. The clinical staff, in the MDT, have more opportunity to work closely with each other, fostering closer working relationships and clear channels of communication before, during, and after the clinic, enabling decisions to be made at the time of the appointment. It is important that the core group agrees to a unified approach to management and that specialists communicate with families using similar language. Specialists working in the MDT recognize the importance of sharing information within the team and providing clear information to young people with GD [8].

Young people accessing the MDT clinic may feel disenfranchised from their family and community. It is very likely that individuals with GD will have experienced stigmatization and discrimination in different settings including home, local community, and school. It is therefore important that young people who have reached the MDT service should feel secure that the clinic represents a non-judgemental space where they can be assured of confidentiality [64].

Treatment options are tailored to the individual but will be guided by the age of the person and staging of puberty, the birth-assigned sex, and capacity to provide consent, among other factors. It is important to recognize that the young people referred to paediatric endocrinologists represent a smaller proportion of the total population of young people with GD. Amongst the total GD population, there will be young people who never seek support of clinical psychologists or paediatric endocrinologists and young people who may only wish to access clinical psychology support without medical intervention.

Psychology Support

Psychosocial support works with young people and their families to help young people explore their gender identity, whilst also addressing the negative impact of GD. Psychosocial interventions include those which empower a young person to explore their gender identity and expression and consider making a “social transition.” Psychosocial interventions work with both parents and young people to promote resilience factors through linking in with available peer and community supports to help improve feelings of belonging and social acceptance.

Treatment in prepubertal children with GD remains contentious, relative to adolescents and adults, as they are less likely to express a stable pattern of gender variance, with the majority no longer having GD by the onset of puberty [65]. The general approach in a prepubertal child with gender variance would be to provide the family with general advice and access to support networks whilst allowing for the developmental trajectory of gender identity to unfold without pursuing or encouraging a specific outcome [65].

For some young people, medical interventions may be useful, including puberty suppression and gender-affirming hormones, alongside ongoing psychological support. Intervention is individualized: not all children and adolescents will want or be suitable for all elements of psychological and medical interventions.

Suppression of Puberty

During puberty, adolescents who fulfil the criteria for suppression of puberty will be referred to a paediatric endocrinologist for discussion of medical interventions to delay pubertal progression with the use of a gonadotrophin-releasing hormone (GnRH) analogue [2]. Through stopping pubertal progression, the GnRH analogue aims to help young people with established GD to alleviate their distress and anxiety, which are both linked to the

appearance of secondary sex characteristics [64, 65]. Thus, suppression of puberty can provide time and space for the young person to explore their gender identity with the support of their mental health professional prior to making decisions on treatments associated with irreversible change. In addition, it will prevent further development of unwanted secondary sex characteristics, obviating the need for future affirming surgeries and making it easier for the person to live in their affirmed gender in the future [66].

Gender-Affirming Hormones

In adolescents wishing to proceed via hormonal transitioning, the treatment involves the use of gender-affirming hormones (oestrogens for transfemales and testosterone for transmales), aiming for the development of secondary sex characteristics of the affirmed gender. Hormonal treatment is initiated progressively (pubertal induction), with the dose increasing gradually, and should occur in parallel with psychological monitoring.

The irreversibility of treatment needs to be considered carefully with a young person and their family prior to commencing gender-affirming hormones. The current consensus on the age of initiation of sex hormone treatment is 16 years [2]. Potential risks of waiting until age 16 years include those to bone health, if puberty is suppressed for many years before initiating sex hormones, and to emotional and social isolation, if a lack of secondary sex characteristics is causing distress. However, there is minimal data and clinical experience in support of the use of gender-affirming hormones in transgender adolescents at a younger age [67].

Gender Affirmation Surgery

After an agreed upon time (known as the social gender role transition) during which the person will live according to their identified gender and beyond the age of 18 years, the option for gender-affirming surgery is offered. However, if social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery, then a referral for surgery should not be made [68].

Impact of Medical Interventions on GD

There are no studies clearly supporting reduction in GD with the introduction of a GnRH analogue in adolescence [69]. However, this might be expected from the outset given that GnRH analogue treatment aims to prevent further development of secondary sex characteristics

and therefore prevent worsening of GD rather than to reduce or resolve it. There is however evidence to suggest that the GnRH analogue improves psychosocial functioning and mood in young people over time [69, 70]. Randomized control trials would allow an exploration of the utility of the GnRH analogue in terms of preventing worsening dysphoria and changing other psychological and biological markers of stress.

In contrast to GnRH analogues, a small number of studies suggest that gender-affirming hormones result in a reduction of GD [71], depression, and anxiety [71–74] and lead to improvements in quality of life [72, 75]. The use of both GnRH analogue and gender-affirming therapy would complicate any assessment of any of HPA, GH-IGF1, and hypothalamic-pituitary-gonadal axis, making a longitudinal assessment of the biological stress response difficult. Sex hormone treatment has been shown to reverse the sex-dependent regulation on the HPA axis following 3 months of gender-affirming hormone therapy in transwomen and transmen such that oestradiol treatment and testosterone withdrawal increase adrenocorticotropin hormone and cortisol secretion in response to corticotropin-releasing hormone in transwomen and testosterone treatment and oestrogen withdrawal decrease adrenocorticotropin hormone and cortisol secretion in response to corticotropin-releasing hormone in transmen [76].

Clinically, we do observe some of the somatic consequences, described in other models of stress, in the follow-up of young people with GD. The contribution of each GD and medical interventions to these are not clear. Adverse outcomes associated with starting GnRH analogue therapy include emotional lability, changes in body composition, decreased height velocity, decreased bone turnover, and decreased bone mineral density (BMD) [77]. Long-term studies of GnRH analogue therapy in central precocious puberty (CPP) report inconsistent findings on treatment-related weight gain and changes in the body mass index. Both transmale and transfemale youths treated with the GnRH analogue have altered body composition relative to cisgender controls, lower lean mass, and higher fat mass [78, 79]. It is not possible to ascertain whether changes in body composition were related solely to treatment or could in part be related to an outcome of chronic stress. Children treated with GnRH analogue therapy for both CPP and GD have diminished bone mineral accrual during treatment [80, 81]. Restoration of BMD in late adolescence, after cessation of treatment, has been documented in CPP [82] but not in young people with GD [83]. Again, it is not possible to ascertain whether changes in BMD are related solely to

treatment or could in part be related to an outcome of chronic stress. It is imperative that future research establishes the longitudinal impact of GnRH analogue therapy but also defines any impact of GD itself through assessments completed prior to and during any intervention.

The use of GnRH analogue therapy is a relatively novel model, thus there is uncertainty whether this pathway leads to individual satisfaction with minimal risk of regret. In addition, concerns have been expressed by healthcare professionals and public that once young people enter this treatment path, they will continue, even if they no longer identify as having GD [69, 84]. A legal complaint lodged against the NHS Gender Identity Development Service in England initially ruled that a person under the age of 16 years would not be competent to give consent to the administration of GnRH analogue treatment, owing to a judgement that they would not have the capacity to understand the long-term risks and uncertainties of treatment [85]. The court also concluded that medical treatment is yet innovative and experimental, in respect of young persons aged 16 years and over, and therefore, clinicians should seek authorization of the court prior to commencing medical treatment [85]. This ruling has subsequently been overturned in an appeal brought forward by the NHS, England. It has been decided that it is more appropriate for clinicians to judge on an individual's capacity to consent to treatment than the high court [86]. These judgements bring to light the complex nature of GnRH analogue treatment and the need to carefully assess the capacity and understanding in young people and their parents/guardians.

Monitoring during treatment with the GnRH analogue should focus on achieving the goals of treatment, whilst preventing or identifying unwanted side effects. During treatment, young people should be reviewed by a paediatric endocrinologist to confirm the efficacy of treatment and the halting of pubertal progression. Ongoing psychological review and support appointments are essential to confirm the persistence of GD and to ensure that suppression of puberty has a psychological benefit for the young person. The uncertainties regarding the effect of puberty suppression on bone health, on growth and adult height, the psychosocial problem of delayed puberty, and possible effects on brain development require regular monitoring of efficacy and safety of the treatment. If the expectations of treatment are not met or if there is a failure to comply with assessments and monitoring, the MDT should review the treatment plan and on consultation with the young person, consider discontinuation of the GnRH analogue [8].

Impact of Medical Interventions on Fertility and Fertility Preservation

A discussion with young people and their families on the consequences of hormonal treatment on fertility is imperative. The discussion will be influenced by the stage of puberty, the birth-assigned sex, and the availability and acceptance of assisted reproductive technologies.

Before starting treatment with GnRH analogue therapy, sperm and oocyte retrieval and banking can be offered to those who are post-pubertal. Young people who commence treatment with the GnRH analogue at Tanner stage 2 and continue to gender-affirming hormones will achieve neither spermatogenesis nor menarche and will therefore not have the opportunity to bank gametes using cryopreservation. If individuals subsequently want to preserve fertility after having started the GnRH analogue, it may take 6 months or more for the reproductive axis to recover, and the reproductive capacity will only be the same as at the point of starting treatment [3].

A majority of young people, after appropriate informed consent, opt not to proceed with fertility preservation despite this service being fully funded in the national health system [8]. There appears to be incongruent numbers of those individuals who wish to have children in the long-term and those who pursue fertility preservation [87, 88]. The reasons behind the poor uptake are largely unknown but are likely related to the young person's prioritization of medical treatment to halt transition. The broader societal shift to parenthood later in life is also relevant to the decisions made by young transgender people regarding fertility preservation options [87, 89]. In this regard, young people are asked to consider the potential of parenthood at an earlier point than their peers and often within the context of less sexual activity than peers. The current reported experience of transgender people with fertility preservation services are mostly negative, and [90] thus, it is essential to identify the barriers the transgender young people face and make the service easier to approach [64, 91, 92].

Future Directions

There is a paucity of research validating a similar stress model for GD as seen in anorexia nervosa, post-traumatic stress disorder, and exercise. Most studies, to date, have focused on the resultant minority stress of having a transgender or gender-diverse identity rather than the specific experience of GD itself. Measures of GD should be included in any future research on transgender individuals.

It would be important to establish if other endocrine axes (gonadal, thyroid, and growth), in addition to the HPA axis, are affected in GD to the same extent as other existing stress models as no prospective studies have yet been published on the long-term impacts of GD in childhood and adolescence. A greater understanding of the impact of GD on biological outcomes will guide clinicians in planning health surveillance, to be cognizant of the potential behavioural and somatic consequences of chronic stress, and to provide screening for possible long-term risks of osteoporosis, cardiovascular disease, obesity, and metabolic syndrome.

There are uncertainties around assessing the benefit from both medical and psychological interventions. Identifying a suitable biomarker of stress could provide additional valuable information, to other measures of GD, of the effects of treatment longitudinally. If measurement is accessible and acceptable to the young people, a biomarker could be a useful adjunct to existing psychological assessments, in a clinical setting, to support the initiation, continuation, or cessation of psychological and medical interventions.

We should be aware of the stress incurred by young people attending both the GD service, for medical and psychology appointments, and referrals for fertility preservation. Discrimination and the fear of being viewed as different may prevent transgender young people from attending the clinic, whilst at the clinic; young people may experience additional anxieties relating to clinical examination corresponding to struggles with body image. Clinicians and clinic staff should work together to provide safe environments for young people to help build self-confidence and reduce anxiety over time. Clinicians should be mindful of the power imbalance that can exist between the patient and clinician and take steps to manage this with their relationship with each young person. Young people should be consulted regularly to help bring improvements to the clinic and referral pathways.

The input from key personnel with specialist knowledge in GD has become more pertinent, owing to the growth in clinic numbers, the complexity of individual cases, the need for a unified approach towards treatment, and the uncertainties around the current clinical approach and the long-term outcome [93, 94]. In addition to providing optimal care, a specialist centre caring for young people with GD should gather data on outcomes to be shared in multicentre registries with the aim of resolving the current uncertainties. This can be aided with the development of national clinical networks, whose remit should be to ensure the provision of equitable state-

of-the-art service for all young people in a region through structured referral pathways. In cases where there is uncertainty at a regional level, there is a need to create links and form international collaborations with experts in GD.

Outside the clinic environment, there are many other settings in daily life that have the potential to evoke stress in young people. Schools, colleges, places of employment, and leisure and sports facilities have a responsibility to enforce anti-discrimination policies to allow transgender young people to feel safe. These policies should be publicized to be more inclusive and welcoming. Health services have a role along with transgender support organizations to provide departments of social work, education, and employment more information and guidance to facilitate such inclusivity. On a societal level, all efforts to create an environment that is inclusive, integrated, and positive for and about all gender non-conforming and gender-diverse people are likely to have a positive effect as a public health measure.

Conclusion

The model of stress is an attractive scaffold on which to base our understanding of the psychological and biological response to GD in young people. We have presented the limited evidence for both the biological and psychological stress response to GD in young people. Fu-

ture studies should define the impact of GD on behavioural and somatic consequences to establish if it behaves similarly to other models of stress and has similar associations with deleterious long-term health. Gaining further understanding of the impact of GD as a stressor in young people will allow a new perspective on how best to manage young people and monitor interventions.

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Author Contributions

A. Mason and A. Kyriakou were responsible for drafting sections – Introduction, GD and the Biological Stress Response, Clinical Management, Future Directions, and Conclusion. E. Crowe, B. Harragan, and S. Smith were responsible for drafting sections – GD and psychological stress in childhood and adolescence and GD and the Biological Stress Response. A. Kyriakou was responsible for the curation of the manuscript. All the authors extensively reviewed the manuscript. All the authors read and approved the final manuscript.

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