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Psychosexual effects resulting from delayed, incomplete, or absent puberty

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Abstract

Puberty is a remarkable period of postnatal development culminating in reproductive capacity. Biological changes of puberty are accompanied by social and emotional changes including psychosexual development. Developmental changes of adolescence are influenced by numerous biological, psychological, and social influences. Work to date has identified associations between disrupted puberty (i.e. delayed, incomplete, or absent) and psychosexual development. This brief review summarizes our current understanding of the psychosexual effects of delayed puberty and congenital hypogonadotropic hypogonadism (Kallmann syndrome). The importance of psychosocial support and transitional care is highlighted, and future directions are discussed.

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Introduction

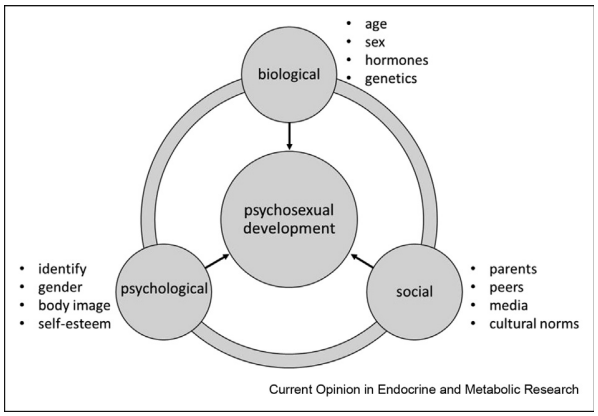
Puberty is a striking period of human development marked by neuroendocrine activation of the hypothalamic–pituitary–gonadal (HPG) axis and culminating in full reproductive capacity [1]. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from specialized hypothalamic neurons triggers the release of luteinizing hormone and follicle-stimulating hormone (FSH) from the gonadotropes in the anterior pituitary. Circulating gonadotropins stimulate the gonads for gametogenesis and production of sex steroids. Testosterone and estradiol are the primary drivers of developing secondary sexual characteristics. The timing of pubertal onset is variable and is influenced by both genetic and environmental factors [2]. Notably, the HPG axis is transiently active during the first six months of neonatal life — termed minipuberty. Circulating sex steroid levels approximate normal adult levels during minipuberty [3]. The physiologic purpose of minipuberty remains to be fully elucidated, yet it appears to play a role in priming the reproductive axis for future fertility [4].

Adolescence is the term used to describe the period of physical and psychological development bridging childhood and adulthood. Adolescence is generally considered to begin with the onset of puberty and is characterized by cognitive, psychological, emotional, and sociocultural changes as youths progressively take on new adult roles. An important aspect of adolescence is psychosexual development that includes changes in sexual desire (libido), arousal, behavior, and function [5]. Psychosexual development is influenced by numerous biological, psychological, and social factors (Figure 1). Accordingly, disrupted (i.e. delayed, incomplete, or absent) puberty and consequent psychosocial sequelae can affect psychosexual development.

Delayed puberty

The first outward sign of puberty is testicular enlargement in males and the appearance of Tanner II breast buds in females. Timing of pubertal onset is variable [6,7]. Delayed puberty is statistically defined as occurring in 2.5% of the population, and males are disproportionately affected [8]. Clinically, delayed puberty in males is marked by testicular volume <4 mL by the age of 14 years and absence of Tanner II breast buds by the age of 13 years in females. Studies examining psychosocial aspects of delayed puberty (i.e. self-esteem, psychopathology, and risky behavior) have focused on the adolescent period. As summarized in a recent review by Zhu and Chan [9], early studies suggested that late-developing boys/girls tend to have more negative beliefs and attitudes about themselves. However, later work indicated this phenomenon is largely driven by short stature rather than delayed puberty *per se*. Notably, the psychological effects of delayed puberty appear to be sexually discordant. Females do not appear to have any

Figure 1



Factors influencing psychosexual development. Schematic depicting diverse biological, psychological, and social factors playing a role in psychosexual development. Inputs form each of these interacting factors can either promote or inhibit a healthy sexual identity and sexual function.

lasting consequence of later menarche [10–12]. In contrast, late-maturing boys have increased body dissatisfaction — primarily related to lack of muscle development [13]. Male body dissatisfaction decreases as appearance becomes more aligned with peers [14] — yet internalized psychological morbidity appears to remain heightened. Psychosocial and psychosexual issues include body image concerns, low self-esteem, depression, and later sexual activity [9,15–17]. Furthermore, delayed puberty is also associated with peer stress and social isolation [8]. Many late-maturing adolescents experience victimization or bullying — experiences that can contribute to depression and mental health problems in adulthood [18]. Cumulatively, these data suggest that delayed puberty in boys is associated with a variety of biological, psychological, and social factors affecting psychosexual development (Figure 1). Importantly, longitudinal data are lacking to determine if psychosexual problems related to delayed puberty persist into adulthood.

Individuals with delayed puberty will eventually initiate and complete puberty. In contrast, patients with congenital hypogonadotropic hypogonadism (CHH) do not progress through puberty spontaneously. Without treatment, patients remain in a state of arrested or absent pubertal development. This extreme phenotype provides a lens to understand how disrupted puberty affects psychosexual development.

Congenital hypogonadotropic hypogonadism

CHH is caused by deficient GnRH secretion or action and clinically manifests as incomplete/absent puberty and infertility [19]. The term Kallman syndrome (KS) describes CHH with anosmia (absent sense of smell). More than 40 loci have been found to underlie CHH/KS, and digenic and oligogenic forms have been described [20]. There is a striking sex discordance in CHH. Approximately, four males are diagnosed for each female case [19]. Importantly, patients with CHH require sex steroid treatment (i.e. testosterone, estradiol) to develop secondary sexual characteristics. Specialized hormone therapies such as gonadotropin therapy (i.e. human chorionic gonadotropin [hCG] + FSH) or pulsatile GnRH therapy via a microinfusion pump can stimulate fertility in 70–80% of cases [21]. However, despite the availability of effective treatments, there is evidence that simply normalizing serum sex steroid levels does not fully ameliorate psychosocial and psychosexual problems [22].

Studies have documented that at the time of diagnosis, male patients exhibit diminished health-related quality of life (HR-QoL) and increased depressive symptoms and anxiety compared with age-matched controls [23,24] (Table 1). After six months of testosterone replacement therapy (TRT) (250 mg of Sustanon q 3 weeks), patients showed improvement in a number of HR-QoL domains, patients exhibited decreased depression/anxiety, and their sexual function was similar to age-matched controls. However, patient scores remained significantly lower that controls in terms of physical role difficulty, emotional role difficulty (mental health), vitality/energy, and satisfaction with general health — and social function remained impaired [23]. Lasaite et al [36] undertook a longer, two-year study. The 19 young men exhibited impaired psychological and social HR-QoL before starting TRT (1,000 mg of testosterone undecanoate q 10–14 weeks). Unfortunately, HR-QoL scores did not significantly improve after two years of treatment (Table 1). Thus, although TRT is effective in ameliorating many of the physical aspects of hypogonadism, it does not seem to fully ameliorate psychological and social aspects of HR-QoL.

A Japanese study of men (n = 31) receiving two years of gonadotropin therapy (hCG + FSH) showed significant improvements in nearly all HR-QoL domains [25]. Notably, patients exhibited normal physical function, physical role, emotional role, vitality, and general health SF-36 (36-item Short Form Survey) scores — all domains unaffected by 6 months of TRT in the study by Aydogan et al [23]. It is important to note that gonadotropin therapy (hCG + FSH) induces testicular growth and fertility — whereas TRT does not. Interestingly, investigators noted the greatest HR-QoL improvements in men who developed sperm in their ejaculate [25]. Cumulatively, these findings underscore the complex interplay of factors affecting HR-QoL and psychosexual well-being. Qualitative interviews with men with CHH point to the important psychological aspect of testicular development that results from fertility-inducing

treatment [26]. Furthermore, even when fertility is not an immediate objective, data support that increased testicular size from gonadotropin therapy (or pulsatile GnRH) seems to mitigate some of body image concerns that can affect psychosexual development in males with CHH. This notion underscores the importance of shared decision-making when selecting treatment as patients may desire testicular development although not actively seeking fertility.

A number of cross-sectional studies have identified impaired HR-QoL as well as increased depressive symptoms and anxiety among men and women with CHH [26–32] (Table 1). These data span numerous countries and suggest that the impact of CHH on psychosexual development is not solely the result of frankly hypogonadal sex steroid levels [22]. Despite the variety of instruments used to assess HR-QoL, depression, and anxiety, the results are strikingly similar. The one exception is a recent Greek study (25 males, 13 females) that found lower anxiety among patients with CHH than among controls [30]. This disparate finding may reflect the limited control group (n = 38) that may not be representative of the general population.

Studies have largely found sexual function in men with CHH to be similar to controls. In contrast, women with CHH seem to differ from controls in several domains of validated sexual function questionnaires (Table 1). Such findings suggest that available general instruments may not be responsive to CHH-specific issues around sexuality and sexual function. Notably, two studies have examined psychosexual aspects in males and females using questions that were co-created with a patient organization [26,32]. Quantitative patient survey data and subsequent qualitative focus group discussions provide evidence of CHH effects on self-esteem, body image, and psychosexual development [26,33]. The findings support the notion that the discordance between chronological age and appearance poses significant barriers for seeking/initiating intimate relationships and sexual activity. Indeed, studies on the largest cohorts to date (n = 101 males, n = 55 females) reveal intimate relationships are 'very difficult' for 70% of males and 59% of females [26,32]. A recent Greek study identified women with CHH on treatment (n = 13) had lower sexual desire than controls [30]. Similarly, a small Spanish study (n = 14) indicated decreased desire, lubrication, orgasm, and increased pain with sexual intercourse among women with CHH — yet 80% had been sexually active [31]. Larger studies indicate that females with CHH are more likely to have ever been sexually active compared to male counterparts (89% vs. 74%, respectively, $p < 0.05$), [32]. In a large cohort of men with CHH (n = 101), more than a quarter of men (26%) had never been sexually active — five times the rate of an age-matched population–based sample [26]. Interestingly, a Finish study demonstrated that men who lacked early HPG activation of minipuberty (i.e. severe CHH as evidenced by cryptorchidism and/or micropenis) had the lowest rates of sexual activity [27]. Androgens have traditionally been the treatment of choice for micropenis [19]. However, there is growing attention to gonadotropin therapy during minipuberty to stimulate penile and testicular growth and potentially prime the reproductive axis for improved fertility later in life [34]. To date, there are no data examining treatment during minipuberty for psychosexual development — yet this is an intriguing area for investigation.

In late-maturing boys, body dissatisfaction and body shame diminishes over time as the gap in physical development with peers shrinks [14]. Patients with CHH are often not diagnosed until late adolescence or early 20s [22]. Thus, body dissatisfaction and body shame appear to persist — often with lasting consequences on psychosexual development. Indeed, body image concerns are pervasive in men with CHH, with 93% of males and 80% of females reporting body shame. Similarly, low self-esteem, shame, feeling 'left behind,' and social isolation are prevalent [16,18,30]. Like delayed puberty, victimization and bullying is not uncommon for patients with CHH — often with corrosive effects on psychological health. In total, 72% of males and 56% of females report having been bullied. Such experiences likely contribute to increased anxiety and depression [26,32,33]. The constellation of emotional and psychological factors has negative effects on psychosexual development that last well into adulthood. Diagnosing CHH is challenging and is a diagnosis of exclusion [19,21]. Patients often undergo a 'diagnostic odyssey,' resulting in late diagnosis and delays in initiating treatment [22]. Earlier identification of CHH and timely initiation of treatment to induce secondary sexual characteristics in line with peers may be an important avenue in improving psychosocial outcomes for patients [22,35].

Support and transitional care

There are ample data supporting that disrupted puberty can have negative consequences on psychosexual development. In congenital disorders (i.e. CHH/KS), clinical management is appropriately focused on hormone replacement and mitigating associated medical problems. However, merely correcting hypogonadal sex steroid levels does not fully ameliorate psychosocial morbidity associated with CHH [23,36]. Patients often struggle with psychosocial aspects of living with a chronic condition as well as the consequences on sexuality and HR-QoL [22,37]. The psychological toll of CHH often manifests in depression and anxiety (Table 1). Unfortunately, depression and anxiety are often under-recognized by clinicians [28,32]. Comprehensive care for CHH should include ongoing assessment of psychosocial well-being and appropriate referrals for psychological counseling as needed. Typically,

Table 1

Studies examining quality of life, depression/anxiety, and sexual function in congenital hypogonadotropic hypogonadism (CHH).

Study	Sample	Age (years)	Reference group	Instruments			Findings
				QoL	dep/anx	sex	
Treatment naïve							
Aydogan et al. [23]	39	22 ± 2	40 controls	SF-36	BDI BAI	ASEX	HR-QoL: ↓ physical function, role-physical, role-emotional, vitality, general health Depression: ← depression and anxiety compared with controls Sex: impaired sexual function compared with controls
Lasaite et al. [24]	34	29 ± 11	34 controls	WHO	POMS	–	HR-QoL: ↓ psychological and social QoL compared with controls Depression: ← depression-dejection, fatigue-inertia, and confusion-bewilderment
After initial treatment							
Aydogan et al. [23]	39	22 ± 2	40 controls	SF-36	BDI BAI	ASEX	6 months of TRT: HR-QoL: improvements yet several domains remained lower vs. controls (role-physical, role-emotional, vitality, general health); social function remained impaired. Depression/anxiety: symptoms improved (similar to controls) Sex: function improved with TRT (like controls)
Lasaite et al. [36]	19	31 ± 13	pre-post	WHO	POMS	–	2 years of TRT: HR-QoL and Depression: no changes after 2 years of treatment
Shiraishi et al. [25]	31	27 ± 9	Population-based	SF-36	–	–	2 years of hCG + FSH: HR-QoL ← to normal range (role-emotional, mental health, vitality, general health), but not social function
Males on long-term treatment							
Varimo et al. [27]	30	Median = 38 (16–61)	Population-based	15D	15D	15D	Depression: ← depression and distress (27% with anxiety/depression diagnosis) Sex: those with absent minipuberty had lowest rates of sexual activity
Dwyer et al. [26,28]	101	37 ± 11	Community base rates	IPQ-R	SDS	Co-created	HR-QoL: CHH had significant emotional impact and negative consequences Depression: ← mild/moderate/severe symptoms (64% with symptoms) Sex: body shame = 93%, difficulty with intimacy = 70%, never sexually active = 26% (5 times the rate in controls); focus groups: absent puberty had lasting psychosexual effects.
Mileski et al. [29]	8	Median = 23 (17–45)	16 controls	WHO	–	–	HR-QoL: not different from controls
Georgopoulos et al. [30]	38[a]	31 ± 10	38 controls	WHO	HADS	IIEF FSFI	HR-QoL: ↓ general health satisfaction Depression: ↓ anxiety compared with controls Sex: males (n = 25), no differences compared with controls; females (n = 13), ↓ sexual desire
Females on long-term treatment							
Ros et al. [31]	21[b]	34 ± 9	41 controls	SF-36	–	FSFI	HR-QoL: ↓ physical function, ← bodily pain Sex: ↓ sex function (arousal, lubrication, orgasm, and pain)
Dzemaili et al. [32]	55	35 ± 10	Community base rates	IPQ-R	SDS	Co-created	HR-QoL: CHH had significant emotional impact and negative consequences Depression: ← mild/moderate/severe symptoms (55% with symptoms) Sex: body shame = 80%, difficulty with intimacy = 58%

Age expressed as mean ± SD, unless noted as median (range).
15D, 15-dimensional survey; ASEX, Arizona Sexual Experiences Scale; BAI, Beck's Anxiety Inventory; BDI, Beck's Depression Inventory; Co-created, instrument co-created with the patient's organization; dep/anx, depression and anxiety instruments; FSFI, Female Sexual Function Index; FSH, follicle-stimulating hormone; HADS, Hospital Anxiety and Depression Scale; hCG, human chorionic gonadotropin, HR-QoL, health-related quality of life; IIEF, International Index of Erectile Function; IPQ-R, Illness Perception Questionnaire-Revised; POMS, Profile of Mood States; SD, standard deviation; SDS, Zung Self-rating Depression Scale; sex, sexuality instruments; SF-36, 36-item Short Form Survey; TRT, testosterone replacement therapy, WHO-Bref, WHO Quality of Life-Bref.
[a] Study combined males with CHH (n = 25) and females with CHH (n = 13) in the analysis.
[b] Study included a mixed population of patients with CHH (n = 14) and 46XX gonadal dysgenesis (n = 7).

CHH is initially evaluated and diagnosed in adolescence or early adulthood. A challenge for clinicians in managing such chronic endocrine disorders is to ensure continuity of care for adolescents and young adults [38]. Transition refers to the planned, purposeful movement of young adults from pediatric to adult-oriented care. Structured transitional care is gaining increasing attention in the field of endocrinology. Care coordination is challenging, given the multiple disciplines involved and the different cultures and attitudes of pediatric and adult care delivery [39]. Several recent publications review transitional care needs for patients with CHH [38,40] and underscore the importance of assessing and attending to psychosexual development. However, psychosexual development in CHH is influenced by wide-ranging biological (i.e. hypogonadal hormone levels), psychological (i.e. body shame, low self-esteem), and social (i.e. cultural body ideals, bullying) factors (Figure 1). Given this complexity, taking a holistic approach often involves collaboration and referral with specialists in psychology, psychiatry, and sex therapy.

Conclusions

Human sexual development is a dynamic process. The activation of the HPG axis and hormonal changes of puberty interact with psychological and social influences on psychosexual development. There is growing attention to psychosexual effects of disrupted puberty and a mounting evidence base. However, many questions remain unanswered (Box 1). Future research directions may include mechanistic studies to elucidate mini-puberty and longitudinal studies to examine if

Box 1. Unanswered questions and future research directions.

Minipuberty
- What is the mechanism(s) by which minipuberty affects future fertility?
- Can hormonal therapy during minipuberty optimize fertility potential in CHH?

Delayed puberty
- Do the psychosocial and psychosexual affects of delayed puberty persist into adulthood?
- Does sex steroid treatment for delayed puberty affect psychosexual development?

Timing of diagnosis
- Can earlier detection and timely initiation of sex steroid therapy improve psychosexual functioning in patients with CHH?

Transitional care
- What is the optimal model for structuring multidisciplinary transitional care, and support?
- Can structured transitional care improve psychosexual outcomes for patients with chronic endocrine disorders?

psychosocial effects of delayed puberty persist into adulthood. Similarly, natural history studies (i.e. patient registries) could help elucidate the impact of timing of diagnosis/treatment initiation. Hormonal treatment has been proposed to treat individuals with absent minipuberty [34]. Appropriately powered, multicenter, controlled trials are needed to evaluate the long-term effect of hormonal treatment during minipuberty on future fertility and psychosexual patient-reported outcomes. Increasing attention is being given to structured approaches to transitional care in endocrinology. To date, it remains unclear how to best organize coordinated multidisciplinary transitional care and if structured approaches promoting continuity of care positively affect psychosexual outcomes. Sexuality is an important aspect of HR-QoL, and attention to psychosexual development is part of comprehensive endocrine care.

Conflict of interest statement

Nothing declared.

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