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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.

Keywords

delayed puberty; hypogonadotropic hypogonadism; Kallmann syndrome; minipuberty; quality of life; transitional care

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 (LH) 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 (T) and estradiol (E2) 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

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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 a 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 occurring in 2.5% of the population and males are disproportionately affected (8). Clinically, delayed puberty in males is marked by testicular volume <4mL by age 14 and absence of Tanner II breast buds by age 13 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 by 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 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). Further, 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 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

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 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. T, E2) to develop secondary sexual characteristics. Specialized hormone therapies such as gonadotropin therapy (i.e. human chorionic gonadotropin + follicle stimulating hormone, hCG+FSH) or pulsatile GnRH therapy via 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 to age-matched controls (23, 24) (Table 1). After six-months of testosterone replacement therapy (TRT) (Sustanon 250mg Q 3wks.), patients had improved a number of HR-QoL domains, exhibited decreased depression/anxiety and their sexual function was similar to age-matched controls. However, patients remained significantly lower 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 and colleagues undertook a longer, two-year study. The 19 young men exhibited impaired psychological and social HR-QoL prior to starting TRT (testosterone undecanoate 1,000mg Q 10–14 wks.). Unfortunately, HR-QoL scores did not significantly improve after two years of treatment (Table 1). Thus, while TRT is effective for 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 scores – all domains unaffected by 6-months of TRT in the study by Aydogan and colleagues (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 wellbeing. Qualitative interviews with CHH men point to the important psychological aspect of testicular development that results from fertility-inducing treatment (26). Further, 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 even though 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 the impact of CHH on psychosexual development is not solely the result of frankly hypogonadal sex steroid levels (22). Despite the variety of instruments employed to assess HR-QoL, depression and anxiety, results are strikingly similar. The one exception is a recent Greek study (25 males, 13 females) that found lower anxiety among CHH patients compared to controls (30). This disparate finding may reflect the limited control group (n=38) that may not be representative of the general population.

Studies in men with CHH have largely found sexual function in CHH men 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). 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 in 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 study 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%, $p<0.05$) (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 on 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 20’s (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 in 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 have negative effects on psychosexual development that lasting 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 to 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 frankly hypogonadal sex steroid levels does not fully ameliorate the 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 wellbeing and appropriate referrals for psychological counseling as needed. Typically, 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 and hormonal changes of puberty interact with psychological and social influences on psychosexual development. There is growing attention to the psychosexual effects of disrupted puberty and a mounting evidence base. However, many unanswered questions remain (Inset Box 1). Future research directions may include mechanistic studies to elucidate minipuberty and longitudinal studies to examine if 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.

References

1. Herbison AE. Control of puberty onset and fertility by gonadotropin-releasing hormone neurons. *Nat Rev Endocrinol*. 2016;12(8):452–66. [PubMed: 27199290]
2. Howard SR. Genetic regulation in pubertal delay. *J Mol Endocrinol*. 2019;63(3):R37–R49. [PubMed: 31394496]
3. Mason KA, Schoelwer MJ, Rogol AD. Androgens during Infancy, Childhood, and Adolescence: Physiology and use in clinical practice. *Endocr Rev*. 2020.** This recent review provides a comprehensive summary of the role of androgens in development from in utero through puberty.
4. Lanciotti L, Cofini M, Leonardi A, Penta L, Esposito S. Up-To-Date Review About Minipuberty and Overview on Hypothalamic-Pituitary-Gonadal Axis Activation in Fetal and Neonatal Life. *Front Endocrinol (Lausanne)*. 2018;9:410. [PubMed: 30093882] ** This review provides an comprehensive, up-to-date summary of studies on minipuberty.
5. Fortenberry JD. Puberty and adolescent sexuality. *Horm Behav*. 2013;64(2):280–7. [PubMed: 23998672]
6. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–12. [PubMed: 9093289]
7. Herman-Giddens ME, Steffes J, Harris D, Slora E, Hussey M, Dowshen SA, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. *Pediatrics*. 2012;130(5):e1058–68. [PubMed: 23085608]
8. Palmert MR, Dunkel L. Clinical practice. Delayed puberty. *N Engl J Med*. 2012;366(5):443–53. [PubMed: 22296078]
9. Zhu J, Chan YM. Adult Consequences of Self-Limited Delayed Puberty. *Pediatrics*. 2017;139(6).** This is a comprehensive and up-to-date review providing a concise summary of the consequences of delayed puberty on long-term health and wellbeing.
10. Day FR, Elks CE, Murray A, Ong KK, Perry JR. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. *Sci Rep*. 2015;5:11208. [PubMed: 26084728]
11. Opoliner A, Carwile JL, Blacker D, Fitzmaurice GM, Austin SB. Early and late menarche and risk of depressive symptoms in young adulthood. *Arch Womens Ment Health*. 2014;17(6):511–8. [PubMed: 25048175]
12. Galvao TF, Silva MT, Zimmermann IR, Souza KM, Martins SS, Pereira MG. Pubertal timing in girls and depression: a systematic review. *J Affect Disord*. 2014;155:13–9. [PubMed: 24274962]
13. Baker JH, Higgins Neyland MK, Thornton LM, Runfola CD, Larsson H, Lichtenstein P, et al. Body dissatisfaction in adolescent boys. *Dev Psychol*. 2019;55(7):1566–78. [PubMed: 30985163]
14. de Guzman NS, Nishina A. A longitudinal study of body dissatisfaction and pubertal timing in an ethnically diverse adolescent sample. *Body Image*. 2014;11(1):68–71. [PubMed: 24331829]
15. Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, et al. Public health implications of altered puberty timing. *Pediatrics*. 2008;121 Suppl 3:S218–30. [PubMed: 18245514]
16. Michaud PA, Suris JC, Deppen A. Gender-related psychological and behavioural correlates of pubertal timing in a national sample of Swiss adolescents. *Mol Cell Endocrinol*. 2006;254–255:172–8.

17. Negri SS EJ Pubertal Timing, Depression, and Externalizing Problems: A Framework, Review, and Examination of Gender Differences. *Journal of Research on Adolescence*. 2011;21(3):717–46.
18. Sweeting JA, Garfin DR, Holman EA, Silver RC. Associations between exposure to childhood bullying and abuse and adulthood outcomes in a representative national U.S. sample. *Child Abuse Negl*. 2020;101:104048. [PubMed: 31945515]
19. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol*. 2015;11(9):547–64. [PubMed: 26194704]
20. Maione L, Dwyer AA, Francou B, Guiochon-Mantel A, Binart N, Bouligand J, et al. GENETICS IN ENDOCRINOLOGY: Genetic counseling for congenital hypogonadotropic hypogonadism and Kallmann syndrome: new challenges in the era of oligogenism and next-generation sequencing. *Eur J Endocrinol*. 2018;178(3):R55–R80. [PubMed: 29330225]
21. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamaki J, et al. Clinical Management of Congenital Hypogonadotropic Hypogonadism. *Endocr Rev*. 2019;40(2):669–710. [PubMed: 30698671]
22. Dwyer AA, Smith N, Quinton R. Psychological Aspects of Congenital Hypogonadotropic Hypogonadism. *Front Endocrinol (Lausanne)*. 2019;10:353. [PubMed: 31333578]
23. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, Basaran Y, et al. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. *Endocr J*. 2012;59(12):1099–105. [PubMed: 22972022] * This interventional study reports findings on the effects of 6-months treatment on 39 young men with CHH.
24. Lasaitte L, Ceponis J, Preiksa RT, Zilaitiene B. Impaired emotional state, quality of life and cognitive functions in young hypogonadal men. *Andrologia*. 2014;46(10):1107–12. [PubMed: 24313565]
25. Shiraishi K, Oka S, Matsuyama H. Assessment of quality of life during gonadotrophin treatment for male hypogonadotropic hypogonadism. *Clin Endocrinol (Oxf)*. 2014;81(2):259–65. [PubMed: 24612103]
26. Dwyer AA, Quinton R, Pitteloud N, Morin D. Psychosexual development in men with congenital hypogonadotropic hypogonadism on long-term treatment: a mixed methods study. *Sex Med*. 2015;3(1):32–41. [PubMed: 25844173] * This study reports findings on the psychosexual effects of CHH in the largest CHH cohort male cohort to date.
27. Varimo T, Hero M, Laitinen EM, Sintonen H, Raivio T. Health-related quality of life in male patients with congenital hypogonadotropic hypogonadism. *Clin Endocrinol (Oxf)*. 2015;83(1):141–3.
28. Dwyer AA, Tiemensma J, Quinton R, Pitteloud N, Morin D. Adherence to treatment in men with hypogonadotropic hypogonadism. *Clin Endocrinol (Oxf)*. 2017;86(3):377–83. [PubMed: 27647266]
29. Mileski KSL, Bottaro M, Grossi-Porto LG, Lofrano-Porto A. Health-related physical fitness and quality of life in men with congenital hypogonadotropic hypogonadism. *Andrologia*. 2018.
30. Georgopoulos NA, Armeni AK, Stamou M, Kentrou A, Tsermpini EE, Iconomou G, et al. Gonadotropin-releasing hormone (GnRH) deficiency under treatment: psychological and sexual functioning impacts. *Hormones (Athens)*. 2018;17(3):383–90. [PubMed: 30168087]
31. Ros C, Alobid I, Balasch J, Mullol J, Castelo-Branco C. Turner's syndrome and other forms of congenital hypogonadism impair quality of life and sexual function. *Am J Obstet Gynecol*. 2013;208(6):484 e1–6. [PubMed: 23313313]
32. Dzemaili S, Tiemensma J, Quinton R, Pitteloud N, Morin D, Dwyer AA. Beyond hormone replacement: quality of life in women with congenital hypogonadotropic hypogonadism. *Endocr Connect*. 2017;6(6):404–12. [PubMed: 28698240] * This study reports findings on the psychosexual effects of CHH in the largest CHH cohort female cohort to date.
33. Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for

- online interventions and peer-to-peer support. *Orphanet J Rare Dis.* 2014;9:83. [PubMed: 24915927]
34. Kohva E, Huopio H, Hietamaki J, Hero M, Miettinen PJ, Raivio T. Treatment of gonadotropin deficiency during the first year of life: long-term observation and outcome in five boys. *Hum Reprod.* 2019;34(5):863–71. [PubMed: 31067328] ** This manuscript provides a summary of studies using gonadotropin therapy in minipuberty and reports initial outcome data on a cohort of patients treated during minipuberty.
35. Swee DS, Quinton R. Congenital Hypogonadotrophic Hypogonadism: Minipuberty and the Case for Neonatal Diagnosis. *Front Endocrinol (Lausanne).* 2019;10:97. [PubMed: 30846970]
36. Lasaitė L, Ceponis J, Preiksa RT, Zilaitienė B. Effects of two-year testosterone replacement therapy on cognition, emotions and quality of life in young and middle-aged hypogonadal men. *Andrologia.* 2017;49(3). * This interventional study reports findings on the effects of 2-years treatment on 19 males with CHH.
37. Garrido Oyarzun MF, Castelo-Branco C. Sexuality and quality of life in congenital hypogonadisms. *Gynecol Endocrinol.* 2016;32(12):947–50. [PubMed: 27809610]
38. Dwyer AA, Phan-Hug F, Hauschild M, Elowe-Gruau E, Pitteloud N. TRANSITION IN ENDOCRINOLOGY: Hypogonadism in adolescence. *Eur J Endocrinol.* 2015;173(1):R15–24. [PubMed: 25653257]
39. Dwyer AA, M Translational Care in Endocrinology In: Betz CC I, editor. *Transition from Pediatric to Adult Healthcare Services for Adolescents and Young Adults with Long-term Conditions.* 1st ed. New York, NY, USA: Springer Nature; 2019.
40. Dwyer AA, Pitteloud N. Transition of Care from Childhood to Adulthood: Congenital Hypogonadotropic Hypogonadism. *Endocr Dev.* 2018;33:82–98. [PubMed: 29886503]

Inset 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?

Figure 1. Factors influencing psychosexual development

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

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

Table 1.

study	sample	age (yrs.)	reference group	instruments:			findings
				QoL	dep/anx	sex	
Treatment naïve							
Aydogan et al. (2014) #23	39	22 ± 2	40 controls	SF-36	BDI BAI	ASEX	HR-QoL: ↓ physical function, role-physical, role-emotional, vitality, general health Depression: depression & anxiety compared to controls Sex: impaired sexual function compared to controls
Lasiate et al. (2014) #24	34	29 ± 11	34 controls	WHO	POMS	-	HR-QoL: ↓ psychological & social QoL compared to controls Depression: depression-dejection, fatigue-inertia & confusion-bewilderment
Post initial treatment							
Aydogan et al. (2014) #23	39	22 ± 2	40 controls	SF-36	BDI BAI	ASEX	6 mos. 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. (2016) #36	19	31 ± 13	pre-post	WHO	POMS	-	2 yrs. TRT: HR-QoL & Depression: no changes post 2yrs treatment
Shiraishi et al. (2014) #25	31	27 ± 9	population-based	SF-36	-	-	2 yrs. 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. (2014) #27	30	Med. 38 (16–61)	population-based	15D	15D	15D	Depression: depression & distress (27% with anxiety/depression diagnosis) Sex: those with absent minipuberty had lowest rates of sexual activity
Dwyer et al. (2015 & 2016) #26, #28	101	37 ± 11	community base rates	IPQ-R	SDS	Co-created	HR-QoL: CHH hadsignificant emotional impact & negative consequences); Depression: mild/moderate/severe symptoms (64% with symptoms); Sex: body shame=93%, difficulty with intimacy=70%, never sexually active=26% (5X rate in controls); Focus Groups: absent puberty had lasting psychosexual effects
Milleski et al. (2017) #29	8	Med. 23 (17–45)	16 controls	WHO	-	-	HR-QoL: not different from controls
Georgopoulos et al. (2018) #30	38*	31 ± 10	38 controls	WHO	HADS	IIEF FSFI	HR-QoL: ↓ general health satisfaction Depression: ↓ anxiety vs. controls Sex: Males (n=25) no differences vs. controls, females (n=13) ↓ sexual desire
Females on long-term treatment							
Ros et al. (2013) #31	21 [†]	34 ± 9	41 controls	SF-36	-	FSFI	HR-QoL: ↓ Physical function, bodily pain Sex: ↓ sex function (arousal, lubrication, orgasm & pain)
Dzemailli et al. (2017) #32	55	35 ± 10	community base rates	IPQ-R	SDS	Co-created	HR-QoL: CHH hadsignificant emotional impact & negative consequences); Depression: mild/moderate/severe symptoms (55% with symptoms) Sex: body shame = 80%, difficulty with intimacy = 58%

Age shown as mean $\pm$ SD unless noted as median (range); QoL: health-related quality of life instruments; SF-36: 36-Item Short Form Survey; WHO-Brief: WHO Quality of Life-Brief; 15D: 15-dimensional Survey; IPQ-R: Illness Perception Questionnaire-Revised; dep/anx: depression and anxiety instruments; POMS: Profile of Mood States; BDI: Beck's Depression Inventory; BAI: Beck's Anxiety Inventory; SDS: Zung Self-rating Depression Scale; HADS: Hospital Anxiety and Depression Scale; Sex: sexuality instruments; ASEX: Arizona Sexual Experiences Scale; FSFI: Female Sexual Function Index; IIEF: International Index of Erectile Function; Co-created: instrument co-created with patient organization; TRT: testosterone replacement therapy, hCG: human chorionic gonadotropin, FSH: follicle stimulating hormone;

* study combined CHH males (n=25) and CHH females (n=13) in the analysis;

[†] study included a mixed population including CHH (n=14) and 46XX gonadal dysgenesis (n=7).