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Infant Minipuberty: Implications for Adult Reproductive Health

Minipubertad del lactante: implicaciones en la salud reproductiva del adulto

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Abstract

Activity of the central hypothalamic–pituitary–gonadal (HPG) axis occurs in three distinct physiological phases across the human lifespan. The initial activation takes place during fetal development, followed by a transient postnatal reactivation in early infancy known as "minipuberty," and a third, sustained activation, beginning at puberty. Once initiated at adolescence, HPG axis activity is maintained throughout adult life. Minipuberty is also observed in mammals including rodents and primates, and is a crucial period of gonadal 'priming', with growth and development of the testes in males and ovarian oocyte maturation in females. Minipuberty is also associated with somatic growth, neural integration in the brain, and potentially has global developmental consequences for lifelong health.

Congenital hypogonadotropic hypogonadism (CHH) is an uncommon inherited condition resulting from impaired secretion or action of hypothalamic gonadotropin-releasing hormone (GnRH). In its most severe forms, CHH is marked by the absence of GnRH pulsatility during all three developmental phases. Failure of fetal HPG axis activation leads to genital anomalies in approximately half of affected male neonates, most commonly presenting as micropenis and/or cryptorchidism. In these infants, the additional absence of postnatal minipuberty further exacerbates testicular underdevelopment. This impaired maturation is reflected by a reduced population of Sertoli cells, which are essential for establishing normal spermatogenic potential later in life. Consequently, disruption of minipuberty is likely to have long-term adverse effects on fertility in affected males. Despite the phenotypic implications in males, CHH frequently goes unrecognized in infancy, and even when identified, there is currently no standardized approach to early treatment. The current data regarding female minipuberty is more limited, and the implications for adult reproductive or non-reproductive health are therefore unclear in females.

This lecture outlines the normal physiology of minipuberty and the impact of central HPG axis dysfunction, proposes strategies for early diagnosis, and examines existing therapeutic approaches aimed at replacing minipuberty in male infants with CHH. Evidence from systematic reviews of clinical series suggests that gonadotropin therapy designed to replicate minipuberty may promote testicular descent and normalize testicular and penile growth. In addition, early hormonal replacement may have broader benefits, addressing both reproductive development and non-reproductive consequences associated with disrupted HPG axis activity.

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Introduction

Minipuberty refers to a brief developmental window in early human infancy marked by increased

gonadal activity. It represents the second phase of hypothalamic-pituitary-gonadal (HPG) axis activation, following the initial activation during fetal life and preceding the permanent reactivation that begins at puberty. From approximately two weeks after birth, pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus increases in both frequency and amplitude, stimulating pituitary release of luteinising hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins drive gonadal maturation and sex steroid synthesis. In male infants, this period of HPG axis activity typically persists until around six months of age, whereas in females it may continue for up to two years after birth[1].

In males, minipuberty plays an essential role in normal sexual development[2]. It contributes to masculinisation of the external genitalia, including increases in penile size, maturation of the scrotum, and completion of testicular descent in infants born with unilateral or bilateral cryptorchidism. Inguinoscrotal descent of the testes is androgen-dependent and regulated by insulin-like peptide 3 (INSL3), along with endogenous testosterone stimulated by either pituitary-derived or exogenous LH, or human chorionic gonadotropin (hCG). This developmental window is also crucial for testicular cellular maturation, stimulating both Leydig and Sertoli cell populations. FSH action during minipuberty promotes expansion of germ cells and Sertoli cells, establishing the cellular foundation necessary for spermatogenesis later in life. Although Sertoli cells proliferate in response to FSH at this stage, they remain functionally immature because they lack androgen receptor expression, with differentiation occurring later under the influence of intratesticular testosterone[3]. As a result of these processes, healthy male infants demonstrate rising levels of anti-Müllerian hormone (AMH) and inhibin B, which serve as markers of Sertoli cell mass and functional capacity.

Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic condition with an estimated prevalence of approximately 1 in 10,000 male births. The clinical manifestations observed in male infants with CHH reflect deficient GnRH secretion and subsequent gonadotropin insufficiency during both prenatal and postnatal development. Early in fetal life, testicular testosterone production is driven primarily by placental hCG, meaning that infants with CHH typically do not present with disorders of sex development such as ambiguous genitalia or hypospadias. However, during the latter half of gestation, when pituitary gonadotropins become the dominant regulators of testicular function, insufficient HPG axis activity may lead to incomplete testicular descent and reduced virilisation of the phallus. After birth, male neonates with CHH exhibit characteristically low concentrations of LH, FSH, testosterone, AMH, and inhibin B during the minipuberty period, supporting the diagnosis when micropenis and/or cryptorchidism (undescended testis or testes) are present. Increasingly, infants born to parents with known CHH are being identified due to successful fertility treatments, enabling earlier clinical assessment. In many centres, access to genetic testing through targeted gene panels or whole exome sequencing allows molecular confirmation of CHH in suspected cases.

In male neonates, the presence of cryptorchidism and micropenis (defined as a stretched penile length > 2.5 standard deviations below the age-adjusted mean) may indicate inadequate activation of the gonadotropic axis during fetal development[4]. CHH (or Kallmann syndrome if associated with olfactory bulb aplasia/hypoplasia and anosmia) is an important underlying diagnosis to consider for infants with this clinical picture. Despite its clinical significance, CHH remains under-recognized, and timely intervention during infancy may confer long-term benefits, particularly in severe cases[5].

Treatment Strategies

Management of cryptorchidism traditionally involves observation for spontaneous testicular descent followed by surgical orchidopexy if required, while micropenis is commonly treated with topical or intramuscular testosterone. However, while leading to penile growth, administration of testosterone alone will have no effect on testicular growth or development. More recently, for male infants with CHH, attention has shifted toward the use of gonadotropin therapy as a means of replicating physiological minipuberty[6].

Gonadotropin-based treatments, such as recombinant human (rh) FSH in combination with rhLH or urinary or rhhCG, are well established within fertility services for the induction of spermatogenesis in men with CHH. More recently, these therapies have also emerged as a potential approach for initiating pubertal development in adolescents and young adults with CHH[7]. The available evidence indicates that gonadotropin therapy is generally effective and well tolerated in this population, although variability between studies limits the strength and generalisability of these findings. Despite increasing adoption of gonadotropin regimens for pubertal induction, testosterone replacement therapy continues to be the most commonly prescribed treatment for inducing puberty in males with CHH. However, delayed or incomplete initiation of hormone replacement during adolescence or adulthood carries recognised limitations, including potential effects on somatic growth, neurocognitive development, and psychological wellbeing[8].

In male infants with CHH, gonadotropin-induced mini-puberty has been shown in a recent systematic review of the published literature to promote increases in penile and testicular size and, in many cases, facilitate spontaneous testicular descent[9]. By promoting

gonadal maturation during this early postnatal period - through expansion of the Sertoli cell population and stimulation of endogenous testosterone synthesis - early intervention is anticipated to enhance later responsiveness to fertility treatments and improve the likelihood of successful spermatogenesis. In addition, LH or hCG mediated stimulation of testicular descent may eliminate the need for surgical orchidopexy in male infants with CHH-associated cryptorchidism. However, the available evidence regarding gonadotropin administration during minipuberty in male infants with CHH remains insufficient to draw firm conclusions about its long-term benefits for reproductive capacity or broader non-reproductive outcomes.

Conclusion

Advancing knowledge in this field, particularly with respect to long-term fertility outcomes following gonadotropin replacement during minipuberty, will depend on the generation of robust longitudinal datasets. Although randomised controlled trials examining gonadotropin therapy in infancy would represent the ideal study design to define optimal timing, dosing strategies, and long-term efficacy, achieving this will necessitate close collaboration among international centres. Standardised clinical guidelines for diagnosis and management, alongside comprehensive and accessible electronic registries capable of capturing long-term follow-up data, are essential components of this effort.

In support of these aims, we have recently established clinical practice recommendations addressing diagnostic pathways and early hormonal replacement in male infants with CHH[6], and developed a dedicated electronic registry for individuals with hypogonadotropic hypogonadism across all age groups and causes (I-HH; the fourth module within the SDM registry framework). Beyond reproductive outcomes, the broader consequences of absent minipuberty remain poorly understood. Substantial further research is required to clarify how gonadotropin exposure during this critical developmental window may influence neurodevelopment, psychosocial functioning, mental health, and other systemic outcomes, including cardiovascular health.

The critical role of early recognition in CHH should be emphasised. Timely diagnosis enables clinicians to offer appropriate therapeutic interventions during infancy, optimise supportive care for patients and their families, and reduce the risk of prolonged diagnostic delay extending into adolescence or adulthood. Early identification also empowers patients and families to participate in informed decision-making and to guide care from childhood through the transition into adult services.

References

1. Johannsen, T.H., et al., *Sex Differences in Reproductive Hormones During Mini-Puberty in Infants With Normal and Disordered Sex Development*. J Clin Endocrinol Metab, 2018. 103(8): p. 3028-3037.

2. Busch, A.S., et al., *Dynamic Changes of Reproductive Hormones in Male Minipuberty: Temporal Dissociation of Leydig and Sertoli Cell Activity*. J Clin Endocrinol Metab, 2022. 107(6): p. 1560-1568.

3. Rey, R.A., et al., *Ontogeny of the androgen receptor expression in the fetal and postnatal testis: its relevance on Sertoli cell maturation and the onset of adult spermatogenesis*. Microsc Res Tech, 2009. 72(11): p. 787-95.

4. Stancampiano, M.R., et al., *Congenital Micropenis: Etiology And Management*. J Endocr Soc, 2022. 6(2): p. bvab172.

5. Nordenstrom, A., *Potential impact of mini-puberty on fertility. Ann Endocrinol* (Paris), 2022. 83(4): p. 250-253.

6. Rohayem, J., et al., *Mini-Puberty, Physiological and Disordered: Consequences, and Potential for Therapeutic Replacement.* Endocr Rev, 2024.

7. Alexander, E.C., et al., *Gonadotropins for pubertal induction in males with hypogonadotropic hypogonadism: systematic review and meta-analysis*. Eur J Endocrinol, 2024. 190(1): p. S1-S11.

8. Dwyer, A.A., N. Smith, and R. Quinton, *Psychological Aspects of Congenital Hypogonadotropic Hypogonadism*. Front Endocrinol (Lausanne), 2019. 10: p. 353.

9. Rhys Evans, S., et al., *Gonadotropin therapy for mini-puberty induction in male infants with hypogonadotropic hypogonadism: a systematic review*. J Clin Endocrinol Metab, 2024.