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Gonadotrophin replacement for induction of fertility in hypogonadal men

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Congenital hypogonadotrophic hypogonadism (CHH) is a rare form of infertility caused by deficient secretion or action of gonadotrophin-releasing hormone. There is no consensus regarding the optimal approach to fertility treatment in CHH men. In most cases, appropriate hormonal treatment with human chorionic gonadotrophin with or without follicle stimulating hormone will induce testicular development, spermatogenesis and fertility. Recent studies have examined sequential treatment with FSH pre-treatment to optimize fertility outcomes in severely affected CHH patients. This paper reviews historical and recent literature to summarize the current evidence on therapeutic approaches for CHH men seeking fertility.

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Introduction

The episodic secretion of gonadotrophin-releasing hormone (GnRH) from specialized hypothalamic neurons is a key neuroendocrine regulator of the human reproductive axis [1]. Pulsatile GnRH stimulates the secretion of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary which in turn triggers testicular development in males as well as testosterone production and reproductive capacity (i.e. spermatogenesis). Accordingly, developmental disorders disrupting the GnRH network can result in congenital hypogonadotrophic hypogonadism (CHH) – a rare condition clinically characterized by absent or partial puberty and infertility [2,3]. In contrast to primary testicular disease, CHH is characterized by hypogonadotropic hypogonadism, and is usually a treatable form of male infertility. However, approaches to induce fertility in these men vary and optimal regimens have yet to be definitively determined. Thus, the focus of this review will be to provide physiologic context for gonadotrophin replacement and summarize the current evidence on therapeutic approaches for CHH men seeking fertility.

The reproductive axis

In humans, the activity of GnRH-induced gonadotrophin secretion changes throughout development. GnRH neurons originate from the olfactory placode and migrate along olfactory guidance fibers to reach the arcuate nucleus of the hypothalamus before birth [2]. In early male fetal life (weeks 10–15) maternal hCG drives the testicular production of testosterone (T) that spurs growth of the phallus and early testicular descent [4]. Then, from the second half of fetal life T production is stimulated via endogenous GnRH-induced LH secretion from the pituitary. This phase is critical for final inguinoscrotal testicular descent and phallic growth. The hypothalamic-pituitary-gonadal (HPG) axis remains active during the first six months of life with hormone levels approaching adult levels [5]. This so-called “mini-puberty” also represents an important window of opportunity to identify CHH among males exhibiting maldescended testes with or without micropenis as low serum T and LH measurement can be utilized to identify congenital GnRH deficiency [6].

The HPG axis appears to be relatively quiescent during childhood yet subtle, important testicular growth occurs as evidenced by studies in primates as well as histologic studies of boys dying in traumatic accidents [7]. The onset of puberty is initially marked by sleep-entrained, pulsatile GnRH-induced LH secretion [8]. The resulting increased serum gonadotrophin and T levels progressively extend into the day as puberty progresses and these hormone dynamics begin a cascade of events culminating in reproductive maturity. The gonadotrophins exert differential effects on the compartments of the testes. Broadly, LH stimulates maturation of the interstitial Leydig cells that secrete T and insulin-like factor 3 (INSL3). Intra-testicular T, in concert with FSH, acts on the Sertoli cells to induce and maintain spermatogenesis. While testosterone's role in male reproduction is well-established, the physiologic role of INSL3 remains unclear yet it is a marker of Leydig cell activity and may have anti-apoptotic effects on germ cells [9].

Follicle stimulating hormone (FSH) is central for development of the tubular compartment, where spermatogenesis occurs. Specifically, FSH stimulates the proliferation of immature Sertoli cells that secrete inhibin B (IB) and antimüllerian hormone (AMH). The FSH-induced proliferation of immature Sertoli cells has far-reaching effects on fertility potential as mature Sertoli cells can support a species-specific number of germ cells [10] and determine final seminiferous tubule length [11,12]. Further, approximately 90% of testicular volume is accounted for by the seminiferous tubules thus testicular volume (TV) is a critical indicator of fertility. AMH is secreted by immature Sertoli cells and is downregulated by T. Accordingly, it is normally high in early puberty and falls with rising serum androgen levels [13,14]. Importantly, during the mini-puberty, Sertoli cells do not express the androgen receptor [15]. Therefore, despite the high intra-testicular T levels induced by LH, Sertoli cells remain immature and so the early neonatal period is a proliferative window for immature Sertoli and germ cells. As puberty progresses, the increasing intra-gonadal T production from the Leydig cells ends the proliferative phase as Sertoli cells mature and the cords develop a lumen noting the transition to tubule, and spermatogenesis is initiated [15]. Notably, T levels at the site of production are much higher than peripheral circulating levels and this is a requisite for spermatogenesis. A fact that was elegantly