

Pubertal induction in prepubertal males with hypogonadotropic hypogonadism: testosterone or gonadotropins?

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Pubertal induction in males with hypogonadotropic hypogonadism (HH) remains challenging. Various treatment strategies using testosterone or gonadotropins have been developed; however, the optimal approach for initiating and sustaining puberty remains uncertain. A comprehensive PubMed search was conducted in July 2024 using the keyword “puberty induction in males” for studies published between January 2004 and July 2024. The inclusion criteria were publication in English including male patients under 18 years of age with HH. Animal studies, adult cohorts, and non-HH groups were excluded. Of the 134 retrieved records, 18 met the inclusion criteria and were analyzed for therapeutic regimens, efficacy, and outcomes. Both testosterone- and gonadotropin-based therapies effectively induced puberty in males with HH. Intramuscular testosterone esters remain the most commonly used approach because of their accessibility and cost-effectiveness, whereas newer long-acting transdermal formulations offer improved tolerability. Gonadotropin-based regimens, including human chorionic gonadotropin, alone or in combination with follicle-stimulating hormone, demonstrated effective virilization and increased testicular growth and spermatogenesis, suggesting potential benefits for future fertility. However, treatment protocols vary widely and no standardized guidelines are currently available. Pubertal induction in HH should aim to mimic physiological puberty and consider psychological and somatic well-being as well as future fertility potential. Although testosterone effectively promotes virilization, gonadotropin therapy enhances testicular development and spermatogenesis. Their formulations, dosages, treatment durations, and modes of administration show considerable heterogeneity. Further multicenter studies are required to establish optimal regimens and clarify long-term fertility outcomes associated with different therapeutic strategies.

Key words: Delayed puberty, Hypogonadotropic hypogonadism, Follicle-stimulating hormone, Luteinizing hormone, Testosterone

Key message

The pubertal induction process in males still poses a challenge for pediatric endocrinologists. The existing literature is limited, and it is not yet possible to make definitive recommendations. We described the various treatment for this condition and tried to analyze the unresolved questions to address the question posed in the title of our manuscript.

Introduction

The hypothalamic-pituitary-gonadal (HPG) axis is physiologically active during intrauterine life as well as the first 6 months of age, a period known as “minipuberty” in which the rise of gonadotropins along with male sex steroids leads to penile development and testicular descent and growth. However, during this phase of life, the Sertoli cells in the testes do not express androgen receptors; consequently, spermatogenesis does not occur.¹⁾ The role of minipuberty is still not fully understood, but current opinion suggests that this imprinting period for various organic functions has long-term consequences for brain development, body composition, and, ultimately, adult gonadal function.^{2,3)}

Reactivation of the HPG axis occurs at the onset of puberty, traditionally in males at 9–14 years of age. A pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) increases the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and finally stimulates the gonadal function and testosterone production. Clinically, this physiological process is responsible for the increase in testicular volume (TV) ≥ 4 mL and appearance of pubertal signs.

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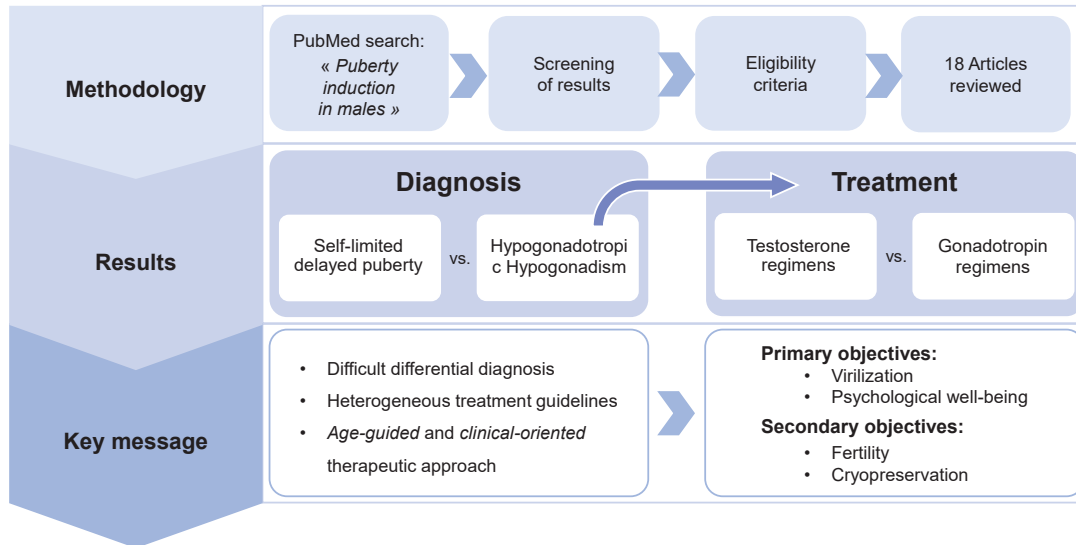
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Graphic abstract. Graphical representation of the methods, results and key messages of our review.

rance of secondary sexual characteristics, with substantial changes in the organism leading to fertility.⁴⁾

Hypogonadotropic hypogonadism (HH) results from deficient GnRH or gonadotropin secretion that leads to diminished or absent male sex steroid gonadal production and, consequently, absent or partial pubertal development. HH is a congenital disorder that may be isolated or comorbid with other pituitary hormone deficits. When combined with olfactory disorders, HH is recognized as Kallmann syndrome. The rarer acquired forms of HH are caused by direct hypothalamic or pituitary damage. Functional HH may occur but is usually due to systemic conditions with a reversible negative effect on the HPG axis.^{5,6)}

In boys with permanent HH, the absence of gonadotropin stimulation during minipuberty and adolescent puberty results in small TV and is frequently associated with micropenis and/or cryptorchidism. Other consequences may include poor bone mass and mineralization, reduced masculinization and sexual function, an impaired pubertal growth spurt, psychological distress, and ultimately infertility.⁷⁾ The prevention of these sequelae represents the aim of pubertal induction therapy in males with HH and usually consists of testosterone prescription. The main outcome of this treatment is virilization; however, it has no effect on testicular development or spermatogenesis. A wide range of strategies for inducing puberty has emerged for boys with permanent HH. In fact, in this group of patients, the possibility of future fertility has increased interest in the use of single or combined gonadotropin treatment, which can stimulate testosterone elevation and promote gamete production, improving adolescent

patients' self-confidence and psychological well-being.⁸⁾ However, a scientifically proven indication for the most effective pubertal induction treatment in HH remains unavailable.

In this narrative review, we report recent therapeutic regimens available for pubertal induction in males with HH and identify the unresolved issues that require addressing.

Methods

In July 2024, we searched PubMed using the keyword "puberty induction in males." We included studies published in the last 20 years (January 2004 to July 2024) and applied the following filters: English publication, human study, and only male subjects. The initial search yielded a total of 134 articles. The results were screened using the following criteria: (1) focus on pubertal induction in males under 18 years of age; and (2) pubertal induction in HH. Further screening of the retrieved titles excluded 104 of them for the following reasons: animal study (n=2), female subjects (n=2), adult subjects (n=3), off-topic study design (n=89), and focus on pubertal induction in clinical conditions other than HH (n=8). Articles for which full-text retrieval was not available were excluded (n=8). A full-text review of the remaining articles eliminated 4 more due to case report design (n=2) or lack of focus on HH (n=2). Thus, a total of 18 articles were included in this review (Fig. 1).

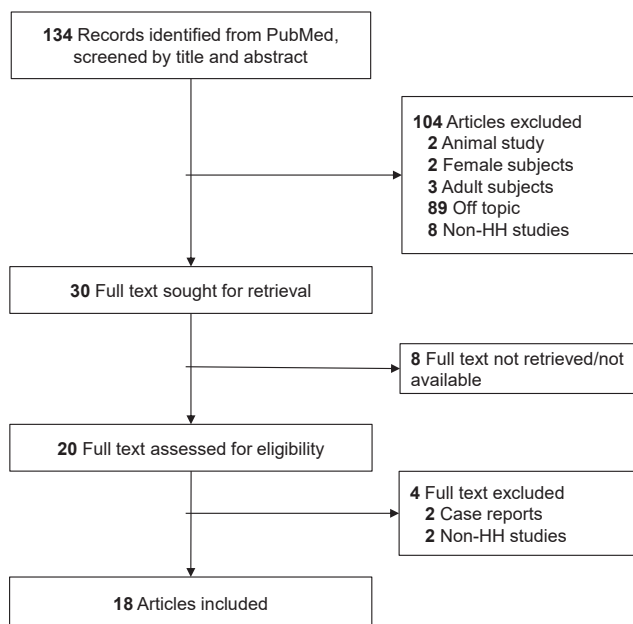


Fig. 1. Flow diagram of the search strategy and selection process used to identify articles suitable for inclusion in this review.

Results

1. Timing of pubertal induction

Regardless of the underlying cause of hypogonadism, pubertal induction should replicate natural physiological processes and promote the development of secondary sexual characteristics, linear growth achievement, and psychological well-being. For boys who show no signs of puberty by the age of 14 years, evaluations (such as bone age, blood examinations, and basal hormonal screening) should be conducted to determine whether pharmacological intervention is necessary. In contrast, in individuals with indicators or conditions suggestive of permanent hypogonadism (i.e., anosmia, deafness, cryptorchidism, and microphallus), pubertal induction often begins before 12 years of age or even earlier. Unfortunately, aside from rare cases in which a medical history suggestive of HH or genetic confirmation is available, no specific markers can reliably differentiate between self-limited delayed puberty (SLDP) and HH. Therefore, in individuals with delayed puberty and diagnostic uncertainty, the initiation of puberty is generally delayed from 14 years of age until late adolescence. The decision should always be tailored to suit the patient's preferences and clinical condition, in consultation with their parents.^{9,10}

2. Testosterone: formulations and regimens

Different testosterone formulations and treatment regimens have been suggested over the years, with many studies focusing on various strategies for using testosterone

to manage HH in adults. However, there is a noticeable lack of research directly comparing these protocols; moreover, no comprehensive evidence-based guidelines have been established. This is particularly evident in children and adolescents, for whom only a limited number of formulations have been tested and even fewer were approved for inducing puberty.

In an analysis of the selected studies, intramuscular (IM) injections of testosterone esters were the preferred strategy for inducing puberty owing to their relatively low cost and simple administration. In most cases, pubertal induction has been observed with intermediate-acting testosterone esters (enanthate or cypionate)¹¹⁻¹⁴ or a mixture of long- and short-acting testosterone esters.¹¹ Formulations for IM injections are most commonly used in pediatric patients because the small doses needed for induction are difficult to administer with other formulations.¹³ Many proposed regimens start treatment with 50–100 mg every 4–6 weeks^{12,15-17} and gradually increase the dose to 50–100 mg every 6–12 months. An adult dosage of 150–250 mg/2–4 weeks is reached within 18–36 months.^{9,10,12,16} Owing to their suboptimal pharmacokinetics leading to wide serum level fluctuations,¹⁴ a slow increase in therapeutic doses is advisable for a more natural mimicking of physiological puberty to maximize the growth spurt and allow psychosexual maturation and the adaptation to physical changes.¹⁶ In contrast, puberty can be induced with a more rapid increase in testosterone levels in patients who seek medical attention in late adolescence, because achieving the final adult height is no longer a priority.¹⁰

A long-acting IM formulation of testosterone undecanoate (TU) ester was recently developed in which the androgen is embedded in an oily compound that allows for prolonged release into the bloodstream, thereby reducing the number of injections and stabilizing serum fluctuations.¹⁴ A 2011 study of older prepubertal adolescents by Giagulli et al.¹⁸ showed the effectiveness of this parenteral formula in promoting pubertal development, although initial priming with oral TU was necessary to ensure a more physiologically progressive increase in testosterone levels. In the proposed regimen, after a short 3-month course with oral TU, 1,000 mg of the long-acting IM ester was administered every 6 weeks for the first 2 injections and then once every 14–12 weeks for the first 1–2 years. Compared with previous IM treatment schemes, fewer injections may improve compliance among adolescent patients, making it a more tolerable treatment. In parallel, its fixed dosage and prolonged half-life hinder the progressive rise of hematic testosterone levels with a hypothetical risk in younger boys with precocious growth plate maturation, limiting its use in older HH patients.^{10,14} Therefore, this formulation could be an efficient alternative to other strategies for long-term use in

adolescents and young adults after puberty.

Despite the existence of many therapeutic schemes and considerable clinical experience, especially in boys with SLDP, no universally accepted formal guidelines have been established for pubertal induction using parenteral testosterone esters in males with HH.

Implantable testosterone preparations in the form of testosterone pellets were among the earliest formulations and are effective and convenient for long-term testosterone delivery.¹²⁾ However, their use in pubertal induction has not yet been studied. Several authors agree that serum testosterone levels produced by this approach might be excessively high for the gradual androgen increase required for pubertal induction; however, it could still offer a safe and tolerable option for lifelong maintenance therapy.^{11,14)}

Another existing testosterone formulation is oral TU, which is absorbed through the lymphatic system and bypasses liver inactivation, thus allowing the administration of smaller doses than older oral molecules. Oral TU has demonstrated efficacy for inducing the maturation of secondary sex features, although its use is limited by inconsistent oral bioavailability, a short half-life, and serum fluctuations.^{10-12,14)} The suggested dosage would start at 40 mg every other day for 3 months and then increase in frequency for 6-12 months before switching to higher doses of 80-120 mg daily within 18-24 months.¹⁰⁾ Despite being more accepted owing to its painless administration, the requirement for multiple daily doses and sensitivity to the lipid content of meals or fasting state make it an unreliable treatment strategy.^{11,12)}

Recently, new oral TU soft capsules, which allow the solubilization and absorption of testosterone without requiring fat-rich meals, have been developed, but no studies have been conducted in prepubertal boys aged <18 years.¹⁴⁾

Other testosterone formulations, such as transdermal patches or gels, are widely used as replacement therapies in postpubertal hypogonadal males; however, their use in pediatric patients is extremely limited. Some experience with daily low doses of testosterone gel (2%) was derived from trials involving patients with SLDP. The benefits of gels include their noninvasive form and availability at low

doses. Furthermore, transdermal absorption bypasses the first-pass metabolism, thereby reducing the risk of hepatic toxicity associated with IM formulations.^{10,14)} Disadvantages include low acceptance among adolescents owing to the need for daily applications and the risk of accidental transfer to others.^{14,19)} Thus, no such formulation has been approved for pubertal induction.¹¹⁻¹³⁾

Finally, modern strategies include the use of intranasal testosterone gels and subcutaneous testosterone esters. Their effectiveness and safety as hormonal replacement therapies have been demonstrated in some trials in adults; however, no studies to date have examined pubertal induction in adolescents.^{10,14)}

Table 1 summarizes the current approaches to using testosterone for pubertal induction in hypogonadal boys.

3. Gonadotropins: formulations and regimens

Several treatment strategies using exogenous gonadotropins have been developed over the past 2 decades. However, to date, only a few randomized studies have evaluated the effectiveness of this approach versus testosterone analogs, making it challenging to determine which regimen is superior or more commonly preferred.⁹⁾

Gonadotropins have been studied as stand-alone and combination treatments, with administration consistently performed via subcutaneous self-injections. FSH, responsible for Sertoli cell proliferation, is present in different preparations, including recombinant human FSH (rhFSH) and human urinary FSH (uFSH), and can be highly purified.¹⁰⁾ A more recent recombinant gonadotropin, corifollitropin alfa (CFA), is a proposed alternative to the above-mentioned FSH formulations.²⁰⁾ Human chorionic gonadotropin (hCG), which has the biological activity of LH but a longer half-life, stimulates Leydig cells to produce endogenous testosterone and increases intratesticular testosterone levels concurrent with FSH to achieve spermatogenesis.¹⁹⁾ Similar to FSH, hCG is available in urinary and recombinant forms.

Unfortunately, only a few of the studies that have explored the use of gonadotropins to induce puberty were prospective multicenter trials or retrospective analyses,

Table 1. Current testosterone types and regimens used for pubertal induction

Formulation	Pubertal induction	Maintenance	Advantages	Side effects
Intramuscular (IM) (T enanthate, cypionate or mixture of T esters)	25-50 mg monthly Increase of 50 mg Every 6-12 m	150-250 mg Every 2-4 wk	Good adherence; most data and clinical experience to support use in adolescents	Not physiological painful
Oral (T undecanoate)	40 mg alternate day or daily	40-80 mg 2-3 times daily	Oral; pain free	Multiple doses needed per day; variable absorption
Transdermal (T gel)	2%: 0.5 g 10 mg T/day	2%: 2-4 g 40-80 mg T/day	Mimics normal physiology; pain free	Potential transfer to another indi- vidual
Subcutaneous (T cypionate)	25 mg subcutaneous every alternate week	50-70 mg subcutaneous every week	Less painful than IM; can be admini- stered at home	Lack of data in hypogonadal boys

T, testosterone.

whereas most were reviews. As shown in Table 2, these studies differed in terms of subject age, which ranged from children to young adults, follow-up duration, and treatment approaches, including the use of hCG alone or combined with FSH.

In 2007, Raivio et al.²¹⁾ conducted a retrospective study of 14 boys (aged 9.9–17.7 years) with HH who were first treated with rhFSH alone, followed by combined rhFSH and hCG. The treatment plan involved initial prepubertal priming with rhFSH (1.5 IU/kg 3 times per week for 2 months to 2.8 years depending on the starting age), followed by pubertal induction through the addition of hCG (500–4,000 IU, 1–3 times per week). The rhFSH priming led to increased TV (0.9 ± 0.7 mL to 1.8 ± 1.1 mL, $P < 0.005$) and inhibin B levels (27 ± 14 pg/mL to 80 ± 57 pg/mL, $P < 0.01$), indicating the proliferation of immature Sertoli cells. Additional increases in both measures were observed in 13 patients after hCG introduction. Boys with a history of absent postnatal activation of the HPG axis had a weaker rhFSH-induced increase of TV and required longer treatment durations (≥ 1 year), suggesting that minipuberty plays a key role in later testicular response to gonadotropins. Despite initially small TV, 6 of the 7 boys who provided semen samples achieved spermatogenesis, highlighting the positive impact of rhFSH priming on testicular function.²¹⁾

A 2010 review by Yin and Swerdloff¹²⁾ of hypogonadism treatment in younger males reported that, in 1999, Barrio et al.²²⁾ achieved normal sexual maturation and significant increases in TV in a group of prepubertal males with HH treated with hCG and FSH administered on alternating days.

An observational study conducted in Australia in 2012 by Zacharin et al.²³⁾ in 2 groups of adolescents/young adults (aged 14.5–31.0 years) treated with hCG alone (500 IU twice/wk increased to 1,500 IU twice/week as puberty progressed) or combined with rhFSH (150–300 IU 3 times per week from the fourth month of the higher hCG dose). Similar Tanner-stage progression and TV increases were observed in both groups (2–8 mL to 3–30 mL, $P = 0.24$ in group 1; 2–8 mL to 8–50 mL, $P = 0.11$ in group 2), with no statistically significant differences in inhibin B or testosterone levels. However, a semen analysis revealed minimal evidence of spermatogenesis at 9 months in 3 of 9 patients treated with hCG alone (range, 0 to $<1 \times 10^6$ /mL); in contrast, all patients who received combination therapy achieved spermatogenesis by 9 months (range, 0.2 – 15×10^6 /mL). This study showed convincing data that combined hCG and FSH treatment, in contrast to hCG monotherapy, in adolescents with HH can lead to testicular growth and may accelerate spermatogenesis within a time frame comparable to that of normal puberty.²²⁾

A further investigation of this treatment strategy was

conducted by Rohayem et al.²⁴⁾ in 2017 in a relatively large group of adolescents with HH from 26 pediatric endocrinology centers throughout Germany. The patients were divided into 2 groups based on whether they had previously received testosterone replacement therapy. Testosterone-naïve adolescents received low starting doses of hCG (250–500 IU twice weekly) in increments of 250–500 IU every 6 months (maximum 2,500 IU/3 times a week), and rhFSH (75–150 IU/3 times a week) was added once serum testosterone reached the targeted pubertal level (1.5 ng/mL). Boys previously treated with testosterone who had already completed pubertal virilization and linear growth received an initial full adult starting dose of hCG in 6-month increments (range, 1,500 IU 2 times weekly to maximum 2,500 IU 3 times weekly), with the addition of the same regimen of rFSH after 3 months of therapy.

This treatment led to a substantial increase in final bi-TV (BTV) in both protocol groups (5 ± 5 mL to 34 ± 3 mL vs. 5 ± 3 mL to 32 ± 3 mL) and the induction of spermatogenesis in the vast majority of patients who provided semen samples (91% vs. 95%). This study adds further clinical data to support previous findings that hCG monotherapy promotes testicular growth and spermatogenesis. However, combining hCG with FSH yielded significantly improved outcomes regardless of prior testosterone replacement therapy or underlying cause. The best results were observed in boys with acquired versus congenital HH.²⁴⁾

In this regard, a 2021 retrospective analysis by Cangiano et al.²⁴⁾ of 19 adolescents with congenital HH undergoing pubertal induction showed that combined uFSH (75 IU 3 times per week) and hCG (250–2,000 IU 2 to three times per week) increased BTV and induced spermatogenesis irrespective of prior testosterone priming or FSH pretreatment. In contrast, posttreatment BTV was significantly associated with cryptorchidism at birth. This likely indicates that the lack of HPG axis activation during the fetal and neonatal stages, which impedes the testes from descending, impairs the ability of the testes to respond effectively to exogenous gonadotropin stimulation later in life. Moreover, this study suggested that a positive genetic background accounting for the complete forms of congenital HH may prevent an optimal testicular response to gonadotropin stimulation.

A study from 2022 by Lambert et al.¹⁶⁾ of 19 patients with congenital HH reported that combined treatment with hCG (2,500–5,000 IU per week) and rhFSH (150 IU 3 times per week) could increase TV and induce spermatogenesis, with better results in boys without a history of cryptorchidism.¹⁶⁾

In a multicenter single-group study by Shankar et al.²⁰⁾ conducted from 2017 to 2020, CFA was used with hCG to induce puberty in adolescent boys aged 14–17.9 years with

Table 2. Summary of included trials of gonadotropins

Study	Country	Study design	Population description	Number	Age range (yr)	Pubertal status at baseline	Therapy and duration	Relevant outcomes
Raivio et al. ²¹⁾ 2007	Finland	Retrospective clinical study	Boys with prepubertal onset of hypogonadotropic hypogonadism (idiopathic, Kallmann, pituitary)	14 HH patients: 4/14 CHH (2 KS, 2 IHH); 10/14 MPHD	9.9–17.7	All had prepubertal onset with TV<3 mL	Pretreatment with rhFSH 1.5 IU/kg, 3/wk (180–450 IU/wk) for 2 mo–2.8 yr, with pubertal induction by adding hCG from 500 IU per 2 wk to 4000 IU/wk, 1–3/wk (after the start of combination treatment, in some patients rhFSH was changed to highly purified FSH)	TV increased from 0.9±0.7 mL to 1.8±1.1 mL ($P<0.005$) and inhibin B levels (27±14 to 80±57 pg/mL, $P<0.01$), indicating the proliferation of immature Sertoli cells. Additional increases in both measures were observed in 13 patients after hCG was introduced. 6/7 patients who provided semen samples achieved spermatogenesis (85.7%); 2/2 IHH patients and 1/2 KS patients.
Zacharin et al. ²³⁾ 2012	Australia and India	Observational study	Males with hypogonadotropic hypogonadism (idiopathic, congenital and acquired)	19 HH patients: 11/19 CHH (5 KS); 8/19 MPHD	14.5–31.0: mean group 1: 18.1; mean group 2: 20.9	100% of patients were prepubertal	Group 1 (n=9): hCG alone, initially 500 IU 2/wk with increases to 1,000 IU at 6 mo and as puberty progressed, to 1,500 IU 2/wk. Group 2 (n=10): 500–1,500 IU hCG 2/wk with addition of 150–300 IU recombinant FSH 3/wk (duration: 9–12 mo).	Tanner stage progression and similar TV increases were observed in both groups (2–8 mL to 3–30 mL, $P=0.24$ in group 1; 2–8 mL to 8–50 mL, $P=0.11$ in group 2). All group 2 patients achieved spermatogenesis by 9 mo (0.2 to 15×10^6 /mL) compared with 3/9 patients in group 1 (0 to $<1\times10^6$ /mL)
Rohayem et al. ²⁴⁾ 2017	Germany	Prospective multicenter study	Hypogonadotropic hypogonadism (Kallmann, congenital, MPHD, CHARGE)	60 HH patients: 34/50 prepubertal (group A); 26/50 previously treated with testosterone (group B)	14–22: group A: median 15.5; group B: median 18.8	34/60 (56.7%) were prepubertal or had early arrested puberty with lack of virilization by testosterone	Prepubertal group: 250–500 IU hCG 2/wk, incremental increases every 6 months to max 2500 IU 3/wk+rhFSH 75–150 IU 3/wk added when adequate testosterone level reached (duration: 24±7 mo). Testosterone virilized group: hCG 1,500 IU 2/wk, increase after 6–9 months to max 2,500 3/wk, +rhFSH 75–150 IU 3/wk added after 3 mo. (duration: 22±6 mo)	Final TV increased in both groups (5±5 mL to 34±3 mL vs 5±3 mL to 32±3 mL). Spermatogenesis was achieved in 91% of patients in group A vs 95% of patients in group B who provided semen samples. hCG/FSH therapy induces testes growth and spermatogenesis regardless of prior TRT.
Cangiano et al. ²⁵⁾ 2021	Italy	Retrospective study	Congenital hypogonadotropic hypogonadism	19 CHH patients (7 KS)	14–23 Yr	15/19 BTV <8 mL=78.9%	uFSH 75 IU 3/wk+hCG 250 IU 2–3/wk increased every 6 mo as puberty progressed, max 2,000 IU 2/wk. 13/19 patients received pretreatment of uFSH 75 IU 3/wk for 4 mo before combination. (duration: 24 mo)	BTV at 18–24 mo increased in all patients. Spermatogenesis was obtained in 68.75% of patients who provided semen samples. uFSH+hCG increase BTV and induce spermatogenesis, irrespective of previous TRT or pretreatment with FSH. A positive genetic background (complete CHH forms) prevents optimal testes response to gonadotropins
Shankar et al. ²⁰⁾ 2022	United States	Multicenter single-group study	Adolescent boys with hypogonadotropic hypogonadism (congenital or prepubertally acquired)	17 HH patients (14 KS)	Mean 15.5±0.9	16/17 (94.1%) genital Tanner stage 1	CFA priming 100–150 ug every 2/wk; at week 12, addition of hCG 500–5000 2/wk titrated to testosterone and estrogen levels; (duration 16 mo)	Treatment induced increase in TV (geometric mean fold increase from baseline in TV was 9.43 (95% CI, 7.44–11.97); arithmetic mean of change from baseline at week 64, 13.0 mL), accompanied by pubertal progression, increased T, and pubertal growth spurt. Spermatogenesis was not assessed due to age of patients; inhibin B was used as a surrogate (inhibin B showed mean increase at week 12, maintained through week 64, consistent with proliferation of Sertoli cells).
Lambert et al. ¹⁶⁾ 2022	France	Prospective study (unpublished data)	Congenital hypogonadotropic hypogonadism	19 HH patients	N/A	N/A	rhFSH: 150 IU 3/wk+hCG 2,500–5,000 IU/wk (in 1 or 2 injections). Adaptation of dose to discretion of child's endocrinologist. (duration: 18–24 mo)	11/19 Patients reached Tanner stage ≥G2 (though only 3/19 reached stage G3). TV under hCG reached T goal in 12/19 patients at 12 mo. 50% reached inhibin B goal >100 pg/mL. 75% of patients obtained spermatogenesis at 24 mo despite nonnormalized TV (50% had oligospermia, 3 patients had severe oligospermia).

BTV, bitesticular volumes; CFA, corifollitropin alfa; CHH, congenital hypogonadotropic hypogonadism; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; IHH, idiopathic hypogonadotropic hypogonadism; IU, international unit; KS, Kallman syndrome; MPHD, multiple pituitary hormone deficit; rhFSH, recombinant FSH; uFSH, highly purified urinary FSH; T, testosterone; TRT, testosterone replacement therapy; TV, testicular volume; N/A, not available.

HH. CFA is a recombinant gonadotropin that targets the same FSH receptor as rhFSH but has a half-life that is twice as long. This allows it to be a substitute for a 2 to 3 times per week regimen of rhFSH with just one CFA injection every 2 weeks. The proposed regimen consisted of a 12-week priming phase with subcutaneous CFA alone (100–150 µg every 2 weeks depending on body weight) followed by 52-week combined treatment with CFA at the exact dosage and hCG (500–5,000 IU twice weekly titrated according to testosterone and estradiol levels). This therapy effectively induces testicular growth and pubertal development. Although semen samples were not collected, the observed increase in inhibin B levels and decrease in anti-Müllerian hormone levels indicated that the Sertoli cells shifted from a proliferative to mature state. The authors suggested that CFA could be a viable alternative to rhFSH that offers fewer injections and potentially results in better treatment compliance. The Endo-ERN clinical practice guidelines for pubertal induction in patients with congenital pituitary hormone deficiency report that combined FSH and hCG therapy, particularly when preceded by rhFSH treatment, may be more effective than hCG alone at stimulating testicular growth and spermatogenesis.⁹⁾ However, no definitive conclusions have been reached regarding optimal treatment approaches. Accordingly, a recent systematic review and meta-analysis provided compelling evidence supporting the effectiveness of this therapy, highlighting that the combination of FSH and hCG outperformed hCG alone by increasing TV and improving spermatogenesis rates.²⁶⁾

Table 3 summarizes the proposed gonadotropin regimens for pubertal induction.

4. Emerging therapies

Another treatment approach involves GnRH delivery in a pulsatile manner through a portable minipump. Delemarre-van de Waal²⁷⁾ demonstrated that this method successfully induces virilization and testicular growth, including spermatogenesis, in male adolescents with HH. However, its high cost and troublesome administration make it an infrequently used option for inducing puberty.¹⁰⁾

Finally, kisspeptin-10, a neuropeptide crucial for regulating the HPG axis, has been investigated as a possible therapy for maintaining puberty in adult men with mild hypogonadism. Although this approach is still in the experimental stage and primarily limited to older patients, it may open new avenues for treatment.¹⁷⁾

Discussion

This review highlighted that both gonadotropins and testosterone can induce puberty in males with HH. However, significant heterogeneity in formulations, dosages, duration, and treatment types makes it challenging to draw clear conclusions regarding the optimal approach to pubertal induction.

The heterogeneity of therapeutic approaches to pubertal induction in HH likely reflects the diversity of the underlying disorders, each with a distinct clinical course. In patients with congenital disorders, such as multiple pituitary deficiencies diagnosed in early childhood or before puberty, a structured treatment plan can facilitate the achievement of their genetic growth potential while preventing psychological difficulties compared to their peers. Conversely, in most cases, HH must be differentiated from SLDP. However,

Table 3. Proposed gonadotropin regimen for pubertal induction

Age	No.	First phase therapy dose frequency	Treatment length (mo)	Second phase or unique phase therapy dose frequency		Treatment length (mo)	Reference
				rhFSH / uFSH	hCG		
9.9–17.7	14	rhFSH: 180–450 3/week	2–33.6	rhFSH: 180–450 3/wk	500–4,000 IU 1–3/wk	N/A	21
Groups (14.5–31.0) 1: mean 18.1 2: mean 20.9	19	n=8: testosterone (prior to study)	6–36	1: N/A 2: rhFSH: 150–300 IU 3/wk from the 4th month of higher hCG dose	1: 500 IU 2/wk, increased to 1,000 IU at 6 mo and to 1,500 IU 2/wk as puberty progressed 2: hCG 500–1,500 IU 2/wk, increased every 6 mo as puberty progressed	9–12	22
Groups (14–22) A: mean 15.5 B: mean 18.8	60 34 26	A: hCG: 250–500 IU 2/wk B: testosterone enanthate IM (prior to study)	A: 250–500 IU (increase every 6 mo) B: 18.0–68.4; mean 30	A: rhFSH 75–150 IU 3/wk (max 150 IU) B: rhFSH 75–150 IU 3/wk (max 150 IU)	A: max 2,500 IU 3/wk B: start 1,500 IU 2/wk (max 2,500 IU 3/wk)	24±7 22±6	23
14–23	19	n=13 uFSH: 75 IU 3/wk n=6 testosterone (prior to study)	4	uFSH: 75 IU 3/wk	250–2,000 2–3/wk	24	24
n/a	19	N/A	N/A	rhFSH: 150 IU 3/wk	2,500–5,000 IU wk (in 1–2 injections)	18–24	16
Mean 15.5±0.9	17	CFA: 100–150 µg Every 2 wk	3	CFA: 100–150 µg Every 2 wk	500–5,000 IU 2/wk	13	20

CFA, corifollitropin alpha; hCG, human chorionic gonadotropin; IM, intramuscular; IU, international units; FSH, follicle-stimulating hormone; rhFSH, recombinant FSH; uFSH, highly purified urinary FSH.

no specific markers reliably distinguish between these 2 conditions, as they share overlapping clinical, biochemical, and radiological features, which often leads to diagnostic delays.^{9,17)} Consequently, rapid pubertal induction may be required to prevent psychological problems, bone mass impairments, and other adverse effects on bone health.^{10,12)} Based on our experience, both chronological and bone ages, as well as the underlying disorder, influence the pace of pubertal induction, even when the same regimen is used. In our cohort (unpublished data), therapy was initiated later than the typical pubertal age, as bone age delay, even in congenital cases, justified postponing treatment to maximize the final height.

The choice of treatment type also contributed to heterogeneity. IM testosterone administration has always been favored and shown efficacy, although it may be painful.^{13,14,17)} Testosterone gel recently became an option, offering the advantage of being painless. However, it carries the risk of steroid transfer to others or skin irritation. Moreover, transdermal treatment requires daily administration, whereas IM injections are administered monthly, making the latter easier to manage in younger patients who rely on their parents to transport them to the clinic.¹⁴⁾ The choice of testosterone formulation depends on factors such as patient age and clinical condition, with oral or subcutaneous testosterone being less commonly used. For example, in our experience with a patient with adrenal hypoplasia, neurological impairment made the self-application of transdermal testosterone infeasible. In this regard, monthly treatment can be more easily managed in a child's daily life, even if it is somewhat painful. Therefore, it is important that the family is directly involved in treatment decisions. Careful clinical monitoring is necessary to track treatment outcomes and identify potential side effects such as gynecomastia, erythrocytosis, mood changes, and, in rare instances, priapism.^{9,10,12,16)}

Although previous treatment with testosterone may be associated with a reduced likelihood of conception in patients with HH,²⁸⁾ other authors concluded the fertility can be successfully induced later in life upon transitioning to gonadotropin therapy. Evidence from adult and adolescent cohorts with congenital HH indicates that prior and extended exposure to testosterone neither precludes spermatogenesis nor causes irreversible impairment of spermatogenic capacity once gonadotropin treatment is initiated. In these patients, spermatogenesis rates are 70%–95%, comparable to those observed in testosterone-naïve individuals,^{23–25,29)} suggesting that the delayed initiation of gonadotropin therapy following testosterone-induced puberty does not compromise future fertility potential. Despite these encouraging data, evidence of sperm retrieval and cryopreservation following testosterone monotherapy

remains limited, as most studies report semen parameters only after gonadotropin initiation and do not explicitly document sperm banking outcomes.

Among the several available treatment regimens for gonadotropin therapy (Table 2), the 2 most common methods include starting with hCG and subsequently introducing FSH, or the reverse.^{9,20)} The latter seems preferable because it more closely mimics the physiological stages of puberty of spermatogenesis onset followed by testosterone production; moreover, it may also benefit testicular microarchitecture development.^{9,10,16)} FSH induces the proliferation of immature Sertoli cells and spermatogonia and sustains TV and spermatogenesis,²¹⁾ whereas hCG presents structural and functional homology with human LH and is used to stimulate the production of endogenous testosterone from testicular Leydig cells. Similar to exogenous testosterone, hCG induces virilization, growth spurts, bone maturity, and psychological development.^{16,20)} Finally, high hCG-induced intratesticular testosterone concentrations act in concert with FSH to stimulate germ and Sertoli cell proliferation and maturation, further promoting spermatogenesis.^{10,16,19)} Consensus is lacking on which gonadotropin regimen is most effective for increasing TV or initiating development and spermatogenesis. Similarly, the literature does not provide clear conclusions regarding whether testosterone or gonadotropins are more suitable for pubertal induction in males.^{9,26)} To date, conclusive scientific evidence is lacking that favors one treatment over the other; therefore, current practice relies on clinical experience.

From a pathophysiological perspective, gonadotropins may be more appropriate for achieving the 2 main goals of pubertal induction of complete physical and psychological maturation (virilization) and fertility. In clinical practice, virilization is usually prioritized, with fertility addressed later if and when the patient desires it. Adolescents with HH are typically more affected by delayed puberty and a lack of virilization than by fertility or changes in TV, especially when they differ from their peers.^{20,24)} However, gonadotropin treatment may facilitate fertility later in life,^{19,23)} and pubertal induction with gonadotropins is complete when adequate spermatogenesis and sperm cryopreservation are achieved. In this context, the key role of pediatric endocrinologists in providing patients and their parents with a comprehensive explanation of the benefits and risks of different fertility treatments must be emphasized. The achievement of fertility begins at this age. Although testosterone therapy has been extensively tested and long-term data are available, gonadotropin therapy is relatively new, and longitudinal studies of long-term fertility outcomes and benefits are lacking. Nevertheless, among a small cohort of 15 patients in our center, 92%

of patients preferred this type of treatment despite the higher costs, while >60% had cryopreserved sperms at the end of therapy (unpublished data).

Although fertility outcomes generally improve regardless of specific treatment schedules, success is not universal. Several studies have attempted to identify clinical and biochemical predictors of poor outcomes in gonadotropin-treated males with congenital HH. Data suggest that the presence of cryptorchidism or micropenis, both indicators of impaired minipuberty, is associated with lower TV gain and delayed or incomplete spermatogenesis despite therapy.^{24,25} Similarly, patients with congenital versus acquired HH tend to show smaller increases in TV and lower sperm detection rates.^{23,24} A pretreatment TV <2 mL, undetectable inhibin B levels, and persistently high anti-Müllerian hormone levels are also proposed as markers of limited Sertoli cell responsiveness.²¹ These findings highlight that prior HPG axis activation during fetal and neonatal life, as reflected by normal minipuberty, plays a key role in determining the gonadal response to gonadotropin stimulation. Such subgroup data may explain why, although overall fertility outcomes improve with combined FSH-hCG therapy, success rates remain variable.

Factors such as complexity, cost, duration, and adverse effects must be considered when selecting a treatment. Gonadotropin treatment involves 2 to 3 subcutaneous injections per week for at least 2-3 years. Once full virilization is achieved and sperm cryopreservation is completed, patients may transition to testosterone therapy for long-term maintenance until fertility is achieved. In contrast, testosterone therapy is more practical, consisting of an injection every 2-4 weeks or daily gel application; however, it remains lifelong.^{9,10,26} Consequently, these patients should express their preferences when choosing a treatment. Compliance improves when adolescents are aware of their treatment and family and psychological support are provided.⁹

Open questions and future perspectives

Pubertal induction in males remains a challenge for pediatric endocrinologists. The existing literature is limited and lacks definitive recommendations.

This review highlights the role of age in therapeutic decision-making. The patient's age at diagnosis, along with other factors such as treatment complexity, duration, cost, and potential side effects, should guide the therapeutic approach. This study's primary objective was to minimize the psychological and somatic consequences of HH, with priority given to managing virilization and supporting psychological well-being, especially in older adolescents.

A key unresolved question concerns the early differentiation of HH from SLDP. A prompt diagnosis enables timely pubertal induction and developmental alignment with peers. Another important issue is the optimal treatment approach for pubertal induction since the current practice largely relies on individual clinical experience. Finally, it remains uncertain whether initiating gonadotropin therapy before testosterone treatment improves fertility in males with HH. Further multicenter studies with more uniform patient populations are required to resolve these issues, establish standardized protocols, and address the broader questions posed by this study.

Footnotes

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References

1. Renault CH, Aksglaede L, Wøjdemann D, Hansen AB, Jensen RB, Juul A. Minipuberty of human infancy - a window of opportunity to evaluate hypogonadism and differences of sex development? *Ann Pediatr Endocrinol Metab* 2020;25: 84-91.
2. Galazzi E, Persani LG. Differential diagnosis between constitutional delay of growth and puberty, idiopathic growth hormone deficiency and congenital hypogonadotropic hypogonadism: a clinical challenge for the pediatric endocrinologist. *Minerva Endocrinol* 2020;45:354-75.
3. Tinggaard J, Mieritz MG, Sørensen K, Mouritsen A, Hagen CP, Aksglaede L, et al. The physiology and timing of male puberty. *Curr Opin Endocrinol Diabetes Obes* 2012;19:197-203.

4. Palmert MR, Dunkel L. Clinical practice. Delayed puberty. *N Engl J Med* 2012;366:443-53.
5. Han TS, Bouloux PM. What is the optimal therapy for young males with hypogonadotropic hypogonadism? *Clin Endocrinol (Oxf)* 2010;72:731-37.
6. Raivio T, Miettinen PJ. Constitutional delay of puberty versus congenital hypogonadotropic hypogonadism: genetics, management and updates. *Best Pract Res Clin Endocrinol Metab* 2019;33:101316.
7. Rohayem J, Alexander EC, Heger S, Nordenström A, Howard SR. Mini-puberty, physiological and disordered: consequences, and potential for therapeutic replacement. *Endocr Rev* 2024;45:460-92.
8. Alenazi MS, Alqahtani AM, Ahmad MM, Almalki EM, AlMutair A, Almalki M. Puberty induction in adolescent males: current practice. *Cureus* 2022;14:e23864.
9. Nordenström A, Ahmed SF, van den Akker E, Blair J, Bonomi M, Brachet C, et al. Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency: an Endo-ERN clinical practice guideline. *Eur J Endocrinol* 2022;186:G9-49.
10. Federici S, Goggi G, Quinton R, Giovanelli L, Persani L, Cangiano B, et al. New and consolidated therapeutic options for pubertal induction in hypogonadism: in-depth review of the literature. *Endocr Rev* 2022;43:824-51.
11. Rogol AD. New facets of androgen replacement therapy during childhood and adolescence. *Expert Opin Pharmacother* 2005;6:1319-36.
12. Yin A, Swerdloff R. Treating hypogonadism in younger males. *Expert Opin Pharmacother* 2010;11:1529-40.
13. Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. *Endocrinol Metab Clin North Am* 2009;38:719-38.
14. Chioma L, Cappa M. Hypogonadism in male infants and adolescents: new androgen formulations. *Horm Res Paediatr* 2023;96:581-89.
15. Hamza RT, Deeb A, Al Saffar H, Alani SH, Habeb A. Timing and regimen of puberty induction in children with hypogonadism: a survey on the practice in Arab countries. *J Pediatr Endocrinol Metab* 2020;33:1197-202.
16. Lambert AS, Bouvattier C. Puberty induction with recombinant gonadotropin: what impact on future fertility? *Ann Endocrinol (Paris)* 2022;83:159-63.
17. Wei C, Crowne EC. Recent advances in the understanding and management of delayed puberty. *Arch Dis Child* 2016;101:481-8.
18. Giagulli VA, Triggiani V, Carbone MD, Corona G, Tafaro E, Licchelli B, et al. The role of long-acting parenteral testosterone undecanoate compound in the induction of secondary sexual characteristics in males with hypogonadotropic hypogonadism. *J Sex Med* 2011;8:3471-8.
19. Zacharin M. Pubertal induction in hypogonadism: current approaches including use of gonadotrophins. *Best Pract Res Clin Endocrinol Metab* 2015;29:367-83.
20. Shankar RR, Shah S, Joeng HK, Mendizabal G, DiBello JR, Guan Y, et al. Corifollitropin alfa combined with human chorionic gonadotropin in adolescent boys with hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 2022;107:2036-46.
21. Raivio T, Wikström AM, Dunkel L. Treatment of gonadotropin-deficient boys with recombinant human FSH: long-term observation and outcome. *Eur J Endocrinol* 2007;156:105-11.
22. Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. *Fertil Steril* 1999;71:244-8.
23. Zacharin M, Sabin MA, Nair VV, Dabadghao P. Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis. *Fertil Steril* 2012;98:836-42.
24. Rohayem J, Hauffa BP, Zacharin M, Kliesch S, Zitzmann M. Testicular growth and spermatogenesis: new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? -a multicentre prospective study of hCG/rFSH treatment outcomes during adolescence. *Clin Endocrinol (Oxf)* 2017;86:75-87.
25. Cangiano B, Goggi G, Federici S, Bresesti C, Cotellessa L, Guizzardi F, et al. Predictors of reproductive and non-reproductive outcomes of gonadotropin mediated pubertal induction in male patients with congenital hypogonadotropic hypogonadism (CHH). *J Endocrinol Invest* 2021;44:2445-54.
26. Alexander EC, Faruqi D, Farquhar R, Unadkat A, Ng Yin K, Hoskyns R, et al. Gonadotropins for pubertal induction in males with hypogonadotropic hypogonadism: systematic review and meta-analysis. *Eur J Endocrinol* 2024;190:S1-11.
27. Delemarre-van de Waal HA. Application of gonadotropin releasing hormone in hypogonadotropic hypogonadism--diagnostic and therapeutic aspects. *Eur J Endocrinol* 2004;151 Suppl 3:U89-94.
28. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. *J Clin Endocrinol Metab* 2009;94:801-8.
29. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, Dunkel L, et al. Expert consensus document: European consensus statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 2015;11:547-64.

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