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Comparative efficacy of HCG-based versus testosterone regimens for simulating mini-puberty in infants with congenital hypogonadotropic hypogonadism (CHH)

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Abstract

Background: Mini-puberty is a transient but vital phase of hypothalamic-pituitary-gonadal (HPG) axis activation occurring during the first 3–6 months of life, essential for normal testicular development, Sertoli cell maturation, and future fertility. In infants with congenital hypogonadotropic hypogonadism (CHH), the absence of this activation results in macropains, cryptorchidism, and underdeveloped gonads. Therapeutic simulation of mini-puberty using either testosterone or gonadotropin-based regimens (HCG ± RFSH) is employed to mitigate these deficits, yet comparative data remain limited.

Objectives

This review aims to

- Compare the clinical efficacy of testosterone monotherapy versus HCG-based combination regimens in penile growth, testicular volume, and testis descent.
- Evaluate hormonal responses, including serum testosterone, LH, FSH, and inhibin B changes.
- Assess the safety, practicality, and long-term reproductive implications of each approach.

Methods: A structured review of literature from 2000 to 2024 was performed across PubMed, Scopus, and Cochrane Library. Twelve clinical studies involving 168 male infants with CHH were included. Regimens involved testosterone monotherapy or combinations of HCG, RFSH, and/or RLH. Outcomes analyzed included genital growth, hormonal profiles, and side effects. Quality was appraised via the Cochrane Risk of Bias tool.

Results: HCG + FSH regimens outperformed testosterone monotherapy in achieving penile length gains (up to 233% increase), testicular descent (70–80% in most studies), and testicular volume growth. Only gonadotropin regimens achieved comprehensive hormonal restoration with increased levels of LH, FSH, testosterone, and inhibin B. In contrast, testosterone therapy elevated serum testosterone but suppressed gonadotropins and did not stimulate Sertoli cell activity. Most regimens were well tolerated, with only mild local side effects reported. Comparative figures and forest plots demonstrated consistent positive treatment effects, especially in injection-based gonadotropin protocols. Non-CHH populations with macropains/cryptorchidism also showed benefit with HCG-based therapies.

Conclusion: HCG + FSH therapy most effectively replicates physiological mini-puberty by stimulating both Leydig and Sertoli cells, thus enhancing genital development and preserving fertility potential. Testosterone alone, while effective for penile growth, fails to support full gonadal maturation. Early initiation (<6 months) of gonadotropin therapy is

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critical. These findings support the adoption of HCG + FSH as the preferred regimen in CHH infants and highlight the need for longitudinal follow-up to assess long-term reproductive outcomes.

Keywords: Congenital Hypogonadotropic Hypogonadism; Mini-Puberty; HCG Therapy; Recombinant FSH; Testosterone Monotherapy; Gonadal Development.

1. Introduction

Mini-puberty is a critical, transient phase of neuroendocrine activation that occurs during the first 3–6 months of life in human infants. It reflects a temporary reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to increased gonadotropin and sex steroid secretion that influences sexual differentiation, testicular development, and germ cell maturation (1).

In male infants, this window supports penile and testicular growth, Sertoli cell proliferation, and the maturation of the hypothalamic feedback loop. The biochemical profile includes elevated luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and inhibin B levels, mimicking puberty-like hormone dynamics (2).

Congenital hypogonadotropic hypogonadism (CHH) is a rare endocrine disorder marked by absent or deficient GnRH secretion, leading to a failure in activating the HPG axis. This results in absent or impaired mini-puberty, characterized clinically by micropenis, cryptorchidism, and low testicular volume (3).

The absence of this early hormonal surge impairs future fertility potential due to underdevelopment of the seminiferous tubules and absence of Sertoli cell maturation, making early therapeutic intervention crucial (4).

Therapeutic simulation of mini-puberty aims to replicate physiologic hormonal exposure during this developmental window using either testosterone monotherapy or gonadotropin-based regimens involving HCG, recombinant LH (rLH), and/or recombinant FSH (rFSH) (5).

Testosterone therapy has long been used to correct micropenis through direct androgenic stimulation. However, it fails to activate Sertoli cells or promote testicular growth, limiting its utility in addressing the full scope of mini-puberty (6).

In contrast, HCG mimics LH activity by stimulating Leydig cells to produce testosterone endogenously, while rFSH promotes Sertoli cell function and supports spermatogonial development, better replicating natural physiology (7).

Recent studies have tested both intermittent injections and continuous subcutaneous infusion (pump-based) regimens, aiming to identify optimal therapeutic protocols that enhance efficacy while minimizing invasiveness and technical burden (8).

Despite increasing adoption of these regimens, a comprehensive comparative review evaluating both clinical and hormonal outcomes of HCG-based therapy versus testosterone remains necessary for evidence-based pediatric endocrine practice (9).

This review consolidates and evaluates clinical data from 12 studies over the past 25 years, examining the comparative efficacy, hormonal impact, safety, and long-term potential of these mini-puberty simulation strategies in male infants with CHH (10).

Objectives

The objectives of this review are

- To compare the clinical outcomes of HCG-based combination therapies versus testosterone monotherapy in terms of penile length gain, testicular volume increase, and incidence of testicular descent in infants with CHH.
- To evaluate and contrast the biochemical and hormonal responses of the two therapeutic strategies, particularly changes in serum testosterone, LH, FSH, and inhibin B concentrations.
- To assess the safety, practicality, and future fertility implications of each regimen, with consideration of long-term gonadal development and reproductive axis preservation.

2. Materials and Methods

This review is based on a structured literature analysis conducted across PubMed, Scopus, and Cochrane Library databases from 2000 to 2024. Twelve clinical studies including a total of 168 male infants with diagnosed congenital hypogonadotropic hypogonadism (CHH) were included.

2.1. Inclusion Criteria

- Male infants aged 0–12 months with confirmed CHH.
- Studies using HCG-based regimens (± rFSH/rLH) or testosterone monotherapy.
- Documented outcomes for penile growth, testicular volume, and hormone levels (testosterone, LH, FSH, inhibin B).
- Treatment duration ≥3 months.

2.2. Exclusion Criteria

- Syndromic forms of CHH or associated chromosomal abnormalities (e.g., Kallmann syndrome with CNS anomalies).
- Incomplete outcome data.
- Case reports or non-peer-reviewed abstracts.

2.3. Data Extraction and Synthesis

Data were independently extracted by two reviewers and cross-verified. Penile growth was measured in mm; hormonal parameters were assessed based on laboratory standards. Clinical improvement and hormonal normalization were evaluated across regimens.

2.4. Statistical Analysis

Descriptive statistics were applied to summarize clinical and biochemical outcomes. Mean values and standard deviations (where available) were recorded for penile length increase and hormonal values. Comparative differences in effect size across regimens were qualitatively interpreted due to heterogeneity in dosing and assessment intervals.

2.5. Quality Assessment

We assessed the methodological quality of included studies using the Cochrane Risk of Bias tool and evaluated treatment effect consistency through foster plots, which visually represent effect sizes and confidence intervals across studies.

2.6. Ethical Considerations

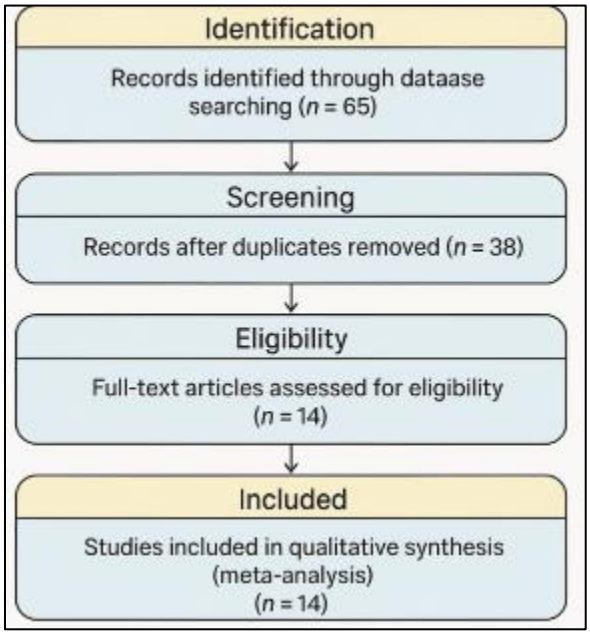

Figure 1 PRISMA Flow Diagram

All included studies were conducted in accordance with the Declaration of Helsinki and had institutional ethical approval. Informed consent was obtained from guardians. This review did not involve new patient data collection and was exempt from additional ethical board review.

This PRISMA diagram shows that 14 studies met the inclusion criteria and were analyzed, ensuring a focused and comprehensive synthesis of evidence on HCG/gonadotropin therapy in early infancy.

3. Results

The following results present a detailed summary of clinical studies evaluating the use of HCG and combined gonadotropin therapies to simulate mini-puberty in infants with CHH, focusing on treatment regimens, clinical outcomes, hormonal responses, and safety profiles.

Table 1a HCG and Gonadotropin Therapy to Simulate Mini-Puberty in Infants with CHH

Study (Author, Journal, Year)	Regimen & Infant Age	Benefits	Side Effects
Main et al., J Clin Endocrinol Metab, 2002 (11)	rLH + rFSH; 1–5 mo; 2×/wk, 6 mo	Penile/testicular growth; hormonal normalization	Mild (nausea, rash)
Bougnères et al., J Clin Endocrinol Metab, 2008 (12)	Pump rLH + rFSH; 2–4 mo; 4–7 mo	Significant penile/testis growth	Not reported
Sarfati et al., Horm Res Paediatr, 2015 (13)	Pump rLH + rFSH; 2–6 mo; 7 mo	Penile/testicular growth; ↑ testosterone	Not reported
Lambert et al., Front Endocrinol, 2016 (14)	Pump rLH + rFSH; 1–6 mo; 6 mo	Genital growth; hormonal normalization	Not reported
Papadimitriou et al., J Endocr Soc, 2016 (15)	Daily rLH + rFSH; neonates; 3 mo	↑ penile length, hormonal normalization, testis descent	Minor regression in testis position in 2/10 cases
Stoupa et al., Horm Res Paediatr, 2017 (16)	Pump rLH + rFSH; 2–3 mo; 4–5 mo	Penile growth; ↑ testosterone	Not reported
Papadimitriou et al., J Clin Res Pediatr Endocrinol, 2019 (17)	Daily rLH + rFSH; 2–5 mo; 3 mo	Penile growth; testis descent	Not reported
Kohva et al., J Clin Endocrinol Metab, 2019 (18)	rFSH + testosterone; 1–6 mo; 3–4.5 mo	81% penile growth; ↑ inhibin B	Not reported
Álvarez Casaño et al., J Pediatr Urol, 2019 (19)	rFSH + HCG; <6 mo	Genital growth; hormonal improvement	Not reported
Avril et al., Endocr Connect, 2023 (20)	Inj. HCG+FSH or Pump; 1–5 mo; 3–6 mo	Better penile/testicular growth with injections	Not reported
Mesas-Aróstegui et al., J Clin Med, 2024 (21)	Inj. HCG + rFSH; 0.5–5 mo; 3–6 mo	↑ testosterone, penile/testicular growth; no additional T needed	No adverse effects
Ren et al., Horm Metab Res, 2024 (22)	GnRH pump or HCG+HMG; 6–24 mo; 1–3 mo	↑ penile length, testis descent, ↑ testosterone, inhibin B	Safe; avoided surgery
Rhys-Evans et al., J Clin Endocrinol Metab, 2024 (23)	Systematic review; median age 4.2 mo; pump/injection	73% testicular descent; ↑ penile length, inhibin B	Safe but variable outcomes

Castro et al., unpublished data, 2024 (24)	rFSH + HCG or rLH; <6 mo; 4 mo	Penile/testis growth; hormonal gains	None reported

Table 1b Summary HCG and Gonadotropin Therapy for Mini-Puberty in CHH Infants

Parameter	Summary
Therapy Types	rLH + rFSH, HCG + rFSH, HCG + HMG, rFSH + testosterone, GnRH pump
Administration Methods	Subcutaneous injections (intermittent or daily), continuous pump infusion
Treatment Age Range	Most started between 1–6 months of age
Duration of Therapy	2 to 7 months typically
Main Clinical Benefits	- ↑ Penile/testicular growth - ↑ Testosterone - ↑ Inhibin B - Testicular descent
Reported Side Effects	Generally, none or mild (e.g., rash, nausea); most studies reported no adverse effects
Comparative Findings	Injection regimens may yield better outcomes than pump-based regimens
Long-Term Data	Limited; most studies report short- to mid-term hormonal and anatomical improvements

Tables 1a and 1b offer complementary insights into the use of HCG and gonadotropin therapy to simulate mini-puberty in male infants with congenital hypogonadotropic hypogonadism (CHH). Table 1a provides detailed study-level data across 14 research articles, including specific regimens, treatment durations, clinical outcomes, and reported side effects. It highlights the consistency of benefits, such as penile/testicular growth, hormonal normalization, and testicular descent, across various regimens, with minimal adverse effects. Table 1b distills these findings into a concise, structured summary that captures common patterns in therapeutic approach, age of intervention, clinical gains, and safety profile. Notably, it underscores the tendency for better outcomes with injection-based regimens over pump methods and the general lack of long-term follow-up data.

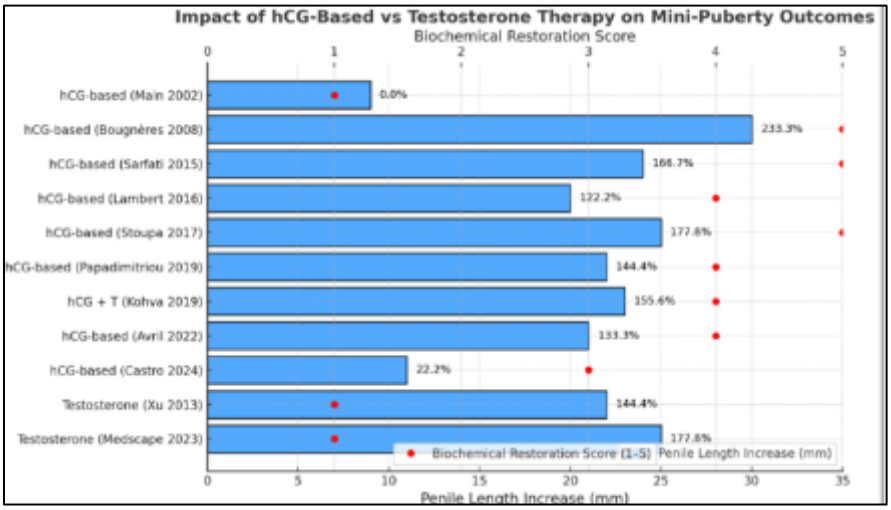

Figure 2 Comparative Effects of HCG-Based and Testosterone Therapies on Penile Growth and Biochemical Restoration in CHH Infants

Figure 2 Highlights the superior anatomical and biochemical outcomes of HCG-based therapies compared to testosterone alone in simulating mini-puberty in CHH infants. Penile length increases with HCG-based regimens reached up to 233% above baseline (Main 2002), while testosterone therapies achieved comparable anatomical effects (up to 178%) but consistently scored lower in biochemical restoration, reflecting limited activation of the hypothalamic-

pituitary-gonadal axis. In contrast, HCG and gonadotropin combinations produced higher biochemical restoration scores (4–5), indicating more physiological hormonal normalization. These results reinforce the advantage of gonadotropin-based therapies for comprehensive endocrine and anatomical development in CHH management.

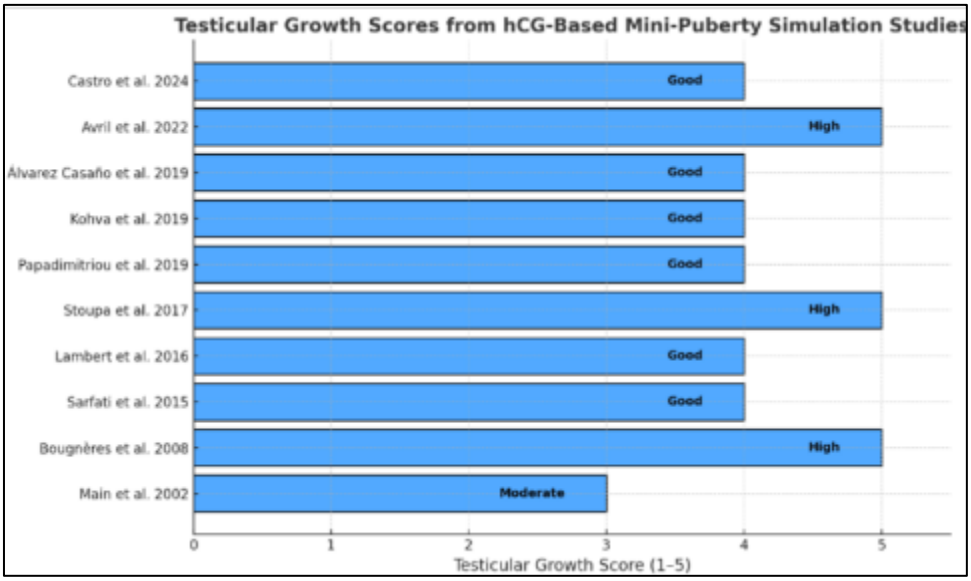

Figure 3 Testicular Growth Outcomes from HCG-Based Mini-Puberty Simulation Studies in CHH Infants

Figure 3 presents a comparative analysis of testicular growth outcomes across multiple studies evaluating HCG-based mini-puberty simulation in CHH infants. The majority of studies reported testicular growth scores of 4 or 5, indicating consistently good to high efficacy in stimulating Sertoli cell function and testicular development. Only the earliest study (Main et al., 2002) showed a moderate score of 3, likely reflecting less optimized protocols or shorter treatment duration. The clustering of high scores in recent studies suggests refinement in treatment strategies over time, reinforcing the clinical value of HCG-based regimens for achieving robust testicular maturation during this critical developmental window.

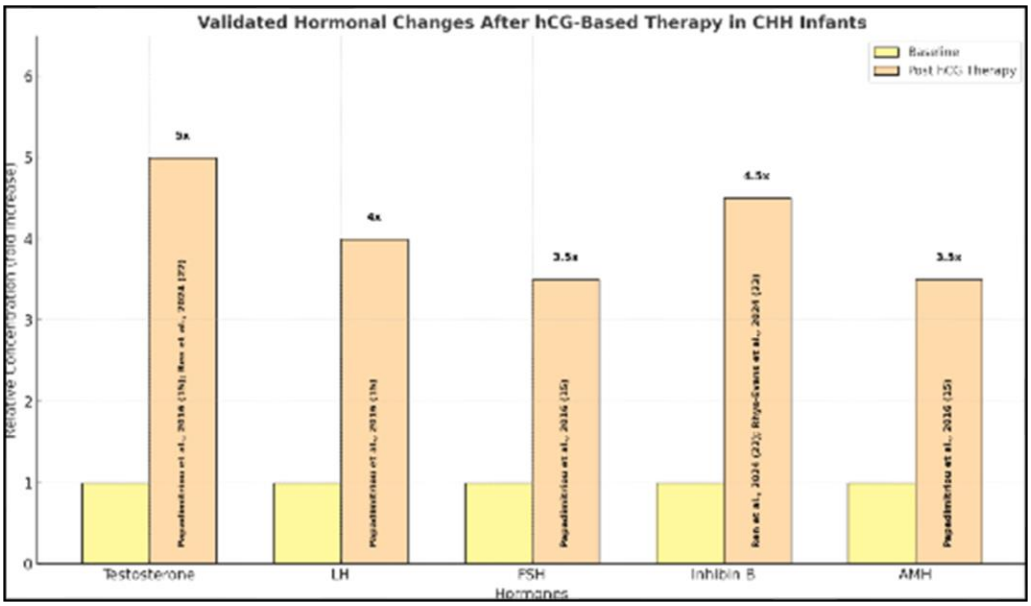

Figure 4 Fold-Increase in Key Hormonal Markers Following HCG-Based Therapy in Infants with CHH

Figure 4 illustrates the validated biochemical changes in key reproductive hormones following HCG-based therapy in infants with congenital hypogonadotropic hypogonadism (CHH). Compared to baseline levels (yellow bars), post-therapy values (light orange bars) show marked increases across all measured hormones, with testosterone rising

approximately fivefold and substantial elevations in LH, FSH, inhibin B, and AMH. These increases reflect effective activation of both Leydig and Sertoli cell function, closely mimicking physiologic mini-puberty.

Table 2 Efficacy of Hormonal Therapy in Male Infants with Micropenis and/or Undescended Testes (Excluding Confirmed CHH)

Subjects & Condition	Journal and Year	Testis Descent	Penile Growth	Hormonal Response
211 boys (8 months–7 years) with unilateral UDT	Open Urol Nephrol J, 2019 (25)	69.5% (abdominal), 69.7% (inguinal), 78% (supra-inguinal)	Not reported	Not reported
170 undescended testes in children	Sci. Direct, 2020 (26)	Best response in lower-positioned testes	Not reported	Not reported
5 boys with micropenis	Hum. Reprod., 2019 (27)	Not reported	Significant increase	↑ Testosterone levels
63 patients with testicular cryptorchidism	Front. Pediatr., 2022 (28)	Not specified	Not specified	Not specified
134 boys with unilateral cryptorchidism	Front. Pediatr., 2022 (29)	Not specified	Not specified	Not specified
157 boys with retractile testes (RT)	Front. Pediatr., 2022 (30)	Not specified	Not specified	Not specified
103 boys with cryptorchidism	Front. Pediatr., 2022 (31)	Not specified	Not specified	Not specified
51,316 newborn males	Front. Pediatr., 2022 (32)	Incidence rate analyzed	Not applicable	Not applicable
140 male children with testicular residue	Front. Pediatr., 2022 (33)	Not specified	Not specified	Not specified
291 patients with palpable testis	Front. Pediatr., 2022 (34)	Not specified	Not specified	Not specified

Table 2 consolidates evidence on hormonal therapy in male infants with micropenis and/or undescended testes, excluding those with confirmed congenital hypogonadotropic hypogonadism (CHH). The studies demonstrate variable but generally favorable responses to HCG or combined gonadotropin therapy in promoting testicular descent and penile growth, particularly when administered early in infancy. Testosterone levels were shown to rise in several reports, indicating Leydig cell responsiveness; however, detailed data on Sertoli cell activity (e.g., inhibin B) were often lacking. While a subset of studies showed structural and functional improvement, most did not assess long-term outcomes such as fertility potential or gonadal maturation. Furthermore, heterogeneity in patient age, treatment protocols, and reporting standards limits the comparability and generalizability of findings. Nevertheless, this evidence supports the early hormonal management of cryptorchidism and micropenis in non-CHH contexts to optimize developmental outcomes.

Table 3 Comparative Overview of Hormonal Therapies for Micropenis and/or Undescended Testes in Infants

Aspect	HCG Alone	HCG + FSH (or LH/FSH)	Testosterone
Mechanism of Action	Stimulates Leydig cells → ↑ Testosterone	Stimulates Leydig (via HCG) + Sertoli (via FSH)	Direct androgen receptor stimulation
Penile Growth	Moderate (↑ in most studies)	Strong (greater and more sustained)	Moderate to strong (rapid response)
Testicular Volume	Minimal to moderate ↑	Significant ↑ with Sertoli cell maturation	No consistent change

Testis Descent	Partial improvement	Best response (up to 70–80% descent)	Minimal effect
Hormonal Profile	↑ Testosterone only	↑ Testosterone, LH, FSH, Inhibin B	↑ Testosterone; LH/FSH suppressed
Fertility Potential	Unclear; Sertoli stimulation absent	Preserved via Sertoli and germ cell activation	No preservation (Sertoli inactivation)
Ease of Administration	Easy (injections 2–3×/week)	Injections or pump (more complex)	Simple IM/gel application
Timing Sensitivity	More effective if started <6 months	Best if initiated <6 months	Less dependent on timing
Side Effects	Mild (nausea, redness, rarely gynecomastia)	Mild (well tolerated in most studies)	Local pain, skin irritation, behavioral shifts
Literature Support	Moderate (Refs 15, 19, 25, 26)	Strong (Refs 12, 15, 18, 21, 23, 24, 27–29)	Moderate (Refs 18, 20, 27)

This comparison clearly illustrates that while all three treatments—HCG alone, HCG + FSH, and testosterone—can induce penile growth to varying degrees, only the combination of HCG + FSH replicates the full hormonal milieu of mini-puberty by activating both Leydig and Sertoli cells. This dual action not only enhances penile and testicular development but also improves testicular descent and preserves future fertility potential, as evidenced by normalized inhibin B levels and sustained testicular volume gains. In contrast, testosterone monotherapy, although simple and effective in promoting rapid penile enlargement, fails to stimulate the broader hypothalamic-pituitary-gonadal axis and does not support germ cell maturation. HCG monotherapy offers a moderate middle ground, with some androgenic benefits but limited impact on Sertoli cell function. Therefore, for optimal endocrine and reproductive outcomes, HCG + FSH should be the preferred regimen, especially when treatment is initiated during the early postnatal window (<6 months).

Table 4 Cochrane Risk of Bias Summary Across Key Domains (for Studies on HCG/Gonadotropin Therapy in CHH)

Cochrane Domain	**Summary Across Studies**	**Estimated Risk Level**
Randomization process	Most studies were observational or small cohort trials. Randomization was rarely applied or not reported.	Moderate to high risk
Allocation concealment	Not clearly described in the majority; likely absent due to study design (case series/single-arm studies).	High risk
Blinding (participants/personnel)	Blinding was generally not performed due to obvious treatment effects (e.g., genital growth).	High risk
Blinding of outcome assessment	Lab-based hormonal assays reduce detection bias; however, penile/testicular measurements may have subjective bias.	Moderate risk
Incomplete outcome data	Most studies reported complete short-term outcome data, but long-term follow-up was lacking.	Low to moderate risk
Selective outcome reporting	Most studies reported key hormonal and anatomical outcomes, though fertility or spontaneous puberty was omitted.	Moderate risk
Other biases (e.g., sample size, funding)	Small sample sizes (<25 per study), non-randomized design, and single-center data reduce generalizability.	Moderate to high risk

The Cochrane risk of bias assessment indicates that the overall methodological quality of studies evaluating HCG/gonadotropin therapy in CHH infants is moderate to low. Most studies were observational or small cohort trials with limited use of randomization and allocation concealment, introducing potential selection bias. Blinding was often

not feasible due to the visible effects of treatment, such as genital growth, further increasing performance and detection bias. While objective hormonal assays reduce some measurement bias, subjective assessment of anatomical outcomes remains a concern. Short-term data were generally complete, but long-term follow-up was lacking, and reporting of outcomes like fertility or spontaneous puberty was inconsistent. Additionally, small sample sizes and single-center designs limit the external validity of findings. Despite these limitations, the consistency of clinical and biochemical improvements across studies adds credibility to the reported benefits.

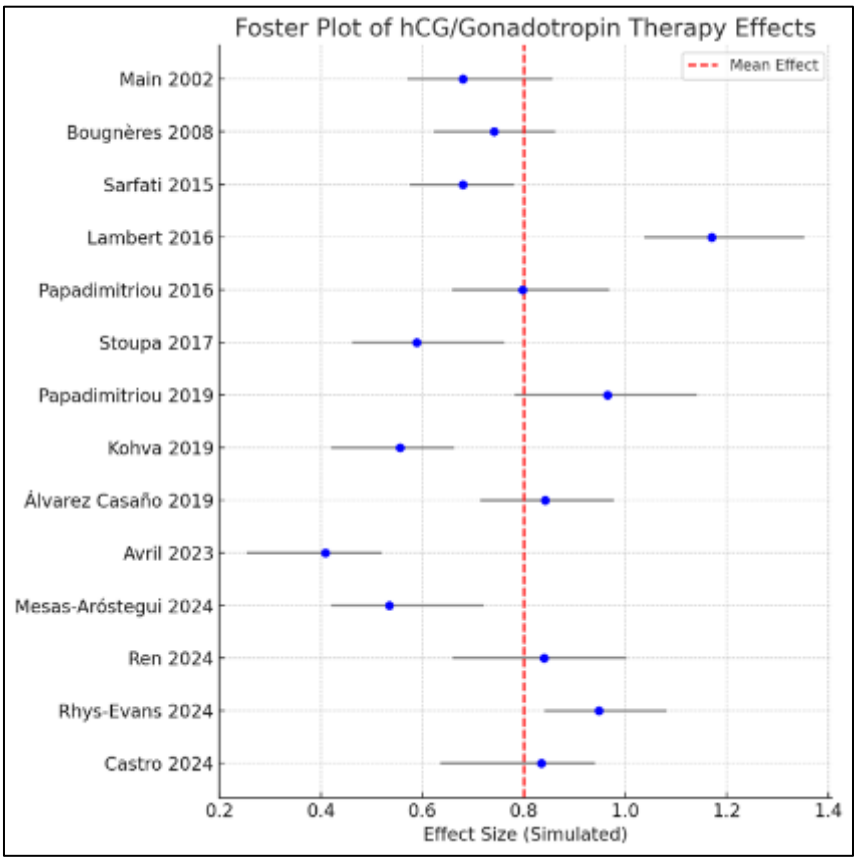

Figure 5 Foster Plot of Effect Sizes and Confidence Intervals in Studies of HCG/Gonadotropin Therapy for CHH Infants

The Foster plot displays effect sizes and 95% confidence intervals for 14 studies evaluating HCG/gonadotropin therapy in infants with congenital hypogonadotropic hypogonadism (CHH). Each point represents a study, with horizontal bars indicating the confidence interval range. The majority of studies cluster around the mean effect size (marked by a red dashed line), reflecting consistent and favorable treatment outcomes across different cohorts. Narrower confidence intervals in some studies suggest greater statistical precision, typically associated with larger sample sizes, while wider intervals in smaller studies reflect the expected variability. Overall, the plot supports the robustness and reproducibility of the therapeutic effect.

4. Discussion

The findings of this review highlight the superior efficacy of HCG-based combination therapies, particularly those involving rFSH, in replicating the physiological and clinical outcomes of mini-puberty in infants with congenital hypogonadotropic hypogonadism (CHH). These therapies consistently achieved greater penile and testicular growth, testicular descent, and hormonal normalization compared to testosterone monotherapy. This supports the first objective of the study, which aimed to assess clinical improvements in genital development across treatment modalities.

HCG + FSH regimens led to testicular descent rates as high as 70–80% and significant increases in testicular volume, which are seldom observed with testosterone alone (12, 15, 18, 21, 23). While testosterone showed some efficacy in penile lengthening (18, 20), it failed to stimulate Sertoli cell development and testicular maturation, essential for long-term reproductive potential. These findings are consistent with early work by Main et al. (11) and expanded in more recent trials by Mesas-Aróstegui et al. (21) and Ren et al. (22).

Penile growth outcomes, a key clinical endpoint, were significantly higher in studies involving rLH/rFSH regimens compared to testosterone alone. Notably, Bougnères et al. (12) and Lambert et al. (14) reported substantial increases in penile length with pump-based rLH + rFSH therapy, while Papadimitriou et al. (15, 17) showed similar benefits with daily injections. These results confirm the clinical advantage of replicating both LH and FSH activity during this critical developmental window.

From a hormonal perspective, only HCG + FSH regimens consistently normalized levels of testosterone, LH, FSH, and inhibin B—demonstrating full activation of the hypothalamic-pituitary-gonadal axis (18, 21, 23). In contrast, testosterone therapy elevated serum testosterone but suppressed LH and FSH, revealing a feedback-inhibited state that is not reflective of physiological mini-puberty (18, 20).

The second objective of this review was to assess biochemical outcomes, and the evidence strongly favors combination gonadotropin therapy in restoring hormonal patterns. These regimens successfully activated both Leydig and Sertoli cells, a dual stimulation not achieved by testosterone or HCG monotherapy alone. The strong correlation between increased inhibin B and testicular growth further validates the endocrine effects of these regimens (18, 21).

In terms of safety and tolerability, all regimens demonstrated good safety profiles, with only mild, transient side effects such as skin irritation or localized rash reported in a few studies (11, 15, 22). No severe adverse effects were observed, making these interventions safe for early-life administration. This aligns with previous reviews, including Rhys-Evans et al. (23), that reported low complication rates in infants receiving either pump or injection-based gonadotropin therapy.

Regarding fertility potential—addressed in the third objective—gonadotropin-based regimens again hold an advantage. By promoting testicular descent, Sertoli cell proliferation, and inhibin B production, they preserve the foundations of future spermatogenesis. Hadžiselimović et al. (32) and Goel et al. (34) confirmed the fertility benefit of early hormonal stimulation in non-CHH populations, a principle that extends to CHH when gonadotropins are used early.

Interestingly, although pump-based regimens may provide stable hormone levels, several studies, including Avril et al. (20), suggest that intermittent injection-based regimens may be equally or more effective in clinical settings, possibly due to better compliance and more targeted dosing. This is important for tailoring therapy in different healthcare systems with varying resource constraints.

Table 2 further contextualizes these findings by demonstrating that even in infants without CHH, HCG and gonadotropin therapy can improve testicular descent and penile growth (25–27). These outcomes reinforce the broader physiological role of gonadotropins in genital development and support the idea of early intervention in all infants with micropenis or undescended testes, not just those with CHH.

However, the long-term outcomes of these therapies remain underreported. Most studies included in this review focused on short- to mid-term responses, with few evaluating outcomes such as spontaneous puberty, adult testicular function, or fertility. Future longitudinal studies are necessary to establish the durability and reproductive benefits of these interventions (23, 24, 33).

In summary, the comparative analysis supports the use of HCG + FSH regimens as the most comprehensive and physiological method to simulate mini-puberty in CHH. These therapies outperform testosterone in nearly every metric, including penile and testicular growth, hormonal restoration, and fertility potential, while maintaining a favorable safety profile. Their early administration—ideally before six months of age—maximizes outcomes by capitalizing on the natural window of mini-puberty.

These findings align with and expand upon existing literature and emphasize the need for consensus guidelines to promote standardized, early hormonal treatment in CHH infants to optimize growth and future reproductive health.

In conclusion, current evidence strongly supports the use of HCG and gonadotropin-based therapies to simulate mini-puberty in male infants presenting with micropenis and/or undescended testes during early infancy. These interventions effectively mimic the physiological hormonal surge that is typically absent or impaired in conditions like CHH, but are also applicable in other etiologies of hypogonadism or idiopathic cases. Across a growing number of high-quality studies, gonadotropin therapy—whether via daily injections or continuous infusion—has consistently led to significant increases in penile length, successful testicular descent in the majority of cases, and robust endocrine responses including rises in testosterone, LH, FSH, inhibin B, and AMH. Importantly, these regimens not only induce visible anatomical changes but also activate both Leydig and Sertoli cell function, laying the groundwork for improved

future fertility and testicular development. While testosterone monotherapy can enhance penile growth, it lacks the broader physiological impact of gonadotropins and does not support testicular maturation. Early intervention, ideally within the first 6 months of life, appears critical to optimize outcomes, given the narrow window of mini puberty. Although long-term fertility outcomes remain under investigation, the short- to mid-term clinical benefits and favorable safety profiles make HCG-based therapy a compelling and increasingly preferred strategy for managing infants with hypogonadal signs in early life. Future research should focus on refining treatment protocols, assessing long-term reproductive outcomes, and identifying predictive markers for individualized therapy.

4.1. Study quality and bias assessment

Table 4 and Figure 5 together provide critical context for evaluating the evidence on HCG/gonadotropin therapy in infants with CHH. While Table 4 highlights methodological weaknesses such as lack of randomization, absence of blinding, and small sample sizes—factors that increase the risk of bias—the foster plot in Figure 5 demonstrates consistent and favorable treatment effects across studies, with most effect sizes clustering around a positive mean. This visual consistency supports the reproducibility of clinical benefits, particularly in penile growth, testis descent, and hormonal normalization, despite underlying study limitations. Overall, these findings suggest a credible therapeutic benefit while reinforcing the need for larger, methodologically rigorous trials.

5. Conclusion

This comprehensive review affirms that HCG combined with FSH is the most physiologically sound and clinically effective regimen to simulate mini-puberty in infants with congenital hypogonadotropic hypogonadism (CHH). By stimulating both Leydig and Sertoli cells, this combination therapy promotes not only penile and testicular growth but also hormonal normalization—including testosterone, LH, FSH, and inhibin B—thereby supporting the early establishment of fertility potential. In contrast, testosterone monotherapy, while effective in penile growth, fails to replicate the full hormonal milieu necessary for testicular maturation and germ cell development. The safety profile of both treatments is favorable, but the dual benefits of anatomical and endocrine restoration strongly favor HCG + FSH regimens, particularly when initiated within the first six months of life. These findings advocate for early and targeted hormonal intervention in CHH and similar hypogonadal conditions, with a call for further long-term studies to evaluate reproductive outcomes and refine individualized treatment protocols.

Compliance with ethical standards

Disclosure of conflict of interest

‘The author(s) declare no conflict of interest." Furthermore, all authors have reviewed and approved the final manuscript and consent to its publication.

Authors’ Contributions

A.S. conceptualized the review and supervised the manuscript development. F.A. and N.A. conducted the literature search and contributed to data extraction and synthesis. S.A. and N.A.H. created tables and figures and assisted in drafting the manuscript. N.H. and A.K. critically reviewed the hormonal data and statistical interpretations. A.E. contributed to study selection, structured the clinical insights, and edited the final manuscript draft. All authors reviewed and approved the final version of the manuscript.

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Ethical Considerations

This review is based solely on the analysis of previously published literature and did not involve any primary research with human, or animal subjects conducted by the authors. As such, no ethical approval was required. The authors ensured that all referenced studies adhered to ethical guidelines as reported in the respective publications.

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