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REVIEW

Current concepts surrounding neonatal hormone therapy for boys with congenital hypogonadotropic hypogonadism

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ABSTRACT

Introduction: Congenital hypogonadotropic hypogonadism (CHH) is a genetic disorder of reproduction and development, characterized by deficient gonadotropin-releasing hormone (GnRH) secretion or action, affecting 1-in-4,000–15,000 males. Micropenis and undescended testes are cardinal features of antenatal GnRH deficiency and could indicate absent minipuberty in the first postnatal months. In this review, we outline the pathophysiology and clinical consequences of absent minipuberty and its implications for optimal approaches to the endocrine management of affected boys.

Areas covered: Deficient GnRH activity during fetal development and neonatal-infancy phase of minipuberty accounts for the diminished mass of Sertoli cells and seminiferous tubules among CHH males, enduring impairment of reproductive function even during gonadotropin replacement in adult life. In overcoming this obstacle, several clinical studies of neonatal gonadotropin replacement have consistently shown positive results in inducing testicular development and correcting cryptorchidism.

Expert opinion: A high index of clinical suspicion, combined with hormonal testing undertaken in the postnatal period of 1–4 months, can reliably confirm or refute the diagnosis of CHH. Timely identification of CHH in affected male infants (having characteristic "red flag' developmental anomalies) opens up the possibility for gonadotropin replacement as a targeted therapy to restore the normal hormonal milieu of minipuberty. Further work is necessary in formulating optimal gonadotropin treatment regimens to be more widely adopted in clinical practice.

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1. Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a reproductive disorder characterized by an isolated deficiency in gonadotropin-releasing hormone (GnRH) activity. Disruption in the embryonal development of the hypothalamic GnRH neuronal regulatory network underlies this complex genetic disorder. When this is coupled with defective olfactory axon pathfinding during embryonic development (causing arrested migration of GnRH neurons from the olfactory placode), impaired sense of smell (anosmia) becomes a key defining feature of the approximately 50% of CHH patients with Kallmann syndrome [1,2]. Male predominance is typically described for CHH with a male:female gender ratio of 3.6: 1 [3] although this cannot be satisfactorily explained on the basis of our current knowledge of the genetics.

CHH is widely regarded as a rare medical disorder, but it has not been possible to accurately ascertain the actual prevalence of CHH because of scarcely available literature. Drawing data from two studies – a French study on young military conscripts [4] and a Finnish nationwide study of hospital records [5] – it can be conservatively estimated that the prevalence of CHH in men is at least 1 in 4,000–15,000.

In the context of combined pituitary hormone deficiency (CPHD), or congenital hypopituitarism, patients may also manifest similar CHH-associated features although they tend to present first with complications of adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), and/or antidiuretic hormone (ADH) deficiency, including poor feeding and weight gain, hypoglycemia, seizures, and prolonged jaundice in the neonatal period [6]. The estimated incidence of CPHD is between 1 in 4,000–10,000 live births [7].

At present, more than 25 verified disease-causing genes have been linked to CHH, accounting for nearly 50% of cases (an up-to-date analysis of CHH genetics by Cangiano et al. reviewed >60 associated genes) [8]. These genetic variants disrupt the central neuroendocrine regulation of reproduction at key points, including the differentiation of GnRH-secreting neurons – *e.g.* genes encoding the receptor-ligand pair fibroblast growth factor receptor 1/fibroblast growth factor 8 (FGFR1/FGF8) [9–11] and NMDA receptor synaptonuclear signaling and neuronal migration factor (NMSF) [12], the migration of GnRH neurons – *e.g.* anosmin-1 (ANOS1) [13] and the ligand-receptor complex prokineticin 2/prokineticin receptor 2 (PROK2/PROKR2) [14,15], or the neuroendocrine control of

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Article highlights

- Congenital hypogonadotropic hypogonadism (CHH) is a rare reproductive disorder characterized by deficiency in gonadotropin-releasing hormone (GnRH) secretion or action that is associated with nonreproductive defects in around 60% of cases; most commonly hyposmia/anosmia defines Kallmann syndrome and more rarely with combined pituitary hormone deficiency.
- An early diagnosis of CHH in childhood facilitates not only timely intervention in normalising genital development but also the implementation of a structured follow-up program to optimize long-term reproductive and psychological health by ensuring timely pubertal-induction around 13 years of age, rather than at the typical 18 years of age reported by patients.
- GnRH deficiency in late pregnancy and neonatal-infancy is chiefly responsible for the defects of virilization, including micropenis, cryptorchidism, and impaired testicular growth, with micropenis and/or bilateral cryptorchidism occurring in 20-50% of CHH boys.
- The presence of a neonatal congenital defect that is strongly associated with CHH should prompt early referral to pediatric endocrinology for timely biochemical evaluation, whether reproductive anomaly (micropenis and/or bilateral cryptorchidism), or nonreproductive (hearing impairment, craniofacial, or digit defect (*e.g.* syndactyly).
- Several clinical studies aiming to replicate minipuberty through combined gonadotropin therapy in neonates and infants with CHH have demonstrated its effectiveness in correcting micropenis, testicular hypoplasia, and cryptorchidism, obviating the need for surgical orchidopexy in almost all cases and potentially improving spermatogenesis-induction outcomes in adulthood.

GnRH secretion – *e.g.* genes encoding the ligand-receptor complexes kisspeptin/kisspeptin receptor 1 (KISS1/KISS1R) and neurokinin B/neurokinin 3 receptor (TAC3/TACR3) [8]. Consequently, genetic evaluation and counseling remain highly challenging because of the underpinning complex genetic architecture, interplay of pathogenic variants and environmental exposure, and variable penetrance frequently observed within the same family [16,17].

2. Clinical manifestations of CHH across ages

CHH manifestations in male individuals vary at different stages of life [18].

Neonates and infants with CHH may present with micropenis and/or undescended testes in the early postnatal months [18]. When compared to the published prevalence of such congenital anomalies in general population, their prevalence in CHH male infants is at least 20- to 30-fold higher; hence, they are aptly considered as 'red flag' features of CHH [19]. This is an important consequence of deficient minipuberty, which not only affects genital development early in life but also has a far-reaching impact on reproductive potential in adulthood.

Besides genital anomalies, several nonreproductive phenotypic features other than anosmia may also be identifiable in patients with CHH ("red flags"), including hearing impairment, synkinesia, midline facial defects, dental and digit anomalies, and renal malformation [20,21]. Clinically and genetically, there is a degree of overlap with the milder end of the CHARGE syndrome spectrum [22,23]. CHARGE syndrome is a rare autosomal dominant disorder due to *CHD7* mutations, characterized by iris coloboma, congenital heart disease, choanal atresia, mental and growth retardation, genital hypoplasia, and ear malformations or deafness [24]. In a study by Xu et al, *CHD7* rare sequencing variants were found to be significantly enriched in a large cohort of CHH probands versus controls, supporting the implication of *CHD7* in CHH [23]. Similarly, the presence of midline developmental abnormalities may be associated with syndromic hypopituitarism *e.g.* septo-optic dysplasia (*HESX1* and *FGFR1/FGF8/PROKR2 mutations*) [25,26], Hartsfield syndrome (*FGFR1 mutation*) [25], and Culler-Jones syndrome (*GLI2 mutation*) [27].

In adolescents, the inactive gonadotropic axis results in failure to initiate or progress through puberty with impaired development of secondary sexual characteristics. Approximately two-thirds of CHH male adolescents do not develop spontaneous puberty at >17 years of age, while rest exhibit features of stalled puberty [21]. Diagnosis tends to be markedly delayed across the board, with meaningful hormonal treatment only being initiated around 18–19 years of age across Europe [28–30], in large part due to the challenge of distinguishing CHH from constitutional delay in growth and puberty (CDGP) [31,32], with the latter being regarded as an extreme of the normal pubertal timing [33]. However, with a history of neonatal cryptorchidism or micropenis, clinicians should have a very high index of suspicion, as the observed prevalence of these in CHH compared to CDGP males is nearly 20-fold elevated [34]. A recent study suggests the possible utility of GnRH-stimulated luteinizing hormone (LH) and inhibin B to differentiate CHH from CDGP, but data remain very limited [35]. Key obstacles to timely diagnosis reported by patients include their own shyness or embarrassment in coming forward, their parents' assumption that they were simply late developers, and the misapplication by pediatricians of a 'watch-and-wait' strategy when there were already very clear "red flag" markers of CHH [36].

Later in adulthood, symptoms of sexual dysfunction and infertility issues are more commonly encountered in clinical practice, and as such, the focus of treatment turns to ensuring adequate long-term testosterone replacement and the induction of spermatogenesis and fertility [18] Much older individuals, who somehow "slipped through the net" when they were younger, occasionally present with osteoporosis, anemia, or sarcopenia.

3. Physiology of fetal genital development, minipuberty, and the impact of their deficiencies

While a majority of CHH males only present clinically from adolescence onward due to pubertal failure, lack of secondary sexual characteristics, sexual dysfunction, and/or infertility, it is important for clinicians to be aware that the disruption in their reproductive tract development occurs much earlier in life due to deficient minipuberty. Indeed, minipuberty plays an integral role in determining long-term testicular function.

Following sexual differentiation at 7–9 weeks of gestation with secretion of testosterone and insulin-like peptide 3 (INSL3) by Leydig cells and anti-Müllerian Hormone (AMH) by Sertoli cells, respectively, masculinization of the fetal external genitalia occurs under the regulation of placental human chorionic gonadotropin (hCG) (first trimester) and fetal

pituitary LH (midgestation) [37]. In the 3rd trimester, fetal GnRH-LH take over the control of fetal Leydig tissue in the production of androgens, creating the necessary hormonal milieu to stimulate penile growth and modulate the inguinoscrotal descent of testes via regression of cranial suspensory ligament and their final anchoring in the scrotal position [38–40]. In addition, deficiency in fetal follicle-stimulating hormone (FSH) could possibly affect utero proliferation of Setoli cells and germ cells [41]. This has important implication in CHH, as the lack of antenatal GnRH activity would bring about micropenis, testicular maldescent, as well as microorchidism at birth [42].

After birth, neonatal GnRH activity recovers robustly following an initial dip due to the inhibitory effect of placental estrogens on the GnRH pulse generator and pituitary gonadotropes, marking the start of minipuberty [43]. This represents the next critical milestone in male reproductive tract development that begins shortly after birth and continues until 6 months postnatal [44]. Not unlike adolescence puberty, GnRH axis activation characterizes minipuberty, which is accompanied by increased pituitary gonadotroph secretion of FSH and LH and, in turn, testicular androgens. A peak in the gonadotropin and gonadal sex steroids and peptides occurs between 1 and 4 months postnatally, reaching adult levels, before declining to the prepubertal range by 6–9 months of age [44,45]. During this period, Leydig and Sertoli cells proliferate substantially [46], with the parallel rise in production of androgens playing a key role in driving male genital development. The Sertoli cells do not fully express androgen receptors under age of 5 years [47] and are thus physiologically insensitive to the concurrent high intratesticular concentration of testosterone [48], thereby allowing germ cell proliferation while preventing premature differentiation, as shown by the rising AMH levels during minipuberty. In contrast, as the AMH level falls during male puberty, Sertoli cells undergo differentiation and begin to instead secrete Inhibin B as they support spermatogenesis [49].

Therefore, it can be appreciated that pulsatile GnRH secretion associated with gonadotropin-stimulated secretion of reproductive hormones during the 3rd trimester and neonatal-infancy period is paramount for normal genital growth and gonadal development [50,51]. In addition, postnatal changes in the position of testes and consolidation of the intrascrotal position are strongly correlated with Leydig and Sertoli cell function [39]. As such, any disease process that blunts activation of the fetal hypothalamic-pituitary-testicular may predispose to neonatal microphallus and cryptorchidism, which, in turn, should be regarded as potential cardinal features of severe gonadotropin deficiency.

Furthermore, in the absence of GnRH activity during fetal life and neonatal-infancy, the diminished proliferation of Sertoli cells and seminiferous tubules that would otherwise normally account for 90% of testicular volume [52] resulting from loss of FSH-signaling result in undeveloped testes. Consequently, the Sertoli cell-derived AMH and Inhibin B levels are substantially depressed, reflecting a sparse Sertoli cell mass, which, in turn, has a huge bearing on future spermatogenic potential if not addressed appropriately. In a recent series, severe GnRH deficiency was found to affect two-thirds of CHH men, who manifested with prepubertal testicular volume [53], and this has consistently been linked to diminished spermatogenic response to gonadotropin therapy in other studies. Knowledge gleaned from research in rhesus monkeys showed that transient switching-off of hypothalamic-pituitary-testicular function during the neonatal period led to stunted testicular growth and sperm production later in life [54], underscoring the far-reaching impact of minipuberty on reproductive function.

4. 'Window of opportunity' in the diagnosis of CHH in infancy

Minipuberty has also been gaining greater attention among clinicians and investigators in recent years because of the recognition of its integral and fundamental role in male genital development [55].

Bypassing the conundrum of distinguishing between CDGP and CHH that clinicians face in the context of delayed puberty in adolescents, the window of opportunity in the first 6 months of life allows CHH to be diagnosed by establishing deficiency in minipuberty-related hormones [44], so that affected individuals could receive pubertal induction with sex steroids or gonadotropins from 12 years of age and, thereby, experience a normal adolescence, rather than the existing ubiquitous state of uncertainty, delay, and procrastination.

Timely evaluation and intervention of children with hypogonadotropic hypogonadism could modify the course of the disease, which, otherwise, if left inappropriately managed, is associated with poor long-term reproductive health and psychological outcomes. Indeed, the responsiveness of Sertoli cells to gonadotropin in spermatogenesis later in life is critically dependent on the priming process that occurred minipuberty, the lack of which conceivably compromises fertility significantly due to the diminished Sertoli cell population and seminiferous tubular mass.

As it is time-sensitive in nature, a protocolized approach incorporating clinical and biochemical assessment (Figure 1) would therefore be helpful in facilitating timely detection and intervention. Based on the normal physiology observed in male minipuberty, a relatively straightforward and cheap biochemical profiling of basal reproductive hormones during this phase in suspected male infants would provide crucial evidence to support or exclude the possibility of CHH. In one study protocol, the absence of neonatal male minipuberty was confirmed with at least three repeated measurements at 8 hours of undetectable LH, FSH, and testosterone from 2 weeks to 3 months of age [56]. Consistent with this approach, in a cohort of male infants with combined pituitary hormone deficiency (CPHD), 14/15 infants with genitalia anomalies were reliably identified to have CHH based on biochemical profiling (low FSH, LH, and testosterone concentrations), in contrast to the other infants with normal genitalia [57]. This demonstrates the high discriminatory value of reproductive hormone evaluation in the first 6 months of life. For greater diagnostic accuracy, investigations could be performed around age 3–3.5 months when sex hormones tend to be most robust, based on the

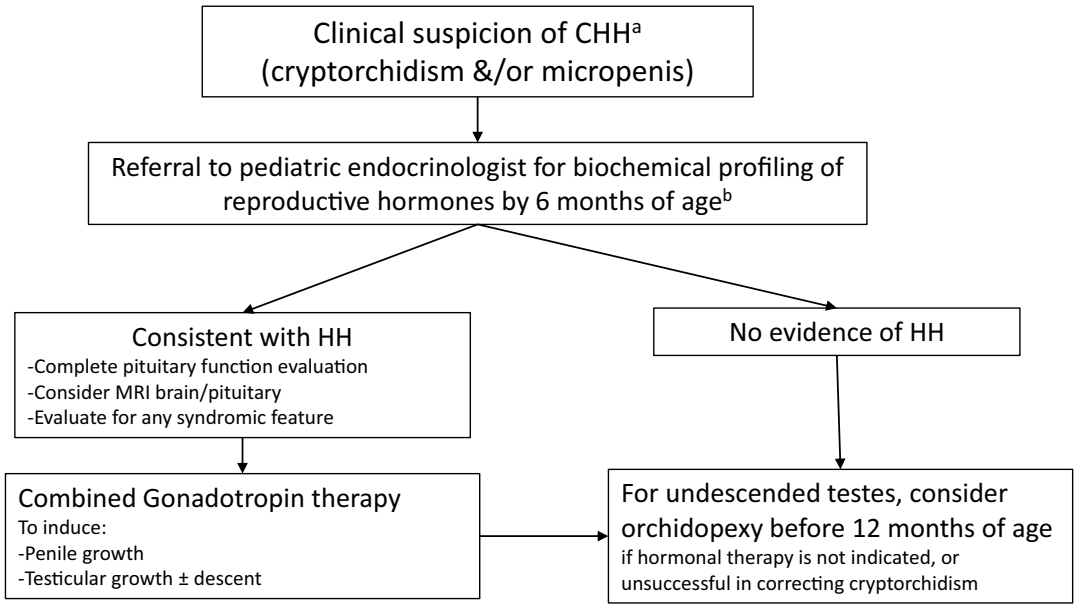


Figure 1. Proposed approach to suspected absent minipuberty in male neonates and infants.

CHH, congenital hypogonadotropic hypogonadism; HH, hypogonadotropic hypogonadism [a]"Red flag" signs of GnRH/gonadotropin deficiency: cryptorchidism, micropenis; Presence of other anterior pituitary deficiencies and/or nonreproductive CHH-associated phenotype including cleft lip/palate, hearing impairment, syndactyly or other anomaly of digits. [b]Serum FSH, LH, Testosterone ± Inhibin B, anti-Müllerian hormone; Male minipuberty peaks between 1 and 4 months.

normative data derived from a large cohort of healthy Danish infants [45]. Besides LH, FSH, and testosterone, the inclusion of AMH and inhibin B levels may be helpful to increase diagnostic confidence. In addition, although non-CHH infants with cryptorchidism may also exhibit hormonal changes, they differ from CHH infants in whom they tend to demonstrate higher FSH, similar testosterone, and slightly depressed inhibin B levels compared to healthy infants [58].

Therefore, it would also be helpful to adopt the targeted strategy that seeks to improve the recognition of infants affected by severe CHH (Figure 1). Male neonates with a significant degree of congenital GnRH deficiency are at high risk of micropenis and/or cryptorchidism at birth. Indeed, persistent cryptorchidism is found in ~40% of CHH infants, compared to less than 2.5% of infants in the general population [59–62], as cryptorchidism in the absence of underlying pathology including gonadotropin deficiency would tend to resolve spontaneously within the first 3 postnatal months [63]. Hence, the presence of such genital anomalies, regarded as some of the "red flag" markers of CHH, should trigger referral to pediatric endocrinologists for evaluation of hypothalamic-pituitary-testicular axis, rather than direct referral to a pediatric urological surgeon.

However, opportunities for early diagnosis and appropriate intervention are often missed due to lack of recognition [64,65]. In a large single-center series, only a third of CHH males with history of bilateral orchidopexy in childhood were referred to pediatric endocrinology for evaluation [20]. Moreover, recommendation on hormonal testing in the management of infants born with genital anomalies remains lacking in published guidance [66,67] although data have since emerged to support such testing during the window of opportunity of minipuberty in the workup of a child with disorder of sex development (DSD) [45]. This is similarly applicable to suspected CHH infants.

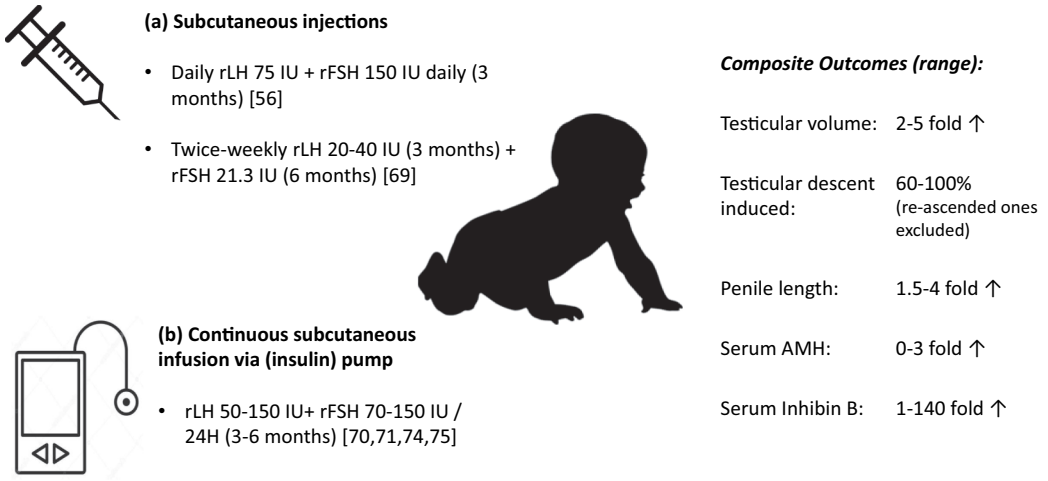
5. Gonadotropin therapy in neonates and infants

5.1. Correcting congenital anomalies

In male neonates and infants with micropenis (stretched penile length of <2.5 cm in term babies) with or without undescended testes, the goal of treatment is to increase the penile length, ensure normal positioning of testes, and maximize fertility potential [42].

Conventionally, the treatment of congenital micropenis involves low-dose testosterone therapy given as either topical gel or intramuscular injections, which is generally expected to achieve desired phallus development [68]. However, it would not be able to overcome gonadotropin-deficient related testicular maldevelopment. Therefore, an important consideration in the use of gonadotropin early in life for the treatment of CHH-associated genital anomalies lies in the possibility of replicating minipuberty physiology to achieve normal development in infancy, with a longer-term view of optimizing reproductive potential. Growing data on the outcomes of such a treatment strategy have been encouraging, making it an increasingly feasible intervention to be carried out in affected boys (Figure 2).

In one of the earliest reported experience, twice-weekly subcutaneous administration of recombinant human LH (rLH) and FSH (rFSH) to a 7.9-month-old child with CHH with micropenis was carried out (Table 1) [69]. Dose of rLH was increased from initial 20 IU to 40 IU after 2 months, while rFSH was maintained at 2.5 IU/kg throughout. Treatment was effective



rLH, recombinant human luteinising hormone; rFSH, recombinant human follicle stimulating hormone; AMH, anti-Müllerian hormone

Figure 2. Combined gonadotropin therapy regimens and outcomes studied in male neonates and infants with congenital hypogonadotropic hypogonadism.

in increasing the penile length by 50% (1.6 cm → 2.4 cm). The substitution of rLH with testosterone suppositories at age 12.2 months further enhanced phallic growth to 2.7 cm. The six-month hormonal therapy also stimulated testicular volume growth from 31 mm^3 to 84 mm^3, along with doubling of serum inhibin B level. Treatment was well tolerated by the child without serious adverse effects.

Bougnères et al. reported their experience with a 6-month continuous subcutaneous infusion of combined gonadotropin therapy in two male infants born with hypogonadotropic hypogonadism (Table 1) [70]. The administration via an insulin pump avoided repeated painful injections. The first child presented at 2 weeks with micropenis (7 mm) and small intrascortal testes (< 10 mm diameter) and was also found to have multiple anterior pituitary deficiencies. The second child was referred at 14 weeks for micropenis (12 mm) with small intrascrotal testes (< 10 mm diameter). At baseline, serum LH, FSH, and testosterone were all below the normal range, while inhibin B and AMH were below or marginally above the lower limit of normal. Following initiation of gonadotropin therapy at age 8 and 20 weeks, respectively, serum testosterone, inhibin B, and AMH rose to high normal ranges during the course of treatment, corresponding to a 4-fold increase in penile length and testicular size in both infants. Doses were derived empirically based on authors' observations: P1 received rLH 56 IU/day and rFSH 67 IU/day and P2 received rLH 50 IU/day and rFSH 125 IU/day. Of note, at the high serum FSH level up to 18-fold, the upper limit of normal was required to attain normal levels of inhibin B and AMH, reflecting a degree of resistance in the Sertoli cells. In the immediate weeks after cessation of gonadotropin therapy, while serum LH, FSH, and testosterone promptly returned to baseline levels, inhibin B fell less sharply to around low-normal range, while AMH persisted at similar concentrations achieved during the treatment phase, mirroring the expanded immature Sertoli cell population.

In a case report by Sarfati et al., a neonate born with micropenis and bilateral microorchidism was given combination rLH 75IU and rFSH 75 IU daily via a subcutaneous infusion pump for 6 months, leading to an increase in the testicular volume (0.33 → 2.3 mL) and penile length (15 → 38 mm) [71]. Given positive family history (mother and maternal uncle), he was tested and confirmed to carry the same *KAL1* mutation, consistent with his other phenotypic features including unilateral renal agenesis, synkinesia, and deafness.

5.2. Inducing testicular descent in CHH infants with cryptorchidism

Induction of testicular descent in infants with CHH-associated cryptorchidism is another potential therapeutic advantage of gonadotropin therapy (Table 2) [72]. First, successful spontaneous descent of testes into the scrotum with hormonal therapy would obviate orchidopexy, thereby avoiding any risk of trauma to the testes during the surgical procedure. Second, gonadotropin therapy seeks to correct the fundamental developmental defects of the testes resulting from deficient minipuberty. This would have important implications on the long-term fertility potential of CHH men, particularly those who are on the more severe end of the spectrum of GnRH deficiency as manifested by cryptorchidism, who typically experience a higher failure rate of spermatogenic response to gonadotropin therapy in adulthood [73].

In a French tertiary pediatric center, continuous subcutaneous infusion of rLH and rFSH was employed in 5 infants with CHH/CPHD with micropenis [74]. They were started on treatment at a mean age of around 4 months. Over the course of treatment, the investigators titrated dose and duration according to clinical response and hormonal parameters. On the whole, the doses needed by the 5 infants were similar: rLH 150 IU/24 h and rFSH 75 IU/24 h. Serum testosterone rose to mean 12.1 nmol/L, along with the 3- and 5-fold increase in serum inhibin B and AMH, respectively. Among the 4 CHH patients with cryptorchidism, 3 had unilateral (high-scrotal or inguinal) and 1 had bilateral (high-scrotal) maldescended testes. Gonadotropin therapy led to spontaneous testicular descent in 2/4 infants (1 unilateral and 1 bilateral) and hence reduced the need for orchidopexy by half. The robustness of

Table 1. Studies of gonadotropin therapy in non-cryptorchid CHH infants.

Study, No. of non-cryptorchid /total CHH subjects	Gonadotropin treatment		Treatment Outcomes (vs pretreatment values)					
	Age at start/ Duration of therapy	Dosing regimen	TV (mL)	PL (mm)	T (nmol/L)	IB (pg/mL)	AMH (pmol/L)	Remarks
Continuous Subcutaneous Infusion								
Bougnères et al. 2008 [70], n = 2/2	2–14 wk/17-28 wk	LH 50–56 IU/d FSH: 67–125 IU/d	2.10 (3.7–4.7x)	21–38 (2.6–4x)	Mean 4.8–7.6 (80–253x)	Mean 426–701 (4–140x)	Mean 608–826 (1.5–2x)	Demonstrated that the a) suppression of AMH secretion by LH-driven T from LCs, which occurs in CHH adults, is not observed in CHH infants. b) SCs of CHH infants are resistant to FSH, requiring levels up to 18-fold ULN to achieve normal IB and AMH.
Sarfati et al. 2015 [71], n = 1/1	1 mo/6 mo	LH 75 IU/d FSH 75 IU/d	2.3 (2x)	38 (2.5x)	-	-	-	Baseline TV enlarged on treatment and remained normal (0.8 ml) for 1 year after treatment ended.
Stoupa et al. 2017 [74], n = 1/5	5.5 mo/3 mo	LH 150 IU/d FSH 75 IU/d	-	45 (3x)	[a]Peak ~3	[a]Peak >800	[a]Peak ~150-200	[a]Estimated from the graph (Figure 1) as no absolute values are provided.
Subcutaneous Injection								
Main et al. 2002 [69], n = 1/1	7.9 mo/5.8 mo	LH: 20 IU 2x/wk x7 wk, then 40 IU 2x/wk x7 wk FSH: 21.3 IU 2x/wk x23 wk	0.084 (2.7x)	24 (1.5x)	< lower limit	2x (absolute value NA)	-	Penile growth occurred despite undetectable T, with further growth (24 → 27 mm) following T suppositories, 1 mg/d for 6 wks.
Kohva et al. 2019 [77], n = 3/5	1.3–4.2 mo/ 3-4.5 mo	LH: nil FSH: 7.5–16.7 IU 2x/wk	Testes ascended	30–35 (1.3–2.2x)	-	[b]77-186 (2.3–5.1x)	-	[b]Data are only available for two subjects. Subjects concurrently received IM T 25 mg 1x/mo x 3 mo. Testes ascended before FSH therapy in 1 subject, and only after FSH therapy, in the other 2 subjects.

CHH, congenital hypogonadotropic hypogonadism; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TV, testicular volume; PL, penile length; IB, inhibin B; AMH, anti-Müllerian hormone; ULN, upper limit of normal; d, day; mo, month; wk, week; IM, intramuscular; T, testosterone; SC, Sertoli cell; LC, Leydig cell.

Table 2. Studies that described testicular descent as an outcome of gonadotropin treatment in CHH neonates/infants.

Mode of gonadotropin delivery	Study, No. of cryptorchid/total CHH subjects	Dosing regimen	Total cumulative dose per patient	Testicular Descent (per total No. testes)			Remarks
				Complete	Partial	No	
Continuous subcutaneous infusion	Lambert and Bougnères et al. 2016 [75], n = 8/8	LH 75 IU/d + FSH 75–150 IU/d x5-6.5 mo	LH: 7,000 IU FSH: 21,000 IU	13/16	3/16	0/16	n = 1 failed to achieve adequate rise in AMH and IB levels during treatment and required orchidopexy after both testes retracted 11 mo following their original complete descent.
	Stoupa et al. 2017 [74], n = 4/5	LH 150 IU/d + FSH 75 IU/d x3-5.5 mo	LH: mean 17,775 IU (13,500–21,375) FSH: mean 9,450 IU (6750–13,500)	3/5	0/5	2/5	U/L (n = 3) and B/L cryptorchidism (n = 1). LH infusion dose increased from 75 to 150 IU /24 hr at 2.5 mo in n = 1. The 2 nonresponders (both U/L cryptorchid) had low to moderate AMH and IB responses. In contrast, the subject with greatest biochemical response had the fastest descent occurring in 3 mo.
Subcutaneous injections	Kohva et al. 2019 [77], n = 3/5[a] (see remarks)	FSH 7.5–16.7 IU 2–3 x/week (3.4–7.5 IU/kg/wk). IM T inj. (25 mg/mo x3 mo). No LH or hCG given	FSH mean 325.2 IU (199.2–601.2)	0/6	0/6	0/6	n = 3 had B/L cryptorchidism prior to FSH therapy[a]. Ascent of testes occurred after FSH treatment (n = 2). All boys required B/L orchidopexy. Compared to other studies, FSH monotherapy without LH/hCG and significantly lower doses were used.
	Papadimitriou et al. 2019 [56], n = 10/10	LH 75 IU/d + FSH 150 IU/d x3 mo	LH: 6,750 IU FSH: 13,500 IU	20/20	0/20	0/20	Fixed doses used for all subjects. Testicular descent occurred in 30% after 1 mo, in 40% after 2 mo, and in 30% after 3 mo (100% cumulative). In n = 2 (septo-optic dysplasia and hypoplastic pituitary), one of 2 testes later retracted to the low inguinal region requiring orchidopexy. At 3–10 yrs follow-up, all testes remained intrascrotal, with slight regression in size (1.0 ml, ranged 0.5–2.0).

CHH, congenital hypogonadotropic hypogonadism; LH, luteinizing hormone; FSH, follicle-stimulating hormone; IB, inhibin B; AMH, anti-Müllerian hormone; d, day; mo, month; IM, intramuscular; T, testosterone; U/L, unilateral and B/L bilateral (cryptorchidism)

biochemical response appears to be associated with a better descent rate.

Separately, another case series from France by Lambert and Bougnères reported favorable experience with the use of subcutaneous combined gonadotropin infusion in inducing testicular descent in bilateral-cryptorchid infants [75]. Eight male infants with CHH, of whom 3 had CPHD, aged 0.25 to 11 months, and had either nonpalpable (5/8) or palpable testes in a high nonscrotal position (3/8). Diagnosis was confirmed by detectably low serum LH and testosterone levels, consistent with that of missing minipuberty. Using an insulin pump system, continuous infusion of rLH and rFSH was delivered at 50 IU and 75–150IU daily, respectively, which served to achieve minipuberty-range gonadotropin and testosterone levels. Similarly, both serum AMH and inhibin B levels reached levels normally expected during minipuberty in most, except in 2 (1 CHH infant with inadequate AMH and inhibin B, and 1 CPHD infant with inadequate inhibin B response). Following therapy, of the 10 nonpalpable (abdominal position) testes in 5 infants, complete descent was observed in 7 testes, whereas incomplete descent occurred in 3 (all high-scrotal position). All the other 3 infants with bilateral high-scrotal testes showed complete descent. Of note, one infant with abdominal testes who had complete response initially experienced reascent of both testes nearly 1 year later, necessitating orchidopexy.

More recently, Papadimitriou et al. reported successful descent of testes into the scrotal position in a cohort of 10 neonates and infants with bilateral cryptorchidism and micropenis following combined gonadotropin therapy (REMAP study) [56]. Prior to treatment, absent minipuberty was all biochemically confirmed by the repeatedly low serum gonadotropins and testosterone levels in the first 3 months after birth. Treatment with a commercially available combined recombinant gonadotropin preparation (LH 75 IU and FSH 150 IU) was initiated at a median age of 0.35 years (0.19–0.78). Parents were trained to administer daily subcutaneous injection at home for 3 months (total of 90 injections). During

the course of treatment, the penile length doubled from a median of 2.0 to 3.8 cm, along with a significant rise in serum levels of testosterone, inhibin B, and AMH.

From these published series (Table 2), combined LH and FSH therapy has emerged to be a highly promising hormonal regimen in inducing complete testicular descent in infants. Of note, the biochemical response (inhibin B and AMH) to gonadotropin therapy tends to correlate with the success rate of descent.

In contrast, the combination of FSH with exogenous testosterone instead of LH does not appear to exert similar effects [76]. In a cohort of five infants treated with concurrent FSH and testosterone replacement, all required bilateral orchidopexy after cryptorchidism failed to correct in 3/5, and testicular ascent occurred in the other two, despite having elicited a good therapeutic response in both Sertoli cell function and penile lengthening [77]. This provides evidence that the synergistic action of both FSH and LH is essential for generating the hormonal milleu for testicular descent and intrascrotal anchoring. Conceivably, exogenous testosterone therapy is incapable of matching the high concentration of intratesticular Leydig cell-derived androgen and INSL3 under LH drive that is necessary for effective paracrine signaling. The alternative explanation is that the FSH doses used were significantly lower (1/40 or less) compared to other studies, which could be grossly inadequate to drive the growth of Sertoli cells. From the inhibin B levels of the 3 subjects provided graphically, it can be estimated that the peak levels achieved ranged from ~50 to just under 300 pg/mL. In comparison, a mean inhibin B level of 368 pg/mL (normal range 254–513) was achieved in the study by Lambert and Bougnères, which administered a total cumulative FSH dose of 21,000 IU per patient [75]. Sertoli cell resistance has been suggested to be present in CHH infants with cryptorchidism due to the lack of FSH stimulation prenatally, hence necessitating higher therapeutic doses [75].

As alluded to earlier, although surgical orchidopexy by 1 year of age is widely recommended to preserve testicular function and prevent germ cell loss [65,67,78], conservative correction of testicular maldescent by hormonal means would be helpful to avoid surgical risks [42], in addition to the benefit of restoring growth of immature Sertoli cells and spermatogonia. Intriguingly, in a recent retrospective study, history of orchidopexy in cryptorchid CHH men was not associated with a more favorable spermatogenic response to gonadotropin treatment as would normally be expected for cryptorchidism from non-CHH etiologies [79]. A plausible explanation could be the inadequacy of orchidopexy to remediate the absence of gonadotropin-mediated transformation of gonocytes into adult dark (Ad) spermatogonia in undescended testes [80,81]. The supply of stem cells for spermatogenesis relies on Ad spermatogonia. These data may further support the role of targeted hormonal intervention in CHH instead of surgical correction to optimally mitigate the sequelae of deficient minipuberty. Even in less successful cases, the increased testicular size following gonadotropin stimulation would aid in facilitating surgical manipulation, thereby minimizing the risk of trauma to testicular tissue, which could result in long-term damage and further diminishes prospect of fertility.

Our own local experience in adolescent CHH males with cryprorchidism is that, even in late teenage years, combined gonadotropin therapy is invariably successful in inducing descent of testes into the scrotum, provided that there has been no prior attempt at surgical orchidopexy [82], similar to a recent report by Sharma et al. (discussed in section 8.1) [83]. However, for those who underwent unsuccessful surgical exploration earlier in childhood, sometimes repeatedly, our experience with combined gonadotropin treatment is both positive and negative; negativity in that medical descent is not achievable, likely due to postsurgical fibrosis in the line of descent, but positivity in that gonadotropin-induced increase in the testicular volume has invariably permitted definitive localization and allowed successful surgery.

It should be emphasized that the success rate of gonadotropin therapy in the treatment of cryptorchidism relies on careful selection of infants with biochemical evidence of gonadotropin deficiency. Studies performed in the setting of CHH/CHPD have demonstrated favorable outcomes without adverse effects. On the other hand, nonselective use of gonadotropins in cases of idiopathic cryptorchidism demonstrated a negligible effect on testicular descent, with possible deleterious consequences on the viability of testicular germ cells [42,84]. Clinicians unfamiliar with such consideration might have misconceptions that gonadotropin therapy should be avoided entirely.

6. Prognostic factors of fertility induction in CHH men

Adult men with congenital causes of HH typically respond less favorably to gonadotropin therapy with regard to spermatogenic parameters compared to those with acquired causes [85,86]. The fundamental reason is the much earlier onset and greater degree of GnRH/gonadotropin deficiency in CHH, leading to disrupted minipuberty-primed testicular development. The efficacy of combined gonadotropin therapy and pulsatile GnRH therapy is comparable and hence does not significantly affect spermatogenic outcomes [86,87].

In a multicenter study of adolescents and young adults with HH receiving gonadotropin (hCG/rFSH) therapy, factors that are found to be associated with poorer therapeutic response (testicular growth and spermatogenesis) would reflect the above are as follows: history of bilateral cryptorchidism, low baseline testicular volumes, and low serum inhibin B and AMH levels [73]. These clinical features represent longstanding severe gonadotropin deficiency with lack of the minipuberty phase of testicular development. Conversely, among CHH adult men who undergo spermatogenic induction by gonadotropin replacement, predictors of success include testicular volume ≥4 mL (vs. <4 mL), higher inhibin B, and the absence of history of cryptorchidism [88,89].

Overall, nearly one-third of men with severe CHH (testicular volume <4 mL) remain persistently azoospermic even with a prolonged course of combined gonadotropin therapy, while those with partial GnRH deficiency (testicular volume ≥4 mL) tend to respond more favorably, with 80% demonstrating sperm in ejaculate during treatment [90]. Therefore, it is clear that a critical volume of seminiferous tubules and germ

cells that attained prepubertal – which would rely on neonatal-infancy minipuberty – at the time of puberty initiation is key to successful testicular maturation and subsequent spermatogenesis.

While testosterone therapy (commonly intramuscular injection of short-acting testosterone formulation) is effective in correcting congenital micropenis, it does not have any significant effect on testicular spermatogenic tissue growth. On the other hand, it was demonstrated in prepubertal boys with CHH in early adolescence that the administration of rFSH alone was successful in inducing at least a 2-fold increase in the testicular volume, along with the rise of serum inhibin B into the healthy range, reflecting the proliferation of Sertoli cells and lengthening of seminiferous tubules that had taken place [91]. Furthermore, the milieu of Leydig cell-derived androgens produced under gonadotropin stimulation may also be beneficial for facilitating spontaneous testicular descent in neonates or infants with CHH-associated cryptorchidism, which conceivably would further improve fertility potential. These changes will not be achieved via exogenous testosterone replacement.

7. Longer-term unmet health needs addressed by early detection and continuous surveillance

The benefit of early diagnosis and intervention extends beyond the provision of targeted hormonal therapy in infancy(36). CHH is a lifelong disorder that would require long-term surveillance for any associated health complications, as well as to ensure appropriate hormonal replacement. Being a rare medical disease, CHH patients would benefit greatly from the watchful eyes of experienced healthcare providers, as nonspecialized centers may lack the expertise to address the gaps in care [92–94]. Evolving genetic landscape in the advent of next-generation sequencing is anticipated to accelerate the understanding of CHH genetics, and patients on follow-up could benefit directly or indirectly from participating in research studies [95].

Psychosocial challenges often confront patients with CHH and have a great impact on quality of life. Surveys conducted revealed high prevalence of psychological comorbidities, moderate to severe depressive symptoms, social isolation, and antidepressant use among CHH men [29,96]. This also negatively impacts the long-term adherence to hormone replacement [28]. Early and continuous engagement with patients and their parents provides opportunities for the multidisciplinary team to intervene and equip them with knowledge and coping strategies. This would allow any issues that could affect their self-esteem and ability to form relationships to be addressed early.

Failure to provide age-appropriate pubertal induction contributes to poor psychological health as well. Issues such as low self-confidence, social withdrawal, poor academic performance, and substance abuse are often associated with delayed puberty [97,98]. A structured follow-up program, therefore, facilitates timely pubertal induction as the children enter adolescence so that they develop secondary sexual characteristics and sexual maturity in tandem with their peers [33], avoiding unnecessary delay due to the diagnostic uncertainty and physician's hesitancy to treat [97]. Furthermore, it is noteworthy that gonadotropin compared to testosterone therapy appears to be associated with better psychological outcomes including emotional and mental health in one study [99], which informs clinicians the importance to discuss treatment options with patients. Where appropriate and desired, timely discussion on fertility prospects and treatment options, including assisted reproductive techniques, in late adolescence and adulthood would serve well to allay unnecessary anxieties. This illustrates the need to tailor treatment according to needs and priorities at different stages of life [18].

8. Gonadotropin therapy – Novel concepts in adolescents and adults

8.1. Induction of testicular descent beyond infancy

Besides being an effective treatment in inducing puberty and genital development in prepubertal adolescents, gonadotropin therapy appears to be capable of promoting testicular descent even in this older age group akin to that of male infants. Cryptorchidism affects between 30 and 50% of CHH males, of whom up to two-thirds have bilateral disease [20,21,53,100], and thus, the feasibility of gonadotropin-induced testicular descent might be important in those who present late with untreated cryptorchidism.

In a small series of CHH patients aged 1.5 to 26 years who received adequate FSH therapy (given as human menopausal gonadotropin (hMG)) either as pretreatment or in combination with LH (given as hCG) from the outset, 5/6 patients with bilateral cryptorchidism experienced successful correction, with all testes descended from the inguinal canal to scrotal position after a mean treatment duration of close to 5 months (Table 3) [83]. Of these five patients, long-term follow-up data were available for 3 patients, which showed maintenance of the scrotal position (testicular volume of 5–8 ml) and successful spermatogenesis induction in 2 men. In the only patient with persistent unilateral right undescended testis, it remained undeveloped at 1 ml despite subsequent orchidopexy, whereas the left intrascrotal testis attained a size of 12ml on long-term follow up. It is noteworthy that in two pediatric patients (age 1.5 and 10.4 years), even hMG alone for 2–4 months could demonstrate partial efficacy, which was not observed in another study with patients on FSH monotherapy (Table 2) [77]. This is presumably due to the LH activity that is provided by hMG in equal potency as its FSH activity.

8.2. Sequential gonadotropin therapy to maximize fertility potential

Among men with CHH who desire fertility, LH (hCG or rLH) and FSH (hMG or rFSH) therapies are the mainstay of treatment [101]. Spermatogenesis is achieved by the concerted actions of FSH and LH-driven intratesticular testosterone [102]. Its efficacy is at least on par with that of the far more complicated pulsatile GnRH therapy, which is not readily accessible in most tertiary centers. However, it should bear in

Table 3. **Single-center experience with gonadotropin-induced testicular descent in CHH beyond infancy** [84].

hMG priming?	Subject: Age (yrs)	Subcutaneous Gonadotrophin Therapy[a]	Outcomes (compared to baseline)				Time to testicular descent (mo)		Remarks; longer term follow-up data (if any)
			TV (ml)		T (nmol/L)	IB (pg/mL)			
			R	**L**			R	L	
Yes	#1: 1.5	hMG 25 IU 3x/wk x2 mo, then hMG 25 IU 3x/wk + hCG 250 IU 2x/week	0.17 -> 0.53 US	0.12 -> 0.64	5.7 (40x)	240 (3x)	5	2	L descended after 2 mo hMG monotherapy
Yes	#2: 10.4	hMG 150 IU 3x/wk x 4mo, then hMG 150 IU 3x/wk + hCG 500 IU 2x/wk	0.5 -> 0.71 US	0.2 -> 0.49	1.4 (5.8x)	152 (17.5x)	4	6	R descended after 4 mo hMG monotherapy
Yes	#3: 14.7	hMG 150 IU 3x/wk x 2 mo, then hMG 150 IU 3x/wk + hCG 500 IU 2x/wk	1 PO, no baseline measurement	1	2.8 (16.7x)	125 (2.4x)	4	4	After 18 mo CGT: TV: 6 ml (R) and 8 ml (L); T 16.6 nmol/L Peak sperm concentration: not examined
No	#4: 12	hMG 75 IU 3x/wk + hCG 1,000 IU 2x/wk	0.2 -> 0.3 US	0.3 -> 0.4	4.2 (3.4x)	-	8	6	After 60 mo CGT: TV: 5 ml *r) and 5 ml (L); T 18.06 nmol/L Peak sperm concentration: 18 x 10^6/mL
No	#5: 25	hMG 75 IU 3x/wk + hCG 2000 IU 3x/wk PO, no baseline measurement	2	2	6.0 (2.3x)	-	4	4	After 28 mo CGT: TV: 8 ml (R) and 6 ml (L); T 17 nmol/L Peak sperm concentration: 32 x 10^6/mL
No	#6: 26	hMG 75 IU 3x/wk + hCG 2000 IU 3x/wk PO, no baseline measurement	1	4	4.6 (21.8x)	-	failed to descend after 42 mo	already in scrotum at baseline	After 32 mo of CGT: TV: 1 ml (R) and 12 ml (L); T 14.56 nmol/L Peak sperm concentration: 5 x 10^6/mL Pregnancy reported in partner

[a]Age-based dosing: (a) <10 yrs: hMG 3 IU/kg/dose 3x/wk + hCG 250 IU 2x/wk and (b) ≥10 yrs: hMG 75–150 IU 3x/wk + hCG 500–1,000 IU 2x/wk (10–20 yrs) or 2,000 IU 3x/wk (>20 yrs); CHH, congenital hypogonadotropic hypogonadism; US: ultrasound; PO: Prader Orchidometer; R: right; L: Left; wk: week; mo: month; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; wk, week; mo, month; TV, testicular volume; CGT, combined gonadotropin treatment; T, testosterone

mind that the order in which gonadotropin therapy is delivered has an impact on the chance of success in achieving spermatogenesis, particularly in those on the more severe end of the CHH disease spectrum.

Early studies of FSH monotherapy in children and adolescents proved its efficacy in promoting testicular growth and Sertoli cell function, as evidenced by increased circulating inhibin B concentrations [91,103]. Additionally, FSH pretreatment before the introduction of hCG demonstrated successful spermatogenesis in 4 out of 5 CHH/CPHD adolescents with a severely low baseline testicular volume of <3 mL [103], which would, otherwise, be typically associated with a substantially poorer response to conventional hCG therapy.

Likewise, FSH priming in adults has been shown in a randomized open-label clinical trial to produce superior spermatogenic outcomes. In this cohort of 13 treatment-naïve CHH men with a prepubertal testicular volume of <4 mL, GnRH treatment was given for 24 months in all subjects, of which seven were randomized to 4-month recombinant FSH pretreatment [104]. During the FSH pretreatment phase, the testicular size doubled along with the rise of inhibin B levels to healthy levels, and all men in this treatment arm developed sperm in ejaculate subsequently on GnRH therapy. In comparison, 2/6 in the GnRH-only treatment arm did not demonstrate spermatogenesis. In addition, the testicular volume, peak sperm counts, and time to appearance of sperm in ejaculate tended to be better in the FSH-primed group. In contrast, hCG monotherapy is typically unsatisfactory in the treatment of CHH men with prepubertal testes (*i.e.* testis volume <4 mL, comprising 2/3 of CHH males). Chen et al. reported a median treatment duration of 3.5 years before the appearance of sperm ejaculate in those who eventually responded to treatment, and it is not surprising that the testicular volume <4 mL and/or cryptorchidism correlated with poor therapeutic response [105].

Therefore, in adolescent or adult men with prepubertal testes due to severe CHH, current limited evidence suggests that it would be beneficial to first maximize the proliferation of Sertoli and germ cells and elongation of seminiferous tubules, similar to the wave of growth normally present during minipuberty, through a 2–4-month period of unopposed FSH therapy. Importantly, such an approach avoids the risk of causing terminal differentiation of an already depleted pool of Sertoli cells arising from the high concentration of intratesticular testosterone from premature introduction of LH (hCG) therapy. Monotherapy with hCG in complete CHH is essentially pointless as the failure rate is exceedingly high [106,107]. On the other hand, FSH pretreatment before combined gonadotropin therapy may be less crucial in partial CHH men with the testicular volume >4 mL [101,108].

9. Conclusions

Growing literature on the effectiveness and safety of gonadotropin therapy in infancy supports the consideration of such treatment in the care of neonates and infants affected by CHH, particularly in the correction of micropenis and undescended and/or underdeveloped testes. In the longer term, by optimizing the prepubertal development of Sertoli cells and seminiferous tubules through minipuberty replacement, response to spermatogenesis-induction therapy is likely to be enhanced in adulthood, thereby improving the fertility prospect.

As such, it is timely to focus efforts on the early diagnosis in male infants with clinical features suggestive of congenital GnRH/gonadotropin deficiency (”red flags”), so that prompt investigations can be undertaken within the narrow window of opportunity (minipuberty phase).

10. Expert opinion

Male CHH is a challenging condition for two key reasons. First, the diagnosis has not always straightforward, and hence, meaningful treatment is typically delayed until late adolescence and even beyond, with resultant long-term consequences to patients’ physical and mental health. In adult life, these men express levels of distress comparable to patients with end-stage cardiorespiratory diseases [109]. Second, while hypogonadotropic hypogonadism (HH) is generally amenable to gonadotropin therapy for fertility induction, the spermatogenic outcomes in men with CHH have been frustratingly dismal compared to those with adult-onset HH, reflecting the critical role and far-reaching impact that GnRH action during *in utero* and neonatal-infancy period has on reproductive capacity in adulthood.

Hence, a different approach is clearly necessary to improve clinical outcomes, and this is supported by growing insights into the fundamental role of minipuberty in reproductive tract development. Minipuberty is a key GnRH-driven developmental phase in neonates and infants who stimulate penile and testicular growth, with a priming role for future maturation and acquisition of spermatogenic function during puberty as well. The lack of minipuberty could therefore manifest early in life as micropenis and/or cryptorchidism (”red flags”).

At present, there remains a lack of consensus in undertaking targeted reproductive hormone evaluation in neonates and infants with suspicious phenotypic features. As near-adult levels of gonadotropins and testosterone are normally expected during the phase of minipuberty, biochemical testing within this window of opportunity could reliably identify or exclude underlying HH. Establishing early diagnosis confers the advantage of instituting timely and appropriate hormonal therapy, thereby avoiding surgical orchidopexy in CHH infants with cryptorchidism.

Indeed, gonadotropin therapy in the first year of life has demonstrated to effectively replicate minipuberty by inducing testicular descent as well as correction of microphallus. Importantly, the concomitant testicular growth from the expansion of Sertoli cells and seminiferous tubules following therapy in childhood potentially addresses the gap in spermatogenic response later in life when these men undergo fertility treatment. While long-term outcomes are not yet available, experience in adult men with CHH has corroborated such a minipuberty-like gonadotropin treatment approach in enhancing spermatogenesis. Furthermore, gonadotropin replacement in neonates and infants has a sound physiological basis and is

well-tolerated in clinical studies. The key barriers to such treatment presently include the lack of awareness among clinicians, limited published data (in large part due to the rarity of the condition and in part to the costs, regulatory burden and funding-gap for undertaking investigator-led clinical trials in children in areas other than cancer), and the absence of guidance on the most optimal strategy to employ gonadotropin therapy in young children.

As illustrated in Figure 2, various administration modes and dosing regimens are reported by different investigators, which may inadvertently create uncertainties. For the field to advance, concerted efforts among tertiary centers with the necessary expertise are crucial to generate a framework for research priorities and to provide guiding principles on diagnostic and therapeutic approaches that are feasible for wider clinical adoption. For instance, in major urological guidelines, surgical orchidopexy before the age of 12 months is the recommended treatment of choice for undescended testis, with indiscriminate hormonal therapy being cautioned against. Incorporating a standardized endocrinological evaluation algorithm (Figure 1) would be helpful to guide clinicians in identifying affected children with underlying HH who might better benefit from gonadotropin therapy instead. With greater case detection among boys with suspicious clinical features, larger clinical studies may be carried out to determine the optimal dosing and duration of gonadotropin treatment and to provide longitudinal data on the long-term benefit of minipuberty-hormone replacement. Importantly, early identification allows patients to benefit from structured long-term follow-up of their growth and development in expert centers. With regard to the mode of gonadotropin delivery, the REMAP study demonstrated the feasibility and efficacy of a commercially available fixed rLH:rFSH dosing that could be subcutaneously administered by parents at home with relative ease [56]. Further studies could explore similar principles that will help to reduce the technical barrier to gonadotropin therapy in young children. In the future, with the expansion in the knowledge of CHH genetics in the current era of next-generation sequencing technologies, it is hopeful that these data would improve disease categorization and individualization of treatment.

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