Clinical Management of Congenital Hypogonadotropic Hypogonadism

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ABSTRACT: The initiation and maintenance of reproductive capacity in humans is dependent on pulsatile secretion of the hypothalamic hormone GnRH. Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder that results from the failure of the normal episodic GnRH secretion, leading to delayed puberty and infertility. CHH can be associated with an absent sense of smell, also termed Kallmann syndrome, or with other anomalies. CHH is characterized by rich genetic heterogeneity, with mutations in >30 genes identified to date acting either alone or in combination. CHH can be challenging to diagnose, particularly in early adolescence where the clinical picture mirrors that of constitutional delay of growth and puberty. Timely diagnosis and treatment will induce puberty, leading to improved sexual, bone, metabolic, and psychological health. In most cases, patients require lifelong treatment, yet a notable portion of male patients (~10% to 20%) exhibit a spontaneous recovery of their reproductive function. Finally, fertility can be induced with pulsatile GnRH treatment or gonadotropin regimens in most patients. In summary, this review is a comprehensive synthesis of the current literature available regarding the diagnosis, patient management, and genetic foundations of CHH relative to normal reproductive development. ***(Endocrine Reviews 40: 669 – 710, 2019)***

Puberty is one of the most striking postnatal developmental processes in humans. It is accompanied by the acquisition of secondary sexual characteristics, the onset of fertility, the attainment of adult height, and imporant psychosocial changes (1). Puberty is initiated by the reawakening of the hypothalamic-pituitary-gonadal (HPG) axis following a relative quiescence during childhood (2). Pulsatile secretion of GnRH by specialized neurons in the hypothalamus stimulates the release of FSH and LH by the pituitary, which in turn stimulate steroidogenesis and gametogenesis in the gonads. Notably, the onset of puberty is preceded by two periods of HPG axis activity: the fetal life and infancy (minipuberty).

The timing of puberty varies largely in the population, and 50% to 80% of this variation is genetically determined (3–5). Delayed puberty is defined as a delay of pubertal onset or progression >2 SD compared with the population mean (6). Constitutional delay of growth and puberty (CDGP) is the most frequent cause of delayed puberty (2% in the general population) and is related to a transient GnRH deficiency. In CDGP, puberty eventually begins and is completed spontaneously. In contrast, congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disease caused by GnRH deficiency. It is characterized by absent or incomplete puberty with infertility (7). This infertility is medically treatable, and

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ESSENTIAL POINTS

- Minipuberty is an important window to assess the activity of the hypothalamic–pituitary–gonadal axis, especially in male neonates with cryptorchidism and/or micropenis, to diagnose neonatal congenital hypogonadotropic hypogonadism (CHH)
- Currently, it is difficult to differentiate CHH from constitutional delay of growth and puberty (CDGP) in early adolescence, as these two conditions have nearly identical clinical presentations and biochemical profiles
- While awaiting the development of novel biomarkers, testicular volume and circulating serum inhibin B levels may be most reliable parameters to date to differentiate CHH from CDGP
- Given the complex genetics of CHH, including oligogenicity, reduced penetrance, and variable expressivity, defining a clear genetic diagnosis for each patient is often daunting
- Treatments are effective to induce secondary sexual characteristics in both sexes; however, the role of gonadotropin therapy during the neonatal and adolescence periods remains unclear
- Infertility in patients with CHH can often be treated successfully with a combination of gonadotropins or pulsatile GnRH, although patients with the most severe form of GnRH deficiency may benefit from a pretreatment with FSH

in fact CHH is one of the few treatable causes of infertility in males. When CHH is associated with anosmia, it is termed Kallmann syndrome (KS).

Considerable differences exist in the terminology surrounding the permanent forms of GnRH deficiency in humans, with idiopathic hypogonadotropic hypogonadism (IHH), isolated GnRH deficiency, and CHH being used almost interchangeably. IHH was the first terminology to appear in print (8); however, “idiopathic” is typically reserved for diseases that appear spontaneously or whose cause is undetermined (9). Several molecular etiologies have since been described underlying this disorder, resulting in the less frequent use of IHH. Isolated GnRH deficiency was first reported in the literature in 1986 (10) and is still widely used in North America. However, the disorder can be due to mutations in the GnRH receptor, resulting in a state of GnRH resistance rather than deficiency. CHH was first used in 1980 (11). Although the diagnosis is often made during adolescence or afterward, the disease is mostly due to developmental defects (*i.e.*, defects in GnRH neuron migration or in the maturation of the GnRH neuronal network) and is often associated with congenital features. The term CHH is commonly used, especially in Europe, and is used in this review.

In this review, we describe the spectrum of clinical presentations in CHH, the diagnostic evaluations including the challenge of differentiating CHH from CDGP, the advances in genetic diagnosis and therapy for CHH, as well as the consequences of a delay in diagnosis. Finally, we discuss the therapeutic options from different perspectives. To achieve these objectives, we also review the normal physiology of the HPG axis.

Fetal Development of the HPG Axis

The HPG axis is active in the midgestational fetus but is quiescent toward term (12). This restraint is removed after birth, leading to a reactivation of the axis and an increase in gonadotropin levels (minipuberty).

Most GnRH-secreting neurons are located in the arcuate nucleus and the preoptic area of the hypothalamus (13). GnRH neurons are an unusual neuronal population, as they originate outside the central nervous system in the olfactory placode, and follow a complex migration route to reach their final destination in the hypothalamus (14, 15). The complex developmental process of GnRH neurons has unfolded through both murine and human genetic studies (16–18).

GnRH neuron fate specification occurs from progenitor cells in the olfactory placode at gestational week (GW) 5 in humans, and days 9.5 to 11 in mice (19). Subsequently, the GnRH neurons begin their migration from the nasal placode, following the axon guidance of the vomeronasal nerve (VNN) and the olfactory nerve until they cross the nasal mesenchyme and cribriform plate. Thereafter, the GnRH neurons follow the guidance of the VNN ventral branch, reaching the forebrain. From here, the GnRH neurons detach from the VNN axons to reach their final destination in the arcuate nucleus and the preoptic area of the hypothalamus. Subsequently, they extend their axons to the median eminence, reaching the fenestrated blood–brain capillaries of the hypothalamo–pituitary portal vessels. By day 16 in the mice and ~15 weeks of gestation in human, GnRH is detected in the hypothalamus and the GnRH neuronal system is largely complete (18, 20).

Recently, studies of GnRH ontogeny in mice and humans using the innovative technique of 3DISCO optical tissue clearing reveal the detailed dynamics of GnRH neuron ontogeny and migration from the nasal compartment to the forebrain. Notably, the number of GnRH neurons in the human fetal brain is much higher (~10,000) than previously anticipated (18).

LH is detected in the human anterior pituitary by GW 9 (21) and is released into the circulation by GW 12 (22–24). The exact timing when pituitary gonadotropin secretion will come under the control of the hypothalamic GnRH is not clear. In anencephalic fetuses without a hypothalamus, pituitary development is normal up to GW 17 to 18 before it involutes, suggesting that hypothalamic signaling is needed for the maintenance of the gonadotropes from this stage (25). Fetal serum gonadotropin levels peak at midgestation in both sexes and decrease near term (26). This decline in the gonadotropins is likely due to the negative feedback mediated by increased placental estrogen (12). However, limited data exist on the hypothalamic–pituitary function in human fetuses after GW 22 (26). Females generally exhibit high circulating FSH and LH levels in the range of postmenopausal women, which is much higher than in male fetuses (22, 23, 26–29). Near term, circulating gonadotropin levels decrease. The latter is thought to be related to the increase of placental estrogens and progesterone, acquisition of sex steroid nuclear receptors by pituitary gonadotropic cells, and subsequent gonadal feedback (22–24, 28, 30).

The differentiation of the gonads into testicles and ovaries occurs between GW 5 and 7. It is a complex process involving a critical role of the *SRY* gene on the Y chromosome for males. During GW 8, the differentiated Sertoli cells in the seminiferous tubules start to produce anti-Müllerian hormone (AMH) under the contol of SOX9, which leads to regression of the Müllerian ducts (31). Placental human chorionic gonadotropin (hCG) during the first trimester and subsequently fetal pituitary LH from midgestation regulate Leydig cell differentiation to produce testosterone (T) from the fetal Leydig cells (32), which is needed for masculinization of the fetus. T is needed for the development of the male internal genitalia, whereas dihydrotestosterone produced by the enzyme 5-α reductase 2 (SRD5A2) induces the formation of the prostate, penis, and scrotum. Until midgestation, T production is driven by placental hCG rather than by GnRH-induced LH secretion by the fetus. This is consistent with the absence of genital differentiation defects in CHH. However, in the third gestational period penile growth and inguinoscrotal testicular descent occur, mediated in part by T stimulated by GnRH-induced LH secretion [reviewed in Refs. (33) and (34)].

In females, the gonads develop into an ovary in the absence of the Y chromosome. However, several active signaling pathways need to be present for a normal differentiation of the ovary (35). Additionally, the differentiation of internal or external genitalia occurs independently of the ovaries. In the absence of AMH, the Müllerian ducts will develop into fallopian tubes, uterus, and a portion of the vagina. In humans, primordial follicles develop in the fetal ovary around GW 15 (36) and are gonadotropin-independent. At this stage, the amount of steroid production from fetal ovaries seems minimal compared with high placental estrogen production (37).

Fetal reproductive development: implications for CHH phenotypes

Disruption of the complex ontogeny of the GnRH neurons and olfactory system can lead to GnRH deficiency and, in severe cases, to CHH with or without anosmia. However, during the first trimester of pregnancy, which is critical for sexual differentiation, the GnRH neuronal system is nonfunctional. Consequently, the differentiation of the genitalia in CHH is normal. In contrast, during late pregnancy GnRH-induced LH secretion stimulates further penile growth and testicular descent. Thus, a higher prevalence of micropenis and cryptorchidism is encountered in CHH [reviewed in Ref. (34)].

Clinical Presentation of CHH

Clinical presentation of CHH during minipuberty

Normal minipuberty

Within minutes of birth, a brief postnatal LH surge leads to an increase in T levels during the first day of life, which then subsides (38).

After the first postnatal week, as serum placental estrogen levels have declined, increased pulsatile GnRH secretion (39) leads to elevated gonadotropins and sex steroid levels in both sexes, with peak levels observed at 1 to 3 months of age (minipuberty) (40–44). During this time, FSH levels are higher in girls, and LH levels are predominant in boys (43). In boys, LH and FSH levels decrease by 6 months of age; however, FSH levels remain elevated up to 3 to 4 years of age in girls (12, 43, 45). A recent study of both full-term and preterm infants suggests that gonadal feedback mediated by sex steroids, as well as inhibin B, can influence the sexual dimorphism for FSH and LH levels during minipuberty (46).

In boys, T levels start to increase after 1 week postnatally, peak between 1 and 3 months, and then decline to low prepubertal levels by ~6 months (12, 43, 45). These changes mirror GnRH-induced LH activation. During minipuberty, T levels correlate with penile growth (47), and postnatal T levels have also been associated with male-type behavior in toddlers (48). Additionally, acne, sebaceous gland hypertrophy, and increased urinary prostate-specific antigen levels are observed, consistent with androgen bioactivity (44, 49). GnRH-induced gonadotropin secretion stimulates the production of inhibin B (a marker of Sertoli cell number and function) (43) and AMH (50) and the Leydig cell product INSL3 (51). High inhibin B levels remain beyond 6 months of age despite the decrease in gonadotropin secretion (43).

Testicular volume (TV) increases during minipuberty (12, 52, 53). One critical event during this time is the proliferation of immature Sertoli cells and spermatogonia induced by FSH, mirroring the increased levels of circulating inhibin B. On average, the Sertoli cell population increases from 260×10^6 at birth to 1500×10^6 by 3 months of age, and this increase constitutes a critical determinant for future sperm-producing capacity in adulthood (53, 54). Despite high levels of intragonadal T and the gonadotropin surge, Sertoli cells and spermatogonia do not undergo differentiation, and spermatogenesis is not initiated. During this period, Sertoli cells express low levels of androgen receptors and thus remain immature despite increased T during minipuberty (50, 55, 56).

In girls, elevated gonadotropin levels result in an increase in ovarian follicular development (44, 49). Estradiol (E2) levels also start to increase after 1 week of age (44) and are associated with increased folliculogenesis (49), and then decrease during the second year of life (44). The high circulating E2 levels in girls lead to palpable breast tissue during minipuberty (44, 57). The postnatal gonadotropin surge also induces the production of the granulosa cell hormonal peptides inhibin B (43) and AMH (49).

In both sexes, T appears to be an important modulator of growth during infancy (58) and influences neurobehavioral sexual differentiation (48). Notably, minipuberty appears enhanced in preterm infants and in those born small for gestational age [reviewed in Ref. (12)].

The biological significance of minipuberty and its consequences on reproductive capacity are not fully understood. This period may be critical for future reproductive health, and thus warrants additional investigation. The exact mechanism that leads to the quiescence of the HPG axis after infancy remains largely unknown. The observation of a similar pattern of gonadotropin secretion occurs in boys with anorchidism indicates that the inhibition of the HPG axis at the end of minipuberty is independent of the gonads (59).

Minipuberty: implications for CHH phenotypes

From a diagnostic perspective, minipuberty offers a unique window of opportunity for the early diagnosis of CHH (60). Although there are no clear clinical signs of GnRH deficiency in female infants, micropenis and cryptorchidism raise a suspicion of CHH in male infants, as these signs may reflect the lack of activation of the HPG axis during fetal and postnatal life. Large retrospective studies on CHH, including KS, have described a frequency of cryptorchidism ranging from 30% to 50% (61, 62), which is higher than the general population [cryptorchidism in full-term male newborns is 1% to 3% worldwide (63) and 9% in Denmark (64)]. This observation is consistent with the role of GnRH-induced T secretion during fetal life and minipuberty in testicular descent. Reports on the frequency of micropenis among patients with CHH is variable, ranging from 20% to 40% in patients with KS, whereas a frequency of 0.015% is reported in the general population (65–67).

Clinical presentation of CHH during adolescence

Normal puberty

Puberty is characterized by sexual maturation, increased growth velocity, changes in body composition, and psychosocial behavior and culminates with the acquisition of reproductive capacity initiated by the reawakening of the GnRH pulse generator after a relative quiescent period during childhood (68, 69). GnRH-induced pulses of LH first occur during the night, but they gradually increase to both day and night, resulting in gonadal maturation and the completion of puberty (70–73). The precise mechanisms that trigger the initiation of puberty remain unclear. Murine studies have shown dynamic remodeling in GnRH neuron morphology occurring at puberty, with the acquistion of >500 spines associated with increasing synaptic inputs contributing to the sharp increase in GnRH neuron activity (74). Increased excitatory input, such as from glutamate, or decreased inhibitory input, such as from γ-aminobutyric acid, appears to be critical for pubertal onset (75). Additionally, the nature of the GnRH pulse generator is still under debate (76). In particular, whether GnRH neurons exhibit an intrinsic pulse generator or whether a neuronal network is required for pulsatile GnRH secretion remains unclear (77). A recent study demonstrated the key role of kisspeptin neurons located in the arcuate nucleus in driving GnRH pulsatility in mice (78). Previous studies performed in girls with Turner syndrome and in agonadal boys have clearly shown that the pubertal reactivation of the gonadotropic axis is independent of the presence of functional gonads (79–83).

The increase in GnRH-induced gonadotropins during puberty is critical to stimulate the production of gametes and thus fertility. In males, FSH secretion stimulates a second wave of proliferation of immature Sertoli cells and spermatogonia prior to seminiferous tubule maturation. This process is associated with an increase in the level of inhibin B, a marker of Sertoli cell number and function (84). Progressively, LH stimulates differentiation of Leydig cells and their steroidogenic capabilities, leading to T production. The concomitant stimulation of Sertoli cells by FSH and the production of intragonadal T by LH lead to the initiation of spermatogenesis and a sharp increase in TV, consisting mainly of maturing germ cells with an increase in the diameter of seminiferous tubules. During this process, AMH levels start a reciprocal decrease in comparison with T and inhibin B (85).

This finding likely reflects changes in androgen receptor expression in immature Sertoli cells, as androgen receptors are present in only 2% to 15% of Sertoli cells until 4 years of age, whereas its expression can be observed in >90% of Sertoli cells after the age of 8 years (55). Notably, AMH levels begin to decline before any notable increase in testis size (85, 86). Additionally, testicular INSL3 secretion increases during the course of puberty with a strong correlation to LH levels (87, 88).

In girls, the early stages of follicular growth are primarily driven by intraovarian factors. However, pubertal onset is characterized by an increase in gonadotropin levels that are necessary for terminal maturation of the follicules, leading to ovulation (89). GnRH-induced LH stimulates the production of androgens by the theca cells, whereas increased FSH is needed for the recruitment of ovarian follicles and the aromatization of androgens to E2 by the granulosa cells (90). AMH concentrations show only minor fluctuations during female puberty (91), whereas inhibin B, similar to boys, increases during puberty (92).

Clinically, puberty consists of a series of changes that typically appear in a predictable sequence. However, considerable variation in the timing of pubertal onset exists even among individuals of a given sex and ethnic origin, ranging roughly from 8 to 13 years in girls (93) and 9 to 14 years in boys (94). Pubertal tempo also exhibits substantial interindividual variation, with slightly faster progression rate in boys than in girls (95–97). Several studies have detected significant correlations between later pubertal onset and faster pubertal tempo in girls (98–101). The latter has been proposed as a compensatory catch-up mechanism.

A longitudinal follow-up of 432 white girls in the United States between 9.5 and 15.5 years old confirmed that the first detectable milestone of puberty is breast development (*i.e.*, thelarche, breast Tanner stage 2). Thelarche occurs at an average of ~10 years of age followed by the appearance of pubic hair (*i.e.*, pubarche) 4 months later (102). Almost concommitantly to thelarche, growth velocity begins to accelerate. The growth spurt lasts ~2 years and allows for the acquisition of ~18% of final height (103). Peak height velocity (PHV) occurs at an average of 11.5 to 12 years of age, ~1 year after thelarche (96). Menarche occurs ~6 months later (99). The median time between the onset of puberty and menarche is ~2.5 years (99, 104). Secondary sexual characteristics development (breast Tanner stage 4 and/or pubic hair stage 5) is completed ~1.5 years after menarche.

In boys, testicular enlargement (volume ≥4 mL) is the first clinically detectable sign of puberty, occurring at ~11.5 years of age and ~6 to 12 months before penis growth (*i.e.*, genital Tanner stage 3) and pubarche (94, 105, 106). The growth spurt begins subsequently with a PHV occurring at age 13.5. In a 7-year longitudinal study, spermatarche, defined as the presence of spermatozoa in the urine, was detected at a median age of 13.4 years (range, 11.7 to 15.3 years) (107). This suggests that spermatarche is a relatively early pubertal event, often preceding PHV. Another milestone of male puberty is the age of first ejaculation. A study of 1582 boys from Bulgaria showed an average age of 13.3 ± 1.1 years for first ejaculation (108). Voice breaking in males is also a distinct event usually occurring between Tanner stages G3 and G4 (97, 109). A retrospective longitudinal study of 463 Danish choir boys showed voice break at an average of 14.0 years (range, 13.9 to 14.6 years) (110). Complete pubertal development is achieved at an average age of 15.5 years or earlier according to the latest European data (94).

Common hallmarks of puberty in both sexes include bone mass acquisition, changes in body composition, and brain development. Bone changes during puberty are detailed in "Bone loss and fracture" below. Changes in body composition have different patterns in girls and boys. In early puberty, the increase in body mass index (BMI) is driven primarily by changes in lean body mass, whereas increases in fat mass are the major contributor in later puberty (111). Sex differences are evident, with girls exhibiting a higher proportion of fat mass gain than boys at all stages, with annual increases in BMI largely due to increases in fat mass after the age of 16 years (112). Hormonal changes during puberty also affect the brain by promoting its remodeling and completing the sexual maturation that begins in the prenatal and early postnatal life (113). This has been clearly demonstrated in animal models (114) and is supported by positive correlations between pubertal markers (physical or hormonal) and structural MRI changes in gray and white matter development in humans, even after removing the confounding effect of age (113).

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Trends in pubertal onset and progression

It is clear that the average age of menarche has decreased significantly between the 19th and the mid-20th centuries in many countries (115). This secular trend is associated with improved general health, nutrition, and lifestyle. A large Danish study comparing puberty in girls in two different periods (1991 to 1993 and 2006 to 2008) demonstrated earlier breast development in girls born more recently, even when adjusting for BMI. However, the central activation of puberty was not proven (93). This advance in breast development might be due to exposure to endocrine disruptors or other factors (116). Studies on the age of puberty in boys have also suggested an advanced age of pubertal onset, although additional research is required to confirm this trend. There are racial differences in pubertal onset (117), although this difference is probably decreasing (118).

Delayed puberty

Delayed puberty is defined as pubertal onset occurring at an age of 2 or 2.5 SD later than the population mean.

The traditional clinical cut-offs applied are 14 years for boys (TV <4 mL) and 13 years for girls (absence of breast development) (6). This definition, however, only focuses on the onset of puberty without considering progression of puberty as diagnostic criteria. Recently, the use of a puberty nomogram evaluating not only the pubertal onset but also pubertal progression (in SD per year) led to a more accurate description of normal puberty and its extremes (precocious and delayed puberty) (119) (Fig. 1).The most common cause of delayed puberty in both sexes is CDGP, which is often considered as an extreme variant of normal pubertal timing. In a large series of 232 patients with delayed puberty investigated in a tertiary US referral center, CDGP accounted for 65% of cases in boys and 30% of girls (120) presenting with a delay in puberty. Relatively similar estimates (82% for boys and 56% for girls) were reported in a recent European study encompassing 244 patients with delayed puberty (121). Although its pathophysiology is not fully understood, CDGP has a clear genetic basis, as 50% to 75% of patients with CDGP have a positive family history (122).

CDGP is a diagnosis of exclusion. Other underlying causes of delayed puberty should be actively investigated and ruled out, including hypergonadotropic hypogonadism [HH (*e.g.*, Klinefelter syndrome or Turner syndrome)], permanent HH (*e.g.*, CHH, tumors, infiltrative diseases), and functional hypogonadotropic hypogonadism (FHH; *e.g.*, systemic illness, anorexia nervosa, excessive exercise). In particular, the differential diagnosis between CDGP and CHH in adolescence is especially difficult, as discussed in detail in "Transient GnRH deficiency: CDGP" below. Management options include expectant observation vs short-term sex steroid replacement (6). The latter targets primarily the induction of secondary sexual characteristics to alleviate psychosocial distress due to pubertal delay and/or short stature.

Hallmarks of CHH in adolescence

Males. In adolescence, male patients with CHH seek medical attention for absent or minimal virilization, low libido, and erectile dysfunction (123). In 75% of patients with CHH, puberty never occurs, leading to severely reduced TV (<4 mL) and the absence of secondary sexual characteristics (*i.e.*, sparse facial and body hair, high-pitched voice). In this group (absent puberty), micropenis and/or cryptorchidism are commonly observed. In contrast, 25% of patients with CHH exhibit partial GnRH deficiency as evidenced by some spontaneous testicular growth (TV >4 mL) with little virilization, which subsequently stalls (61, 124). Most patients do not have any ejaculate in the setting of severe hypogonadism. Indeed, T is needed for seminal and prostatic fluid production and optimal ejaculate volume.

Most patients with CHH have eunuchoidal proportions with arm spans typically exceeding height by ≥5 cm, reflecting the delayed closure of the epiphysis of long bones in the absence of gonadal steroids. The lack of increased sex steroid levels leads to steady linear growth (125) without a growth spurt; however, final height is rarely affected (126). Several studies report that adult height in men with CHH exceeds the height of healthy control men (127–129). Other studies show that CHH adolescents, on average, achieve their midparental height (126, 130). In a study of 41 men with CHH, a positive correlation was found between the delay of puberty prior to treatment and adult height, such that 6 years or more of pubertal delay was associated with ~5 cm greater adult height

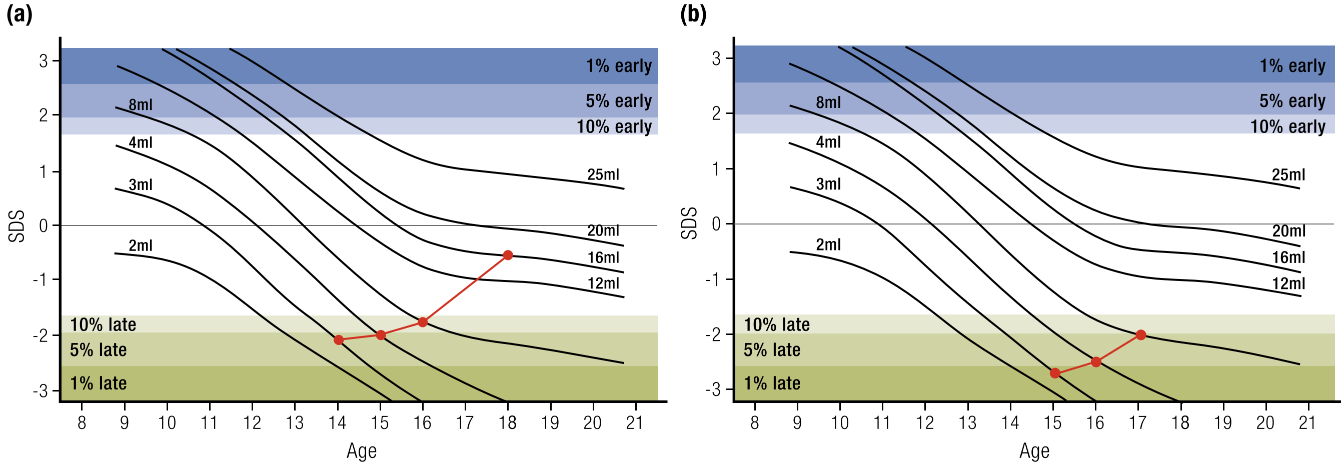


Figure 1. Pubertal progression in two male patients with delayed puberty. TV was plotted on the age-matched puberty nomogram. (a) Patient 1 was diagnosed with delayed puberty at age 14 (TV 3 mL) and completed pubertal development at age 18 (TV 16 mL), confirming CDGP diagnosis. (b) Patient 2 was diagnosed at age 15 (TV 3 mL) and discharged at age 17 (TV 8 mL), despite the fact that his progression was still abnormal (below −2 SD) using the pubertal nomogram. Thus, the differential diagnosis between CDGP and partial CHH is still unclear. [Pubertal nomogram obtained courtesy of Dr. Van Buuren from http://vps.stefvanbuuren.nl/puberty/].

(128). Alternatively, Dickerman *et al.* (129) reported the growth of 50 adolescents with CHH and found no differences in the achieved normal adult height between boys who were referred before 16 years of age or thereafter. Boys in both groups exceeded their predicted final height by 4.9 cm (referred before 16 years of age), and by 6.3 cm (referred after 16 years of age).

Typical changes of body composition in boys with CHH include decreased muscle mass and female body habitus with a gynoid pattern of fat distribution. Mild gynecomastia can be seen in untreated patients due to the imbalance of the T/E2 ratio. Bone maturation is impaired, with delayed bone age and lower bone density observed relative to peers. There are no reported data on bone microarchitecture of males with CHH, and the risk of fracture is difficult to assess given the lack of large multicenter prospective studies on bone health in CHH.

Females. The most prevalent complaint is primary amenorrhea in nearly 90% of women with CHH (131–134). Less than 10% of women with CHH had some menstrual bleeding (131, 133, 135), which in most cases involved one or two episodes of bleeding during adolescence (primary-to-secondary amenorrhea) before chronic amenorrhea sets in (131–134). Chronic oligomenorrhea has been reported, although at a considerably low frequency (136, 137).

Several studies have shown that absent breast development is observed in a minority of women with CHH prior to estrogen replacement therapy (131–133). Only one single multicenter retrospective study described absent breast development in most women with CHH (134). However, this study included only female patients with CHH without breast development.

Pubarche also shows great variability, ranging from absent to almost normal pubic hair (131, 133). Varying degrees of GnRH defciency may impact ovarian androgen production differently (132) (see below). Furthermore, adrenarche leading to increase production of adrenal androgen (*i.e.*, dehydroepiandrosterone, androstenedione) could also contribute to pubarche (132, 138).

Linear growth and final height in women with CHH has been evaluated in relatively few studies (129, 139). The scant published data indicate that the final height in these women is similar to that of the reference population. In Dickerman *et al.*'s (129) series, the growth of 16 females with CHH was unremarkable, whereas a slight mid-childhood deceleration in the growth rate of girls carrying *FGFR1* mutations was recently reported (124, 139).

Clinical presentation of CHH in adulthood

Although the clinical presentation of CHH in adolescence is more common, some patients do not seek medical attention until adulthood. At this point, low libido, infertility, or less commonly bone loss and fractures are the most common complaints. Although male patients usually exhibit prepubertal or small degrees of spontaneous testicular growth, larger TV with preserved spermatogenesis is observed in a subset of male patients (called "fertile eunuch syndrome"). These patients exhibit low serum levels of T in the setting of detectable gonadotropins. The presence of low amplitude and/or low frequency or sleep-entrained GnRH pulses is thought to be sufficient to support intratesticular T production, but unable to achieve normal circulating T levels for full virilization (140). Very rarely, CHH is diagnosed at older age. Recently, Patderska *et al.* (141) described six cases of men who were diagnosed with CHH after 50 years of age and who had long-term uncorrected hypogonadism. These patients exhibited adverse health events such as osteoporosis (six of six), hypercholesterolemia (four of six), and anemia (two of six). Body composition and cardiovascular events were not documented. To the best of our knowledge, there is no report on undiagnosed female patients until age of menopause. Furthermore, data on the natural history of CHH in older men and women are lacking.

Additionally, a small subset of patients present with adult-onset hypogonadotropic hypogonadism (AHH). These patients report normal pubertal development followed later by the complete inhibition of the HPG axis leading to severe HH. No central nervous system abnormalities or risk factors for functional GnRH deficiencies have been identified (142), and follow-up studies on AHH have shown the absence of recovery (143).

The psychological impact of CHH is often neglected. The absence of sexual hormones and its impact on physical appearance constitute major sources of psychological distress for hypogonadal males (144). Specifically, CHH can be accompanied by anxiety and depression (124, 145), and these symptoms are frequently underestimated by physicians (146). Low self-esteem and altered body image have also been reported (147) and can prevent adequate psychosexual development (124, 148). Similarly, pschological distress is observed in female patients with CHH. A recent online survey suggests a negative perception of women with CHH on their health status, with a tendency toward depression (149). This same study suggests that care providers often do not adequately address these issues, and according to patients even have a tendency to dismiss the psychological consequences of their poor pubertal development (149). It is also quite possible that the erroneous perception of their potential infertility (see below) is also a major contributor to their malaise.

CHH reversal

Although CHH was previously considered as a lifelong condition, it is now known that a subset of patients with CHH spontaneously recover function of their reproductive axis following treatment (150–153). Reversibility occurs in both male and female patients with CHH, and it appears to be more common (~10% to 20% in males, and a few case reports for females) than previously thought (150–152). Patients with reversal span the range of GnRH deficiency from mild to severe, and many harbor mutations in genes underlying CHH. However, to date there are no clear clinical factors for predicting reversible CHH. Similarly, the genetic signature for reversal remains unclear, although an enrichment of *TAC3*/*TACR3* mutations has been observed in one series of patients (151, 154). Importantly, recovery of reproductive axis function may not be permanent, as some patients experience a relapse to a state of GnRH deficiency (151, 153), and therefore long-term monitoring of reproductive function is needed. Thus, patients with CHH experiencing reversal (i) represent the mild end of the clinical spectrum, (ii) demonstrate the plasticity of the GnRH neuronal system, and (iii) highlight the importance of the effects of environmental (or epigenetic) factors such as sex steroid treatment on the reproductive axis. Indeed, treatment with sex steroids was the only common denominator in patients experiencing reversal. Normalization of the sex steroid milieu may trigger maturation of the GnRH neuronal network at least in a subgroup of patients, as the expression of critical genes for GnRH ontogeny are sex steroid responsive (155, 156).

CHH-associated phenotypes

CHH can be associated with nonreproductive phenotypes. Anosmia (*i.e.*, lack of sense of smell) is observed in ~50% of CHH cases (157, 158), and this co-occurrence is termed KS. The interconnected link between the GnRH and olfactory systems during early developmental stages explains this association (see "Fetal Development of the HPG Axis" above) (159).

Other phenotypes are also associated with CHH, although at a lower prevalence. They include mirror movements (synkinesia), unilateral renal agenesis, eye movement disorders, sensorineural hearing loss, midline brain defects (including absence of the corpus callosum), cleft lip/palate, dental agenesis, skeletal defects, and cardiovascular defects (7, 157, 158, 160) [Fig. 2 (161–164)]. Three large studies have evaluated the prevalence of these associated phenotypes in CHH, although these studies were retrospective without a systematic evaluation for CHH-associated phenotypes (157, 158, 160). A summary of these studies along with the frequency of these phenotypes in the general population are found in Table 1 (157, 158, 160, 165–170). The presence of specific phenotypes can lead to the diagnosis of syndromic forms of CHH (*e.g.*, CHARGE syndrome, Waardenburg syndrome, and 4H syndrome). A search for hypogondotropic hypogonadism in OMIM (http://www.omim.org/) finds 46 complex syndromes that include this trait. In this review, we have compiled a table of syndromes having both a clinical and genetic overlap with CHH [Table 2 (162–164, 171–191].

Epidemiology

There is no rigorous epidemiological study on the prevalence of CHH. Two historical studies examining military records provided some estimation of the prevalence of this disease. One study examined 600,000 Sardinian conscripts during their military checkup and identified 7 cases with normal karyotype presenting bilateral testicular atrophy and anosmia (considered as KS cases), and thus estimated that the prevalence of KS is 1 in 86,000 in that population (192). A second study identified 4 cases of HH among 45,000 French men presenting for military service, and thus determined that the prevalence of CHH is 1 in 10,000 (193). There is no study on the prevalence of females with CHH. In the series from the Massachusetts General Hospital of 250 consecutive CHH cases, the male-to-female ratio is 3.9:1. However, this ratio drops to 2.3:1 when the familial cases were analyzed separately (140). A recent epidemiological study examining the discharge registers of all five university hospitals in Finland estimated that the prevalence of KS is 1 in 48,000 in the Finnish population, with a clear difference between males (1 in 30,000) and females (1 in 125,000) (65).

Bias regarding the reduced prevalence of CHH in females

The prevalence of CHH has historically been considered to be skewed toward a male predominance (male-to-female ratio of 5:1) (157, 158). Recent work suggests that the sex ratio is closer to 2:1 (133, 134). Furthermore, analysis of the sex ratio for CHH in families with autosomal inheritance demonstrates that the sex ratio is close to being equal (194, 195). Importantly, partial CHH may still be underdiagnosed due to subtle clinical presentation that resembles functional hypothalamic amenorrhea (131, 196).

Several possible explanations for the underdiagnosis of CHH in females follow:

1. During the last decade, there has been a refinement of the spectrum of GnRH deficiency in CHH in both males and females, as the hallmarks of CHH were for a long time absent puberty, leading to an underevaluation of the prevalence of CHH in the past (131, 133).
2. In the 1990s, it was thought that X-linked CHH was prevalent and thus that female patients with CHH were rare. This dogmatic view was progressively challenged by the first descriptions of female patients with CHH harboring biallelic *GNRHR* mutations, with variable degrees of breast development (135, 137, 197, 198). Later, a variable degree of pubertal development was

Figure 2. Nonreproductive, nonolfactory signs associated with KS. (a) Coronal CT scan showing the normal palatine bone in a normal subject (yellow circle). (b) Cleft palate (yellow arrow) in a patient with KS carrying a heterozygous *FGFR1* mutation. (c) Iris depigmentation of left eye in a patient with *SOX10* mutation. (d) Oculomotor nerve palsy suggesting left VI cranial nerve damage in a teenager with KS and a heterozygous *CHD7* mutation. (e) Ear pavilion abnormality suggesting CHARGE syndrome in a male patient with CHH initially referred for KS. (f) Inner ear CT scan showing hypoplastic semicircular canals in a male patient with KS and deafness resulting from a heterozygous *SOX10* mutation (g) Postnatal kidney ultrasound; left posterior fossa view showing absent left kidney in a male neonate with an *ANOS1* mutation. s, spleen. (h) Right kidney ultrasound in same patient revealing compensatory hypertrophy (dotted line indicates kidney length of 65 mm). [(a and b) Adapted with permission from Maione L, Benadjaoud S, Eloit C, et al. Computed tomography of the anterior skull base in Kallmann syndrome reveals specific ethmoid bone abnormalities associated with olfactory bulb defects. J Clin Endocrinol Metab 2013; 98:E537-E546. Illustration presentation copyright by the Endocrine Society. (c and f) Reproduced with permission from Maione L, Brailly-Tabard S, Nevoux J, et al. Letter to the editor: Reversal of congenital hypogonadotropic hypogonadism in a man with Kallmann syndrome due to SOX10 mutation. Clin Endocrinol (Oxf) 2016; 85:988-989. (g and h) Reproduced with permission from Sarfati J, Bouvattier C, Bry-Gauillard H, et al. Kallmann syndrome with FGFR1 and KAL1 mutations detected during fetal life. Orphanet J Rare Dis 2015; 10:71.]

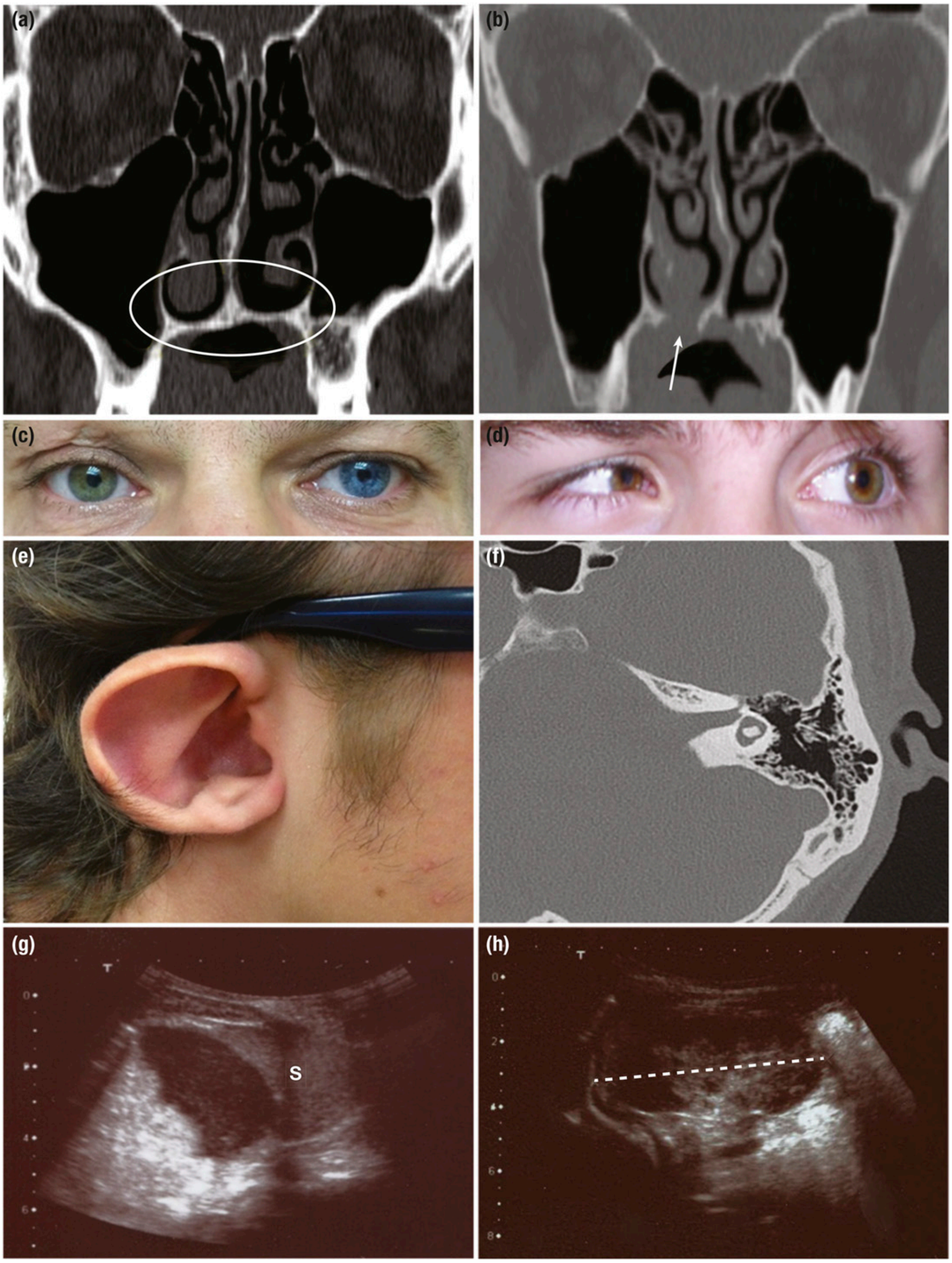


Table 1. Prevalence of Main Nonreproductive Phenotypes in CHH vs General Population

	All CHH		KS		
Phenotypes	Waldstreicher *et al.* (157) (n = 106)	Quinton *et al.* (158) (n = 215)	Quinton *et al.* (158) (n = 112)	Costa-Barbosa *et al.* (160) (n = 219)	General Population
Anosmia/hyposmia	55%	52%	100%	100%	0.01%
Mirror movement	NA	20%	31%	19%	0.0001%
Unilateral renal agenesis	NA	10%	15%	8%	0.05%
Eye movement disorders	3%	20%	27%	NA	0.02%–0.0002%
Hearing loss	6%	5%[a]	8%[a]	15%	0.02%
Cleft lip/palate	7%	5%	4%	6%	0.1% (165)
Dental agenesis	NA	NA	NA	14%	4%–7% (166)
Syndactyly, polydactyly, camptodactyly	NA	NA	NA	5%	0.03%–0.1% (167)
					0.2%–1.3% (168)
					1% (169)
Scoliosis	NA	NA	NA	13%	0.05%–0.1% (170)

Prevalence in the general population: anosmia data are from the National Institutes of Health Genetic and Rare Disease Information Center (https://rarediseases.info.nih.gov/, accessed in January 2018); for mirror movement, eye movement disorders, and hearing loss, data were obtained from the National Institutes of Health Genetics Home Reference (https://ghr.nlm.nih.gov, accessed in January 2018); unilateral renal agenesis data are from Orphanet (http://www.orpha.net/consor/cgi-bin/index.php, accessed in January 2018).
Abbreviation: NA, not assessed.
[a]Only sensorineural hearing loss is included.

described for females with CHH carrying mutations in autosomal genes (*e.g.*, *FGFR1*, *PROK2/PROKR2*, or *SOX10*) (65, 136, 164, 180, 199–201).

3. Finally, in some countries, patients with mild, nonsyndromic forms of CHH are more likely to be treated with contraceptives or hormone replacement therapy (HRT) by their general practitioner or gynecologist rather than receiving a complete workup and accurate diagnosis.

Diagnosis of CHH

Clinical diagnosis

Minipuberty

Minipuberty provides a brief window of opportunity to diagnose CHH. For male infants, micropenis with or without cryptorchidism can be suggestive of CHH. In such cases, hormone testing at 4 to 12 weeks of life may be used to assist in the diagnosis (60, 136, 202–207).

Typically, low serum T, LH, and FSH levels are reported [Table 3 (136, 202–207)] based on comparisons with established reference ranges (43, 208). However, hormonal testing is not routinely prescribed for male infants with micropenis or cryptorchidism. A recent study reported the normative reproductive hormonal data from a large group of healthy infants (209), which will facilitate the interpretation of hormonal results. Neonates born from one parent with CHH should undergo hormonal evaluation during minipuberty. The lack of typical clinical features in female infants suggesting CHH explains why the diagnosis of CHH in neonatals is only rarely made in this sex (7, 139, 205).

Childhood

During childhood, the diagnosis of CHH is very challenging, as childhood is a physiologically hypogonadal period, consistent with the relative quiescence of the GnRH pulse generator.

Adolescence and early adulthood

Delayed puberty is the hallmark of CHH diagnosis in adolescence. Patients can exhibit absent (TV <4 mL) or partial puberty (119). Typically, the hormonal profile shows hypogonadal T or E2 levels and low/normal serum levels of gonadotropins due to GnRH deficiency. However, CHH remains a diagnosis of exclusion (see "Differential Diagnosis of CHH" below). Between 14 and 16 years of age, CHH is difficult to differentiate from CDGP, a common cause of delayed puberty (see "Transient GnRH deficiency: CDGP" below).

Evaluation of CHH-associated phenotypes

It is important to evaluate the presence of CHH-associated phenotypes that may indicate a diagnosis of CHH and have specific utility for genetic counseling:

1. History of cryptorchidism with or without micropenis
2. Decreased or absent sense of smell, suggesting KS, is present in approximately half of the CHH population and should be evaluated using a standardized olfactory test (158). Formal smell testing is especially critical, as 50% of CHH who self-reported a normal sense of smell are in fact hyposmic or anosmic by standardized testing (210); in very young children or in the absence of available olfactometry, MRI imaging may be useful as a surrogate for smell testing when it shows olfactory bulb hypoplasia or aplasia (see below)
3. Congenital sensorineural hearing impairment should be systematically evaluated with an audiogram, as hearing loss is usually mild or unilateral, and thus patients may be unaware of their deficit
4. Bimanual synkinesia (mirror movements)
5. Dental agenesis best assessed by panoramic dental X-ray
6. Cleft lip and/or palate, as well as other midline defects
7. Unilateral renal agenesis or malformation of the urinary tract, both of which should be assessed by renal ultrasound
8. Skeletal anomalies such as scoliosis, polydactyly, and clinodactyly
9. Pigmentation defects
10. Other stigmata of syndromic forms of CHH, *e.g.*, heart malformation, outer ear anomalies, and coloboma for CHARGE syndrome (see Table 2)

Biochemical testing

Gonadotropins

Most men and women with CHH have very low circulating gonadotropin levels (61, 123, 132), and most patients with absent puberty exhibit apulsatile patterns of LH secretion (61). Patients with partial puberty can have low-normal circulating gonadotropins levels, which is inappropriate in the setting of low sex hormones (T or E2) (131, 132) (Fig. 3).

Estradiol

Females. Circulating E2 levels in women with CHH are usually low or in the lower end of the normal range during the follicular phase when using sensitive assays with a detection threshold of 10 pg/mL (132, 211) (Fig. 3). In contrast, the more commonly used immunoassays have poor sensitivity and thus are not accurate in this clinical setting (131, 134). Insensitive E2 assays may even result in misdiagnosis or confusion with other causes of anovulation (211).

Males. Although serum E2 levels are not needed for the clinical diagnosis of CHH, they are consistently lower in males with CHH as compared with normal males using sensitive assays (138, 212) and could have an impact on bone and metabolic health (213–215).

Testosterone

Males. Circulating T levels in patients with CHH are usually low, that is, <3 nmol/L (86.5 ng/dL). This is usually also the case for patients with CHH with partial puberty and larger TVs (61).

Females. Low circulating androgen levels (androstenedione and T) are reported in women with

Table 2. Complex Syndromes With Clinical and Genetic Overlap With CHH

Syndrome	Major Signs	Minor Signs	Genetic Overlap With CHH[a]
CHARGE syndrome	Coloboma, choanal atresia, semicircular canal dysplasia	*Hypothalamic-pituitary defect*, *sensorineural hearing loss*, ear malformation, mental retardation, congenital heart defect	*CHD7* (162, 171–174); *SEMA3E* (175, 176)
Waardenburg syndrome	*Sensorineural hearing loss*, abnormal pigmentation	*HH*, *anosmia with olfactory bulb aplasia/hypoplasia*, facial dysmorphism, megacolon, semicircular canal dysplasia, congenital heart defect	*SOX10* (163, 164, 177, 178)
Hartsfield syndrome	*Split hand/foot malformation*, holoprosencephaly	*Anosmia*, *hypothalamic-pituitary defect*, *syndactyly*, facial dysmorphism	*FGFR1* (179–182)
Adrenal hypoplasia congenita	*HH*, adrenal hypoplasia	—	*NR0B1* (*DAX1*) (183, 184)
4H syndrome	*HH*, *hypodontia*, hypomyelination	—	*POLR3B* (185, 186)
Septo-optic dysplasia	Optic nerve hypoplasia, *hypothalamic-pituitary defect*, *midline brain defect*	—	*HESX1* (187, 188)
			SOX2 (189–191)

Phenotypes that overlap between these syndromes and CHH are highlighted in italics.
Abbreviations: 4H syndrome, hypomyelination, HH, and hypodontia.
[a]List of genes mutated in both syndromic and nonsyndromic forms of CHH, with landmark studies cited as references.

Table 3. Clinical and Biochemical Characteristics of Neonatal Males With CHH Reported in the Literature

	Clinical Signs		Hormonal Testing						
Case No.	Neonatal Signs	Family History	Age (mo)	T (nmol/L)	LH (IU/L)	FSH (IU/L)	Diagnosis	Neonatal Treatment	References
1	Micropenis	Hyposmia	4	n.d.	n.d.	0.18	CHH	hCG, T	(202)
2	Ascending testis	CPHD	3.5	n.d.	0.07	0.18	CPHD	T	
3	Micropenis	None	0-7.9	n.d.	n.d.	0.05–0.17	CHH	rFSH + rLH, T	(203)
4	Micropenis	n.r.	2	0.03	0.19	0.19	CPHD	rFSH + rLH	(204)
5	Micropenis	n.r.	3.5	0.06	0.03	0.12	CHH	rFSH + rLH	
6	Micropenis, cryptorchidism, CLP, SHFM	CHH, CLP	2	n.d.	n.d.	0.4	CHH	rFSH + rLH	(207)
7	Micropenis	KS	1	0.1	0.04	0.18	KS	rFSH + rLH	(136)
8	Micropenis, cryptorchidism	None	3	0.3	n.d.	n.d.	CHH	T	(205)
9	Micropenis, cryptorchidism	n.r.	6	0.2	0	0.4	CPHD	rFSH + rLH	(206)
10	Micropenis, cryptorchidism	n.r.	4.5	0.2	0.4	1	CHH	rFSH + rLH	
11	Micropenis, cryptorchidism	n.r.	2.5	0.1	0.1	0.8	CHH	rFSH + rLH	
12	Cryptorchidism	n.r.	5	0.1	n.d.	0.3	CHH	rFSH + rLH	
13	Micropenis, cryptorchidism	n.r.	0.25	0.2	n.d.	0.21	CHH	rFSH + rLH	

Abbreviations: CLP, cleft lip palate; n.d., not detectable; n.r., not reported; SHFM, split hand/foot malformation.

CHH despite normal circulating dehydroepiandrosterone sulfate concentrations (132). This relative androgen deficiency is likely subsequent to the inadequate stimulation of theca cells by low circulating LH. Indeed, serum T levels increase in women with CHH during combined recombinant LH (rLH) plus recombinant FSH (rFSH) stimulation, whereas T levels do not change with rFSH alone (132).

GnRH test

Pituitary gonadotropin response to a GnRH challenge test has been specifically evaluated in men and women with CHH (137).

Males. In men with CHH, the LH response is highly variable and correlates with the severity of gonadotropin deficiency. However, the latter is already clinically reflected by the degree of testicular atrophy, which questions the added value of the GnRH stimulation test (135, 201, 216, 217).

Females. Pituitary gonadotrope response to the GnRH test has only been evaluated in a few case reports (137, 139). In most women with GnRH deficiency, the peak LH response to GnRH stimulation was blunted relative to normal women (137).

Inhibin B

Males. Inhibin B is a hormone secreted by Sertoli cells and reflects Sertoli cell number and function (218, 219). Inhibin B is under the control of FSH (220, 221). Healthy seminiferous tubules after puberty also regulate inhibin B production, likely through the control of spermatids (222). Most men with CHH with absent puberty with/without micropenis and cryptorchidism exhibit low serum inhibin B levels (<30-60 pg/mL), indicating a reduced Sertoli cell population (66, 123, 223). This is consistent with the absence of GnRH-induced FSH stimulation of the seminiferous tubules during fetal life and minipuberty (45, 66, 217, 224). Higher serum inhibin B levels are encountered in a minority of patients with absent puberty but are found in most patients with partial puberty (61) or acquired HH (225), consistent with a robust activation of the HPG axis during minipuberty. Serum inhibin B levels correlated well with testicular size (61), and low inhibin B level is a negative predictor of fertility (66). Furthermore, a few studies demonstrated a good discriminative value of serum inhibin B to differentiate severe CHH from CDGP (see below) (121).

Females. Inihibin B is a marker of the number of antral follicles and is secreted by the granulosa cells (226). Very few studies have investigated circulating inhibin B levels in females with CHH (132). Low inhibin B concentrations are reported in the range of prepubertal girls (227–229). One study demonstrated the critical role of FSH to stimulate ovarian inhibin B secretion as evidenced by increased inhibin B levels in response to rFSH alone, but no additional change in response to both rFSH and rLH (132).

Anti-Müllerian hormone

Males. Circulating AMH levels in male patients with CHH have been studied during the neonatal period and in adulthood (before and after gonadotropin or T treatment) (204, 223, 230). During minipuberty, CHH infants have low AMH levels, which can be normalized by rFSH and rLH treatment (34, 204). Untreated adults with CHH have high AMH levels when compared with normal men, but in the low to normal range of the prepubertal levels in normal boys, indicating the immaturity of the Sertoli cell population (223). rFSH treatment in previously untreated patients with CHH induces proliferation of immature Sertoli cells, and thus increases AMH levels, whereas subsequent hCG treatment will increase intratesticular T levels and dramatically decreases AMH levels (223).

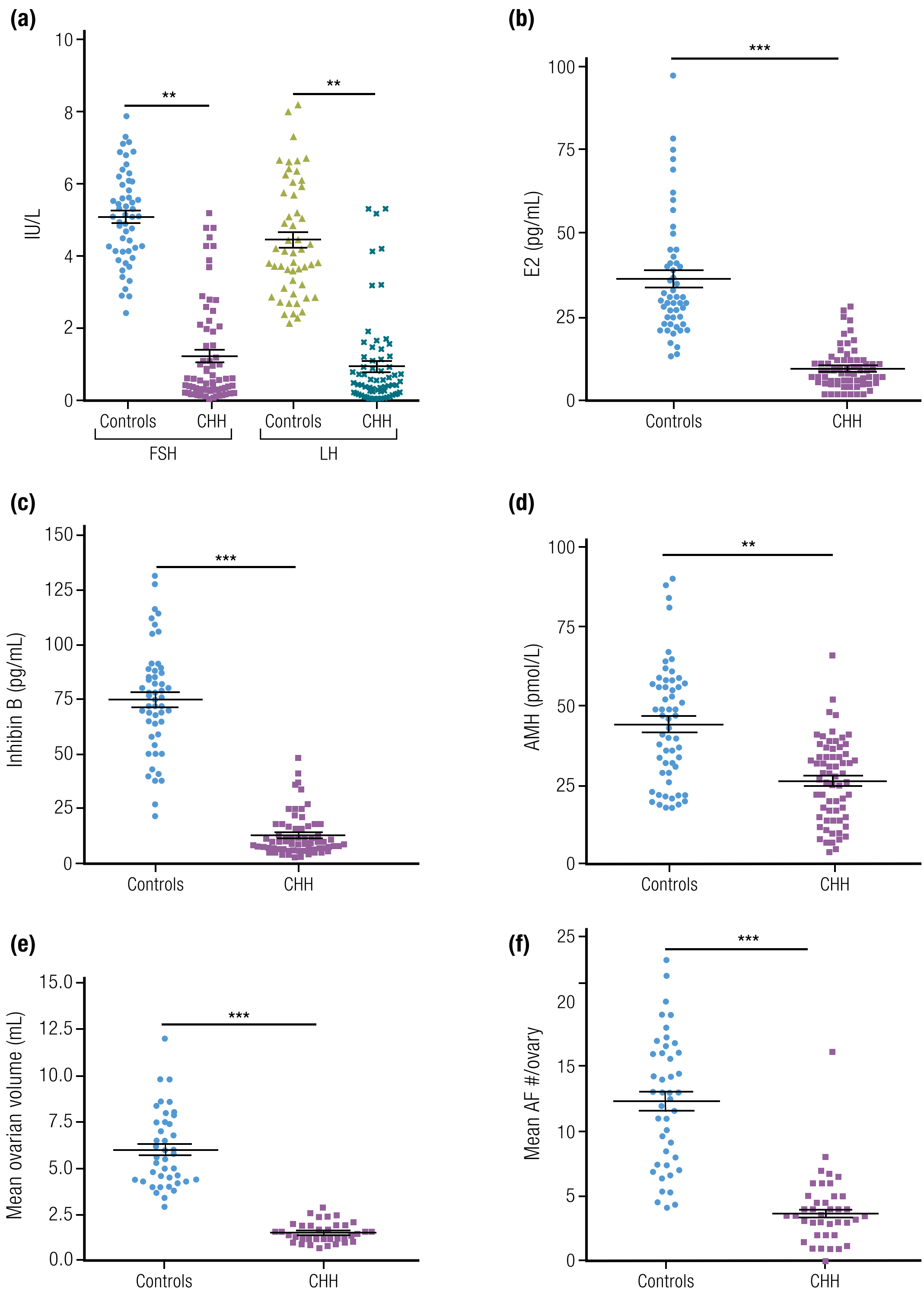


Figure 3. Hormone levels and ultrasound features in female patients with CHH compared with healthy controls. (a) Serum FSH and LH, (b) E2, (c) serum ovarian peptide inhibin B, and (d) AMH levels in untreated women with CHH (n = 68, aged from 18 to 34 y) and age-matched healthy young women (controls, n = 52). (e) Mean OV and (f) total mean AF number in ovary in untreated women with CHH (n = 39) and in healthy women (n = 41). ***P* < 0.01; ****P* < 0.0001. [Adapted with permission from Bry-Gauillard H, Larrat-Ledoux F, Levaillant J-M, et al. Anti-Mullerian hormone and ovarian morphology in women with isolated hypogonadotropic hypogonadism/Kallmann syndrome: effects of recombinant human FSH. J Clin Endocrinol Metab 2017; 102(4):1102-1111.]

Females. Mean serum AMH concentrations are significantly lower in women with CHH than in healthy women (Fig. 3) (132), although two-thirds of patients display serum AMH levels within the normal range. The subgroup of women with CHH with the lowest ovarian volume (OV) and antral follicular count had significantly lower AMH levels consistent with lower FSH levels. However, low AMH levels should not be considered a poor fertility prognosis, as both pulsatile GnRH and gonadotropin administration can lead to fertilty and will be accompanied with an increase in serum AMH levels.

Other pituitary hormones

In the evaluation of CHH, it is important to rule out other pituitary defects by performing an exploration of the complete pituitary axis (*e.g.*, to rule out hyperprolactinemia) (231) (see "Genetics of CHH" below). A baseline profile including measurements of prolactin, free T4, TSH, morning cortisol, and IGF1 should be performed and the growth curve should be analyzed. In case of suspected pituitary insufficiency, appropriate dynamic challenge tests and diencephalic imaging should be performed (231).

Radiological examination

Pelvic ultrasound

Studies on uterine morphologies in women with CHH are limited (131, 132, 232). Pelvic or transvaginal ultrasound (when appropriate) demonstrated a significant reduction in mean OV compared with healthy adult women of a similar age (131–133, 232). OV correlates with the severity of E2 deficiency (232) and endometrial atrophy (233). Notably, the decrease in OV is greater in KS than in normosmic CHH with a trend toward lower serum gonadotropin levels in KS, suggesting a more severe GnRH deficiency (131). The only study that quantified the number of ovarian antral follicles (AFs) showed a significant decrease in the average number of AFs compared with normal, age-matched women, consistent with the low levels of AMH (132). Thus, a combined decrease in OV and AF count is a phenotypic characteristic of women with CHH and is often mistakenly considered a poor fertility prognosis. However, OV and AFs respond favorably to gonadotropin stimulation in females with CHH (see below).

Testicular ultrasound

The measurement of testicular size is important to determine the severity of GnRH deficiency and track the progress of testicular maturation during fertility treatment. Although an orchidometer is often used in clinical practice, testicular ultrasound has the advantage to assess not only size but also testicular localization. Both methods were equally accurate in the hands of an experienced clinician (234, 235). As expected, an orchidometer overestimates TV by ~6 mL in comparison with ultrasound, likely due to the interference of surrounding soft tissues, and it has low sensitivity in detecting testicular asymmetry (185). Thus, ultrasound has the added benefit during baseline evaluation to simultaneously assess testicular size in detail and rule out renal malformations during a single evaluation. However, subsequent evaluations can be conducted reliably with an orchidometer.

Brain MRI is performed at baseline to exclude hypothalamic–pituitary lesions and to assess defects in the olfactory bulbs, corpus callosum, semicircular canals, cerebellum (207, 236), and midline (237). Patients with KS will typically exhibit unilateral or bilateral olfactory bulb agenesis, olfactory tract agenesis, and/or gyrus malformation associated with their anosmia/hyposmia (238). However, a few patients with KS have normal olfactory structures despite clinically confirmed anosmia. In this minority of patients, it seems useful to search for other causes of congenital or acquired anosmia (*e.g.*, viral infections, trauma). Furthermore, an anomaly of the semicircular canals is an important finding, as it suggests the diagnosis of CHARGE syndrome (239).

Bone density and microarchitecture

A CHH workup should include the measurement of bone mass via dual-energy X-ray absorptiometry (DXA) to assess bone mineral density (BMD) (7). Bone quality can be evaluated by processing a trabecular bone score or by performing a high-resolution peripheral quantitative CT. The latter provides a more detailed assessment of bone microarchitecture at peripheral sites (*e.g.*, distal radius, tibia) (240). Alternatively, trabecular bone score is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture, readily available from the DXA scan (241). Bone workup should be done at baseline and repeated at least 2 years after HRT to assess the beneficial effect of sex steroids on bone mass and guide subsequent monitoring. The use of FRAX, a clinical algorithm for assessment of fracture risk, has not been validated in this particular population (242).

Other tests

Olfaction

Olfactory function represents a hallmark in the clinical assessment of CHH, as ~50% of patients have a defect in the sense of smell (KS, also known as "olfactogenital dysplasia") (243). Olfactory function is assessed using semiquantitative methods such as the UPSIT score (210) or the Sniffin' Sticks (244, 245) tests, which give age- and sex-matched scores relative to a reference population. Alternatively, volatile-stimulated chemosensory evoked potentials can be used (246), although they are less practical in a clinical setting. Partial or subtle olfactory impairment may be seen in some patients (*i.e.*, hyposmia or microsmia), raising the question of a continuum rather than a binary classification (210, 247). Whereas a self-report of anosmia is sensitive and specific, the self-reporting of a normal sense of smell is unreliable (210). Therefore, formal smell testing should be pursued for all patients with CHH.

Hearing

The prevalence of hearing loss in CHH is reported to be between 5% and 15% (Table 1). Nevertheless, there are no large studies with systematic evaluations of hearing in patients with CHH, as an audiogram is seldom performed during baseline evaluation. Hearing defects range from unilateral, mild hearing loss to complete bilateral sensorineural deafness; however, conductive hearing loss is seldom encountered (158). Notably, the association of CHH with hearing loss points to mutations in specific genes (*e.g.*, *CHD7*, *SOX10*, *IL17RD*) (7, 160).

Spermiogram

A spermiogram is defined as the quantitative and qualitative analysis of semen to assess male fertility potential (248). Among the primary parameters, ejaculate volume (which is T-dependent) as well as sperm motility and morphology are the most critical. The latest World Helath Organization (WHO) criteria for interpretation of semen analysis were published in 2010 (249) based on semen samples from >4500 men in 14 countries and defined the lower reference limits for the following parameters: 1.5 mL for semen volume, 15 million/mL for sperm count, 40% for total motility, and 4% for normal morphology. Most patients with CHH at baseline (particularly those with severe hypogonadism) exhibit severe erectile dysfunction and an absence of ejaculate, rendering a spermiogram impossible. However, with fertility treatment most males with CHH will develop sperm in their ejaculate. Interestingly, the concentration of sperm needed for fertilization in patients with CHH is much lower compared with the WHO guidelines (250). In conclusion, a spermiogram is indicated at baseline (when possible) and serially after the initiation of fertility treatment.

Genetics of CHH

Genetic determinants of pubertal timing

The timing of puberty varies widely in the general population and is influenced by genetic, environmental, and epigenetic factors (3). The studies of pubertal timing in families and twins provide evidence that 50% to 80% of this variation is caused by genetic factors (3–5). Recent genome-wide association studies (GWASs) in large populations shed light on the genetic determinants underlying the heritability of pubertal timing. By studying ~370,000 women of European ancestry, Day *et al.* (251) reported ~400 independent loci robustly associated with the age at menarche. The individual effect size of each locus ranges from 1 week to 1 year; however, the cumulative effect of all identified genetic signals only explains 7.4% of population variance in age at menarche. Similar results are seen in GWASs on pubertal timing in males using age at voice breaking as a proxy for pubertal timing. A large number of the identified loci are implicated in BMI, height, and epigenetic regulation consistent with the critical links between energy balance, growth and development, and reproduction. Furthermore, a subset of loci implicated in the timing of puberty are located in imprinted regions (*e.g.*, *MKRN3* and *DLK1*), which exhibit important effects when paternally inherited (251). Notably, a few menarche loci are enriched in or near genes that underlie CHH (*e.g.* *FGF8*, *GNRH1*, *KAL1*, *KISS1*, *NR0B1*, *TACR3*) or central precocious puberty (*MKRN3*). In conclusion, pubertal timing is a highly polygenic trait, likely involving many individual genetic loci. Further studies on larger cohorts with well-studied phenotypes are needed to uncover genetic players and determine the contribution of gene–environmental interactions.

Genetics of CHH

Several recent reviews have focused exclusively on the genetics of CHH, including the review by Stamou *et al.* (252) in this journal (194). During the last year, four additional genes have been reported to underly CHH: *KLB* (253), *SMCHD1* (254), *DCC*, and its ligand *NTN1* (255). Herein, we summarize the complexity of CHH genetics.

Since the first description of "The genetic aspects of primary eunuchoidism" by Dr. Franz Kallmann, in 1944 (256), the genetic complexity of the disease has unfolded. Mirroring the clinical heterogeneity of CHH, genetic heterogenity also prevails, with mutations in >30 genes identified to date. These genes have been critical in unraveling the complex ontogeny of GnRH neurons: (i) defects in GnRH fate specification; (ii) defects in GnRH neuron migration/olfactory axon guidance; (iii) abnormal neuroendocrine secretion and homeostasis; and (iv) gonadotrope defects (Fig. 4) (7, 140, 194, 252, 257). However, >50% of cases remain without an identified genetic cause.

The genetic complexity of CHH is also reflected in its different modes of inheritance: X-linked, autosomal dominant, and autosomal recessive (7, 140, 194, 252). Incomplete penetrance and variable expressivity are also observed [Fig. 5 (258)]. In addition to the Mendelian modes of inheritance, oligogenicity has also been reported in CHH. In 2007, loss-of-function mutations in two CHH genes acting in concert was

"A positive family history of CDGP cannot rule out CHH..."

described in two probands (259). The systematic screening of eight CHH genes in 2010 in a large cohort of CHH identified oligogenicity in 2.5% of probands (260). Subsequent studies screening increasingly more CHH genes demonstrated even larger degrees of oligogenicity, ranging from 7% (261) to 15% (262). The advent of high-throughput sequencing dramatically enhances the ability to detect multiple rare variants in a patient. However, the assessment of a single variant's pathogenicity and the synergistic effects between variants remains challenging.

The genetic complexity of CHH is further exemplified by pleiotropic genes that can exhibit different roles during development. Indeed, the phenotypic richness found in "syndromic CHH" is not always linked to a continguous gene syndrome (*e.g.*, large deletion in Xp22.31 in a patient with KS, chondrodysplasia punctate, and ichthyosis, including *ANOS1*, *ARSE*, and *STS*) (263). Rather, it may arise from mutations in pleiotropic genes that can influence unrelated phenotypic traits. For example, dominant *FGFR1* mutations can cause CHH with or without anosmia (180, 181), Pfeiffer syndrome (264), holoprosencephaly (265), Hartsfield syndrome (179), or CHH with split hand/foot malformation (207). These diverse phenotypes may arise by different mechanisms such as the type of mutations (loss or gain of function, haploinsufficiency, dominant negative) or, alternatively, be influenced by modifier genes, consistent with an oligogenic model of inheritance. Furthermore, different constellations of CHH-associated phenotypes define "CHH syndromes" with both clinical and genetic overlap [*e.g.*, mutations in *SOX10* causing Waardenburg syndrome (177, 266) or KS (CHH with anosmia) (164)] (Table 2). Refining these CHH-associated phenotypes greatly enhances the diagnostic yield of targeted gene screening. Indeed, whereas *FGFR1* mutations occur in ~10% of patients with CHH, they are present in 87% of patients with both CHH and split hand/foot malformation (207). Similarly, whereas *SOX10* mutations underlie 4% of KS, *SOX10* mutations are found in 30% of patients with KS and hearing loss (7). These genetic advances challenge the traditional phenotypic classification of syndromes.

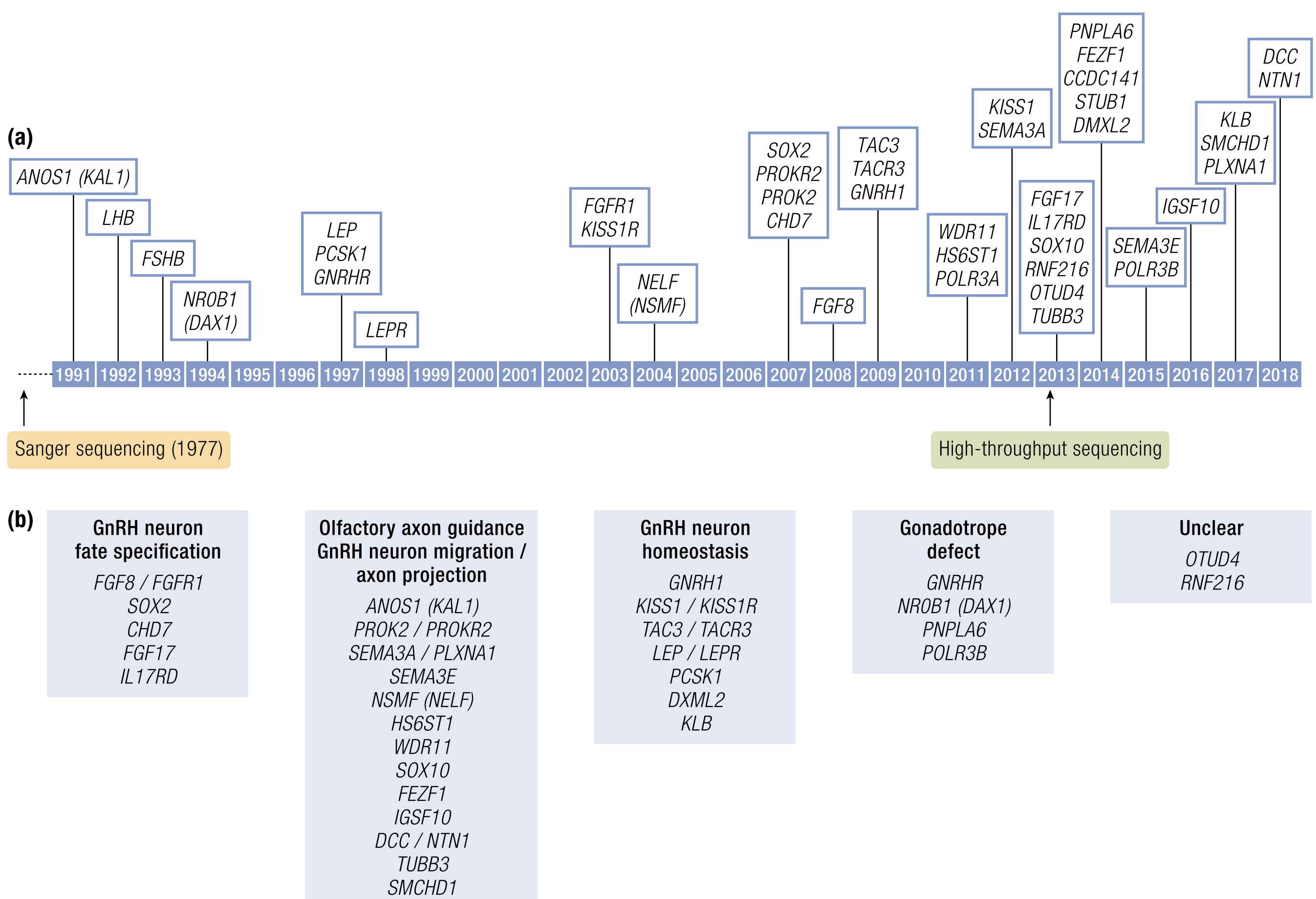


Figure 4. Genetics in CHH. (a) Timeline of gene discovery in CHH and CHH-overlapping syndromes. (b) Biological involvement of CHH genes in GnRH neuronal system.

Differential Diagnosis of CHH

Structural causes

Structural causes affecting the hypothalamic–pituitary axis may lead to acquired HH. These causes can be classified into tumors (pituitary adenomas, craniopharyngeomas, and other central nervous system tumors), irradiation, surgery, apoplexy, or infiltrative diseases (*i.e.*, hemochromatosis, sarcoidosis, and histiocytosis). Less commonly, head trauma or subarachnoidal hemorrhage can be associated with acquired HH (267–269). Most patients with structural causes have multiple pituitary hormone deficiencies in addition to acquired HH (268). In early adolescence, a brain MRI is indicated in patients with delayed puberty and HH when there is a break in growth spurt, pituitary hormone deficiency (including diabetes insipidus), and hyperprolactinemia, and when there are symptoms of mass effect (headache, visual impairment, or visual field defects). In late adolescence or adulthood, a brain MRI is indicated in patients with isolated severe HH (T $<$5 nmol/L, high suspicion of CHH) and in patients with combined pituitary hormone deficiency (CPHD), hyperprolactinemia, or symptoms suggestive of a sellar mass (267, 268, 270).

Genetic causes: CPHD

CPHD is a rare congenital disorder characterized by impaired production of pituitary hormones affecting at least two anterior pituitary hormone lineages with variable clinical manifestations. CPHD may manifest as (i) isolated pituitary hormone deficiencies, (ii) a component of other syndromes (*i.e.*, septo-optic dysplasia, which combines CPHD with hypoplasia of the optic nerve or midline defects), or (iii) pituitary stalk interruption syndrome with ectopic posterior pituitary gland (271). To differentiate CPHD from CHH, biochemical assessment of pituitary function with measurements of IGF1, morning cortisol, TSH, and free T4 and prolactin is needed in addition to evaluating specific clinical manifestations of selective anterior pituitary hormone deficiency. Even subtle indications of insufficiency for one of the pituitary hormones warrants further testing with appropriate dynamic challenge tests and brain MRI (231).

Transient GnRH deficiency: CDGP

During early adolescence, distinguishing CHH from CDGP is extremely challenging, as a delay in puberty is a hallmark of both diseases, and HH is present in both. Whereas GnRH deficiency is permanent in most cases of CHH, CDGP is a state of transient GnRH deficiency where puberty eventually begins and is completed without hormonal treatment (6). Additionally, CDGP is a common cause of delayed puberty, whereas CHH is considerably more rare. Differentiating CHH from CDGP is crucial to allow an early diagnosis of CHH, avoid delay regarding hormonal replacement, and alleviate the psychological burden associated with delayed sexual maturation (7). Additionally, from a prognostic point of view, to differentiate a transient condition from a chronic disease will affect the patient's quality of life (7). We review some features that may assist in this differential diagnosis, noting that although individual indicators may not provide a definitive resolution, a combination of multiple indicators and clinical observation will strengthen arguments for or against a particular diagnosis (Fig. 6):

Growth velocity was recently suggested to help differentiate the different etiologies of delayed puberty (6), but it was subsequently shown to offer no additional diagnostic value in separating between CDGP and CHH (121, 126).

Testicular size may discriminate boys with CHH from those with CDGP. In a retrospective study of 174 boys with delayed puberty at the age of 14 to 15 years, a cut-off of TV at 1.1 mL (measured clinically) showed a 100% sensitivity and 91% specificity to distinguish CHH from CDGP (121).

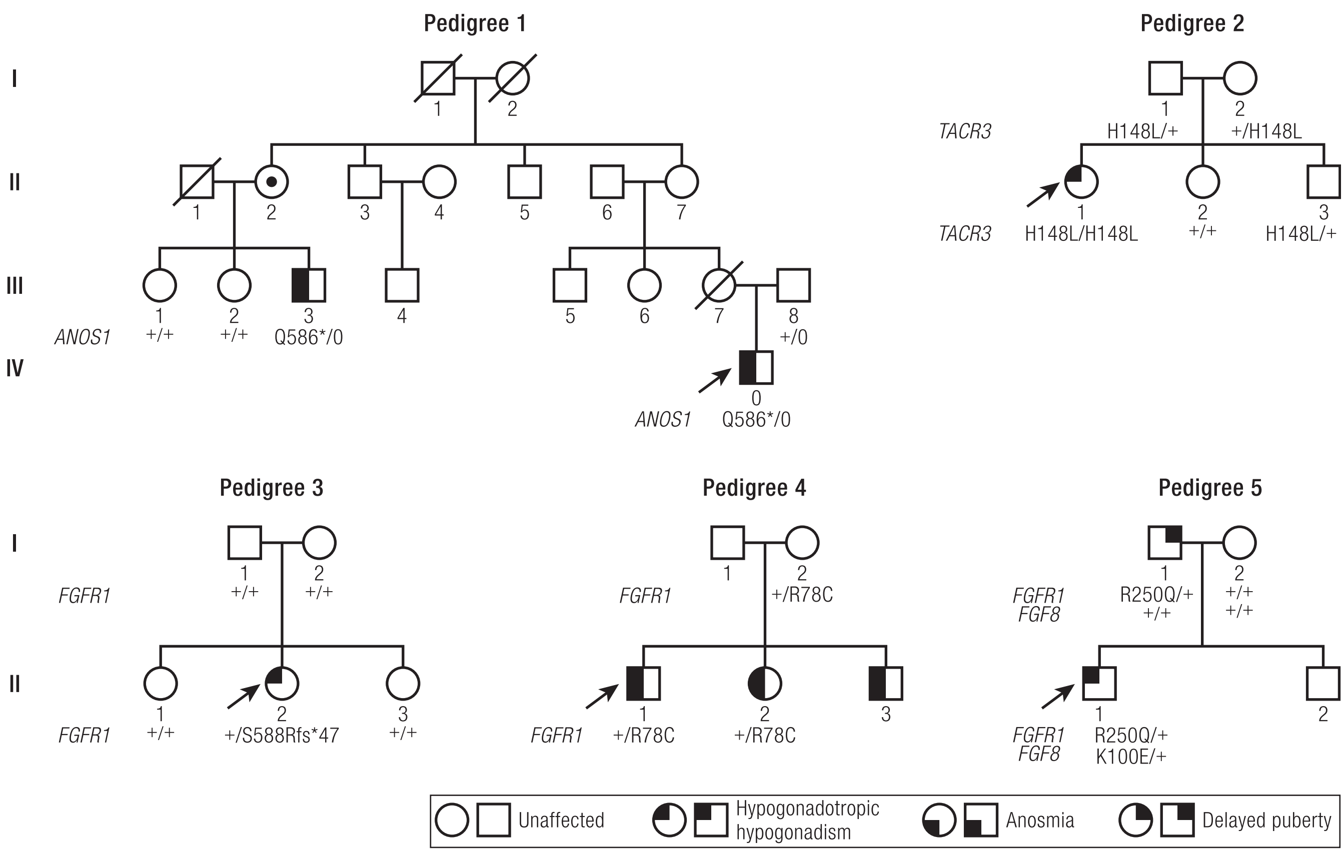
The presence of cryptorchidism and/or micropenis strongly argues in favor of CHH, reflecting the absence of gonadotropins and sexual hormones during both fetal life and minipuberty (6, 121). In a series of 174 boys referred to a tertiary center for evaluation of delayed puberty, cryptorchidism was present in 36% of boys with CHH and only in 2% of boys with CDGP (126).

CHH-associated phenotypes argue against a diagnosis of CDGP. Most notably, congenital anosmia (*i.e.*, unrelated to facial trauma, surgery, or chemical exposure) favors a diagnosis of KS. The presence of anosmia or other CHH-associated phenotypes may favor a diagnosis of CHH, but must also be weighed against their frequency in the general population (Table 1).

A positive family history of CDGP cannot rule out CHH, as CHH families are often enriched for family members with CDGP (157). Additionally, autosomal dominant inheritance is seen in both CHH and CDGP (122).

Biochemical evaluation: To date, no biochemical marker can fully differentiate CHH from CDGP (272) in early adolescence. A GnRH test might be useful for identifying severe cases of CHH. Indeed, when a GnRH-stimulated LH response is blunted, CHH is highly probable. A recent study included 19 patients with CHH and 181 patients with CDGP and demonstrated a cut-off of GnRH-stimulated LH of 4.3 IU/L to detect CHH with a sensitivity of 100% and specificity of 75% (121). Inhibin B levels are also a useful diagnostic adjunct, with low values ($<$60 pmol/mL) suggesting severe GnRH deficiency (121). Nevertheless, some

Figure 5. Pedigrees and gene mutations in patients with CHH and patients with KS. All gene variants listed are rare (minor allele frequency <0.5%) and predicted to be damaging by standard protein prediction algorithms (SIFT and/or PolyPhen2). All variants are classified as pathogenic or likely pathogenic according to American College of Medical Genetics recommendations (258). Pedigree 1: X-linked KS caused by *ANOS1* mutation. Pedigree 2: Autosomal recessive mode of inheritance. Pedigree 3: *De novo* mutation. Pedigree 4: Autosomal dominant with reduced penetrance. Pedigree 5: Oligogenic mutation with *de novo* mutation in *FGF8*. Circles denote females, squares denote males, and arrows indicate probands. A diagonal slash through a symbol means the subject is deceased. Regarding the gene mutations, + represents a wild-type (reference) sequence, and a 0 is present in hemizygous male subjects for genes on the X chromosome.



overlap exists especially between partial CHH, CDGP, and healthy controls (273, 274), thereby highlighting the need for larger prospective studies. Higher AMH is suggestive for CHH, although the cut-off is not clear (274, 275). Furthermore, other markers such as INSL3, dehydroepiandrosterone sulfate, and IGF-1 do not improve accuracy for differential diagnosis.

Genetic testing is a promising prospect; however, evidence as to whether CHH and CDGP exhibit common or distinct genetic backgrounds remains unclear. Mutations in *IGSF10* have been reported in both CDGP and CHH families (276). A shared genetic basis is also partly supported by previous work identifying putative pathogenic mutations of known CHH genes in 14% of CDGP probands (277), which was significantly higher than in controls. Furthermore, meta-analysis of GWASs including 370,000 women on the age of menarche revealed >400 loci associated with the timing of puberty, several of which overlap with known CHH genes, such as *TACR3* and *GNRHR* (251). Nevertheless, a recent study using whole-exome sequencing in two cohorts of CHH and CDGP probands suggested distinct genetic architectures (262), with CDGP resembling the control population in terms of both the frequency of pathogenic variants in known CHH genes and the presence of oligogenicity. Confirmation of these results with larger studies is needed and could lead to a broader use of genetic testing to complement clinical and biochemical data for the diagnosis of CHH in adolescence.

Transient GnRH deficiency: FHH

Similar to CDGP (see above), FHH is difficult to differentiate from CHH. FHH (frequently termed as functional hypothalamic amenorrhea in females) is a reversible form of GnRH deficiency, often induced by stressors such as caloric deficits, psychological distress, and/or excessive exercise (278, 279). In adolescents, the frequency of FHH is rising [3% to 5% of the population among young women (280)] and can manifest as primary amenorrhea (281), further complicating its distinction from CHH. There is a genetic susceptibility in the inhibition of the HPG axis in the presence of predisposing factors, and a shared genetic basis of CHH and functional hypothalamic amenorrhea in women has been described (282).

For both sexes, malnutrition due to an organic disorder such as celiac disease, inflammatory bowel disease (*e.g.*, Crohn disease, ulcerative colitis) or other chronic inflammatory and infectious states should be ruled out as the primary cause underlying a patient's HH before rendering a diagnosis of CHH (7).

Opioid-induced HH

Opioid use is a major cause of functional/reversible HH in males and females (283, 284). In the central nervous system, endogenous opioids inhibit pulsatile GnRH release (285) and suppress LH secretion, resulting in low sex steroid production and clinical hypogonadism (284, 286–288). Opioid misuse and addiction is an ongoing and rapidly evolving public health crisis (289). It is therefore likely that the

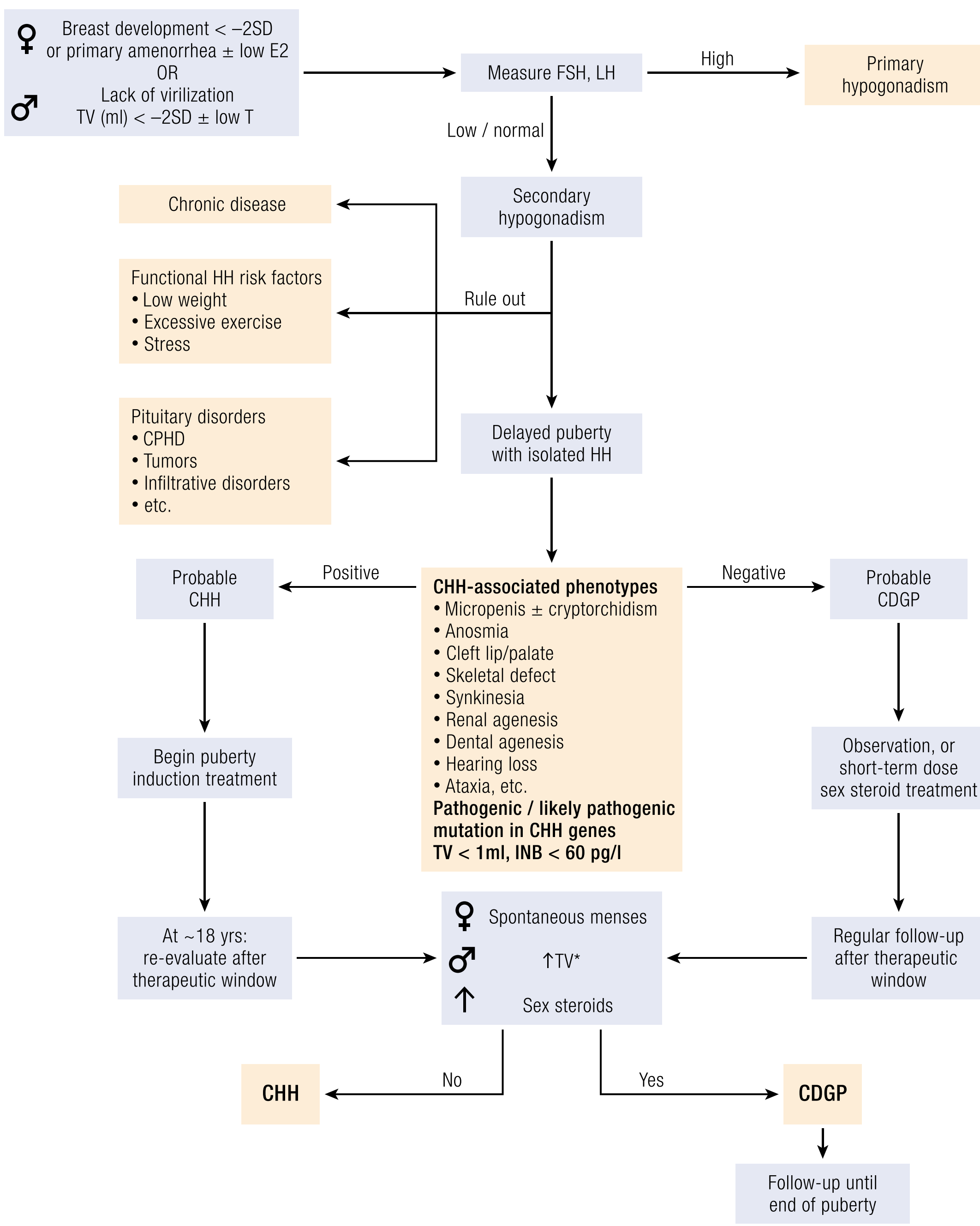


Figure 6. Practical algorithm of clinical management for patients with delayed puberty. The asterisk (*i.e.*, ↑TV*) indicates an increase of TV under T treatment or after a therapeutic window highly indicative of CDGP. INB, inhibin B.

prevalence of HH related to the consumption of these drugs will increase and become a growing diagnostic issue, particularly among adolescents and young people.

HH associated with metabolic defects

Late-onset HH is associated with metabolic syndrome, obesity, and/or diabetes (290). Contrary to CHH, this disorder is characterized by mild GnRH deficiency, most commonly occurring after puberty (290). The physiopathology of obesity-related HH is multifactorial and depends on the severity of the underlying metabolic defect (291). A decrease of SHBG is the major factor responsible for low T levels in men with moderate obesity, whereas men with severe obesity (BMI >40 kg/m^2) exhibit low total and free T and reduced GnRH-induced LH pulsatility (291). Increased aromatization of T to E2 in adipose tissue with subsequent enhanced negative feedback, insulin resistance, and hypothalamic inflammation are thought to be causative factors that alter the function of GnRH neurons and/or pituitary gonadotroph cells (292). Notably, with the increasing incidence of childhood obesity, obesity-related HH is also on the rise in early adolescence, especially in boys, and can be characterized by delayed puberty (293–295).

HH associated with hemochromatosis

Hemochromatosis is part of the differential diagnosis for CHH, as it can often result in HH with no additional pituitary deficiencies and often preceeds cardiac and hepatic defects (296). Juvenile hemochromatosis (type 2A) can present with delayed puberty or permenant hypogonadtropic hypogonadism due to mutations in hemojuvelin (297, 298). Hemochromatosis is confirmed by serum measurement of iron, ferritin, and transferrin saturation coefficient and molecular diagnosis (299). Family history of hemochromatosis also points toward this etiology. It is important not to miss the diagnosis of hemochromatosis, as a reversal of the associated HH may occur after repeated phlebotomy (300).

Treatment of CHH

With appropriate HRT, patients with CHH can develop secondary sexual characteristics, maintain normal sex hormone levels and a healthy sexual life, and achieve fertility. Several regimens of treatment with different administrative routes exist. The choice of treatment depends on the therapeutic goal, the timing of treatment, and the personal preference of each patient. It is important to know that randomized controlled trials on hormonal treatment in CHH are scarce, and data on clinical observational studies are also limited. There is no uniform treatment regimen used internationally. The advantages and disadvantages of available treatment regimens are summarized in Palmert and Dunkel (6) and Dunkel and Quinton (301) and in Tables 4 and 5.

Neonatal treatment of CHH

To date, hormonal therapy during the neonatal period is only applied in male patients exhibiting micropenis/cryptorchidism and HH (34, 136, 203, 204, 206, 303). An equivalent therapy is not proposed in female patients, as the consequences of severe GnRH deficiency during the late fetal period and minipuberty in females are unclear.

In male infants with severe GnRH deficiency, the main goals of hormonal treatment are to increase the penile size and to stimulate testicular growth. Early reports in 1999 and in 2000 described the benefit of early androgen therapy in boys with either CHH or CPHD (202, 303). T treatment can increase penile size and stimulate scrotal development.

hCG therapy with or without a combination of nasal spray of GnRH has been shown to be effective to treat cryptorchidism in neonates and prepubertal boys (304, 305). This finding could represent a further benefit of neonatal treatment of children with CHH, as cryptorchidism is a factor of poor prognosis for adult fertility and is also a risk factor for testicular malignancy. Alternatively, orchidopexy—surgery to move an undescended testicle into the scrotum—is the current treatment of choice of cryptorchidism. Some publications point to a deleterious effect of isolated hCG therapy in boys with cryptorchidism (306). A concern for high-dose hCG treatment is its potentially deleterious effect on germ cells with increased apoptosis, and thus negative consequences for future fertility (306). However, the deleterious effect of hCG has not been demonstrated in males with CHH with cryptorchidism.

In 2002, Main *et al.* (203) reported the effects of subcutaneous (SC) injections of rLH and rFSH during the first year of life in an infant with CHH born with micropenis. This treatment led to an increase in penile length (1.6 to 2.4 cm), as well as a 170% increase in TV accompanied by an increase in inhibin B levels. Similarly, Bougnères *et al.* (204) reported the use of gonadotropin infusion in two neonates, one diagnosed with CHH and the other with CPHD. In this study, rLH and rFSH were administered SC via a pump for 6 months. This treatment not only corrected the micropenis in both patients (8 to 30 mm and 12 to 48 mm, respectively), but also induced testicular growth (0.57 to 2.1 mL and 0.45 to 2.1 mL, respectively). Serum LH and FSH levels increased to normal or supranormal levels, leading to an endogenous secretion of T, inhibin B, and AMH. Similarly, Sarfati *et al.* (136) reported another case with a perinatal diagnosis of KS based on the presence of an *ANOS1* (*KAL1*) mutation, the detection of renal

Table 4. Medical Treatment of Puberty Induction, Hypogonadism, and Infertility in Female Patients With CHH

Treatment	Dosing and Administration	Advantages	Disadvantages
Induction of puberty in girls			
17β-estradiol (tablets)	Initial dose: 5 μg/kg daily orally	Natural estrogen	Less preferable than transdermal route
	↑ 5 μg/kg increments every 6–12 mo		
	Up to 1–2 mg/d		
17β-estradiol (patch)	Inital dose: 0.05–0.07 μg/kg, only nocturnal	Natural estrogen	Small dose patch not available; need to cut the patch of 25 μg/24 h
	↑ to 0.08–0.12 μg/kg every 6 mo	No hepatic passage (decrease thromboembolic risk)	
	Up to 50–100 μg/24 h		
Progesterone	Added after full breast development or breakthrough bleeding, during the last 14 d of menstrual cycle		
Treatment of hypogonadism in adult females			
Estroprogestin therapy (tablets)	17β-Estradiol 1 or 2 mg	Mimic the physiological hormone changes	
	Progestin: during the last 14 d of the month micronized progestin at 200 mg/d orally, or dydrogesterone at 10 mg/d orally		
Estroprogestin therapy (patch or gel)	17β-Estradiol patch 50–100 μg/24 h daily, OR	Mimic the physiological hormone changes	
	17β-Estradiol gel 7.5–15 mg daily		
	Progestin: during the last 14 d of the month, micronized progestin at 200 mg/d orally, or dydrogesterone at 10 mg/d orally		
Treatment of fertility in adult females			
Pulsatile GnRH	*IV pump:* 75 ng/kg per pulse every 90 min	Most physiological treatment	Not available in many countries
	Dose adapted based on response, up to 500 ng/kg per pulse	Possibility to adjust pulse frequency in IV pump	Require centers with expertise
	SC pump: 15 μg per pulse every 90 min	High success rate	Risk of phlebitis for IV treatment (rare)
	Dose adapted based on response, up to 30 μg per pulse	Less risk in multiple pregnancy	Pituitary resistance (rare)
	Luteal phase: continue GnRH pump, OR		
	hCG 1500 U every 3 d for three times		
Gonadotropins	hMG (FSH + LH) 75 to 150 IU SC daily, dose adapted based on follicular growth	Available around the world	More expensive
	Induction of ovulation by hCG 6500 IU SC injection	Self-injection	Higher risk of overstimulation
	Luteal phase:		Requires close monitoring of E2 and ultrasound
	hCG 1500 U every 3 d for three times		Higher risk of multiple pregnancy
	Progesterone 200 mg intravaginally daily		

Table 5. Medical Treatment of Puberty Induction, Hypogonadism, and Infertility in Male Patients With CHH

Treatment	Dosing and Administration	Advantages	Disadvantages
Induction of puberty in boys			
T enanthate	Initial dose: 50 mg IM monthly	Standard care with long clinical experience	Premature epiphyseal closure (high dose)
	↑ 50 mg increments every 6–12 mo	Aromatizable to E2: promote bone maturation	Could inhibit TV and spermatogenesis
	Up to 250 mg/mo		Impact on future fertility unknown
Gonadotropin	hCG: initial dose 250 IU SC twice weekly,	Stimulate TV growth and spermatogenesis	Not standard treatment
	↑ 250–500 IU increments every 6 mo	Pre-FSH treatment can be beneficial in patients with TV <4 mL or history of cryptorchidism	Need good compliance in adolescent patients
	Up to 1500 IU three times weekly		Need studies in larger cohorts
	rFSH: dose 75–150 IU SC three times weekly,		
Hypogonadism treatment in adult males			
T enanthate	250 mg IM every 2 to 4 wk	Cost-effective	Relatively frequent IM injection
	Interval adjusted based on trough T	Available around the world	SC route under investigation (302)
		Self-injection	
T undecanoate	1000 mg IM every 10 to 14 wk	Cost-effective	Interval of treatment highly variable; follow-up of trough T is important
	Interval adjusted based on trough T	Infrequent injection	Injections by nurses
T gel	50–80 mg/d transdermally	Noninvasive	Risk of transmission by skin contact
		Self-administered	
Treatment of infertility in adult males			
Pulsatile GnRH	SC pump: 25 ng/kg per pulse every 120 min	Most physiological treatment	Not available in many countries
	Dose adapted based on serum T		Require centers with expertise
	Up to 600 ng/kg per pulse		Pituitary resistance (rare)
Gonadotropin	hCG: dose 500–1500 IU SC three times weekly,	Available around the world	Relatively expensive for rFSH
	Dose adjusted based on trough T	For patients with absent puberty (TV <4 mL):	Frequent injections
	rFSH: dose 75–150 IU SC three times weekly,	Pre-rFSH treatment increases fertility prognosis	
	Dose adjusted based on serum FSH, sperm count		

agenesis during fetal life, and the presence of micropenis at birth. The combined gonadotropins infusion from 1 to 7 months of age induced the normalization of testicular size (0.33 to 2.3 mL) and penis length (15 to 38 mm). Recently, Lambert and Bougnères (206) reported the effect of combined rLH and rFSH injections in a series of eight male infants with either CHH or CPHD. All patients presented with either cryptorchidism or high scrotal testis at diagnosis and were treated with gonadotropin infusion. Apart from the increase in both penile length and testicular size, the authors observed complete testicular descent in six out of eight cases. However, the effect of combined gonadotropin treatment on cryptorchidism in CHH infants will need to be formally assessed by randomized controlled trials. Furthermore, the effect of such treatment on males with cryptorchidism without hypogonadism remains unknown.

Collectively, these studies suggest that combined gonadotropin therapy in male patients with CHH during the neonatal period can have a beneficial effect on both testicular endocrine function and genital development. This treatment may be superior to androgen therapy, as it stimulates Sertoli cell proliferation and the growth of seminiferous tubules, as evidenced by the marked increase in TV and in serum inhibin B concentrations (34).

It is possible that the normalization of penis size in the neonate will lead to a normal adult penis size during subsequent pubertal virilization with exogenous T or hCG, thus preventing the feeling of inadequacy often reported by males with CHH with micropenis (147). In parallel, the increase in testicular size, which correlates with the increase in Sertoli cell mass, could lead to better outcomes in terms of sperm output during fertility induction in adolescence or adulthood (34). Taken together, these data imply that combined gonadotropin therapy in males during the neonate period may attenuate the psychological effects of micropenis later in adolescence, and potentially improve fertility in adulthood. Thus, randomized controlled trials with a larger number of patients are needed to rigorously assess the effect of gonadotropins on cryptorchidism in male neonates. Furthermore, longitudinal studies are warranted to determine the long-term benefits on reproductive function of hormonal intervention during infancy. However, there are no data to support such a treatment in female patients with CHH.

Pubertal induction

Induction of female secondary sexual characteristics

The literature focusing on the induction of puberty in teenagers (and adult women) with CHH is limited. However, the therapeutic objectives are well defined (7, 301, 307): to achieve breast development, to ensure external and internal genital organ maturity and other aspects of feminine appearance, and to promote psychosexual development with respect to emotional life and sexuality (149). Additionally, puberty induction also increases uterine size, which is important for future pregnancy. Finally, optimizing growth to achieve a final height close to the predicted parental mean target is important, along with acquiring normal BMD (301, 308).

Most therapeutic regimens inducing feminization in CHH are not evidence based. Instead, they arise from expert opinions (7, 301, 309–311) partly due to the paucity of patients (308, 311–314). Furthermore, regimens have often mirrored Turner syndrome treatment (315). Thus, a dogmatic attitude is to be avoided. We propose that the choice of treatment integrates the patient's opinion while maintaining a favorable risk/benefit balance.

In practice, E2 therapy (oral or transdermal) induces feminization; however, available protocols vary widely (312, 313). As transdermal estrogen in adulthood is associated with a good efficacy profile and reduced cardiovascular events, it is reasonable to prioritize this formulation for pubertal induction (308). Additionally, a recent randomized trial in a small number of hypogonadal girls has shown that transdermal E2 resulted in higher E2 levels and more effective feminization compared with oral conjugated equine estrogen (314).

Transdermal E2 administration is often started at low doses (*e.g.*, 0.05 to 0.07 μg/kg nocturnally, from 11 years), with the goal of mimicking E2 levels during early puberty. In older girls with CHH when breast development is a priority, transdermal E2 is started at 0.08 to 0.12 μg/kg (301, 308, 316). The E2 dosage should then be increased gradually during 12 to 24 months. After maximizing breast development and/or after the breakthrough bleeding, cyclic progestagen is added. In most females with CHH, estroprogestin (EP) therapy is effective to induce harmonious development of the breasts and genitals. In turn, the restoration of normal secondary sex characteristics likely contributes to a more satisfactory emotional and sexual life (149). Estrogen treatment also increases uterine size (133), and EP therapy induces monthly withdrawal bleeding. However, this treatment does not restore ovulation. Finally, estrogen therapy induces a growth spurt and increases bone density in most female adolescents with CHH and older women with CHH (317). The treatment options are summarized in Table 4.

Induction of male secondary sexual characteristics

Therapeutic goals in the adolescent male with CHH are also well defined: to induce virilization, to reach optimal adult height, to acquire normal bone mass and body composition, to achieve normal psychosocial development, and to gain fertility. However, available treatment regimens may not always cover all of these aspects. The hormonal treatment options for the induction of puberty in males with CHH are presented in Table 5.

As with girls with CHH, there is a paucity of literature and a lack of randomized studies comparing different treatment modalities, with only one randomized study including several patients with CHH (318). Difficulties also arise from studies aggregating heterogeneous cohorts of patients with CHH in terms of clinical presentation (*i.e.*, degree of spontaneous puberty) and genetics.

Early treatment is crucial and usually involves an injectable T ester such as T enanthate (123, 301, 319). Pediatric endocrinologists treating younger patients (from 12 years of age) typically begin treatment with low-dose T (*e.g.*, 50 mg of T enanthate monthly) and gradually increase to full adult dose (250 mg every 2 to 4 weeks) during the course of ~24 months. For patients with CHH seeking treatment in later adolescence or early adulthood, a higher dose of T can be used to induce rapid virilization. Initial T doses (such as 100 mg of T enanthate monthly) can be quickly increased to 250 mg intramuscularly (IM) monthly. Such regimens induce secondary sexual characteristics and maximize final height (301, 320). Side effects for T treatment include erythrocytosis, premature closure of the epiphysis (when doses are too high during the first year of treatment), and occasional pain and erythema at the injection site. Of note, T treatment does not stimulate testicular growth or spermatogenesis (123, 319), because intragonadal T production is needed to stimulate spermatogenesis. In contrast, increased testicular growth during T treatment indicates CHH reversal and requires treatment withdrawal followed by hormone profiling (152).

Induction of testicular maturation. Gonadotropins are used for fertility treatments in adult patients with CHH, but can also be used to induce pubertal maturation in adolescent males with CHH. An additional advantage of gonadotropin treatment compared with T treatment is the stimulation of testicular growth and spermatogenesis. Therefore, gonadotropin treatment may offer important psychological reassurance in adolescents and enhance self-confidence. Varying treatment protocols including hCG alone or in combination with FSH have been used to induce puberty in boys (321–325). In a retrospective analysis of boys with CHH, Bistritzer *et al.* (321) showed a comparable virilizing effect of monthly T injections and weekly hCG injections (5000 IU/wk), but testicular growth was significantly larger in boys treated with hCG.

Rohayem *et al.* (325) studied a relatively large group of adolescents with delayed puberty, most of them with absent puberty (n = 34). The adolescents received low-dose hCG (250 to 500 IU twice weekly) with increasing increments of 250 to 500 IU every 6 months, and rFSH was added once serum T achieved targeted pubertal level (5.2 nmol/L). This treatment led to a substantial increase in TV (bitesticular volumes, 5 ± 5 to 34 ± 3 mL) and induction of spermatogenesis in 91% of patients (325).

Pretreatment with FSH in adolescents with severe GnRH deficiency. The rationale behind priming with FSH alone in patients with severe GnRH deficiency is that the mass of Sertoli cells is a predictor of future sperm output. FSH induces proliferation of immature Sertoli cells prior to seminiferous tubule maturation in rats (326), *Macaca mulatta* (327), and probably also in humans (328). Conversely, adult men with biallelic inactivating *FSHR* mutations exhibit small testicular size and variable degrees of spermatogenesis failure (329). Additionally, it has been suggested that patients with CHH with absent puberty with/without micropenis and cryptorchidism likely have a suboptimal Sertoli cell complement due to lack of minipuberty, as evidenced by low serum inhibin B levels, and could thus benefit from pretreatment with FSH. A study of 14 boys with gonadotropin deficiency treated with rFSH priming showed significant increases in inhibin B and TV in the absence of an increase in intragonadal T production consistent with proliferation of Sertoli cells (330). Spermatogenesis was achieved in six out of seven boys who provided semen samples, with a maximal sperm count ranging from 2.9 to 92 million/mL (median, 8.5 million/mL) (330). A subsequent randomized controlled study (see below) showed similar results in young adults (331). Thus, pretreatment with FSH prior to testicular maturation appears to compensate for the suboptimal Sertoli cell proliferation during late fetal life and minipuberty, and thus might be beneficial in adolescent males for future fertility. However, this treatment is intensive, requires frequent injections and close follow-up, and might not be optimal for all adolescent patients with CHH. A large multicenter study to evaluate the benefits and cost-effectiveness of pretreatment with FSH in severe cases of adolescents and adults with CHH is warranted.

Hypogonadism treatment in adults

Females

Hormonal treatment is required in adult females with CHH for maintaining bone health, increasing feminine appearance, improving emotional and sexual life, and promoting general well-being. Studies on hormonal treatment in adult patients with CHH are limited and several centers favor EP replacement therapy instead of oral contraceptive pills. Indeed, the effect of ethinylestradiol on bone health of hypogonadal women is less established than the effect of 17β-estradiol. Additionally, long-term EP replacement preserves BMD in another population of young hypogonadal women with Turner syndrome (332). More recently, a 2-year randomized trial comparing HRT vs oral contraceptive pills in hypogonadal women with primary ovarian insufficiency revealed significantly higher BMD of the lumbar spine in the HRT group (333). Additionally, there has been no report of increased risk for thromboembolic events in females with CHH on EP substitution. E2 can be given either orally (at a dose of 1 to 2 mg) or transdermally (50 μg daily by patch or 2 pumps of 0.06% gel daily) with a cyclic progestin regimen (*i.e.*, micronized progesterone at 200 mg or dydrogesterone at 10 mg, daily during the last 14 days of the cycle) to avoid endometrial hyperplasia. EP treatment induces monthly withdrawal bleeding but does not restore ovulation. This treatment should be maintained at least until the natural age of menopause.

Males

Long-term androgen treatment is required in male patients with CHH to maintain normal serum T levels, libido, sexual function, bone density, and general well-being. The different regimens of T replacement therapy are summarized in Table 5.

T can be given as an injectable formulation (aromatizable androgen such as enanthate, cypionate, or undecanoate) or transdermal application (123, 319, 334). The maintenance dose of T is usually 250 mg of

T enanthate IM every 2 to 4 weeks, 1 g of T undecanoate IM every 3 to 4 months, or 50 to 80 mg of T gel daily (Table 5). The surveillance of trough serum T levels is important, as there exists considerable variation regarding the metabolism of exogenous T products among patients with CHH (154). For T injections, the frequency of injections should be assessed according to the trough serum T measurement, targeting the lower end of the normal range. IM T injections may cause substantial differences between the peak and trough T levels. Pilot studies have shown that a weekly SC injection of low doses of T cypionate or T enanthate can induce a more steady profile of plasma T (302, 335). For patients treated with T gel, the target for random serum T level is the middle of the normal range. The advantage of T gel is its pharmacokinetics with a more stable T concentration within the normal adult range, and the lack of minimally invasive injections. However, patients on T gel should avoid skin contact with others (partners or children), as there are known risks for hyperandrogenism in women (336) or for precocious puberty in children (337). Among the reported disadvantages of transdermal T are the high cost and the lack of reimbursement in some countries. Whichever treatment is used, men with CHH are challenged to adhere to long-term treatment, and poor adherence may contribute to adverse effects on bone, sexual, and psychological health (146).

Fertility treatment

Induction of fertility in females with CHH

Infertility in women with CHH is caused by impaired pituitary secretion of both gonadotropins, LH and FSH, leading to an impaired ovarian stimulation. Specifically, GnRH deficiency leads to an impairment in follicular terminal growth and maturation, resulting in chronic anovulation. However, there is no evidence of a decreased follicular reserve (132). This point must be emphasized to patients and their families as soon as the diagnosis is made. Indeed, the combination of small ovaries, decreased antral follicular count, and low circulating AMH concentrations observed in women with CHH could wrongly suggest an alteration in ovarian reserve and a poor fertility prognosis (132). In contrast, these patients should be informed that ovulation induction will lead to a fairly good outcome in terms of fertility in the absence of a male factor of infertility or advanced age (>35 years) (132, 133, 338–340).

Before considering ovulation induction, sonohysterosalpingography or traditional hysterosalpingography could be performed to evaluate both the integrity and the permeability of the uterine cavity and fallopian tubes (341). Alternatively, sono-hysterosalpingography could be performed after a couple of cycles of successful ovulation in the absence of pregnancy. Additionally, an associated male infertility factor should be ruled out by obtaining a semen analysis (340). Couples should be advised on the optimal timing of sexual intercourse during the ovulation induction, as this first-line therapy does not require *in vitro* fertilization (132, 133, 338, 339).

The goal of ovulation induction therapy in female patients with CHH is to obtain a mono-ovulation to avoid multiple pregnancies. Ovulation can be achieved either with pulsatile GnRH therapy or stimulation with gonadotropins. The latter includes either extractive or rFSH treatment followed by hCG or rLH to trigger ovulation (342). The therapeutic choice will depend on the expertise of each center and the local availability of the different medical therapeutics.

Pulsatile GnRH treatment. Pulsatile GnRH therapy via a pump was first proposed by Leyendecker *et al.* (343–345) to induce ovulation in women with different causes of hypogonadotropic amenorrhea (WHO I, anovulation). Given its remarkable efficiency in acquired forms of HH, pulsatile GnRH was successfully applied to women with CHH (346) and other causes of acquired HH (347–349). Both SC and IV routes for GnRH administration are appropriate to restore fertility (347, 350). Pulsatile GnRH restores the physiological secretion of pituitary gonadotropins, which in turn induces ovulation in patients with CHH (351–355). The major advantage of pulsatile GnRH therapy compared with gonadotropin treatment is the decreased risk of multiple pregnancy or ovarian hyperstimulation (347, 348, 355). Consequently, it requires less monitoring and surveillance during treatment. Therefore, when pulsatile GnRH treatment is available within the region the patient is being treated, it should be considered the first line of therapy in females with CHH, given that it is the most physiological regimen and results in fewer side effects.

"CHH is one of the few medically treatable causes of male infertility..."

Physiologically, GnRH pulse intervals vary throughout the menstrual cycle, as evidenced by LH pulse studies in a large series of women with regular menses (356). Based on this study, the frequency of GnRH pulses is set for every 90 minutes during the early follicular phase of treatment, and subsequently accelerated to every 60 minutes during the middle and late follicular phase. After ovulation, the frequency is reduced to every 90 minutes. Finally, during the late luteal phase, there is a further decrease to every 4 hours that will favor FSH secretion over LH. However, pulsatile GnRH at a constant frequency of 90 minutes also induces maturation of ovarian follicles, an LH surge, and ovulation (350).

The dosage of GnRH required to restore normal ovulation has been well studied in females with CHH or functional hypothalamic amenorrhea. IV doses of 75 ng/kg per pulse are considered a physiological dose to induce adequate pituitary gonadotropin secretion and ovarian stimulation (357). In 30% of females with CHH, pituitary resistance is present at the first cycle, requiring increased GnRH doses and longer stimulation (354). Once ovulation is achieved, the corpus luteum must be stimulated to produce progesterone, which is mandatory for embryo implantation. The pulsatile GnRH pump is able to maintain endogenous pulsatile LH secretion sufficient to ensure progesterone release by the corpus luteum until the endogenous secretion of hCG from the placenta begins (355, 358). Another treatment option for luteal support is hCG (SC injections of 1500 IU every 3 days for three times), which is less costly and well tolerated. The success rate of ovulation induction is excellent in females with CHH, reaching 90% ovulation per cycle, and 27.6% conception per ovulatory cycle. The number of cycles needed to obtain a pregnancy is quite variable, ranging from one to six cycles (350, 355). The multiple pregnancy rate is slightly higher than the general population at 5% to 8% (357), but much lower than with gonadotropin therapy. Notably, the pulsatile GnRH pump can be effective even in the presence of GnRH resistance, such as in women with CHH who harbor partial loss-of-function mutations in *GNRHR* (351, 354).

When administered SC, higher doses (15 μg per pulse) are needed, and typically the frequency of pulses are kept at one every 90 minutes. The success rate is slightly lower at 70% of ovulation rate per cycle (359). However, the SC administration has no risk of phlebitis and is more convenient.

GnRH pulse treatment is discontinued when pregnancy occurs, and adverse effects in early pregnancy have not been reported (360). After several unsuccessful cycles of GnRH stimulation, gonadotropin therapy should be proposed (see below) (338, 339) to bypass a potential pituitary resistance associated or not with loss-of-function *GNRHR* mutations (197, 354).

Gonadotropin treatment. In women with CHH, ovulation can also be achieved with FSH treatment followed by hCG or rLH to trigger ovulation. However, women with severe GnRH deficiency have very low gonadotropin levels, thus requiring both FSH and LH during the follicular phase. LH stimulates the ovarian theca cells to produce androgen substrates, allowing sufficient secretion of E2 by the maturing follicles (132, 233, 338, 361). E2 is necessary for optimal endometrial thickness and cervical mucus production, which in turn are needed for sperm transit and embryo implantation (132). Typically, SC human menopausal gonadotropins (hMGs; FSH plus hCG) doses of 75 to 150 IU/d are sufficient to induce ovulation. Usually, a dominant follicle (>18 mm) will mature in ~12 days. The starting dose of hMG is often increased or decreased depending on the ovarian response, as assessed by repeated serum E2 measurements or by using ultrasonography to count and measure maturing follicles every other day. This regimen minimizes the risk of multiple pregnancy and ovarian hyperstimulation syndrome. After ovulation, progesterone production can be stimulated by repeated hCG injections, or direct administration of progesterone during the post-ovulatory phase until the end of the luteal phase.

***In vitro* fertilization.** If conception fails after repeated successful ovulation induction in females with CHH, *in vitro* fertilization may be an alternative (362, 363).

Induction of fertility in males with CHH

CHH is one of the few medically treatable causes of male infertility, and fertility treatments have very good outcomes. Fertility induction can be accomplished either by long-term pulsatile GnRH therapy or with combined gonadotropin therapy.

Pulsatile GnRH treatment. Pulsatile GnRH treatment is a logical approach in patients with CHH seeking fertility. Physiological GnRH secretion is episodic, and therefore GnRH treatment requires IV or SC GnRH administration in a pulsatile manner via a mini-infusion pump (364). This therapy will stimulate pituitary gonadotropin secretion and in turn intragonadal T production, resulting in the initiation and maintenance of spermatogenesis as evidenced by increased TV and sperm output by 12 months of treatment on average. The common initial dose is 25 ng/kg per pulse every 2 hours, with a subsequent titration to normalize serum T to the adult normal range (66, 365–367). Response to treatment varies according to the degree of GnRH deficiency, with normalization of TV and successful induction of spermatogenesis for all patients with partial puberty. On the contrary, TV and sperm counts are lower in patients with absent puberty, and 20% of these patients remained azoospermic despite 12 to 24 months of pulsatile GnRH treatment (66). A systematic literature review on this issue is listed in Table 6 (66, 250, 325, 330, 364, 366, 368–402).

Gonadotropin treatment. Gonadotropin treatment (hCG alone or combined with rFSH) is another treatment option for fertility induction in male patients with CHH. Whereas IM injections were prescribed in the past, SC gonadotropin injections are currently preferred, and various formulations are used. Typical doses vary from 500 to 2500 IU two to three times a week for hCG, and from 75 to 225 IU two to three times a week for FSH preparations, namely hMG, highly purified urinary FSH, or rFSH. The dosage of hCG is adjusted based on trough serum T, and rFSH dosage is titrated based on serum FSH levels and sperm counts.

Fertility outcomes in men with CHH. From the early 1970s to 2017, a series of 40 papers were published that address fertility and spermatogenesis in patients with CHH, and included >1000 patients with CHH (Table 6). More than 80% of the patients have been treated by combined gonadotropin therapy. Although the GnRH pump is an effective therapy to induce spermatogenesis in the absence of pituitary defect, the substantial use of gonadotropins may indicate that GnRH therapy is not available in several countries, including the United States, where it has been largely used only in a research setting. Furthermore, this therapy is expensive and likely less comfortable than gonadotropin injections given the long period (1 to 3 years) needed to mature the testes.

Both pulsatile GnRH and gonadotropin therapy are effective to induce spermatogenesis and fertility in men with CHH (403–405); however, no clear superiority of GnRH vs gonadotropins was observed. Similarly, none of the available FSH preparations appears to differ in terms of sperm output.

The overall success rate in terms of sperm output is variable across studies (64% to 95% success), with sperm counts ranging from zero to several hundred million per milliliter. The weighted average median time to achieve sperm production was slightly more than a year (Table 6). It is well established that even low sperm concentrations in men with CHH are sufficient to impregnate partners (250). Pregnancy was successfully achieved in 175 partners of patients with CHH (Table 6), and successful pregnancies were reported in 16% to 57% of patients with CHH desiring fertility. As reported (Table 6), most pregnancies obtained were by natural conception. In a minority, *in vitro* fertilization was necessary because of the existence of concomitant ovarian or uterotubal abnormalities in the partner (see references quoted in Table 6). Conversely, 192 patients were not able to produce sperm despite long-term gonadotropin treatment (median, 24 months), corresponding to 12% to 40% depending on the study. In patients with azoospermia after treatment or poor sperm quality, more invasive treatments such as testicular sperm extraction were proposed followed by intracytoplasmic spermatozoid injection (390); however, the outcomes are not clearly outlined in these studies.

The major limitations of most studies are (i) the often small population size; (ii) the inclusion of all types of patients with HH (*i.e.*, severe, partial, or AHH, which are known to have different outcomes in terms of fertility); (iii) the inclusion or exclusion in some studies of men with cryptorchidism with variable dates of postnatal surgery that could also impact prognosis; (iv) the absence of studies taking into account the genetic mutations as a predictor for treatment outcome; and (v) the absence of prospective randomized studies comparing head-to-head gonadotropin treatment to pulsatile GnRH therapy.

Despite these limitations, there are some lessons to be learned: (i) sperm counts may improve but rarely normalize in patients with CHH based on WHO criteria; (ii) low sperm concentration does not always preclude fertility in men with CHH; and (iii) several predictive factors have been identified in this population:

Testicular volume. TV is an indicator of the degree of GnRH deficiency and is a positive predictor of sperm output (66). When we consider the entire population of patients with CHH treated for infertility (n = 994), the average testicular size was 3.5 mL at baseline and increased to 8.6 mL by the last visit. However, the spectrum of TV at baseline varies widely within and across studies. Thus, it is not surprising that studies including patients with milder forms of GnRH deficiency had the best sperm output (Table 6). In contrast, studies in which most men with CHH exhibited prepubertal testes tended to have the poorest results. These patients usually lack the beneficial stimulatory effects of gonadotrope activation during the minipuberty and could benefit from a pretreatment with rFSH prior to GnRH [see below (331)].

Cryptorchidism. The presence of unilateral or bilateral undescended testes reflects the severity of gonadotrope axis deficiency, and is thus one of the main features of antenatal-onset GnRH deficiency. Cryptorchidism is recognized as a negative predictor of sperm output, and patients with bilateral cryptorchidism have lower sperm counts than do those with the unilateral variant or those without cryptorchidism. Also, patients with cryptorchidism require a longer time to attain spermatogenesis (66). Despite >1000 men with CHH included in the various studies focusing on spermatogenesis/fertility, only 19% had cryptorchidism. Furthermore, in 42% of studies no patients with cryptorchidism were included. Furthermore, 30% of studies explicitly excluded cryptorchidism because of an expected poorer spermatogenesis prognosis. A number of factors may be involved in the cryptorchidism-related germ cell depletion, including apoptosis of germ cells in a testis that remains too long in the abdomen (406). In this setting, a surgical correction should be recommended as early as 6 months to 1 year of age (407).

Prior exposure to androgens. A single study considered prior androgen therapy to be associated with a poorer prognosis (393), but this result was not reproduced in subsequent studies (66, 389, 397, 408, 409). Thus, the impact of prior androgen treatment on fertility remains controversial.

"HRT is the first-line treatment of CHH-asociated bone loss..."

Pretreatment with FSH. The fertility outcome with GnRH or classical gonadotropin therapy is suboptimal, especially in patients with severe GnRH deficiency. In 2013, a randomized study explored the addition of rFSH pretreatment to standard GnRH pulsatile therapy in 13 young adults with severe GnRH deficiency (TV <4 mL) and no prior gonadotropin therapy (331). Patients with cryptorchidism were excluded in this study. After 4 months of rFSH alone, mean TV doubled from 1 to 2 mL in the absence of

Table 6. Fertility Outcomes in Male Patients With CHH: Summary of 44 Published Studies

Study No.	CHH (n)	nCHH (n)	KS (n)	CHH With Cryptorchidism (n)	Median Basal TV (mL)	Median Max. TV (mL)	Median Max. Sperm Count (10^6/mL)	Median TTS (mo)	Therapy Failure (Persistent Azoospermia) (n)	Therapies Used	Pregnancies[a] (n)	Refs.
Combined gonadotropin therapy												
1	10	8	2	NA	NA	NA	NA	16	1	hMG + hCG	4	(368)
2	36	25	11	NA	NA	NA	5.1	5	9	hPG	12	(369)
3	15	7	8	7	NA	NA	8.5	10	5	hMG + hCG	8	(370)
4	13	7	6	4	2.4	6.9	1.3	11.5	1	hMG + hCG	2 (7)	(371)
5	13	13	0	0	1.2	3.1	3.0	NA	2	hMG + hCG	3	(372)
6	24	17	7	Excluded	6.8	13.9	16.7	7.6	Not included	hMG + hCG	22	(250)
7	8	NA	NA	NA	2.1	9	1.0	24	2	hMG + hCG	1 (8)	(373)+
8	18	9	9	5	2.5	8	4	12	9	hMG + hCG	1	(374)[++]
9	16	8	8	4	3.5	13.3	6.0	23.1	2	hMG + hCG	NA	(375)
10	18	NA	NA	Excluded	3.7	14.9	2.6	34.2	4	hCG + hMG	7 (10)	(376)
11	10	4	6	Excluded	4	12	18.5	24	NA	hMG + hCG	3 (4)	(377)
12	7	6	1	6	1.2	9	10.0	11.8	1	hMG + hCG	3	(378)
13	9	7	2	0	2.2	8	8.0	14	2	hMG + hCG	4	(379)
14	26	12	14	13	1.5	3.8	2.2	12.2	12	hMG + hCG	3	(380)
15	35	19	16	Excluded	4.3	11.1	14.0	5	12	uFSH + hCG	1 (4)	(381)
16	27	16	11	Excluded	3.6	10.5	16.5	9	3	uFSH + hCG	2 (10)	(382)
17	18	9	9	8	4.4	15.3	1.2	6	2	hMG + hCG	3	(383)[+++]
18	10	8	2	Excluded	3.5	9.6	5.0	6.6	2	rhFSH + hCG	2	(384)
19	26	17	9	Excluded	2	12	1.5	9	4	rhFSH + hCG	4 (7)	(385)
20	20	13	7	5	8	NA	5	5.5	NA	rhFSH /uFSH + hCG	NC	(386)
21	9	8	1	4	3	7.5	5.1	16.8	NA	hMG + hCG	NA	(387)
22	26	11	15	11	5.7	12	5.0	7	10	rhFSH + hCG	NA	(388)
23	23	18	5	9	1.6	4.85	1.0	52	7	hMG + hCG	NA	(389)
24	4	4	0	0	4.1	6.8	2.05	12	0	hMG + hCG	3	(390)
25	4	2	2	2	1	5.5	3.0	10	1	rhFSH + hCG	NA	(330)
26	25	16	9	Excluded	NA	14	5.2	5.1	1	rhFSH + hCG	5 (30)	(391)
27	77	48	29	Excluded	3.4	11.7	8.2	18	13	rhFSH + hCG	14 (51)	(392)
28	51	34	17	12	6.5	NA	8.0	23	NA	rhFSH/uFSH + hCG	38	(393)
29	10	9	1	0	NA	9	7.0	9.8	1	hMG/rhFSH + hCG	4	(394)
30	31	22	9	Excluded	3.8	9	22.8	12	NA	rhFSH/uFSH + hCG	10 (22)	(395)
31	19	8	11	9	4.5	10.2	7.1	11	1	hMG + hCG	5 (11)	(396)
32	223	112	111	40	2.1	8.1	11.7	15	80	hMG + hCG	17	(397)

(*Continued*)

Table 6. ***Continued***

Study No.	CHH (n)	nCHH (n)	KS (n)	CHH With Cryptor-chidism (n)	Median Basal TV (mL)	Median Max. TV (mL)	Median Max. Sperm Count (10^6/mL)	Median TTS (mo)	Therapy Failure (Persistent Azoospermia) (n)	Therapies Used	Pregnancies[a] (n)	Refs.
33	38	18	20	19	2.5	16.5	15.0	55	3	rhFSH + hCG	0	(325)
Subtotal	**899**	**515**	**358**	**158**					**190**		**181**[a]	
Pulsatile GnRH therapy												
34	5	3	2	NA	3	4.5	4.1	3	3	GnRH[b]	1	(364)
35	10	6	4	NA	NA	NA	4.2	12	1	GnRH	3	(398)
36	30	NA	NA	0	5	18	68	5	1	GnRH	18 (30)	(399)
37	5	NA	NA	NA	2.4	11.5	0.1	24	3	GnRH	2 (5)	(373)[+]
38	10	8	2	1	4	14	19.2	12	0	GnRH	NA	(366)
39	18	10	8	4	2	10	4.7	5	4	GnRH	1	(374)[++]
40	28	17	11	13	2	12	2	10.7	7	GnRH	3	(400)
41	6	4	2	3	6.8	14.9	1.6	4	1	GnRH	3	(383)[+++]
42	52	26	26	21	3.3	12	15.0	24	9	GnRH	NA	(66)
43	35	12	23	9	2.3	9	NA	12	9	GnRH	NA	(401)
44	20	9	11	4	2.9	10.8	14.2	15.6	NA	GnRH	5 (14)	(402)
Subtotal	**219**	**95**	**89**	**55**					**38**		**36**[a]	
Total, n	**1118**	**610**	**447**	**213**					**228**		**217**[a]	
Mean					**3.4**	**9.8**	**7.59**	**15.3**				
Weighted mean[c]					**3.51**	**10.8**	**9.83**	**15.2**				

Data are reported as number or medians, as appropriate. Please note that because of the wide range of some parameters (notably sperm count, which may range from 0.01 to >300 million/mL), we chose to show medians instead of means. "Excluded" indicates patients with CHH/KS with cryptorchidism who were excluded from the study design. +, ++, and +++ indicate data from the same study.

Abbreviations: hMG, FSH + LH; hPG, human pituitary gonadotropin (mixture of FSH and LH); KS, patients with KS; NA, not available; NC, noncalculable; nCHH, CHH without reported KS features; rhFSH, recombinant human FSH; TTS, time to induce sperm appearance in ejaculate (mo); uFSH, urinary highly purified FSH.

[a]Pregnancies obtained (number in parentheses indicates the total number of patients treated who wanted children).

[b]For GnRH treatment, the GnRH agonist gonadorelin was used (pulsatile administration via a pump).

[c]To emphasize the importance of the population size, we also calculated the weighted means of the median values [*i.e.*, we calculated weighted means of 8489.9 10^6/mL (patients × sperm count) and 10,341.4 mL (patients × TVs)]. The weighted means were then divided by the total number of patients to whom these numbers refer (864 for the sperm count and 956 for the TVs, respectively).

increased intragonadal T with a concomitant increase in inhibin B levels into the normal range. Furthermore, histological findings demonstrated an increase in the diameter of the seminiferous tubules compared with baseline without any sign of maturation, as well as enhanced proliferation of immature Sertoli cells and spermatogonia (331). Following 2 years of pulsatile GnRH, both groups (with and without rFSH pretreatment) normalized serum T levels and exhibited significant testicular growth. All patients in the pretreatment group developed sperm in their ejaculate (vs four out of six in the GnRH-only group) and showed trends toward higher maximal sperm counts, TVs, and serum inhibin B levels, although it did not reach statistical significance mainly due to the small sample size. Thus, larger prospective multicenter studies are needed to support the superiority of pretreatment with FSH prior to classical treatment (GnRH or hCG plus FSH) on improving fertility outcomes in patients with severe GnRH deficiency, with and without cryptorchidism, and to assess the cost-effectiveness of pretreatment with FSH.

Management of adverse health events related to CHH

Bone loss and fracture

A recent mixed longitudinal study of 2014 healthy children has substantially improved our understanding of skeletal development. McCormack *et al.* (410) showed that (i) at age 7 years, healthy children had obtained only 30% to 38% of maximal observed whole body mineral content (BMC); (ii) during puberty, a significant gain in BMC occurred; (iii) the mean age at peak rate of whole BMC aquisition was 14.0 years in boys, and 12 to 12.5 years in girls, which was, on average, 0.6 to 1.2 years after the PHV; and (iv) another 7% to 11% of maximal observed BMC was gained after linear growth had ceased.

The relative roles of androgens and estrogens in bone metabolism in bone health were recently investigated in adult men. Endogenous sex steroids were suppressed with goserelin acetate, and the patients were subsequently treated with increasing doses of T only, or in combination with aromatase inhibitor anastrozole to suppress conversion of T to E2 (411). The results from this study demonstrated that bone resorption increased markedly once E2 levels were low, even when serum T was substantially elevated (411). E2 deficiency primarily affected the cortical bone. Cutoffs of <10 pg/mL for E2 and <200 ng/dl (6.9 nmol/L) for T (with intact aromatization) were suggested as undesirable for bone health (411).

Consistent with these data, low BMD is present in most patients with CHH. However, important variability exists regarding the degree of bone involvement in CHH, as illustrated by a recent report of older never-treated patients with CHH with low to near-normal BMD and no significant difference compared with patients treated by HRT (412). These data suggest that the beneficial effect of sex steroid replacement therapy on bone status in this specific population may be smaller than previously thought. However, the authors could not completely rule out the possibility of occasional hormone treatment in the past in older "never treated CHH." Similarly, they could not exclude the possibility of suboptimal adherence to chronic hormone therapy in the "treated" patients with CHH.

Bone remodeling is low in CHH, as suggested by the only study that performed iliac crest bone biopsies in patients with CHH with low bone mass (413). Data on bone remodeling markers are inconclusive and do not always correlate with BMD (414). Evidence on fracture incidence is scarce, with some reports of incidental vertebral fractures but no comparison of the prevalence against controls (414, 415).

HRT is the first-line treatment of CHH-associated bone loss, with antiresorptive drugs (bisphosphonates, denosumab) as second-line therapeutic choices (416). Given the male sex predominance of CHH, the effect of gonadal steroid replacement has been principally studied in males receiving T and/or gonadotropins. T increases BMD in CHH (413, 417) and mixed hypogonadal cohorts (418–421). Increased levels of bone formation markers such as P1NP, usually observed early in the course of treatment, possibly reflect the anabolic effects of androgens (422, 423). It remains unclear whether T replacement fully reverses the bone phenotype (418) or only partially improves BMD (417). Age at onset of HRT might be a crucial prognostic factor for the therapeutic response. In the first study exploring the link between CHH and bone, Finkelstein *et al.* (413) described bone densities measured by CT in 21 men with CHH, of whom 15 initially had fused epiphyses and 6 had open epiphyses. Most patients had received prior androgen treatment. After bringing T levels to within the normal range, the younger group increased both cortical and trabecular bone densities, whereas those with initially fused epiphyses displayed only an increase in cortical bone density (413). The authors hypothesized that this difference reflects the physiological bone accretion that occurs during normal sexual maturation. These data imply that there is a critical period of skeletal response to sex steroids, which would further stress the importance of timely diagnosis of CHH. Nevertheless, another study focusing on older patients with CHH (median age of 56 years) revealed substantial bone response to T replacement despite delayed diagnosis and onset of HRT (141). Therapeutic adherence may also explain the variability observed. Highlighting the importance of compliance to HRT, Laitinen *et al.* (414) demonstrated that prolonged cessations in HRT (>5 years in total) were associated with decreased BMD in the lumbar spine, hip, femoral neck, and whole body, although no difference was observed in fracture prevalence.

Note that some genes involved in CHH may also have direct implications on bone health, which may confound the results reported from the small series of men with CHH. Specific genetic causes that may directly affect bone include mutations in *FGF8*, *FGFR1*, and *SEMA3A* (182, 424).

Despite the importance of estrogen for the male skeleton, measurement of E2 is not routinely performed in patients with CHH with bone defects. This attitude is based on the fact that standard T treatment is aromatizable and corrects low estrogen levels (212). However, this should be considered in cases with suboptimal response to HRT and after excluding more frequent causes such as inadequate compliance.

As in other causes of secondary osteoporosis, adequate calcium intake (>1000 mg/d) should be assured. Vitamin D deficiency is prevalent in the CHH population (415) and should also be corrected. Targeting levels >30 μg/L (75 nmol/L) is reasonable in the presence of low BMD. A small retrospective study suggested that the central hypogonadism as seen in CHH might lead to worse bone outcomes as compared with primary hypogonadism independently of gonadal steroids levels (425). The authors postulated that severe vitamin D deficiency in CHH is due to decreased LH-dependent vitamin D 25-hydroxylation in the testes. Nevertheless, no difference in vitamin D levels was detected in a larger cohort of patients with CHH in comparison with age- and BMI-matched controls (426). Further studies addressing this issue should focus on removing the bias of seasonal variation of vitamin D.

Metabolic defects

Metabolic defects are present in patients with CHH and are commonly thought to be secondary to sex steroid deficiency (292, 427). The prevalence of overweight and obesity in patients with CHH is between 40% and 50% according to a recent nationwide Italian cohort of patients (134), similar to the general Italian population (428). However, another study detected increased prevalance of metabolic syndrome in CHH in comparison with the general population (429). The latter compared 332 young patients with CHH without prior androgen treatment vs 395 age- and BMI-matched controls and revealed a significantly increased prevalence of all components of metabolic syndrome (*i.e.*, waist circumference, arterial blood pressure, fasting glucose, homeostatic model assessment of insulin resistance, serum triglyceride levels).

T therapy in CHH leads to an improvement in insulin sensitivity (430, 431), a reduction in high-sensitivity C-reactive protein levels (430) and low-density lipoprotein cholesterol (432), as well as increased lean mass and decreased visceral adiposity (431). Furthermore, short-term withdrawal of T therapy in male patients with CHH causes mild insulin resistance and increased fasting glucose levels (427). Similar to T therapy in male patients with CHH, gonadotropin replacement therapy is accompanied by increased lean mass, reduced body fat and waist-to-hip ratio, increased insulin sensitivity, and reduced triglycerides levels (433).

It is possible that genetic determinants predispose certain patients with CHH to metabolic disturbances. Leptin deficiency or resistance leads to defective signaling of different metabolic cues to the hypothalamus, which normally regulates both energy homeostasis and reproductive capacity (434). Recently, the FGF21/KLB/FGFR1 pathway was also highlighted as an important player underlying the link between reproduction and metabolism (253). In this study, most probands with CHH harboring *KLB* mutations (9 of 13) exhibited some degree of metabolic defect (*i.e.* overweight, insulin resistance, and/or dyslipidemia), consistent with the potential role of this pathway in metabolic health.

Conclusions

Despite a set of relatively straightforward diagnostic criteria, the phenotypic spectrum of CHH is broad. This includes a notable proportion of reversal cases, an overlap with common reproductive disorders such as CDGP and FHH, and the presence of CHH as a component of more complex entities such as CHARGE and Waardenburg syndromes. Timely diagnosis is critical; however, the clinical presentation and biochemical profiles are often not fully informative in early adolescence, as the presentation of CHH closely resembles that of CDGP. One possible opportunity for earlier diagnosis is during minipuberty, but currently the importance of evaluating minipuberty is not known. The advance of biochemical testing with minimal blood samples (*e.g.*, blood dry spots) offers the potential to assess the HPG axis function in neonates in normal and disease states.

Finally, the discovery of genes involved in GnRH ontogeny have helped to elucidate the pathophysiology as well as improve genetic counseling of the disease, and have assisted in rendering an accurate diagnosis. The advent of high-throughput sequencing technologies have substantially increased the identification of rare variants. However, this results in a specific challenge to classify for pathogenicity, especially in the context of the oligogenicity seen in CHH. Large, multinational studies are required to define CHH genetic risks associated with the spectrum of rare variants.

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Abbreviations

AF, antral follicle; AHH, adult-onset hypogonadotropic hypogonadism; AMH, anti-Müllerian hormone; BMC, body mineral content; BMD, bone mineral density; BMI, body mass index; CDGP, constitutional delay of growth and puberty; CHH, congenital hypogonadotropic hypogonadism; CPHD, combined pituitary hormone deficiency; DXA, dual-energy X-ray absorptiometry; E2, estradiol; EP, estroprogestin; FHH, functional hypogonadotropic hypogonadism; GW, gestational week; GWAS, genome-wide association study; hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; hMG, human menopausal gonadotropin; HPG, hypothalamic-pituitary-gonadal; HRT, hormone replacement therapy; IHH, idiopathic hypogonadotropic hypogonadism; IM, intramuscular(ly); KS, Kallmann syndrome; OV, ovarian volume; PHV, peak height velocity; rLH, recombinant LH; rFSH, recombinant FSH; SC, subcutaneous(ly); T, testosterone; TV, testicular volume; VNN, vomeronasal nerve; WHO, World Health Organization.