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The initiation and maintenance of reproductive capacity in humans is dependent upon pulsatile secretion of the hypothalamic hormone gonadtropin-releasing 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 more than 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 significant portion of male patients (around 10-20%) exhibit a spontaneous recovery of their reproductive function. Finally, fertility can be induced with pulsatile GnRH treatment or gonadotropin regimens in a majority of patients. In summary, this review is a comprehensive synthesis of the current literature available regarding the diagnosis, patient management and genetic foundations of congenital hypogonadotropic hypogonadism relative to normal reproductive development.

Essential points

- Minipuberty is an important window to assess the activity of the HPG axis, especially in male neonates with cryptorchidism and/or micropenis in order to diagnose neonatal CHH.
- Currently, it is difficult to differentiate CHH from 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 differentiate CHH from CDGP to date.

- 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 sex, however the role of gonadotropin therapy during the neonatal and adolescence periods remains unclear.
- Infertility in CHH patients 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.

1. Introduction

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 re-awakening of the hypothalamic-pituitary-gonadal (HPG) axis following a relative quiescence during childhood (2). Pulsatile secretion of gonadotropin-releasing hormone (GnRH) by specialized neurons in the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (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 the hypothalamic-pituitary-gonadal (HPG) axis activity: the fetal life and infancy (minipuberty).

The timing of puberty varies largely in the population, and 50-80% of this variation is genetically determined (3-5). Delayed puberty is defined as a delay of pubertal onset or progression greater than 2SD compared to the population mean (6). Constitutional delay in 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 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 (IGD), and congenital hypogonadotropic hypogonadism (CHH) being used almost interchangeable. IHH was the first terminology to appear in print (8), however "idiopathic" is typically reserved for diseases which 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 after, 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 often associated with congenital features. The term CHH is commonly used especially in Europe, and will be 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 therapeutical options from different perspectives. To achieve these objectives, we also review the normal physiology of the HPG axis.

2. Fetal development of the hypothalamic-pituitary-gonadal axis

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

The majority of 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 neurons 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 around 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 nasal compartment to 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 17-18 before it involutes, suggesting that hypothalamic signalling is needed for the maintenance of the gonadotropes from this stage (25). Fetal serum gonadotropin levels peak at mid-gestation 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 gestational week 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 steroids 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 5-7. 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 hCG (human chorionic gonadotropin) during the first trimester and subsequently fetal pituitary LH from mid-gestation regulate Leydig cell differentiation to produce testosterone (T) from the fetal Leydig cells (32), which is needed for masculinization of the fetus. Testosterone is needed for the development of the male internal genitalia, while dihydrotestosterone produced by the enzyme 5-α reductase 2 (SRD5A2) induces the formation of the prostate, penis and scrotum. Until mid-gestation, testosterone 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 inguino-scrotal testicular descent occur, mediated in part by testosterone stimulated by GnRH-induced LH secretion (reviewed in (33) and (34)).

In females, the gonads develop into an ovary in the absence of the Y chromosome. However, several active signalling pathways need to be present for a normal differentiation of the ovary (35). In addition, 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 to 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 non-functional. 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 (34)).

3. Clinical presentation of CHH

3.1 Clinical presentation of CHH during the minipuberty

3.1.1 Normal minipuberty

Within minutes of birth, a brief postnatal LH surge leads to an increase in testosterone 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- 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 3-4 years of life in girls (12,43,45). A recent study of both full-term and pre-term infants suggests that gonadal feedback mediated by sex steroids, and 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 1-3 months, and then decline to low prepubertal levels by approximately 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 behaviour in toddlers (48). In addition, 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 significant 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 x 10^6 at birth to 1500 x 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 level of androgen receptors (AR) and thus remain immature despite increased testosterone 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 one 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, testosterone appears to be a significant 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 (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 anorchid boys indicates that the inhibition of the HPG axis at the end of minipuberty is independent of the gonads (59).

3.1.2 Minipuberty: Implications for CHH phenotypes

From a diagnostic perspective, minipuberty offers a unique window of opportunity for the early diagnosis of CHH (60). While 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 30-50% (61,62), which is higher than the general population (cryptorchidism in full-term male newborns: 1-3% 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 CHH patients is variable, ranging from 20-40 % in KS patients while a frequency of 0.015% is reported in the general population (65-67).

3.2 Clinical presentation of CHH during adolescence

3.2.1 Normal puberty

Puberty is characterized by sexual maturation, increased growth velocity, changes in body composition and psycho-social 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 gradually increase to both day and night resulting in gonadal maturation and the completion of puberty (70-73). The precise mechanisms that triggers the initiation of puberty remain unclear. Murine studies have shown dynamic remodelling in GnRH neuron morphology occuring at puberty with the acquistion of more than 500 spines associated with increasing synaptic inputs contributing to the sharp increase in GnRH neuron activity (74). Increased excitatory input like glutamate or decreased inhibitory input like aminobutyric acid (GABA) appear to be critical for pubertal onset (75). In addition, the nature of the GnRH pulse generator is still a 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 arcuate nucleus in driving GnRH pulsatility in mice (78). Previous works performed in girls with Turner syndrome and in agonadal boys have clearly showed that the pubertal reactivation of 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 cells number and function (84). Progressively, LH stimulates Leydig cell differentiation and their steroidogenic capabilities leading to testosterone production. The concomitant stimulation of Sertoli cells by FSH and the production of intragonadal testosterone by LH leads to the initiation of spermatogenesis and a sharp increase in testicular volume 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 to testosterone and inhibin B (85). This finding likely reflects changes in androgen receptor expression in immature Sertoli cells, since androgen receptors are present in only 2-15% of Sertoli cells until 4 years of age, whereas its expression can be observed in > 90% of Sertoli cells after the age of eight years (55). Notably, AMH levels begin to decline before any notable increase in testis size (85,86). In addition, 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 intra-ovarian 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, while increased FSH is needed for the recruitment of ovarian follicles and the aromatisation of androgens to estradiol by the granulosa cells (90). AMH concentrations show only minor fluctuations during female puberty (91), while 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 significant inter-individual 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 Caucasian 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 old 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 approximately 2 years and allows for the acquisition of approximately 18% of final height (103). Peak height velocity (PHV) occurs at an average of 11.5-12 years old, approximately one year after thelarche (96). Menarche occurs approximately 6 months later (99). The median time between the onset of puberty and menarche is approximately 2.5 years (99,104). Secondary sexual characteristics development (breast Tanner stage 4 and/or pubic hair stage 5) is completed approximately 1.5 year after menarche.

In boys, testicular enlargement (volume ≥ 4 ml) is the first clinically detectable sign of puberty, occuring at ~11.5 years, and approximately 6-12 months before penis growth (i.e. genital Tanner stage 3) and pubarche (94,105,106). The growth spurt begins subsequently with a PHV occuring 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, 11.7-15.3 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 13.9-14.6 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 genders include bone mass acquisition, changes in body composition, and brain development. Bone changes during puberty are detailed in Section 8.5.1. 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). Gender 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 magnetic resonance imaging (MRI) changes in grey and white matter development in humans, even after removing the confounding effect of age (113).

3.2.2 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 (1991–1993 and 2006–2008) demonstrated earlier breast development in the 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), though this difference is probably decreasing (118).

3.2.3 Delayed puberty

Delayed puberty is defined as pubertal onset occuring 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 (testicular volume < 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/year) led to a more accurate description of normal puberty and its extremes (precocious and delayed puberty) (119) (Figure 1).The most common cause of delayed puberty in both sexes is the constitutional delay of growth and puberty (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). Though its pathophysiology is not fully understood, CDGP has a clear genetic basis, as 50-75% of CDGP patients 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 (e.g. Klinefelter syndrome or Turner syndrome), permanent hypogonadotropic hypogonadism (e.g. CHH, tumors, infilitrative diseases) and functional hypogonadotropic hypogonadism (e.g. systemic illness, anorexia nervosa, excessive exercise). In particular, the differential

diagnosis between CDGP and CHH in adolescence is particularly difficult as discussed in detail in Section 7.3. Management options include expectant observation versus short-term sex steroid replacement (6). The latter targets primarily the induction of secondary sexual characteristics in order to alleviate psychosocial distress due to pubertal delay and/or short stature.

3.2.4 Hallmarks of CHH in adolescence

In males

In adolescence, CHH male patients seek medical attention for absent or minimal virilization, low libido, and erectile dysfunction (123). In 75% of CHH patients, puberty never occurs, leading to severely reduced testicular volume (< 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 CHH patients 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, testosterone is needed for seminal and prostatic fluids production and optimal ejaculate volume.

The majority of CHH patients 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 steroids 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 CHH men exceeds the height of healthy control men (127-129). Other studies show that CHH adolescents, on average, achieve their mid-parental height (126,130). Studying 41 CHH men, 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 (128). On the other hand, Dickerman et al. 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 (129). 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).

Typical changes of body composition in CHH boys 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 testosterone/estradiol ratio. Bone maturation is impaired, with delayed bone age and lower bone density observed relative to peers. There are no reported data on bone micro-architecture of CHH males, and the risk of fracture is difficult to assess given the lack of large multi-center prospective studies on bone health in CHH.

In females

The most prevalent complaint is primary amenorrhea in nearly 90% of CHH women (131-134). Less than 10% of CHH women had some menstrual bleeding (131,133,135), which in most cases involved one or two episodes of bleeding during adolescence (primary-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 CHH women prior to estrogen replacement therapy (131-133). Only one single multicenter retrospective study described absent breast development in the majority of CHH women (134). However, this study included only female CHH patients 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). Further, adrenarche leading to increase production of adrenal androgen (i.e. DHEA, 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's series, the growth of 16 females with CHH was unremarkable (129), whereas a slight mid-childhood deceleration in the growth rate of girls carrying *FGFR1* mutations was recently reported (124,139).

3.3 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 testicular volume with preserved spermatogenesis is observed in a subset of male patients (called 'fertile eunuch syndrome'). These patients exhibit low serum levels of testosterone 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 intra-testicular testosterone production, but unable to achieve normal circulating testosterone levels for full virilization (140). Very rarely, CHH is diagnosed at older age. Recently, Patderska *et al*. described six cases of men who were diagnosed with CHH after 50 years of age, and who had long-term uncorrected hypogonadism (141). These patients exhibited adverse health events such as osteoporosis (6/6), hypercholestelemia (4/6) and anemia (2/6). 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. Further, data on the natural history of CHH in older men and women is lacking.

In addition, 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 hypogonadotropic hypogonadism (HH). No central nervous system abnormalities or risk factors for functional GnRH deficiencies have been identified (142), and follow-up studies in 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 constitutes a major source 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 CHH patients. A recent online survey suggests a negative perception of CHH women on their health status, with a tendency towards 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.

3.4 CHH reversal

Although CHH was previously considered as a life-long condition, it is now known that a subset of CHH patients spontaneously recover function of their reproductive axis following treatment (150-153). Reversibility occurs in both male and female CHH patients, and appears to be more common (~10-20% 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), therefore long-term monitoring of reproductive function is needed. Thus, CHH patients 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).

3.5 CHH-associated phenotypes

CHH can be associated with non-reproductive phenotypes. Anosmia (i.e. lack of sense of smell) is observed in approximately 50% of CHH cases (157,158), and this co-occurrence is termed Kallmann syndrome (KS). The interconnected link between the GnRH and olfactory systems during early developmental stages explains this association (see above, Section 2) (159).

Other phenotypes are also associated with CHH, although at a lower prevalence. They include mirror movements (synkinesia), unilateral renal agenesis, eye movement disorders, sensori-neural hearing loss, midline brain defects (including absence corpus callosum), cleft lip/palate, dental agenesis, skeletal defects, and cardiovascular defects (7,157,158,160) (Figure 2). 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 can be found in Table 1. 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 which include this trait. In this review, we have compiled a table of syndromes having both a clinical and genetic overlap with CHH (Table 2).

4. 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 seven 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 hypogonadotropic hypogonadism 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 female CHH. In the series from the Massachusetts General Hospital of 250 consecutive CHH cases, the male to female ratio is 3.9 to 1. However, this ratio drops to 2.3 to 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 the prevalence of KS is 1:48,000 in the Finnish population, with a clear difference between males (1:30,000) and females (1:125,000) (65).

Bias regarding the reduced prevalence of CHH in females

The prevalence of CHH has historically been considered to be skewed towards a male predominance (male/female ratio of 5:1) (157,158). Recent work suggests that the sex ratio is closer to 2:1 (133,134). Further, analysis of sex ratio for CHH in families with autosomal

inheritance demonstrates that the sex ratio is close to being equal (194,195). Importantly, partial congenital hypogonadotropic hypogonadism may still be underdiagnosed due to subtle clinical presentation that resembles functional hypothalamic amenorrhea (131,196).

Several reasons could help to explain the underdiagnosis of CHH females:

(i) Over 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 longtime absent puberty, leading to an underevaluation of the prevalence of CHH in the past (131,133).

(ii) In the 1990s, it was thought that X-linked CHH is prevalent and thus that female CHH patients were rare. This dogmatic view was progressively challenged by the first descriptions of female CHH patients harboring biallelic *GNRHR* mutations, with variable degrees of breast development (135,137,197,198). Later, a variable degree of pubertal development was described for female CHH carrying mutations in autosomal genes (e.g. *FGFR1, PROK2* / *PROKR2* or *SOX10*)(65,136,164,180,199-201).

(iii) Finally, in some countries, patients with mild, non-syndromic 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 work-up and accurate diagnosis.

5. Diagnosis of CHH

5.1 Clinical diagnosis

5.1.1 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 4–12 weeks of life may be used to assist in the diagnosis (60,136,202-207).

Typically, low serum testosterone, LH and FSH levels are reported (Table 3) 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 CHH parent should undergo hormonal evaluation during minipuberty. The lack of typical clinical features in female infants suggesting CHH explains why the diagnosis of neonatal CHH is only rarely made in this gender (7,139,205).

5.1.2 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.

5.1.3 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 show hypogonadal T or E2 levels and low/normal serum levels of gonadotropins due to GnRH deficiency. However, CHH remains a diagnosis of exclusion (see Section 7). Between ages 14-16, CHH is difficult to differentiate from CDGP, a common cause of delayed puberty (See section 7.3).

5.1.4 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 significant utility for genetic counselling:

1. History of cryptorchidism with or without micropenis
2. Decreased or absent sense of smell, suggesting Kallmann syndrome, 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 if it shows olfactory bulbs hypoplasia or aplasia (see below)

3. Congenital sensori-neural 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, and 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, clinodactyly, etc
9. Pigmentation defects
10. Other stigmata of syndromic forms of CHH, e.g. heart malformation, outer ear anomalies and coloboma for CHARGE syndrome, etc (see Table 2)

5.2 Biochemical testing

5.2.1 Gonadotropins

Most men and women with CHH have very low circulating gonadotropin levels (61,123,132), and the majority of 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) (Figure 3).

5.2.2 Estradiol

Females:

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

Males:

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

5.2.3 Testosterone:

Males:

Circulating testosterone levels in CHH patients are usually low, i.e. less than 3 nmol/L (86.5 ng/dL). This is usually also the case for CHH patients with partial puberty and larger testicular volumes (61).

Females:

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

5.2.4 GnRH test

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

Males:

In CHH men, 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 GnRH deficient women, the peak LH response to GnRH stimulation was blunted relative to normal women (137).

5.2.5 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 CHH men with absent puberty +/- 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 (see above, Section 4.2.1.) (45,66,217,224). Higher serum inhibin B levels are encountered in a minority of patients with absent puberty, but in the majority of patients with partial puberty (61) or acquired hypogonadotropic hypogonadism (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 levels is a negative predictor of fertility (66). Further, a few studies demonstrated a good discrimative 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 follicules, and is secreted by the granulosa cells (226). Very few studies have investigated circulating inhibin B levels in CHH females (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).

5.2.6 Anti-Müllerian Hormone (AMH):

Males:

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

Females:

Mean serum AMH concentrations are significantly lower in women with CHH than in healthy women (Figure 3) (132), although two-thirds of patients display serum AMH levels within the normal range. The subgroup of CHH women with the lowest ovarian volume and antral follicular count had significantly lower AMH levels consistent with lower FSH levels. However, low AMH 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.

5.2.7 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 also Section 6). A baseline profile including measurments of prolactin, free T4, TSH, morning

cortisol and IGF1 should be performed and growth curve should be analysed. In case of suspected pituitary insufficiency, appropriate dynamic challenge tests and diencephalic imaging should be performed (231).

5.3 Radiological examination

Pelvic ultrasound

Studies on uterine morphologies in CHH women are limited (131,132,232). Pelvic or transvaginal ultrasound (when appropriate) demonstrated a significant reduction in mean ovarian volume (OV) compared to healthy adult women of a similar age (131-133,232). OV correlates with the severity of estradiol deficiency (232) and endometrial atrophy (233). Notably, the decrease in OV is greater in KS than in normosmic CHH with a trend towards lower serum gonadotropin levels in KS, suggesting a more severe GnRH deficiency (131). The only study that quantified the number of ovarian antral follicles (AF) showed a significant decrease in the average number of AF compared to 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 CHH women, and is often mistakenly considered a poor fertility prognosis. However, OV and AF respond favorably to gonadotropin stimulation in female 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. While an orchidometer is often used in clinical practice, testicular ultrasound (US) 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, orchidometer overestimates testicular volume by approximately 6 cc in comparison to ultrasound, likely due to the interference of surrounding soft tissues and 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). KS patients 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 KS patients 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 (i.e. viral infections, trauma etc.). Further, an anomaly of the semicircular canals is an important finding, as it suggests the diagnosis of CHARGE syndrome (239).

Bone density and microarchitecture:

CHH work-up 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 (TBS) or by performing a high-resolution peripheral quantitative computed tomorgraphy (HR-pQCT). The latter provides a more detailed assessment of bone microarchitecture at peripheral sites (e.g. distal radius, tibia) (240). On the other hand, TBS is a textural index that evaluates pixel grey-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture, readily available from the DXA scan (241). Bone work-up should be done at baseline and repeated at least two 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).

5.4 Other tests

5.4.1 Olfaction

Olfactory function represents a hallmark in the clinical assessment of CHH, as approximately 50% of patients have a defect in the sense of smell (Kallmann syndrome, also known as "olfacto-genital dysplasia") (243). Olfactory function is assessed using semi-quantitative methods such as the UPSIT score (210) or the Sniffin' Sticks (244,245) tests which gives age- and gender-matched scores relative to a reference population. Alternatively, volatile-stimulated chemosensory evoked potentials can be used (246), although 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). While 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 CHH patients.

5.4.2 Hearing

The prevalence of hearing loss in CHH is reported to be between 5-15% (Table 1). Nevertheless, there are no large studies with systematic evaluations of hearing in CHH patients, 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).

5.4.3 Spermiogram

Spermiogram is defined as the quantitative and qualitative analysis of semen in order to assess male fertility potential (248). Among the primary parameters, ejaculate volume (which is testosterone 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 over 4500 men in 14 countries and defined the lower reference limits for the following parameters: 1.5 ml for semen volume, 15 million per ml for sperm count, 40% for total motility and 4% for normal morphology. Most CHH patients at baseline (particularly those with severe hypogonadism) exhibit severe erectile dysfunction and an absence of ejaculate, rendering a spermiogram impossible. However, with fertility treatment the majority of CHH males will develop sperm in their ejaculate. Interestingly, the concentration of sperm needed for fertilization in CHH patients is much lower compared to the WHO guidelines (250). In conclusion, spermiogram is indicated at baseline (when possible) and serially after the initiation of fertility treatment.

6. Genetics of CHH

6.1 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 50–80% of this variation is caused by genetic factors (3-5). Recent genome-wide association studies (GWAS) 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*. reported ~400 independent loci robustly associated with the age at menarche (251). 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 GWAS 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. Further, a subset of loci implicated in the timing of puberty are located in imprinted regions (e.g. *MKRN3* and *DLK1*) which exhibit significant 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*, etc.) 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.

6.2 Genetics of CHH

Several recent reviews have focused exclusively on the genetics of CHH including the review by Stamou *et al*. in this journal (194,252). Over 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 more than 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 (Figure 4) (7,140,194,252,257). Yet, more than 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 is also observed (Figure 5). In addition to the Mendelian modes of inheritance, oligogenicity has also been reported in CHH. In 2007, loss-of-function mutations in 2 CHH genes acting in concert was described in 2 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 significantly 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 patients with KS, chondrodysplasia punctata 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), holoproencephaly (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. Further, 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+anosmia)(164) (Table 2). Refining these CHH-associated phenotypes greatly enhances the diagnostic yield of targeted gene screening. Indeed, while *FGFR1* mutations occur in approximately 10% of CHH patients, they are present in 87% of patients with both

CHH and SHFM (207). Similarly, while *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.

7. Differential diagnosis of CHH

7.1 Structural causes

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

7.2 Genetic causes : Combined pituitary hormone deficiency (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).

7.3 Transient GnRH deficiency: constitutional delay of growth and puberty (CDGP)

During early adolescence, distinguishing CHH from CDGP is extremely challenging, as a delay in puberty is a hallmark of both diseases, and hypogonadotropic hypogonadism is present in both. While 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). In addition, CDGP is a common cause of delayed puberty, whereas CHH is considerably more rare. Differentiating CHH from CDGP is crucial in order to allow an early diagnosis of CHH, avoid delay regarding hormonal replacement, and alleviate the psychological burden associated with delayed sexual maturation (7). In addition, 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 will review some features that may assist in this differential diagnosis, noting that while 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 (Figure 6):

Growth velocity was recently suggested to help differentiate the different etiologies of delayed puberty (6), but 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 age 14-15 years, a cut-off of TV 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% 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. GnRH test might be useful for identifying severe cases of CHH. Indeed, when GnRH stimulated LH response is blunted, CHH is highly probable. A recent study included 19 CHH and 181 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 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). Further, other markers such as INSL3, DHEAS, 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. Further, meta-analysis of GWAS studies including 370,000 women on the age of menarche revealed more than 400 loci associated with the timing of puberty, several of which overlap with known CHH genes, such as *TACR3, GNRHR*, etc (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.

7.4 Transient GnRH deficiency: functional hypogonadotropic hypogonadism

Similar to CDGP (see above), functional hypogonadotropic hypogonadism (FHH) is difficult to differentiate from CHH. FHH (frequently termed as functional hypothalamic amenorrhea [FHA] 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 (3-5% of the population among young woman, (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 FHA in women has been described (282).

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

7.5 Opioid-induded hypogonadotropic hypogonadism

Opioids use is a major cause of functional/reversible hypogonadotropic hypogonadism 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 prevalence of HH related to the consumption of these drugs will increase and become a growing diagnostic issue particularly among adolescents and young people.

7.6 Hypogonadotropic hypogonadism associated with metabolic defects

Late-onset hypogonadotropic hypogonadism is associated with metabolic syndrome, obesity and/or diabetes. (290). Contrary to CHH, this disorder is characterized by mild GnRH deficiency most commonly occuring 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 sex hormone-binding globulin (SHBG) is the major factor responsible for low T levels in moderately obese men, while severely obese men (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).

7.7 Hypogonadotropic hypogonadism associated with hemochromatosis

Hemochromatosis is part of the differential diagnosis for CHH as it can often result in hypogonadotropic hypogonadism 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 towards this etiology. It is important not to miss the diagnosis hemochromatosis, as a reversal of the associated hypogonadotropic hypogonadism may occur after repeated phlebotomy (300).

8. Treatment of CHH

With appropriate hormonal replacement therapy, CHH patients 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 (6,301) Table 4 & 5.

8.1 Neonatal treatment of CHH

To date, hormonal therapy during the neonatal period is only applied in male patients exhibiting micropenis/cryptorchidism and hypogonadotropic hypogonadism (34,136,203,204,206,303). An equivalent therapy is not proposed in female patients, as the consequences of severe GnRH deficiency during late fetal period and minipuberty in females is 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 have described the benefit of early androgen therapy in boys with either CHH or CPHD (202,303). Testosterone treatment can increase penile size and stimulate scrotal development.

hCG therapy with or without 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. On the other hand, 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 of 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 CHH males with cryptorchidism.

In 2002, Main *et al*. reported the effect of subcutaneous injections of rLH and rFSH during the first year of life in a CHH infant born with micropenis (203). This treatment led to an increase in penile length (1.6 to 2.4 cm), and a 170% increase in testicular volume accompanied by an increase in inhibin B levels. Similarly, Bougnères *et al*. reported the use of gonadotropin infusion in two neonates—one diagnosed with CHH and the other with CPHD (204). In this study, rLH and rFSH were administrated subcutaneously 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*. reported another case with a perinatal diagnosis of KS based on presence of an *ANOS1* (*KAL1)* mutation, the detection of renal agenesis during fetal life, and the presence of micropenis at birth (136). 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 & Bougneres reported the effect of combined rLH and rFSH injections in a series of eight male infants with either CHH or CPHD (206). 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 6 out of 8 cases. However, the effect of combined gonadotropin treatment on cryptorchidism in CHH infants will need to be formally assessed by randomized controlled trials. Further, the effect of such treatment on cryptorchid males without hypogonadism remains unknown.

Collectively, these studies suggest that combined gonadotropin therapy in male CHH patients 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 testosterone or hCG, thus preventing the feeling of inadequacy often reported by CHH males 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 larger number of patients are needed to rigorously assess the effect of gonadotropins on cryptorchidism in male neonates. Further, longitudinal studies are warranted to determine the long-term benefits on reproductive function of hormonal

intervention during infancy. However, there is no data to support such a treatment in female CHH patients.

8.2 Pubertal induction

8.2.1 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). In addition, puberty induction also increases uterine size, which is important for future pregnancy. Finally, optimizing growth in order to achieve a final height close to the predicted parental mean target is important, along with acquiring normal bone mineral density (301,308).

Most therapeutic regimens inducing feminization in CHH are not evidenced-based. Instead, they arise from expert opinions (7,301,309-311) partly due to the paucity of patients (308,311-314). Further, 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, estradiol 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). In addition, a recent randomized trial in a small number of hypogonadal girls have shown that transdermal estradiol resulted in higher estradiol levels and more effective feminization compared to oral conjugated equine estrogen (314).

Transdermal estradiol administration is often started at low doses (for instance 0.05–0.07 µg/kg nocturnally, from 11 years), with the goal of mimicking estradiol levels during early puberty. In older CHH girls when breast development is a priority, transdermal estradiol is started at 0.08–0.12 µg/kg (301,308,316). The estradiol dosage should then be increased gradually over 12–24 months. After maximizing breast development and/or after the break-through bleeding, cyclic progestagen is added. In the majority of CHH females, estroprogestin 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 estroprogestin therapy induces monthly withdrawal bleeding. However, this treatment does not restore ovulation. Finally, estrogen therapy induces a growth spurt and increases bone density in the majority of CHH female adolescent and older women (317). The treatment options are summarized in Table 4.

8.2.2 Induction of male secondary sexual characteristics

Therapeutic goals in the adolescent CHH male 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 male CHH are presented in Table 5.

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

Early treatment is crucial and usually involves an injectable testosterone ester such as testosterone enanthate (123,301,319). Pediatric endocrinologists treating younger patients (from 12 years of age) typically begin treatment with low-dose testosterone (for example, 50 mg of testosterone enanthate monthly) and gradually increase to full adult dose (250 mg every 2-4 weeks) over the course of approximately 24 months. For CHH patients seeking treatment in later adolescence or early adulthood, a higher dose of testosterone can be used to induce rapid virilization. Initial testosterone doses (such as 100 mg testosterone enanthate monthly) can be quickly increased to 250 mg 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 (if doses are too high during the first year of treatment), and occasional pain and erythema at the injection site. Of note, testosterone treatment does not stimulate testicular growth or spermatogenesis (123,319), since intragonadal T production is needed to stimulate spermatogenesis. In contrast, increased testicular growth during testosterone 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 CHH patients, but can also be used to induce pubertal maturation in adolescent CHH males. An additional advantage of gonadotropin treatment compared to testosterone 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 CHH boys, Bistrizer *et al*. showed a comparable virilizing effect of monthly testosterone injections and weekly hCG injections (5000 IU/week), but testicular growth was significantly larger in boys treated with hCG (321).

Rohayem *et al*. studied a relatively large group of adolescents with delayed puberty, most of them with absent puberty (n = 34) (325). The adolescents received low dose hCG (250-500 IU twice weekly) with increasing increments of 250-500 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 (bi-testicular 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 deficient is that the mass of Sertoli cells is a predictor of future sperm output. FSH induces proliferation of immature Sertoli cells prior to seminiferous tubules 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). In addition, it has been suggested that CHH patients with absent puberty +/- 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 pre-treatment with FSH. A study of 14 gonadotropin-deficient boys 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 6 out of 7 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 CHH patients. A large multicenter study to evaluate the benefits and cost-effectiveness of pre-treatment with FSH in severe cases of adolescent and adult CHH is warranted.

8.3 Hypogonadism treatment in adults

8.3.1 Females

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

8.3.2 Males

Long-term androgen treatment is required in male CHH patients 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.

Testosterone 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 testosterone is usually 250 mg of T enanthate IM every 2-4 weeks, 1g of T undecanoate IM every 3-4 months, or 50-80 mg of testosterone gel daily (Table 5). The surveillance of trough serum T levels is important, as there exists considerable variation regarding the metabolism of exogenous testosterone products among CHH patients (154). For testosterone injections, the frequency of injections should be assessed according to the trough serum testosterone measurement, targeting the lower end of normal range. Intra-muscular T injections may cause significant differences between the peak and trough T levels. Pilot studies have shown that weekly subcutaneous injection of low doses of T cypionate or T enanthate can induce a more steady profile of plasma T (335),(302). For patients treated with testosterone gel, the target for random serum T level is the middle of 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 testosterone are the high cost and the lack of reimbursement in some countries. Whichever treatment is used, CHH men are challenged to adhere to long-term treatment and poor adherence may contribute to adverse effects on bone, sexual and psychological health (146).

8.4 Fertility treatment

8.4.1 Induction of fertility in females 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 significantly advanced age (> 35 years) (132,133,338-340).

Before considering ovulation induction, sono-hysterosalpingography or traditional hysterosalpingography could be performed in order 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. In addition, 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*. to induce ovulation in women with different causes of hypogonadotropic amenorrhea (WHO I, anovulation) (343-345). Given its remarkable efficiency in acquired forms of HH, pulsatile GnRH was successfully applied to CHH women (346) and other causes of acquired HH (347-349). Both subcutaneous and intravenous 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 CHH patients (351-355). The major advantage of pulsatile GnRH therapy compared to 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, if pulsatile GnRH treatment is available within the region the patient is being treated, it should be considered the first-line of therapy in CHH females, given that it is the most physiological regimen and results in fewer side effects.

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 mid 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. Intravenous doses of 75 ng per kg per pulse are considered a physiological dose to induce adequate pituitary gonadotropin

secretion and ovarian stimulation (357). In 30% of CHH females, 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 (subcutaneous injections of 1500 IU every 3 days for 3 times) which is less costly and well tolerated. The success rate of ovulation induction is excellent in CHH females, 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 5-8% (357), but much lower than with gonadotropin therapy. Notably, 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 subcutaneously, 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 subcutaneous 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 CHH women, 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 estradiol by the maturing follicles (132,233,338,361). Estradiol is necessary for optimal endometrial thickness and cervical mucus production, which in turn are needed for sperm transit and embryo implantation (132). Typically, subcutaneous hMG (human menopausal gonadotropins, FSH + hCG) doses of 75–150 IU per day are sufficient to induce ovulation. Usually, a dominant follicle (>18 mm) will mature in approximately 12 days. The starting dose of hMG is often increased or decreased depending on the ovarian response, as assessed by repeated serum estradiol measurements or by using ultrasonography to count and measure maturing follicles every other day. This regimen minimizes the risk of multiple pregnancies 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 CHH females, *in vitro* fertilization may be an alternative (362,363).

8.4.2. Induction of fertility in CHH males

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 intravenous or subcutaneous GnRH administration in a pulsatile manner via mini-infusion

pump (364). This therapy will stimulate pituitary gonadotropin secretion and in turn intragonadal testosterone production, resulting in the initiation and maintenance of spermatogenesis as evidenced by increased testicular volume 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 testosterone 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 12-24 months of pulsatile GnRH treatment (66). A systematic literature review on this issue is listed in Table 6.

Gonadotropin treatment

Gonadotropin treatment (hCG alone or combined with rFSH) is another treatment option for fertility induction in male CHH patients. While intramuscular (IM) injections were prescribed in the past, subcutaneous gonadotropin injections are currently preferred, and various formulations are used. Typical doses vary from 500 to 2,500 UI 2-3 times a week for hCG, and from 75 UI to 225 UI 2-3 times a week for FSH preparations, namely hMG, highly purified urinary FSH (uFSH) or recombinant FSH (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 CHH men

From the early 1970s to 2017, a series of forty papers were published that address fertility and spermatogenesis in CHH patients, and included more than one thousand CHH patients (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 significant use of gonadotropins may indicate that GnRH therapy is not available in several countries, including the US where it has been largely used only in a research setting. Further, this therapy is expensive and likely less comfortable than gonadotropin injections given the long period (1-3 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 versus gonadotropins was observed. Similarly, none of the available FSH preparations appear to differ in terms of sperm output.

The overall success rate in term of sperm output is variable across studies (64 to 95% success), with sperm counts ranging from zero to several hundred million/ml. The weighted average median time to achieve sperm production was slightly over a year (Table 6). It is well established that even low sperm concentrations in CHH men are sufficient to impregnate partners (250). Pregnancy was successfully achieved in 175 CHH patients' partners (Table 6), and successful pregnancies were reported in 16 to 57% of CHH patients desiring fertility. As reported (Table 6), the majority of the pregnancies obtained were by natural conception. In a minority, *in vitro* fertilization was necessary because of the existence of concomitant ovarian or utero-tubal abnormalities in the partner (references quoted in Table 6). Conversely, 192 patients were not able to produce sperm despite long-term gonadotropin treatment (median 24 months), corresponding to 12-40% depending upon 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 (ICSI) (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 hypogonadotropic hypogonadism (i.e. severe, partial, or AHH, which are known to have different outcome in terms of fertility); (iii) the inclusion or exclusion in some studies of cryptorchid men 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 CHH patients 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 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 the majority of CHH men 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 pre-treatment 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 those with the unilateral variant or those without cryptorchidism. Also, cryptorchid patients require a longer time to attain spermatogenesis (66). Despite >1,000 CHH men included in the various studies focusing on spermatogenesis/fertility, only 19% had cryptorchidism. Further, 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.

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 pre-treatment 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 increased intragonadal T with a concomitant increase in inhibin B levels into the normal range. Further, histological findings demonstrated an increase in the diameter of the seminiferous tubules compared to 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 pre-treatment) normalized serum T levels and exhibited significant testicular growth. All patients in the pre-treatment group developed sperm in their ejaculate (versus 4 out of 6 in the GnRH-only group) and showed trends toward higher maximal sperm counts, testicular volumes 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 pre-treatment with FSH prior to classical treatment (GnRH or hCG+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.

8.5 Management of adverse health events related to CHH

8.5.1 Bone loss and fracture

A recent mixed longitudinal study of 2014 healthy children has significantly improved our understanding of skeletal development. McCormack *et al*. showed that (i) at age 7 years, healthy children had obtained only 30%-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 12-12.5 years in girls (410) which was, on average, 0.6-1.2 years after the peak height velocity, and (iv) another 7% to 11% of maximal observed BMC was gained after linear growth had ceased (410).

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

Consistent with these data, low BMD is present in the majority of CHH patients. Yet, important variability exists regarding the degree of bone involvement in CHH, as illustrated by a recent report of older never-treated CHH patients 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" CHH patients.

Bone remodeling is low in CHH as suggested by the only study that performed iliac crest bone biopsies in CHH patients 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 for CHH-associated bone loss, with anti-resorptive drugs (bisphosphonates, denosumab) as second-line therapeutic choices (416). Given the male gender predominance of CHH, the effect of gonadal steroid replacement has been principally studied in males receiving testosterone and/or gonadotropins. Testosterone 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 testosterone 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* described bone densities measured by computed tomography in 21 CHH men, of whom 15 initially had fused epiphyses and 6 had open epiphyses. The majority of patients had received prior androgen treatment. After bringing testosterone 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 CHH patients (median age of 56 years) revealed substantial bone

response to testosterone 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* demonstrated that prolonged cessations in HRT (more than 5 years in total) were associated with decreased bone mineral density in the lumbar spine, hip, femoral neck and whole body, although no difference was observed in fracture prevalence (414).

It should be noted 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 CHH men. 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 estradiol is not routinely performed in CHH patients with bone defects. This attitude is based on the fact that standard testosterone 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/day) 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 to 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 CHH patients 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.

8.5.2 Metabolic defects

Metabolic defects are present in CHH patients and are commonly thought to be secondary to sex steroid deficiency (292,427). The prevalence of overweight and obesity in CHH patients is between 40-50% 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 to the general population (429). The latter compared 332 young CHH patients without prior androgen treatment versus 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, HOMA-IR, serum triglyceride levels).

Testosterone therapy in CHH leads to an improvement in insulin sensitivity (430,431), a reduction in high-sensitivity C-reactive protein levels (430) and LDL cholesterol (432), as well as increased lean mass and decreased visceral adiposity (431). Further, short term withdrawal of testosterone therapy in male CHH patients causes mild insulin resistance and increased fasting glucose levels (427). Similar to testosterone therapy in male CHH patients, 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 CHH patients to metabolic disturbances. Leptin deficiency or resistance leads to defective signaling of different metabolic cues to the hypothalamus which normally regulate 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, the majority of CHH probands harboring *KLB* mutations (9/13) 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.

9. Conclusions

Despite a set of relatively straight-forward diagnostic criteria, the phenotypic spectrum of CHH is broad. This includes a significant 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.

And 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 significantly 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, multi-national studies are required to define CHH genetic risks associated with the spectrum of rare variants.

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The authors have nothing to disclose

Reference

1. Ojeda SR, Lomniczi A. Puberty in 2013: Unravelling the mystery of puberty. Nat Rev Endocrinol 2014; 10:67-69
2. Plant TM. Neuroendocrine control of the onset of puberty. Front Neuroendocrinol 2015; 38:73-88
3. Gajdos ZK, Henderson KD, Hirschhorn JN, Palmert MR. Genetic determinants of pubertal timing in the general population. Mol Cell Endocrinol 2010; 324:21-29
4. Dauber A, Hirschhorn JN. Genome-wide association studies in pediatric endocrinology. Hormone research in paediatrics 2011; 75:322-328
5. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocrine reviews 2003; 24:668-693
6. Palmert MR, Dunkel L. Clinical practice. Delayed puberty. The New England journal of medicine 2012; 366:443-453
7. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, Dwyer AA, Giacobini P, Hardelin JP, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2015; 11:547-564
8. Reitano JF, Caminos-Torres R, Snyder PJ. Serum LH and FSH responses to the repetitive administration of gonadotropin-releasing hormone in patients with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1975; 41:1035-1042
9. Venes D, Taber CW. Taber's cyclopedic medical dictionary. Ed. 22, illustrated in full color / ed. Philadelphia: F.A. Davis.
10. Norman RJ, Naidoo C, Reddi K, Khatree M, Joubert SM. Clinical studies in black women with isolated gonadotrophin-releasing hormone deficiency. S Afr Med J 1986; 69:546-548
11. Rogol AD, Mittal KK, White BJ, McGinniss MH, Lieblich JM, Rosen SW. HLA-compatible paternity in two "fertile eunuchs" with congenital hypogonadotropic hypogonadism and anosmia (the Kallmann syndrome). J Clin Endocrinol Metab 1980; 51:275-279
12. Kuiri-Hanninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Hormone research in paediatrics 2014; 82:73-80
13. Silverman AJ, Jhamandas J, Renaud LP. Localization of luteinizing hormone-releasing hormone (LHRH) neurons that project to the median eminence. J Neurosci 1987; 7:2312-2319
14. Schwanzel-Fukuda M, Pfaff DW. Origin of luteinizing hormone-releasing hormone neurons. Nature 1989; 338:161-164
15. Teixeira L, Guimiot F, Dode C, Fallet-Bianco C, Millar RP, Delezoide AL, Hardelin JP. Defective migration of neuroendocrine GnRH cells in human arrhinencephalic conditions. The Journal of clinical investigation 2010; 120:3668-3672
16. Wray S, Grant P, Gainer H. Evidence that cells expressing luteinizing hormone-releasing hormone mRNA in the mouse are derived from progenitor cells in the olfactory placode. Proceedings of the National Academy of Sciences of the United States of America 1989; 86:8132-8136
17. Schwarting GA, Wierman ME, Tobet SA. Gonadotropin-releasing hormone neuronal migration. Semin Reprod Med 2007; 25:305-312
18. Casoni F, Malone SA, Belle M, Luzzati F, Collier F, Allet C, Hrabovszky E, Rasika S, Prevot V, Chedotal A, Giacobini P. Development of the neurons controlling fertility in humans: new insights from 3D imaging and transparent fetal brains. Development (Cambridge, England) 2016; 143:3969-3981

19. Chung WC, Tsai PS. Role of fibroblast growth factor signaling in gonadotropin-releasing hormone neuronal system development. Front Horm Res 2010; 39:37-50
20. Polin RA, Abman SH. Fetal and Neonatal Physiology. 4th ed: Elsevier.
21. Hagen C, McNeilly AS. The gonadotrophins and their subunits in foetal pituitary glands and circulation. J Steroid Biochem 1977; 8:537-544
22. Reyes FI, Boroditsky RS, Winter JS, Faiman C. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. J Clin Endocrinol Metab 1974; 38:612-617
23. Clements JA, Reyes FI, Winter JS, Faiman C. Studies on human sexual development. III. Fetal pituitary and serum, and amniotic fluid concentrations of LH, CG, and FSH. J Clin Endocrinol Metab 1976; 42:9-19
24. Winter JS. Hypothalamic--pituitary function in the fetus and infant. Clin Endocrinol Metab 1982; 11:41-55
25. Pilavdzic D, Kovacs K, Asa SL. Pituitary morphology in anencephalic human fetuses. Neuroendocrinology 1997; 65:164-172
26. Kaplan SL, Grumbach MM. The ontogenesis of human foetal hormones. II. Luteinizing hormone (LH) and follicle stimulating hormone (FSH). Acta Endocrinol (Copenh) 1976; 81:808-829
27. Beck-Peccoz P, Padmanabhan V, Baggiani AM, Cortelazzi D, Buscaglia M, Medri G, Marconi AM, Pardi G, Beitins IZ. Maturation of hypothalamic-pituitary-gonadal function in normal human fetuses: circulating levels of gonadotropins, their common alpha-subunit and free testosterone, and discrepancy between immunological and biological activities of circulating follicle-stimulating hormone. J Clin Endocrinol Metab 1991; 73:525-532
28. Debieve F, Beerlandt S, Hubinont C, Thomas K. Gonadotropins, prolactin, inhibin A, inhibin B, and activin A in human fetal serum from midpregnancy and term pregnancy. J Clin Endocrinol Metab 2000; 85:270-274
29. Guimiot F, Chevrier L, Dreux S, Chevenne D, Caraty A, Delezoide AL, de Roux N. Negative fetal FSH/LH regulation in late pregnancy is associated with declined kisspeptin/KISS1R expression in the tuberal hypothalamus. J Clin Endocrinol Metab 2012; 97:E2221-2229
30. Kaplan SL, Grumbach MM. Pituitary and placental gonadotrophins and sex steroids in the human and sub-human primate fetus. Clin Endocrinol Metab 1978; 7:487-511
31. De Santa Barbara P, Bonneaud N, Boizet B, Desclozeaux M, Moniot B, Sudbeck P, Scherer G, Poulat F, Berta P. Direct interaction of SRY-related protein SOX9 and steroidogenic factor 1 regulates transcription of the human anti-Mullerian hormone gene. Mol Cell Biol 1998; 18:6653-6665
32. Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab 2011; 25:221-238
33. Virtanen HE, Cortes D, Rajpert-De Meyts E, Ritzen EM, Nordenskjold A, Skakkebaek NE, Toppari J. Development and descent of the testis in relation to cryptorchidism. Acta Paediatr 2007; 96:622-627
34. Bouvattier C, Maione L, Bouligand J, Dode C, Guiochon-Mantel A, Young J. Neonatal gonadotropin therapy in male congenital hypogonadotropic hypogonadism. Nat Rev Endocrinol 2012; 8:172-182
35. Brennan J, Capel B. One tissue, two fates: molecular genetic events that underlie testis versus ovary development. Nat Rev Genet 2004; 5:509-521
36. Kurilo LF. Oogenesis in antenatal development in man. Hum Genet 1981; 57:86-92
37. Cole B, Hensinger K, Maciel GA, Chang RJ, Erickson GF. Human fetal ovary development involves the spatiotemporal expression of p450c17 protein. J Clin Endocrinol Metab 2006; 91:3654-3661

38. Corbier P, Dehennin L, Castanier M, Mebazaa A, Edwards DA, Roffi J. Sex differences in serum luteinizing hormone and testosterone in the human neonate during the first few hours after birth. J Clin Endocrinol Metab 1990; 71:1344-1348
39. Waldhauser F, Weissenbacher G, Frisch H, Pollak A. Pulsatile secretion of gonadotropins in early infancy. Eur J Pediatr 1981; 137:71-74
40. Forest MG, Cathiard AM, Bertrand JA. Evidence of testicular activity in early infancy. J Clin Endocrinol Metab 1973; 37:148-151
41. Forest MG, Sizonenko PC, Cathiard AM, Bertrand J. Hypophyso-gonadal function in humans during the first year of life. 1. Evidence for testicular activity in early infancy. The Journal of clinical investigation 1974; 53:819-828
42. Winter JS, Hughes IA, Reyes FI, Faiman C. Pituitary-gonadal relations in infancy: 2. Patterns of serum gonadal steroid concentrations in man from birth to two years of age. J Clin Endocrinol Metab 1976; 42:679-686
43. Andersson AM, Toppari J, Haavisto AM, Petersen JH, Simell T, Simell O, Skakkebaek NE. Longitudinal reproductive hormone profiles in infants: peak of inhibin B levels in infant boys exceeds levels in adult men. J Clin Endocrinol Metab 1998; 83:675-681
44. Kuiri-Hanninen T, Haanpaa M, Turpeinen U, Hamalainen E, Seuri R, Tyrvainen E, Sankilampi U, Dunkel L. Postnatal ovarian activation has effects in estrogen target tissues in infant girls. J Clin Endocrinol Metab 2013; 98:4709-4716
45. Bergada I, Milani C, Bedecarras P, Andreone L, Ropelato MG, Gottlieb S, Bergada C, Campo S, Rey RA. Time course of the serum gonadotropin surge, inhibins, and anti-Mullerian hormone in normal newborn males during the first month of life. J Clin Endocrinol Metab 2006; 91:4092-4098
46. Kuiri-Hanninen T, Dunkel L, Sankilampi U. Sexual dimorphism in postnatal gonadotrophin levels in infancy reflects diverse maturation of the ovarian and testicular hormone synthesis. Clin Endocrinol (Oxf) 2018; 89:85-92
47. Bolton NJ, Tapanainen J, Koivisto M, Vihko R. Circulating sex hormone-binding globulin and testosterone in newborns and infants. Clin Endocrinol (Oxf) 1989; 31:201-207
48. Lamminmaki A, Hines M, Kuiri-Hanninen T, Kilpelainen L, Dunkel L, Sankilampi U. Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls. Horm Behav 2012; 61:611-616
49. Kuiri-Hanninen T, Kallio S, Seuri R, Tyrvainen E, Liakka A, Tapanainen J, Sankilampi U, Dunkel L. Postnatal developmental changes in the pituitary-ovarian axis in preterm and term infant girls. J Clin Endocrinol Metab 2011; 96:3432-3439
50. Aksglaede L, Sorensen K, Boas M, Mouritsen A, Hagen CP, Jensen RB, Petersen JH, Linneberg A, Andersson AM, Main KM, Skakkebaek NE, Juul A. Changes in anti-Mullerian hormone (AMH) throughout the life span: a population-based study of 1027 healthy males from birth (cord blood) to the age of 69 years. J Clin Endocrinol Metab 2010; 95:5357-5364
51. Bay K, Main KM, Toppari J, Skakkebaek NE. Testicular descent: INSL3, testosterone, genes and the intrauterine milieu. Nat Rev Urol 2011; 8:187-196
52. Cassorla FG, Golden SM, Johnsonbaugh RE, Heroman WM, Loriaux DL, Sherins RJ. Testicular volume during early infancy. J Pediatr 1981; 99:742-743
53. Cortes D, Muller J, Skakkebaek NE. Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. Int J Androl 1987; 10:589-596
54. Plant TM, Marshall GR. The functional significance of FSH in spermatogenesis and the control of its secretion in male primates. Endocrine reviews 2001; 22:764-786
55. Chemes HE, Rey RA, Nistal M, Regadera J, Musse M, Gonzalez-Peramato P, Serrano A. Physiological androgen insensitivity of the fetal, neonatal, and early infantile testis is explained by the ontogeny of the androgen receptor expression in Sertoli cells. J Clin Endocrinol Metab 2008; 93:4408-4412

56. Boukari K, Meduri G, Brailly-Tabard S, Guibourdenche J, Ciampi ML, Massin N, Martinerie L, Picard JY, Rey R, Lombes M, Young J. Lack of androgen receptor expression in Sertoli cells accounts for the absence of anti-Mullerian hormone repression during early human testis development. J Clin Endocrinol Metab 2009; 94:1818-1825
57. Schmidt IM, Chellakooty M, Haavisto AM, Boisen KA, Damgaard IN, Steendahl U, Toppari J, Skakkebaek NE, Main KM. Gender difference in breast tissue size in infancy: correlation with serum estradiol. Pediatr Res 2002; 52:682-686
58. Kiviranta P, Kuiri-Hanninen T, Saari A, Lamidi ML, Dunkel L, Sankilampi U. Transient Postnatal Gonadal Activation and Growth Velocity in Infancy. Pediatrics 2016; 138
59. Grinspon RP, Ropelato MG, Bedecarras P, Loreti N, Ballerini MG, Gottlieb S, Campo SM, Rey RA. Gonadotrophin secretion pattern in anorchid boys from birth to pubertal age: pathophysiological aspects and diagnostic usefulness. Clin Endocrinol (Oxf) 2012; 76:698-705
60. Grumbach MM. A window of opportunity: the diagnosis of gonadotropin deficiency in the male infant. J Clin Endocrinol Metab 2005; 90:3122-3127
61. Pitteloud N, Hayes FJ, Boepple PA, DeCruz S, Seminara SB, MacLaughlin DT, Crowley WF, Jr. The role of prior pubertal development, biochemical markers of testicular maturation, and genetics in elucidating the phenotypic heterogeneity of idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2002; 87:152-160
62. Trabado S, Maione L, Bry-Gauillard H, Affres H, Salenave S, Sarfati J, Bouvattier C, Delemer B, Chanson P, Le Bouc Y, Brailly-Tabard S, Young J. Insulin-like peptide 3 (INSL3) in men with congenital hypogonadotropic hypogonadism/Kallmann syndrome and effects of different modalities of hormonal treatment: a single-center study of 281 patients. J Clin Endocrinol Metab 2014; 99:E268-275
63. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, Diaz M, Lee PA, Seashore CJ, Tasian GE, Barthold JS, American Urological A. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014; 192:337-345
64. Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, Chellakooty M, Damgaard IN, Mau C, Reunanen M, Skakkebaek NE, Toppari J. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet 2004; 363:1264-1269
65. Laitinen EM, Vaaralahti K, Tommiska J, Eklund E, Tervaniemi M, Valanne L, Raivio T. Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland. Orphanet journal of rare diseases 2011; 6:41
66. Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF, Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2002; 87:4128-4136
67. Nelson CP, Park JM, Wan J, Bloom DA, Dunn RL, Wei JT. The increasing incidence of congenital penile anomalies in the United States. J Urol 2005; 174:1573-1576
68. Wu FC, Butler GE, Kelnar CJ, Huhtaniemi I, Veldhuis JD. Ontogeny of pulsatile gonadotropin releasing hormone secretion from midchildhood, through puberty, to adulthood in the human male: a study using deconvolution analysis and an ultrasensitive immunofluorometric assay. J Clin Endocrinol Metab 1996; 81:1798-1805
69. Schally AV, Arimura A, Kastin AJ, Matsuo H, Baba Y, Redding TW, Nair RM, Debeljuk L, White WF. Gonadotropin-releasing hormone: one polypeptide regulates secretion of luteinizing and follicle-stimulating hormones. Science (New York, NY) 1971; 173:1036-1038
70. Boyar RM, Rosenfeld RS, Kapen S, Finkelstein JW, Roffwarg HP, Weitzman ED, Hellman L. Human puberty. Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. The Journal of clinical investigation 1974; 54:609-618

71. Wu FC, Butler GE, Kelnar CJ, Sellar RE. Patterns of pulsatile luteinizing hormone secretion before and during the onset of puberty in boys: a study using an immunoradiometric assay. J Clin Endocrinol Metab 1990; 70:629-637
72. Dunkel L, Alfthan H, Stenman UH, Selstam G, Rosberg S, Albertsson-Wikland K. Developmental changes in 24-hour profiles of luteinizing hormone and follicle-stimulating hormone from prepuberty to midstages of puberty in boys. J Clin Endocrinol Metab 1992; 74:890-897
73. Chipman JJ, Moore RJ, Marks JF, Fevre M, Segel T, Ramsey J, Boyar RM. Interrelationship of plasma and urinary gonadotropins: correlations for 24 hours, for sleep/wake periods, and for 3 hours after luteinizing hormone-releasing hormone stimulation. J Clin Endocrinol Metab 1981; 52:225-230
74. Cottrell EC, Campbell RE, Han SK, Herbison AE. Postnatal remodeling of dendritic structure and spine density in gonadotropin-releasing hormone neurons. Endocrinology 2006; 147:3652-3661
75. Terasawa E, Fernandez DL. Neurobiological mechanisms of the onset of puberty in primates. Endocrine reviews 2001; 22:111-151
76. Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. Science (New York, NY) 1978; 202:631-633
77. Knobil E. The neuroendocrine control of the menstrual cycle. Recent Prog Horm Res 1980; 36:53-88
78. Clarkson J, Han SY, Piet R, McLennan T, Kane GM, Ng J, Porteous RW, Kim JS, Colledge WH, Iremonger KJ, Herbison AE. Definition of the hypothalamic GnRH pulse generator in mice. Proceedings of the National Academy of Sciences of the United States of America 2017; 114:E10216-E10223
79. Lustig RH, Conte FA, Kogan BA, Grumbach MM. Ontogeny of gonadotropin secretion in congenital anorchism: sexual dimorphism versus syndrome of gonadal dysgenesis and diagnostic considerations. J Urol 1987; 138:587-591
80. Nathwani NC, Hindmarsh PC, Massarano AA, Brook CG. Gonadotrophin pulsatility in girls with the Turner syndrome: modulation by exogenous sex steroids. Clin Endocrinol (Oxf) 1998; 49:107-113
81. Gravholt CH, Naeraa RW, Andersson AM, Christiansen JS, Skakkebaek NE. Inhibin A and B in adolescents and young adults with Turner's syndrome and no sign of spontaneous puberty. Hum Reprod 2002; 17:2049-2053
82. Hagen CP, Main KM, Kjaergaard S, Juul A. FSH, LH, inhibin B and estradiol levels in Turner syndrome depend on age and karyotype: longitudinal study of 70 Turner girls with or without spontaneous puberty. Hum Reprod 2010; 25:3134-3141
83. Quigley CA, Wan X, Garg S, Kowal K, Cutler GB, Jr., Ross JL. Effects of low-dose estrogen replacement during childhood on pubertal development and gonadotropin concentrations in patients with Turner syndrome: results of a randomized, double-blind, placebo-controlled clinical trial. J Clin Endocrinol Metab 2014; 99:E1754-1764
84. Valeri C, Schteingart HF, Rey RA. The prepubertal testis: biomarkers and functions. Current opinion in endocrinology, diabetes, and obesity 2013; 20:224-233
85. Hero M, Tommiska J, Vaaralahti K, Laitinen EM, Sipila I, Puhakka L, Dunkel L, Raivio T. Circulating antimullerian hormone levels in boys decline during early puberty and correlate with inhibin B. Fertil Steril 2012; 97:1242-1247
86. Edelsztein NY, Grinspon RP, Schteingart HF, Rey RA. Anti-Mullerian hormone as a marker of steroid and gonadotropin action in the testis of children and adolescents with disorders of the gonadal axis. International journal of pediatric endocrinology 2016; 2016:20

87. Ferlin A, Garolla A, Rigon F, Rasi Caldogno L, Lenzi A, Foresta C. Changes in serum insulin-like factor 3 during normal male puberty. J Clin Endocrinol Metab 2006; 91:3426-3431
88. Wikstrom AM, Bay K, Hero M, Andersson AM, Dunkel L. Serum insulin-like factor 3 levels during puberty in healthy boys and boys with Klinefelter syndrome. J Clin Endocrinol Metab 2006; 91:4705-4708
89. Gougeon A. Regulation of ovarian follicular development in primates: facts and hypotheses. Endocrine reviews 1996; 17:121-155
90. Richards JS, Ren YA, Candelaria N, Adams JE, Rajkovic A. Ovarian Follicular Theca Cell Recruitment, Differentiation, and Impact on Fertility: 2017 Update. Endocrine reviews 2018; 39:1-20
91. Hagen CP, Aksglaede L, Sorensen K, Main KM, Boas M, Cleemann L, Holm K, Gravholt CH, Andersson AM, Pedersen AT, Petersen JH, Linneberg A, Kjaergaard S, Juul A. Serum levels of anti-Mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. J Clin Endocrinol Metab 2010; 95:5003-5010
92. Hagen CP, Mieritz MG, Nielsen JE, Anand-Ivell R, Ivell R, Juul A. Longitudinal assessment of circulating insulin-like peptide 3 levels in healthy peripubertal girls. Fertil Steril 2015; 103:780-786 e781
93. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics 2009; 123:e932-939
94. Sorensen K, Aksglaede L, Petersen JH, Juul A. Recent changes in pubertal timing in healthy Danish boys: associations with body mass index. J Clin Endocrinol Metab 2010; 95:263-270
95. Marceau K, Ram N, Houts RM, Grimm KJ, Susman EJ. Individual differences in boys' and girls' timing and tempo of puberty: modeling development with nonlinear growth models. Dev Psychol 2011; 47:1389-1409
96. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969; 44:291-303
97. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45:13-23
98. de Ridder CM, Thijssen JH, Bruning PF, Van den Brande JL, Zonderland ML, Erich WB. Body fat mass, body fat distribution, and pubertal development: a longitudinal study of physical and hormonal sexual maturation of girls. J Clin Endocrinol Metab 1992; 75:442-446
99. Biro FM, Huang B, Crawford PB, Lucky AW, Striegel-Moore R, Barton BA, Daniels S. Pubertal correlates in black and white girls. J Pediatr 2006; 148:234-240
100. Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. J Pediatr 1997; 131:618-621
101. Pantsiotou S, Papadimitriou A, Douros K, Priftis K, Nicolaidou P, Fretzayas A. Maturational tempo differences in relation to the timing of the onset of puberty in girls. Acta Paediatr 2008; 97:217-220
102. Susman EJ, Houts RM, Steinberg L, Belsky J, Cauffman E, Dehart G, Friedman SL, Roisman GI, Halpern-Felsher BL, Eunice Kennedy Shriver NECCRN. Longitudinal development of secondary sexual characteristics in girls and boys between ages 91/2 and 151/2 years. Arch Pediatr Adolesc Med 2010; 164:166-173
103. Abbassi V. Growth and normal puberty. Pediatrics 1998; 102:507-511
104. Christensen KY, Maisonet M, Rubin C, Holmes A, Flanders WD, Heron J, Ness A, Drews-Botsch C, Dominguez C, McGeehin MA, Marcus M. Progression through puberty in girls enrolled in a contemporary British cohort. J Adolesc Health 2010; 47:282-289

105. Biro FM, Lucky AW, Huster GA, Morrison JA. Pubertal staging in boys. J Pediatr 1995; 127:100-102
106. Herman-Giddens ME, Steffes J, Harris D, Slora E, Hussey M, Dowshen SA, Wasserman R, Serwint JR, Smitherman L, Reiter EO. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. Pediatrics 2012; 130:e1058-1068
107. Nielsen CT, Skakkebaek NE, Richardson DW, Darling JA, Hunter WM, Jorgensen M, Nielsen A, Ingerslev O, Keiding N, Muller J. Onset of the release of spermatozoa (spermarche) in boys in relation to age, testicular growth, pubic hair, and height. J Clin Endocrinol Metab 1986; 62:532-535
108. Tomova A, Lalabonova C, Robeva RN, Kumanov PT. Timing of pubertal maturation according to the age at first conscious ejaculation. Andrologia 2011; 43:163-166
109. Harries ML, Walker JM, Williams DM, Hawkins S, Hughes IA. Changes in the male voice at puberty. Arch Dis Child 1997; 77:445-447
110. Juul A, Magnusdottir S, Scheike T, Prytz S, Skakkebaek NE. Age at voice break in Danish boys: effects of pre-pubertal body mass index and secular trend. Int J Androl 2007; 30:537-542
111. Maynard LM, Wisemandle W, Roche AF, Chumlea WC, Guo SS, Siervogel RM. Childhood body composition in relation to body mass index. Pediatrics 2001; 107:344-350
112. Gasser T, Ziegler P, Kneip A, Prader A, Molinari L, Largo RH. The dynamics of growth of weight, circumferences and skinfolds in distance, velocity and acceleration. Ann Hum Biol 1993; 20:239-259
113. Herting MM, Sowell ER. Puberty and structural brain development in humans. Front Neuroendocrinol 2017; 44:122-137
114. Juraska JM, Sisk CL, DonCarlos LL. Sexual differentiation of the adolescent rodent brain: hormonal influences and developmental mechanisms. Horm Behav 2013; 64:203-210
115. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. The New England journal of medicine 1982; 306:1033-1035
116. Lee Y, Styne D. Influences on the onset and tempo of puberty in human beings and implications for adolescent psychological development. Horm Behav 2013; 64:250-261
117. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, Sun SS. Age at menarche and racial comparisons in US girls. Pediatrics 2003; 111:110-113
118. Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Hiatt RA, Kushi LH, Wolff MS. Onset of breast development in a longitudinal cohort. Pediatrics 2013; 132:1019-1027
119. Gerner Lawaetz J, Hagen CP, Grunnet Mieritz M, Blomberg Jensen M, Holm Petersen J, Juul A. Evaluation of 451 Danish Boys with Delayed Puberty: Diagnostic use of a new Puberty Nomogram and Effects of Oral Testosterone Therapy. J Clin Endocrinol Metab 2015:jc20143631
120. Sedlmeyer IL, Palmert MR. Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab 2002; 87:1613-1620
121. Varimo T, Miettinen PJ, Kansakoski J, Raivio T, Hero M. Congenital hypogonadotropic hypogonadism, functional hypogonadotropism or constitutional delay of growth and puberty? An analysis of a large patient series from a single tertiary center. Hum Reprod 2017; 32:147-153
122. Wehkalampi K, Widen E, Laine T, Palotie A, Dunkel L. Patterns of inheritance of constitutional delay of growth and puberty in families of adolescent girls and boys referred to specialist pediatric care. J Clin Endocrinol Metab 2008; 93:723-728
123. Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. The Journal of clinical endocrinology and metabolism 2012; 97:707-718

124. Varimo T, Hero M, Laitinen EM, Sintonen H, Raivio T. Health-related Quality of Life in Male Patients with Congenital Hypogonadotropic Hypogonadism. Clin Endocrinol (Oxf) 2014;
125. Van Dop C, Burstein S, Conte FA, Grumbach MM. Isolated gonadotropin deficiency in boys: clinical characteristics and growth. J Pediatr 1987; 111:684-692
126. Varimo T, Hero M, Laitinen EM, Miettinen PJ, Tommiska J, Kansakoski J, Juul A, Raivio T. Childhood growth in boys with congenital hypogonadotropic hypogonadism. Pediatr Res 2016; 79:705-709
127. Raboch J, Reisenauer R. Analysis of body height in 829 patients with different forms of testicular pathology. Andrologia 1976; 8:265-268
128. Uriarte MM, Baron J, Garcia HB, Barnes KM, Loriaux DL, Cutler GB, Jr. The effect of pubertal delay on adult height in men with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1992; 74:436-440
129. Dickerman Z, Cohen A, Laron Z. Growth in patients with isolated gonadotrophin deficiency. Arch Dis Child 1992; 67:513-516
130. Moorthy B, Papadopolou M, Shaw DG, Grant DB. Depot testosterone in boys with anorchia or gonadotrophin deficiency: effect on growth rate and adult height. Arch Dis Child 1991; 66:197-199
131. Shaw ND, Seminara SB, Welt CK, Au MG, Plummer L, Hughes VA, Dwyer AA, Martin KA, Quinton R, Mericq V, Merino PM, Gusella JF, Crowley WF, Jr., Pitteloud N, Hall JE. Expanding the phenotype and genotype of female GnRH deficiency. J Clin Endocrinol Metab 2011; 96:E566-576
132. Bry-Gauillard H, Larrat-Ledoux F, Levaillant JM, Massin N, Maione L, Beau I, Binart N, Chanson P, Brailly-Tabard S, Hall JE, Young J. Anti-Mullerian Hormone and Ovarian Morphology in Women With Isolated Hypogonadotropic Hypogonadism/Kallmann Syndrome: Effects of Recombinant Human FSH. J Clin Endocrinol Metab 2017; 102:1102-1111
133. Tang RY, Chen R, Ma M, Lin SQ, Zhang YW, Wang YP. Clinical characteristics of 138 Chinese female patients with idiopathic hypogonadotropic hypogonadism. Endocr Connect 2017; 6:800-810
134. Bonomi M, Vezzoli V, Krausz C, Guizzardi F, Vezzani S, Simoni M, Bassi I, Duminuco P, Di Iorgi N, Giavoli C, Pizzocaro A, Russo G, Moro M, Fatti L, Ferlin A, Mazzanti L, Zatelli MC, Cannavo S, Isidori AM, Pincelli AI, Prodam F, Mancini A, Limone P, Tanda ML, Gaudino R, Salerno M, Francesca P, Maghnie M, Maggi M, Persani L, Italian Network on Central H. Characteristics of a nationwide cohort of patients presenting with isolated hypogonadotropic hypogonadism (IHH). Eur J Endocrinol 2018; 178:23-32
135. de Roux N, Young J, Misrahi M, Genet R, Chanson P, Schaison G, Milgrom E. A family with hypogonadotropic hypogonadism and mutations in the gonadotropin-releasing hormone receptor. The New England journal of medicine 1997; 337:1597-1602
136. Sarfati J, Bouvattier C, Bry-Gauillard H, Cartes A, Bouligand J, Young J. Kallmann syndrome with FGFR1 and KAL1 mutations detected during fetal life. Orphanet journal of rare diseases 2015; 10:71
137. Brioude F, Bouligand J, Trabado S, Francou B, Salenave S, Kamenicky P, Brailly-Tabard S, Chanson P, Guiochon-Mantel A, Young J. Non-syndromic congenital hypogonadotropic hypogonadism: clinical presentation and genotype-phenotype relationships. Eur J Endocrinol 2010; 162:835-851
138. Giton F, Trabado S, Maione L, Sarfati J, Le Bouc Y, Brailly-Tabard S, Fiet J, Young J. Sex steroids, precursors, and metabolite deficiencies in men with isolated hypogonadotropic hypogonadism and panhypopituitarism: a GCMS-based comparative study. J Clin Endocrinol Metab 2015; 100:E292-296

139. Hero M, Laitinen EM, Varimo T, Vaaralahti K, Tommiska J, Raivio T. Childhood growth of females with Kallmann syndrome and FGFR1 mutations. Clin Endocrinol (Oxf) 2015; 82:122-126
140. Seminara SB, Hayes FJ, Crowley WF, Jr. Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. Endocrine reviews 1998; 19:521-539
141. Pazderska A, Mamoojee Y, Artham S, Miller M, Ball SG, Cheetham T, Quinton R. Safety and tolerability of one-year intramuscular testosterone regime to induce puberty in older men with CHH. Endocr Connect 2018; 7:133-138
142. Nachtigall LB, Boepple PA, Pralong FP, Crowley WF, Jr. Adult-onset idiopathic hypogonadotropic hypogonadism--a treatable form of male infertility. The New England journal of medicine 1997; 336:410-415
143. Dwyer AA, Hayes FJ, Plummer L, Pitteloud N, Crowley WF, Jr. The long-term clinical follow-up and natural history of men with adult-onset idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2010; 95:4235-4243
144. Huffer V, Scott WH, Connor TB, Lovice H. Psychological Studies of Adult Male Patients with Sexual Infantilism before and after Androgen Therapy. Annals of internal medicine 1964; 61:255-268
145. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, Basaran Y, Uzun O, Bolu E, Saglam K. Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. Endocrine journal 2012; 59:1099-1105
146. Dwyer AA, Tiemensma J, Quinton R, Pitteloud N, Morin D. Adherence to treatment in men with hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf) 2017; 86:377-383
147. Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet journal of rare diseases 2014; 9:83
148. Dwyer AA, Quinton R, Pitteloud N, Morin D. Psychosexual development in men with congenital hypogonadotropic hypogonadism on long-term treatment: a mixed methods study. Sexual medicine 2015; 3:32-41
149. Dzemaili S, Tiemensma J, Quinton R, Pitteloud N, Morin D, Dwyer AA. Beyond hormone replacement: quality of life in women with congenital hypogonadotropic hypogonadism. Endocr Connect 2017; 6:404-412
150. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, Cole LW, Pearce SH, Lee H, Boepple P, Crowley WF, Jr., Pitteloud N. Reversal of idiopathic hypogonadotropic hypogonadism. The New England journal of medicine 2007; 357:863-873
151. Sidhoum VF, Chan YM, Lippincott MF, Balasubramanian R, Quinton R, Plummer L, Dwyer A, Pitteloud N, Hayes FJ, Hall JE, Martin KA, Boepple PA, Seminara SB. Reversal and relapse of hypogonadotropic hypogonadism: resilience and fragility of the reproductive neuroendocrine system. J Clin Endocrinol Metab 2014; 99:861-870
152. Dwyer AA, Raivio T, Pitteloud N. MANAGEMENT OF ENDOCRINE DISEASE: Reversible hypogonadotropic hypogonadism. Eur J Endocrinol 2016; 174:R267-274
153. Santhakumar A, Balasubramanian R, Miller M, Quinton R. Reversal of isolated hypogonadotropic hypogonadism: long-term integrity of hypothalamo-pituitary-testicular axis in two men is dependent on intermittent androgen exposure. Clin Endocrinol (Oxf) 2014; 81:473-476
154. Gan EH, Bouloux PM, Quinton R. Unexpectedly prolonged washout period of exogenous testosterone after discontinuation of intramuscular testosterone undecanoate depot

injection (Nebido((R)) or Reandron((R))) in men with congenital hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf) 2016; 84:947-950
155. Kim J, Semaan SJ, Clifton DK, Steiner RA, Dhamija S, Kauffman AS. Regulation of Kiss1 expression by sex steroids in the amygdala of the rat and mouse. Endocrinology 2011; 152:2020-2030
156. Welter H, Wollenhaupt K, Einspanier R. Developmental and hormonal regulated gene expression of fibroblast growth factor 2 (FGF-2) and its receptors in porcine endometrium. J Steroid Biochem Mol Biol 2004; 88:295-304
157. Waldstreicher J, Seminara SB, Jameson JL, Geyer A, Nachtigall LB, Boepple PA, Holmes LB, Crowley WF, Jr. The genetic and clinical heterogeneity of gonadotropin-releasing hormone deficiency in the human. J Clin Endocrinol Metab 1996; 81:4388-4395
158. Quinton R, Duke VM, Robertson A, Kirk JM, Matfin G, de Zoysa PA, Azcona C, MacColl GS, Jacobs HS, Conway GS, Besser M, Stanhope RG, Bouloux PM. Idiopathic gonadotrophin deficiency: genetic questions addressed through phenotypic characterization. Clin Endocrinol (Oxf) 2001; 55:163-174
159. Schwanzel-Fukuda M, Bick D, Pfaff DW. Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal (Kallmann) syndrome. Brain research Molecular brain research 1989; 6:311-326
160. Costa-Barbosa FA, Balasubramanian R, Keefe KW, Shaw ND, Al-Tassan N, Plummer L, Dwyer AA, Buck CL, Choi JH, Seminara SB, Quinton R, Monies D, Meyer B, Hall JE, Pitteloud N, Crowley WF, Jr. Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. J Clin Endocrinol Metab 2013; 98:E943-953
161. Maione L, Benadjaoud S, Eloit C, Sinisi AA, Colao A, Chanson P, Ducreux D, Benoudiba F, Young J. 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:E537-546
162. Marcos S, Sarfati J, Leroy C, Fouveaut C, Parent P, Metz C, Wolczynski S, Gerard M, Bieth E, Kurtz F, Verier-Mine O, Perrin L, Archambeaud F, Cabrol S, Rodien P, Hove H, Prescott T, Lacombe D, Christin-Maitre S, Touraine P, Hieronimus S, Dewailly D, Young J, Pugeat M, Hardelin JP, Dode C. The prevalence of CHD7 missense versus truncating mutations is higher in patients with Kallmann syndrome than in typical CHARGE patients. J Clin Endocrinol Metab 2014; 99:E2138-2143
163. Maione L, Brailly-Tabard S, Nevoux J, Bouligand J, Young J. Reversal of congenital hypogonadotropic hypogonadism in a man with Kallmann syndrome due to SOX10 mutation. Clin Endocrinol (Oxf) 2016; 85:988-989
164. Pingault V, Bodereau V, Baral V, Marcos S, Watanabe Y, Chaoui A, Fouveaut C, Leroy C, Verier-Mine O, Francannet C, Dupin-Deguine D, Archambeaud F, Kurtz FJ, Young J, Bertherat J, Marlin S, Goossens M, Hardelin JP, Dode C, Bondurand N. Loss-of-function mutations in SOX10 cause Kallmann syndrome with deafness. American journal of human genetics 2013; 92:707-724
165. Tompach PC, Zeitler DL. Kallmann syndrome with associated cleft lip and palate: case report and review of the literature. J Oral Maxillofac Surg 1995; 53:85-87
166. Polder BJ, Van't Hof MA, Van der Linden FP, Kuijpers-Jagtman AM. A meta-analysis of the prevalence of dental agenesis of permanent teeth. Community dentistry and oral epidemiology 2004; 32:217-226
167. Malik S. Syndactyly: phenotypes, genetics and current classification. European journal of human genetics : EJHG 2012; 20:817-824
168. Finley WH, Gustavson KH, Hall TM, Hurst DC, Barganier CM, Wiedmeyer JA. Birth defects surveillance: Jefferson County, Alabama, and Uppsala County, Sweden. Southern medical journal 1994; 87:440-445

169. Salazard B, Quilici V, Samson P. [Camptodactyly]. Chirurgie de la main 2008; 27 Suppl 1:S157-164
170. Shands AR, Jr., Eisberg HB. The incidence of scoliosis in the state of Delaware; a study of 50,000 minifilms of the chest made during a survey for tuberculosis. J Bone Joint Surg Am 1955; 37-A:1243-1249
171. Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 2004; 36:955-957
172. Janssen N, Bergman JEH, Swertz MA, Tranebjaerg L, Lodahl M, Schoots J, Hofstra RMW, Van Ravenswaaij-Arts CMA, Hoefsloot LH. Mutation update on the CHD7 gene involved in CHARGE syndrome. Human mutation 2012; 33:1149-1160
173. Kim HG, Kurth I, Lan F, Meliciani I, Wenzel W, Eom SH, Kang GB, Rosenberger G, Tekin M, Ozata M, Bick DP, Sherins RJ, Walker SL, Shi Y, Gusella JF, Layman LC. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. Am J Hum Genet 2008; 83:511-519
174. Balasubramanian R, Crowley WF, Jr. Reproductive endocrine phenotypes relating to CHD7 mutations in humans. Am J Med Genet C Semin Med Genet 2017; 175:507-515
175. Lalani SR, Safiullah AM, Molinari LM, Fernbach SD, Martin DM, Belmont JW. SEMA3E mutation in a patient with CHARGE syndrome. Journal of medical genetics 2004; 41:e94
176. Cariboni A, Andre V, Chauvet S, Cassatella D, Davidson K, Caramello A, Fantin A, Bouloux P, Mann F, Ruhrberg C. Dysfunctional SEMA3E signaling underlies gonadotropin-releasing hormone neuron deficiency in Kallmann syndrome. The Journal of clinical investigation 2015; 125:2413-2428
177. Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, Herbarth B, Hermans-Borgmeyer I, Legius E, Matthijs G, Amiel J, Lyonnet S, Ceccherini I, Romeo G, Smith JC, Read AP, Wegner M, Goossens M. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet 1998; 18:171-173
178. Vaaralahti K, Tommiska J, Tillmann V, Liivak N, Kansakoski J, Laitinen EM, Raivio T. De novo SOX10 nonsense mutation in a patient with Kallmann syndrome and hearing loss. Pediatr Res 2014; 76:115-116
179. Simonis N, Migeotte I, Lambert N, Perazzolo C, de Silva DC, Dimitrov B, Heinrichs C, Janssens S, Kerr B, Mortier G, Van Vliet G, Lepage P, Casimir G, Abramowicz M, Smits G, Vilain C. FGFR1 mutations cause Hartsfield syndrome, the unique association of holoprosencephaly and ectrodactyly. Journal of medical genetics 2013; 50:585-592
180. Dode C, Levilliers J, Dupont JM, De Paepe A, Le Du N, Soussi-Yanicostas N, Coimbra RS, Delmaghani S, Compain-Nouaille S, Baverel F, Pecheux C, Le Tessier D, Cruaud C, Delpech M, Speleman F, Vermeulen S, Amalfitano A, Bachelot Y, Bouchard P, Cabrol S, Carel JC, Delemarre-van de Waal H, Goulet-Salmon B, Kottler ML, Richard O, Sanchez-Franco F, Saura R, Young J, Petit C, Hardelin JP. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nature genetics 2003; 33:463-465
181. Pitteloud N, Acierno JS, Jr., Meysing A, Eliseenkova AV, Ma J, Ibrahimi OA, Metzger DL, Hayes FJ, Dwyer AA, Hughes VA, Yialamas M, Hall JE, Grant E, Mohammadi M, Crowley WF, Jr. Mutations in fibroblast growth factor receptor 1 cause both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. Proceedings of the National Academy of Sciences of the United States of America 2006; 103:6281-6286
182. Miraoui H, Dwyer A, Pitteloud N. Role of fibroblast growth factor (FGF) signaling in the neuroendocrine control of human reproduction. Mol Cell Endocrinol 2011; 346:37-43

183. Guo W, Mason JS, Stone CG, Jr., Morgan SA, Madu SI, Baldini A, Lindsay EA, Biesecker LG, Copeland KC, Horlick MN, et al. Diagnosis of X-linked adrenal hypoplasia congenita by mutation analysis of the DAX1 gene. JAMA 1995; 274:324-330
184. Merke DP, Tajima T, Baron J, Cutler GB, Jr. Hypogonadotropic hypogonadism in a female caused by an X-linked recessive mutation in the DAX1 gene. The New England journal of medicine 1999; 340:1248-1252
185. Tetreault M, Choquet K, Orcesi S, Tonduti D, Balottin U, Teichmann M, Fribourg S, Schiffmann R, Brais B, Vanderver A, Bernard G. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. Am J Hum Genet 2011; 89:652-655
186. Richards MR, Plummer L, Chan YM, Lippincott MF, Quinton R, Kumanov P, Seminara SB. Phenotypic spectrum of POLR3B mutations: isolated hypogonadotropic hypogonadism without neurological or dental anomalies. Journal of medical genetics 2017; 54:19-25
187. Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Martensson IL, Toresson H, Fox M, Wales JK, Hindmarsh PC, Krauss S, Beddington RS, Robinson IC. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet 1998; 19:125-133
188. Newbern K, Natrajan N, Kim HG, Chorich LP, Halvorson LM, Cameron RS, Layman LC. Identification of HESX1 mutations in Kallmann syndrome. Fertil Steril 2013; 99:1831-1837
189. Kelberman D, Rizzoti K, Avilion A, Bitner-Glindzicz M, Cianfarani S, Collins J, Chong WK, Kirk JM, Achermann JC, Ross R, Carmignac D, Lovell-Badge R, Robinson IC, Dattani MT. Mutations within Sox2/SOX2 are associated with abnormalities in the hypothalamo-pituitary-gonadal axis in mice and humans. The Journal of clinical investigation 2006; 116:2442-2455
190. Stark Z, Storen R, Bennetts B, Savarirayan R, Jamieson RV. Isolated hypogonadotropic hypogonadism with SOX2 mutation and anophthalmia/microphthalmia in offspring. European journal of human genetics : EJHG 2011; 19:753-756
191. Shima H, Ishii A, Wada Y, Kizawa J, Yokoi T, Azuma N, Matsubara Y, Suzuki E, Nakamura A, Narumi S, Fukami M. SOX2 nonsense mutation in a patient clinically diagnosed with non-syndromic hypogonadotropic hypogonadism. Endocrine journal 2017; 64:813-817
192. Filippi G. Klinefelter's syndrome in Sardinia. Clinical report of 265 hypogonadic males detected at the time of military check-up. Clinical genetics 1986; 30:276-284
193. Fromantin M, Gineste J, Didier A, Rouvier J. [Impuberism and hypogonadism at induction into military service. Statistical study]. Problemes actuels d'endocrinologie et de nutrition 1973; 16:179-199
194. Maione L, Dwyer AA, Francou B, Guiochon-Mantel A, Binart N, Bouligand J, Young J. GENETICS IN ENDOCRINOLOGY: Genetic counseling for congenital hypogonadotropic hypogonadism and Kallmann syndrome: new challenges in the era of oligogenism and next-generation sequencing. Eur J Endocrinol 2018; 178:R55-R80
195. Francou B, Paul C, Amazit L, Cartes A, Bouvattier C, Albarel F, Maiter D, Chanson P, Trabado S, Brailly-Tabard S, Brue T, Guiochon-Mantel A, Young J, Bouligand J. Prevalence of KISS1 Receptor mutations in a series of 603 patients with normosmic congenital hypogonadotrophic hypogonadism and characterization of novel mutations: a single-centre study. Hum Reprod 2016; 31:1363-1374
196. Hietamaki J, Hero M, Holopainen E, Kansakoski J, Vaaralahti K, Iivonen AP, Miettinen PJ, Raivio T. GnRH receptor gene mutations in adolescents and young adults presenting with signs of partial gonadotropin deficiency. PLoS One 2017; 12:e0188750

197. de Roux N, Young J, Brailly-Tabard S, Misrahi M, Milgrom E, Schaison G. The same molecular defects of the gonadotropin-releasing hormone receptor determine a variable degree of hypogonadism in affected kindred. J Clin Endocrinol Metab 1999; 84:567-572
198. Beranova M, Oliveira LM, Bedecarrats GY, Schipani E, Vallejo M, Ammini AC, Quintos JB, Hall JE, Martin KA, Hayes FJ, Pitteloud N, Kaiser UB, Crowley WF, Jr., Seminara SB. Prevalence, phenotypic spectrum, and modes of inheritance of gonadotropin-releasing hormone receptor mutations in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2001; 86:1580-1588
199. Pitteloud N, Meysing A, Quinton R, Acierno JS, Jr., Dwyer AA, Plummer L, Fliers E, Boepple P, Hayes F, Seminara S, Hughes VA, Ma J, Bouloux P, Mohammadi M, Crowley WF, Jr. Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. Mol Cell Endocrinol 2006; 254-255:60-69
200. Raivio T, Sidis Y, Plummer L, Chen H, Ma J, Mukherjee A, Jacobson-Dickman E, Quinton R, Van Vliet G, Lavoie H, Hughes VA, Dwyer A, Hayes FJ, Xu S, Sparks S, Kaiser UB, Mohammadi M, Pitteloud N. Impaired fibroblast growth factor receptor 1 signaling as a cause of normosmic idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2009; 94:4380-4390
201. Sarfati J, Guiochon-Mantel A, Rondard P, Arnulf I, Garcia-Pinero A, Wolczynski S, Brailly-Tabard S, Bidet M, Ramos-Arroyo M, Mathieu M, Lienhardt-Roussie A, Morgan G, Turki Z, Bremont C, Lespinasse J, Du Boullay H, Chabbert-Buffet N, Jacquemont S, Reach G, De Talence N, Tonella P, Conrad B, Despert F, Delobel B, Brue T, Bouvattier C, Cabrol S, Pugeat M, Murat A, Bouchard P, Hardelin JP, Dode C, Young J. A comparative phenotypic study of kallmann syndrome patients carrying monoallelic and biallelic mutations in the prokineticin 2 or prokineticin receptor 2 genes. J Clin Endocrinol Metab 2010; 95:659-669
202. Main KM, Schmidt IM, Skakkebaek NE. A possible role for reproductive hormones in newborn boys: progressive hypogonadism without the postnatal testosterone peak. J Clin Endocrinol Metab 2000; 85:4905-4907
203. Main KM, Schmidt IM, Toppari J, Skakkebaek NE. Early postnatal treatment of hypogonadotropic hypogonadism with recombinant human FSH and LH. Eur J Endocrinol 2002; 146:75-79
204. Bougneres P, Francois M, Pantalone L, Rodrigue D, Bouvattier C, Demesteere E, Roger D, Lahlou N. Effects of an early postnatal treatment of hypogonadotropic hypogonadism with a continuous subcutaneous infusion of recombinant follicle-stimulating hormone and luteinizing hormone. J Clin Endocrinol Metab 2008; 93:2202-2205
205. Xu C, Lang-Muritano M, Phan-Hug F, Dwyer AA, Sykiotis GP, Cassatella D, Acierno J, Jr., Mohammadi M, Pitteloud N. Genetic testing facilitates prepubertal diagnosis of congenital hypogonadotropic hypogonadism. Clinical genetics 2017; 92:213-216
206. Lambert AS, Bougneres P. Growth and descent of the testes in infants with hypogonadotropic hypogonadism receiving subcutaneous gonadotropin infusion. International journal of pediatric endocrinology 2016; 2016:13
207. Villanueva C, Jacobson-Dickman E, Xu C, Manouvrier S, Dwyer AA, Sykiotis GP, Beenken A, Liu Y, Tommiska J, Hu Y, Tiosano D, Gerard M, Leger J, Drouin-Garraud V, Lefebvre H, Polak M, Carel JC, Phan-Hug F, Hauschild M, Plummer L, Rey JP, Raivio T, Bouloux P, Sidis Y, Mohammadi M, de Roux N, Pitteloud N. Congenital hypogonadotropic hypogonadism with split hand/foot malformation: a clinical entity with a high frequency of FGFR1 mutations. Genetics in medicine : official journal of the American College of Medical Genetics 2015; 17:651-659

208. Lahlou N, Fennoy I, Carel JC, Roger M. Inhibin B and anti-Mullerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. J Clin Endocrinol Metab 2004; 89:1864-1868
209. Johannsen TH, Main KM, Ljubicic ML, Jensen TK, Andersen HR, Andersen MS, Petersen JH, Andersson AM, Juul A. Sex-Differences in Reproductive Hormones during Mini-Puberty in Infants with Normal and Disordered Sex Development. J Clin Endocrinol Metab 2018;
210. Lewkowitz-Shpuntoff HM, Hughes VA, Plummer L, Au MG, Doty RL, Seminara SB, Chan YM, Pitteloud N, Crowley WF, Jr., Balasubramanian R. Olfactory phenotypic spectrum in idiopathic hypogonadotropic hypogonadism: pathophysiological and genetic implications. J Clin Endocrinol Metab 2012; 97:E136-144
211. Rosner W, Hankinson SE, Sluss PM, Vesper HW, Wierman ME. Challenges to the measurement of estradiol: an endocrine society position statement. J Clin Endocrinol Metab 2013; 98:1376-1387
212. Trabado S, Maione L, Salenave S, Baron S, Galland F, Bry-Gauillard H, Guiochon-Mantel A, Chanson P, Pitteloud N, Sinisi AA, Brailly-Tabard S, Young J. Estradiol levels in men with congenital hypogonadotropic hypogonadism and the effects of different modalities of hormonal treatment. Fertil Steril 2011; 95:2324-2329, 2329 e2321-2323
213. Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ. Gonadal steroids and body composition, strength, and sexual function in men. The New England journal of medicine 2013; 369:1011-1022
214. Chen Z, Wang O, Nie M, Elison K, Zhou D, Li M, Jiang Y, Xia W, Meng X, Chen S, Xing X. Aromatase deficiency in a Chinese adult man caused by novel compound heterozygous CYP19A1 mutations: effects of estrogen replacement therapy on the bone, lipid, liver and glucose metabolism. Mol Cell Endocrinol 2015; 399:32-42
215. Jones ME, Boon WC, McInnes K, Maffei L, Carani C, Simpson ER. Recognizing rare disorders: aromatase deficiency. Nat Clin Pract Endocrinol Metab 2007; 3:414-421
216. Barkan AL, Reame NE, Kelch RP, Marshall JC. Idiopathic hypogonadotropic hypogonadism in men: dependence of the hormone responses to gonadotropin-releasing hormone (GnRH) on the magnitude of the endogenous GnRH secretory defect. J Clin Endocrinol Metab 1985; 61:1118-1125
217. Salenave S, Chanson P, Bry H, Pugeat M, Cabrol S, Carel JC, Murat A, Lecomte P, Brailly S, Hardelin JP, Dode C, Young J. Kallmann's syndrome: a comparison of the reproductive phenotypes in men carrying KAL1 and FGFR1/KAL2 mutations. J Clin Endocrinol Metab 2008; 93:758-763
218. Rivier C, Corrigan A, Vale W. Effect of recombinant human inhibin on gonadotropin secretion by the male rat. Endocrinology 1991; 129:2155-2159
219. Carroll RS, Kowash PM, Lofgren JA, Schwall RH, Chin WW. In vivo regulation of FSH synthesis by inhibin and activin. Endocrinology 1991; 129:3299-3304
220. Illingworth PJ, Groome NP, Byrd W, Rainey WE, McNeilly AS, Mather JP, Bremner WJ. Inhibin-B: a likely candidate for the physiologically important form of inhibin in men. J Clin Endocrinol Metab 1996; 81:1321-1325
221. Anawalt BD, Bebb RA, Matsumoto AM, Groome NP, Illingworth PJ, McNeilly AS, Bremner WJ. Serum inhibin B levels reflect Sertoli cell function in normal men and men with testicular dysfunction. J Clin Endocrinol Metab 1996; 81:3341-3345
222. Pierik FH, Vreeburg JT, Stijnen T, De Jong FH, Weber RF. Serum inhibin B as a marker of spermatogenesis. J Clin Endocrinol Metab 1998; 83:3110-3114
223. Young J, Chanson P, Salenave S, Noel M, Brailly S, O'Flaherty M, Schaison G, Rey R. Testicular anti-mullerian hormone secretion is stimulated by recombinant human FSH in

patients with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2005; 90:724-728
224. O'Shaughnessy PJ, Baker PJ, Monteiro A, Cassie S, Bhattacharya S, Fowler PA. Developmental changes in human fetal testicular cell numbers and messenger ribonucleic acid levels during the second trimester. J Clin Endocrinol Metab 2007; 92:4792-4801
225. Young J, Couzinet B, Chanson P, Brailly S, Loumaye E, Schaison G. Effects of human recombinant luteinizing hormone and follicle-stimulating hormone in patients with acquired hypogonadotropic hypogonadism: study of Sertoli and Leydig cell secretions and interactions. J Clin Endocrinol Metab 2000; 85:3239-3244
226. Andersen CY, Schmidt KT, Kristensen SG, Rosendahl M, Byskov AG, Ernst E. Concentrations of AMH and inhibin-B in relation to follicular diameter in normal human small antral follicles. Hum Reprod 2010; 25:1282-1287
227. Kottler ML, Chou YY, Chabre O, Richard N, Polge C, Brailly-Tabard S, Chanson P, Guiochon-Mantel A, Huhtaniemi I, Young J. A new FSHbeta mutation in a 29-year-old woman with primary amenorrhea and isolated FSH deficiency: functional characterization and ovarian response to human recombinant FSH. Eur J Endocrinol 2010; 162:633-641
228. Tommiska J, Toppari J, Vaaralahti K, Kansakoski J, Laitinen EM, Noisa P, Kinnala A, Niinikoski H, Raivio T. PROKR2 mutations in autosomal recessive Kallmann syndrome. Fertil Steril 2013; 99:815-818
229. Sehested A, Juul AA, Andersson AM, Petersen JH, Jensen TK, Muller J, Skakkebaek NE. Serum inhibin A and inhibin B in healthy prepubertal, pubertal, and adolescent girls and adult women: relation to age, stage of puberty, menstrual cycle, follicle-stimulating hormone, luteinizing hormone, and estradiol levels. J Clin Endocrinol Metab 2000; 85:1634-1640
230. Young J, Rey R, Couzinet B, Chanson P, Josso N, Schaison G. Antimullerian hormone in patients with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1999; 84:2696-2699
231. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet 2016; 388:2403-2415
232. Tsilchorozidou T, Conway GS. Uterus size and ovarian morphology in women with isolated growth hormone deficiency, hypogonadotrophic hypogonadism and hypopituitarism. Clin Endocrinol (Oxf) 2004; 61:567-572
233. Schoot DC, Coelingh Bennink HJ, Mannaerts BM, Lamberts SW, Bouchard P, Fauser BC. Human recombinant follicle-stimulating hormone induces growth of preovulatory follicles without concomitant increase in androgen and estrogen biosynthesis in a woman with isolated gonadotropin deficiency. J Clin Endocrinol Metab 1992; 74:1471-1473
234. Taskinen S, Taavitsainen M, Wikstrom S. Measurement of testicular volume: comparison of 3 different methods. J Urol 1996; 155:930-933
235. Diamond DA, Paltiel HJ, DiCanzio J, Zurakowski D, Bauer SB, Atala A, Ephraim PL, Grant R, Retik AB. Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. J Urol 2000; 164:1111-1114
236. Jongmans MC, van Ravenswaaij-Arts CM, Pitteloud N, Ogata T, Sato N, Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman JE, Brunner HG, Crowley WF, Jr., Hoefsloot LH. CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. Clinical genetics 2009; 75:65-71
237. Sarfati J, Saveanu A, Young J. Pituitary stalk interruption and olfactory bulbs aplasia/hypoplasia in a man with Kallmann syndrome and reversible gonadotrope and somatotrope deficiencies. Endocrine 2014;
238. Hacquart T, Ltaief-Boudrigua A, Jeannerod C, Hannoun S, Raverot G, Pugeat M, Brac de la Perriere A, Lapras V, Nugues F, Dode C, Cotton F. Reconsidering olfactory bulb

magnetic resonance patterns in Kallmann syndrome. Ann Endocrinol (Paris) 2017; 78:455-461
239. Xu C, Cassatella D, van der Sloot AM, Quinton R, Hauschild M, De Geyter C, Fluck C, Feller K, Bartholdi D, Nemeth A, Halperin I, Pekic Djurdjevic S, Maeder P, Papadakis G, Dwyer AA, Marino L, Favre L, Pignatelli D, Niederlander NJ, Acierno J, Jr., Pitteloud N. Evaluating CHARGE syndrome in congenital hypogonadotropic hypogonadism patients harboring CHD7 variants. Genetics in medicine : official journal of the American College of Medical Genetics 2017;
240. Nishiyama KK, Shane E. Clinical imaging of bone microarchitecture with HR-pQCT. Curr Osteoporos Rep 2013; 11:147-155
241. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res 2014; 29:518-530
242. Cauley JA, El-Hajj Fuleihan G, Luckey MM, Members FPDC. FRAX(R) International Task Force of the 2010 Joint International Society for Clinical Densitometry & International Osteoporosis Foundation Position Development Conference. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 2011; 14:237-239
243. De Morsier G. Median craioencephalic dysraphias and olfactogenital dysplasia. World Neurol 1962; 3:485-506
244. Maione L, Cantone E, Nettore IC, Cerbone G, De Brasi D, Maione N, Young J, Di Somma C, Sinisi AA, Iengo M, Macchia PE, Pivonello R, Colao A. Flavor perception test: evaluation in patients with Kallmann syndrome. Endocrine 2016; 52:236-243
245. Wolfensberger M, Schnieper I, Welge-Lussen A. Sniffin'Sticks: a new olfactory test battery. Acta Otolaryngol 2000; 120:303-306
246. Hummel T, Pietsch H, Kobal G. Kallmann's syndrome and chemosensory evoked potentials. Eur Arch Otorhinolaryngol 1991; 248:311-312
247. Hudson R, Laska M, Berger T, Heye B, Schopohl J, Danek A. Olfactory function in patients with hypogonadotropic hypogonadism: an all-or-none phenomenon? Chem Senses 1994; 19:57-69
248. Sanchez V, Wistuba J, Mallidis C. Semen analysis: update on clinical value, current needs and future perspectives. Reproduction 2013; 146:R249-258
249. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, Haugen TB, Kruger T, Wang C, Mbizvo MT, Vogelsong KM. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010; 16:231-245
250. Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril 1988; 50:343-347
251. Day FR, Thompson DJ, Helgason H, Chasman DI, Finucane H, Sulem P, Ruth KS, Whalen S, Sarkar AK, Albrecht E, Altmaier E, Amini M, Barbieri CM, Boutin T, Campbell A, Demerath E, Giri A, He C, Hottenga JJ, Karlsson R, Kolcic I, Loh PR, Lunetta KL, Mangino M, Marco B, McMahon G, Medland SE, Nolte IM, Noordam R, Nutile T, Paternoster L, Perjakova N, Porcu E, Rose LM, Schraut KE, Segre AV, Smith AV, Stolk L, Teumer A, Andrulis IL, Bandinelli S, Beckmann MW, Benitez J, Bergmann S, Bochud M, Boerwinkle E, Bojesen SE, Bolla MK, Brand JS, Brauch H, Brenner H, Broer L, Bruning T, Buring JE, Campbell H, Catamo E, Chanock S, Chenevix-Trench G, Corre T, Couch FJ, Cousminer DL, Cox A, Crisponi L, Czene K, Davey Smith G, de Geus E, de Mutsert R, De Vivo I, Dennis J, Devilee P, Dos-Santos-Silva I, Dunning AM, Eriksson JG, Fasching PA, Fernandez-Rhodes L, Ferrucci L, Flesch-Janys D, Franke L, Gabrielson M, Gandin I, Giles GG, Grallert H, Gudbjartsson DF, Guenel P, Hall P, Hallberg E, Hamann U, Harris TB,

Hartman CA, Heiss G, Hooning MJ, Hopper JL, Hu F, Hunter DJ, Ikram MA, Im HK, Jarvelin MR, Joshi PK, Karasik D, Kellis M, Kutalik Z, LaChance G, Lambrechts D, Langenberg C, Launer LJ, Laven JSE, Lenarduzzi S, Li J, Lind PA, Lindstrom S, Liu Y, Luan J, Magi R, Mannermaa A, Mbarek H, McCarthy MI, Meisinger C, Meitinger T, Menni C, Metspalu A, Michailidou K, Milani L, Milne RL, Montgomery GW, Mulligan AM, Nalls MA, Navarro P, Nevanlinna H, Nyholt DR, Oldehinkel AJ, O'Mara TA, Padmanabhan S, Palotie A, Pedersen N, Peters A, Peto J, Pharoah PDP, Pouta A, Radice P, Rahman I, Ring SM, Robino A, Rosendaal FR, Rudan I, Rueedi R, Ruggiero D, Sala CF, Schmidt MK, Scott RA, Shah M, Sorice R, Southey MC, Sovio U, Stampfer M, Steri M, Strauch K, Tanaka T, Tikkanen E, Timpson NJ, Traglia M, Truong T, Tyrer JP, Uitterlinden AG, Edwards DRV, Vitart V, Volker U, Vollenweider P, Wang Q, Widen E, van Dijk KW, Willemsen G, Winqvist R, Wolffenbuttel BHR, Zhao JH, Zoledziewska M, Zygmunt M, Alizadeh BZ, Boomsma DI, Ciullo M, Cucca F, Esko T, Franceschini N, Gieger C, Gudnason V, Hayward C, Kraft P, Lawlor DA, Magnusson PKE, Martin NG, Mook-Kanamori DO, Nohr EA, Polasek O, Porteous D, Price AL, Ridker PM, Snieder H, Spector TD, Stockl D, Toniolo D, Ulivi S, Visser JA, Volzke H, Wareham NJ, Wilson JF, Spurdle AB, Thorsteindottir U, Pollard KS, Easton DF, Tung JY, Chang-Claude J, Hinds D, Murray A, Murabito JM, Stefansson K, Ong KK, Perry JRB. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. Nat Genet 2017; 49:834-841

252. Stamou MI, Cox KH, Crowley WF, Jr. Discovering Genes Essential to the Hypothalamic Regulation of Human Reproduction Using a Human Disease Model: Adjusting to Life in the "-Omics" Era. Endocrine reviews 2016; 2016:4-22

253. Xu C, Messina A, Somm E, Miraoui H, Kinnunen T, Acierno J, Jr., Niederlander NJ, Bouilly J, Dwyer AA, Sidis Y, Cassatella D, Sykiotis GP, Quinton R, De Geyter C, Dirlewanger M, Schwitzgebel V, Cole TR, Toogood AA, Kirk JM, Plummer L, Albrecht U, Crowley WF, Jr., Mohammadi M, Tena-Sempere M, Prevot V, Pitteloud N. KLB, encoding beta-Klotho, is mutated in patients with congenital hypogonadotropic hypogonadism. EMBO Mol Med 2017; 9:1379-1397

254. Shaw ND, Brand H, Kupchinsky ZA, Bengani H, Plummer L, Jones TI, Erdin S, Williamson KA, Rainger J, Stortchevoi A, Samocha K, Currall BB, Dunican DS, Collins RL, Willer JR, Lek A, Lek M, Nassan M, Pereira S, Kammin T, Lucente D, Silva A, Seabra CM, Chiang C, An Y, Ansari M, Rainger JK, Joss S, Smith JC, Lippincott MF, Singh SS, Patel N, Jing JW, Law JR, Ferraro N, Verloes A, Rauch A, Steindl K, Zweier M, Scheer I, Sato D, Okamoto N, Jacobsen C, Tryggestad J, Chernausek S, Schimmenti LA, Brasseur B, Cesaretti C, Garcia-Ortiz JE, Buitrago TP, Silva OP, Hoffman JD, Muhlbauer W, Ruprecht KW, Loeys BL, Shino M, Kaindl AM, Cho CH, Morton CC, Meehan RR, van Heyningen V, Liao EC, Balasubramanian R, Hall JE, Seminara SB, Macarthur D, Moore SA, Yoshiura KI, Gusella JF, Marsh JA, Graham JM, Jr., Lin AE, Katsanis N, Jones PL, Crowley WF, Jr., Davis EE, FitzPatrick DR, Talkowski ME. SMCHD1 mutations associated with a rare muscular dystrophy can also cause isolated arhinia and Bosma arhinia microphthalmia syndrome. Nat Genet 2017; 49:238-248

255. Bouilly J, Messina A, Papadakis G, Cassatella D, Xu C, Acierno JS, Tata B, Sykiotis G, Santini S, Sidis Y, Elowe-Gruau E, Phan-Hug F, Hauschild M, Bouloux PM, Quinton R, Lang-Muritano M, Favre L, Marino L, Giacobini P, Dwyer AA, Niederlander NJ, Pitteloud N. DCC/NTN1 complex mutations in patients with congenital hypogonadotropic hypogonadism impair GnRH neuron development. Hum Mol Genet 2018; 27:359-372

256. Kallmann FJ, Schoenfeld WA, Barrera SE. The genetic aspects of primary eunuchoidism. Am J Mental Deficiency 1944; XLVIII:203-236

257. Sykiotis GP, Pitteloud N, Seminara SB, Kaiser UB, Crowley WF, Jr. Deciphering genetic disease in the genomic era: the model of GnRH deficiency. Science translational medicine 2010; 2:32rv32
258. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics 2015; 17:405-424
259. Pitteloud N, Quinton R, Pearce S, Raivio T, Acierno J, Dwyer A, Plummer L, Hughes V, Seminara S, Cheng YZ, Li WP, Maccoll G, Eliseenkova AV, Olsen SK, Ibrahimi OA, Hayes FJ, Boepple P, Hall JE, Bouloux P, Mohammadi M, Crowley W. Digenic mutations account for variable phenotypes in idiopathic hypogonadotropic hypogonadism. The Journal of clinical investigation 2007; 117:457-463
260. Sykiotis GP, Plummer L, Hughes VA, Au M, Durrani S, Nayak-Young S, Dwyer AA, Quinton R, Hall JE, Gusella JF, Seminara SB, Crowley WF, Jr., Pitteloud N. Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. Proceedings of the National Academy of Sciences of the United States of America 2010; 107:15140-15144
261. Miraoui H, Dwyer AA, Sykiotis GP, Plummer L, Chung W, Feng B, Beenken A, Clarke J, Pers TH, Dworzynski P, Keefe K, Niedziela M, Raivio T, Crowley WF, Jr., Seminara SB, Quinton R, Hughes VA, Kumanov P, Young J, Yialamas MA, Hall JE, Van Vliet G, Chanoine JP, Rubenstein J, Mohammadi M, Tsai PS, Sidis Y, Lage K, Pitteloud N. Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are identified in individuals with congenital hypogonadotropic hypogonadism. Am J Hum Genet 2013; 92:725-743
262. Cassatella D, Howard S, Acierno J, Xu C, Papadakis G, Santoni FA, Dwyer AA, Santini S, Sykiotis G, Chambion C, Meylan J, Marino L, Favre L, Li J, Liu X, Zhang JG, Bouloux P, De Geyter C, De Paepe A, Dhillo WS, Ferrara JM, Hauschild M, Lang-Muritano M, Lemke J, Fluck CE, Nemeth A, Phan-Hug F, Pignatelli D, Popovic V, Pekic S, Quinton R, Szinnai G, l'Allemand D, Konrad D, Sharif S, Iyidir OT, Stevenson BJ, Yang H, Dunkel L, Pitteloud N. Congenital Hypogonadotropic Hypogonadism and Constitutional Delay of Growth and Puberty Have Distinct Genetic Architectures. Eur J Endocrinol 2018;
263. Bick D, Curry CJ, McGill JR, Schorderet DF, Bux RC, Moore CM. Male infant with ichthyosis, Kallmann syndrome, chondrodysplasia punctata, and an Xp chromosome deletion. Am J Med Genet 1989; 33:100-107
264. Muenke M, Schell U, Hehr A, Robin NH, Losken HW, Schinzel A, Pulleyn LJ, Rutland P, Reardon W, Malcolm S, et al. A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome. Nat Genet 1994; 8:269-274
265. Dubourg C, Carre W, Hamdi-Roze H, Mouden C, Roume J, Abdelmajid B, Amram D, Baumann C, Chassaing N, Coubes C, Faivre-Olivier L, Ginglinger E, Gonzales M, Levy-Mozziconacci A, Lynch SA, Naudion S, Pasquier L, Poidvin A, Prieur F, Sarda P, Toutain A, Dupe V, Akloul L, Odent S, de Tayrac M, David V. Mutational Spectrum in Holoprosencephaly Shows That FGF is a New Major Signaling Pathway. Human mutation 2016; 37:1329-1339
266. Southard-Smith EM, Angrist M, Ellison JS, Agarwala R, Baxevanis AD, Chakravarti A, Pavan WJ. The Sox10(Dom) mouse: modeling the genetic variation of Waardenburg-Shah (WS4) syndrome. Genome research 1999; 9:215-225
267. Basaria S. Male hypogonadism. Lancet 2014; 383:1250-1263
268. Silveira LF, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2013; 98:1781-1788

269. Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 2007; 298:1429-1438
270. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force ES. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010; 95:2536-2559
271. Kelberman D, Rizzoti K, Lovell-Badge R, Robinson IC, Dattani MT. Genetic regulation of pituitary gland development in human and mouse. Endocrine reviews 2009; 30:790-829
272. Harrington J, Palmert MR. Clinical review: Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests. J Clin Endocrinol Metab 2012; 97:3056-3067
273. Coutant R, Biette-Demeneix E, Bouvattier C, Bouhours-Nouet N, Gatelais F, Dufresne S, Rouleau S, Lahlou N. Baseline inhibin B and anti-Mullerian hormone measurements for diagnosis of hypogonadotropic hypogonadism (HH) in boys with delayed puberty. J Clin Endocrinol Metab 2010; 95:5225-5232
274. Adan L, Lechevalier P, Couto-Silva AC, Boissan M, Trivin C, Brailly-Tabard S, Brauner R. Plasma inhibin B and antimullerian hormone concentrations in boys: discriminating between congenital hypogonadotropic hypogonadism and constitutional pubertal delay. Medical science monitor : international medical journal of experimental and clinical research 2010; 16:CR511-517
275. Rohayem J, Nieschlag E, Kliesch S, Zitzmann M. Inhibin B, AMH, but not INSL3, IGF1 or DHEAS support differentiation between constitutional delay of growth and puberty and hypogonadotropic hypogonadism. Andrology 2015; 3:882-887
276. Howard SR, Guasti L, Ruiz-Babot G, Mancini A, David A, Storr HL, Metherell LA, Sternberg MJ, Cabrera CP, Warren HR, Barnes MR, Quinton R, de Roux N, Young J, Guiochon-Mantel A, Wehkalampi K, Andre V, Gothilf Y, Cariboni A, Dunkel L. IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty. EMBO Mol Med 2016; 8:626-642
277. Zhu J, Choa RE, Guo MH, Plummer L, Buck C, Palmert MR, Hirschhorn JN, Seminara SB, Chan YM. A shared genetic basis for self-limited delayed puberty and idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2015; 100:E646-654
278. Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. The New England journal of medicine 2010; 363:365-371
279. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, Murad MH, Santoro NF, Warren MP. Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017; 102:1413-1439
280. Meczekalski B, Katulski K, Czyzyk A, Podfigurna-Stopa A, Maciejewska-Jeske M. Functional hypothalamic amenorrhea and its influence on women's health. J Endocrinol Invest 2014; 37:1049-1056
281. Liu JH, Bill AH. Stress-associated or functional hypothalamic amenorrhea in the adolescent. Ann N Y Acad Sci 2008; 1135:179-184
282. Caronia LM, Martin C, Welt CK, Sykiotis GP, Quinton R, Thambundit A, Avbelj M, Dhruvakumar S, Plummer L, Hughes VA, Seminara SB, Boepple PA, Sidis Y, Crowley WF, Jr., Martin KA, Hall JE, Pitteloud N. A genetic basis for functional hypothalamic amenorrhea. The New England journal of medicine 2011; 364:215-225
283. Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, Adriaensen H, Verlooy J, Van Havenbergh T, Smet M, Van Acker K. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab 2000; 85:2215-2222

284. Reddy RG, Aung T, Karavitaki N, Wass JA. Opioid induced hypogonadism. BMJ (Clinical research ed) 2010; 341:c4462
285. Bottcher B, Seeber B, Leyendecker G, Wildt L. Impact of the opioid system on the reproductive axis. Fertil Steril 2017; 108:207-213
286. Fraser LA, Morrison D, Morley-Forster P, Paul TL, Tokmakejian S, Larry Nicholson R, Bureau Y, Friedman TC, Van Uum SH. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. Exp Clin Endocrinol Diabetes 2009; 117:38-43
287. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocrine reviews 2010; 31:98-132
288. O'Rourke TK, Jr., Wosnitzer MS. Opioid-Induced Androgen Deficiency (OPIAD): Diagnosis, Management, and Literature Review. Curr Urol Rep 2016; 17:76
289. Collins FS, Koroshetz WJ, Volkow ND. Helping to End Addiction Over the Long-term: The Research Plan for the NIH HEAL Initiative. JAMA 2018; 320:129-130
290. Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Vanderschueren D, Huhtaniemi IT, Wu FC, Group E. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab 2010; 95:1810-1818
291. Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. J Clin Endocrinol Metab 1994; 79:997-1000
292. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. Nat Rev Endocrinol 2009; 5:673-681
293. Crocker MK, Stern EA, Sedaka NM, Shomaker LB, Brady SM, Ali AH, Shawker TH, Hubbard VS, Yanovski JA. Sexual dimorphisms in the associations of BMI and body fat with indices of pubertal development in girls and boys. J Clin Endocrinol Metab 2014; 99:E1519-1529
294. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002; 110:903-910
295. Kaplowitz P. Delayed puberty in obese boys: comparison with constitutional delayed puberty and response to testosterone therapy. J Pediatr 1998; 133:745-749
296. El Osta R, Grandpre N, Monnin N, Hubert J, Koscinski I. Hypogonadotropic hypogonadism in men with hereditary hemochromatosis. Basic Clin Androl 2017; 27:13
297. Pelusi C, Gasparini DI, Bianchi N, Pasquali R. Endocrine dysfunction in hereditary hemochromatosis. J Endocrinol Invest 2016; 39:837-847
298. De Gobbi M, Roetto A, Piperno A, Mariani R, Alberti F, Papanikolaou G, Politou M, Lockitch G, Girelli D, Fargion S, Cox TM, Gasparini P, Cazzola M, Camaschella C. Natural history of juvenile haemochromatosis. Br J Haematol 2002; 117:973-979
299. Brissot P, Cavey T, Ropert M, Guggenbuhl P, Loreal O. Genetic hemochromatosis: Pathophysiology, diagnostic and therapeutic management. Presse Med 2017; 46:e288-e295
300. Kelly TM, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. Ann Intern Med 1984; 101:629-632
301. Dunkel L, Quinton R. TRANSITION IN ENDOCRINOLOGY: Induction of puberty. Eur J Endocrinol 2014; 170:R229-R239
302. Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic Profile of Subcutaneous Testosterone Enanthate Delivered via a Novel, Prefilled Single-Use Autoinjector: A Phase II Study. Sexual medicine 2015; 3:269-279

303. Bin-Abbas B, Conte FA, Grumbach MM, Kaplan SL. Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size why sex reversal is not indicated. J Pediatr 1999; 134:579-583
304. Nane I, Ziylan O, Esen T, Kocak T, Ander H, Tellaloglu S. Primary gonadotropin releasing hormone and adjunctive human chorionic gonadotropin treatment in cryptorchidism: a clinical trial. Urology 1997; 49:108-111
305. Christiansen P, Muller J, Buhl S, Hansen OR, Hobolth N, Jacobsen BB, Jorgensen PH, Kastrup KW, Nielsen K, Nielsen LB, et al. Treatment of cryptorchidism with human chorionic gonadotropin or gonadotropin releasing hormone. A double-blind controlled study of 243 boys. Hormone research 1988; 30:187-192
306. Dunkel L, Taskinen S, Hovatta O, Tilly JL, Wikstrom S. Germ cell apoptosis after treatment of cryptorchidism with human chorionic gonadotropin is associated with impaired reproductive function in the adult. The Journal of clinical investigation 1997; 100:2341-2346
307. Dwyer AA, Phan-Hug F, Hauschild M, Elowe-Gruau E, Pitteloud N. TRANSITION IN ENDOCRINOLOGY: Hypogonadism in Adolescence. Eur J Endocrinol 2015;
308. Kenigsberg L, Balachandar S, Prasad K, Shah B. Exogenous pubertal induction by oral versus transdermal estrogen therapy. Journal of pediatric and adolescent gynecology 2013; 26:71-79
309. de Muinck Keizer-Schrama SM. Introduction and management of puberty in girls. Hormone research 2007; 68 Suppl 5:80-83
310. Divasta AD, Gordon CM. Hormone replacement therapy and the adolescent. Curr Opin Obstet Gynecol 2010; 22:363-368
311. Hindmarsh PC. How do you initiate oestrogen therapy in a girl who has not undergone puberty? Clin Endocrinol (Oxf) 2009; 71:7-10
312. Kiess W, Conway G, Ritzen M, Rosenfield R, Bernasconi S, Juul A, van Pareren Y, de Muinck Keizer-Schrama SM, Bourguignon JP. Induction of puberty in the hypogonadal girl--practices and attitudes of pediatric endocrinologists in Europe. Hormone research 2002; 57:66-71
313. Drobac S, Rubin K, Rogol AD, Rosenfield RL. A workshop on pubertal hormone replacement options in the United States. Journal of pediatric endocrinology & metabolism : JPEM 2006; 19:55-64
314. Shah S, Forghani N, Durham E, Neely EK. A randomized trial of transdermal and oral estrogen therapy in adolescent girls with hypogonadism. International journal of pediatric endocrinology 2014; 2014:12
315. Klein KO, Rosenfield R, Santen RJ, Gawlik A, Backeljauw P, Gravholt CH, Sas T, Mauras N. Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations. J Clin Endocrinol Metab 2018;
316. Norjavaara E, Ankarberg-Lindgren C, Kristrom B. Sex Steroid Replacement Therapy in Female Hypogonadism from Childhood to Young Adulthood. Endocr Dev 2016; 29:198-213
317. MacGillivray MH. Induction of puberty in hypogonadal children. Journal of pediatric endocrinology & metabolism : JPEM 2004; 17 Suppl 4:1277-1287
318. Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. Clin Endocrinol (Oxf) 1981; 14:49-61
319. Han TS, Bouloux PM. What is the optimal therapy for young males with hypogonadotropic hypogonadism? Clinical endocrinology 2010; 72:731-737
320. Lawaetz JG, Hagen CP, Mieritz MG, Blomberg Jensen M, Petersen JH, Juul A. Evaluation of 451 Danish boys with delayed puberty: diagnostic use of a new puberty

nomogram and effects of oral testosterone therapy. J Clin Endocrinol Metab 2015; 100:1376-1385
321. Bistritzer T, Lunenfeld B, Passwell JH, Theodor R. Hormonal therapy and pubertal development in boys with selective hypogonadotropic hypogonadism. Fertil Steril 1989; 52:302-306
322. Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. Fertil Steril 1999; 71:244-248
323. Zacharin M, Sabin MA, Nair VV, Dabadghao P. Addition of recombinant follicle-stimulating hormone to human chorionic gonadotropin treatment in adolescents and young adults with hypogonadotropic hypogonadism promotes normal testicular growth and may promote early spermatogenesis. Fertil Steril 2012; 98:836-842
324. Sinisi AA, Esposito D, Maione L, Quinto MC, Visconti D, De Bellis A, Bellastella A, Conzo G, Bellastella G. Seminal anti-Mullerian hormone level is a marker of spermatogenic response during long-term gonadotropin therapy in male hypogonadotropic hypogonadism. Hum Reprod 2008; 23:1029-1034
325. Rohayem J, Hauffa BP, Zacharin M, Kliesch S, Zitzmann M. Testicular growth and spermatogenesis: new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? -a multicentre prospective study of hCG/rFSH treatment outcomes during adolescence. Clin Endocrinol (Oxf) 2017; 86:75-87
326. Meachem SJ, McLachlan RI, de Kretser DM, Robertson DM, Wreford NG. Neonatal exposure of rats to recombinant follicle stimulating hormone increases adult Sertoli and spermatogenic cell numbers. Biol Reprod 1996; 54:36-44
327. Arslan M, Weinbauer GF, Schlatt S, Shahab M, Nieschlag E. FSH and testosterone, alone or in combination, initiate testicular growth and increase the number of spermatogonia and Sertoli cells in a juvenile non-human primate (Macaca mulatta). J Endocrinol 1993; 136:235-243
328. Raivio T, Toppari J, Perheentupa A, McNeilly AS, Dunkel L. Treatment of prepubertal gonadotrophin-deficient boys with recombinant human follicle-stimulating hormone. Lancet 1997; 350:263-264
329. Tapanainen JS, Aittomaki K, Min J, Vaskivuo T, Huhtaniemi IT. Men homozygous for an inactivating mutation of the follicle-stimulating hormone (FSH) receptor gene present variable suppression of spermatogenesis and fertility. Nat Genet 1997; 15:205-206
330. Raivio T, Wikstrom AM, Dunkel L. Treatment of gonadotropin-deficient boys with recombinant human FSH: long-term observation and outcome. Eur J Endocrinol 2007; 156:105-111
331. Dwyer AA, Sykiotis GP, Hayes FJ, Boepple PA, Lee H, Loughlin KR, Dym M, Sluss PM, Crowley WF, Jr., Pitteloud N. Trial of recombinant follicle-stimulating hormone pretreatment for GnRH-induced fertility in patients with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2013; 98:E1790-1795
332. Cleemann L, Hjerrild BE, Lauridsen AL, Heickendorff L, Christiansen JS, Mosekilde L, Gravholt CH. Long-term hormone replacement therapy preserves bone mineral density in Turner syndrome. Eur J Endocrinol 2009; 161:251-257
333. Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab 2016; 101:3497-3505
334. Santhakumar A, Miller M, Quinton R. Pubertal induction in adult males with isolated hypogonadotropic hypogonadism using long-acting intramuscular testosterone undecanoate 1-g depot (Nebido). Clin Endocrinol (Oxf) 2014; 80:155-157

335. Spratt DI, Stewart, II, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients. J Clin Endocrinol Metab 2017; 102:2349-2355
336. de Ronde W. Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies. Hum Reprod 2009; 24:425-428
337. Martinez-Pajares JD, Diaz-Morales O, Ramos-Diaz JC, Gomez-Fernandez E. Peripheral precocious puberty due to inadvertent exposure to testosterone: case report and review of the literature. Journal of pediatric endocrinology & metabolism : JPEM 2012; 25:1007-1012
338. Shoham Z, Smith H, Yeko T, O'Brien F, Hemsey G, O'Dea L. Recombinant LH (lutropin alfa) for the treatment of hypogonadotrophic women with profound LH deficiency: a randomized, double-blind, placebo-controlled, proof-of-efficacy study. Clin Endocrinol (Oxf) 2008; 69:471-478
339. Kaufmann R, Dunn R, Vaughn T, Hughes G, O'Brien F, Hemsey G, Thomson B, O'Dea LS. Recombinant human luteinizing hormone, lutropin alfa, for the induction of follicular development and pregnancy in profoundly gonadotrophin-deficient women. Clin Endocrinol (Oxf) 2007; 67:563-569
340. Tournaye H, Krausz C, Oates RD. Concepts in diagnosis and therapy for male reproductive impairment. Lancet Diabetes Endocrinol 2017; 5:554-564
341. Dreyer K, van Rijswijk J, Mijatovic V, Goddijn M, Verhoeve HR, van Rooij IAJ, Hoek A, Bourdrez P, Nap AW, Rijnsaardt-Lukassen HGM, Timmerman CCM, Kaplan M, Hooker AB, Gijsen AP, van Golde R, van Heteren CF, Sluijmer AV, de Bruin JP, Smeenk JMJ, de Boer JAM, Scheenjes E, Duijn AEJ, Mozes A, Pelinck MJ, Traas MAF, van Hooff MHA, van Unnik GA, de Koning CH, van Geloven N, Twisk JWR, Hompes PGA, Mol BWJ. Oil-Based or Water-Based Contrast for Hysterosalpingography in Infertile Women. The New England journal of medicine 2017; 376:2043-2052
342. Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev 2016; 4:CD003719
343. Leyendecker G, Struve T, Plotz EJ. Induction of ovulation with chronic intermittent (pulsatile) administration of LH-RH in women with hypothalamic and hyperprolactinemic amenorrhea. Arch Gynecol 1980; 229:177-190
344. Leyendecker G, Wildt L. From physiology to clinics--20 years of experience with pulsatile GnRH. Eur J Obstet Gynecol Reprod Biol 1996; 65 Suppl:S3-12
345. Leyendecker G, Wildt L, Hansmann M. Pregnancies following chronic intermittent (pulsatile) administration of Gn-RH by means of a portable pump ("Zyklomat")--a new approach to the treatment of infertility in hypothalamic amenorrhea. J Clin Endocrinol Metab 1980; 51:1214-1216
346. Crowley WF, Jr., McArthur JW. Simulation of the normal menstrual cycle in Kallman's syndrome by pulsatile administration of luteinizing hormone-releasing hormone (LHRH). J Clin Endocrinol Metab 1980; 51:173-175
347. Mason P, Adams J, Morris DV, Tucker M, Price J, Voulgaris Z, Van der Spuy ZM, Sutherland I, Chambers GR, White S, et al. Induction of ovulation with pulsatile luteinising hormone releasing hormone. Br Med J (Clin Res Ed) 1984; 288:181-185
348. Martin KA, Hall JE, Adams JM, Crowley WF, Jr. Comparison of exogenous gonadotropins and pulsatile gonadotropin-releasing hormone for induction of ovulation in hypogonadotropic amenorrhea. J Clin Endocrinol Metab 1993; 77:125-129
349. Santoro N, Elzahr D. Pulsatile gonadotropin-releasing hormone therapy for ovulatory disorders. Clin Obstet Gynecol 1993; 36:727-736

350. Christin-Maitre S, de Crecy M. [Pregnancy outcomes following pulsatile GnRH treatment: results of a large multicenter retrospective study]. J Gynecol Obstet Biol Reprod (Paris) 2007; 36:8-12
351. Seminara SB, Beranova M, Oliveira LM, Martin KA, Crowley WF, Jr., Hall JE. Successful use of pulsatile gonadotropin-releasing hormone (GnRH) for ovulation induction and pregnancy in a patient with GnRH receptor mutations. J Clin Endocrinol Metab 2000; 85:556-562
352. Bouligand J, Ghervan C, Tello JA, Brailly-Tabard S, Salenave S, Chanson P, Lombes M, Millar RP, Guiochon-Mantel A, Young J. Isolated familial hypogonadotropic hypogonadism and a GNRH1 mutation. The New England journal of medicine 2009; 360:2742-2748
353. Francou B, Bouligand J, Voican A, Amazit L, Trabado S, Fagart J, Meduri G, Brailly-Tabard S, Chanson P, Lecomte P, Guiochon-Mantel A, Young J. Normosmic congenital hypogonadotropic hypogonadism due to TAC3/TACR3 mutations: characterization of neuroendocrine phenotypes and novel mutations. PLoS One 2011; 6:e25614
354. Abel BS, Shaw ND, Brown JM, Adams JM, Alati T, Martin KA, Pitteloud N, Seminara SB, Plummer L, Pignatelli D, Crowley WF, Jr., Welt CK, Hall JE. Responsiveness to a physiological regimen of GnRH therapy and relation to genotype in women with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2013; 98:E206-216
355. Christou F, Pitteloud N, Gomez F. The induction of ovulation by pulsatile administration of GnRH: an appropriate method in hypothalamic amenorrhea. Gynecol Endocrinol 2017; 33:598-601
356. Filicori M, Santoro N, Merriam GR, Crowley WF, Jr. Characterization of the physiological pattern of episodic gonadotropin secretion throughout the human menstrual cycle. J Clin Endocrinol Metab 1986; 62:1136-1144
357. Martin K, Santoro N, Hall J, Filicori M, Wierman M, Crowley WF, Jr. Clinical review 15: Management of ovulatory disorders with pulsatile gonadotropin-releasing hormone. J Clin Endocrinol Metab 1990; 71:1081a-1081g
358. Letterie GS, Coddington CC, Collins RL, Merriam GR. Ovulation induction using s.c. pulsatile gonadotrophin-releasing hormone: effectiveness of different pulse frequencies. Hum Reprod 1996; 11:19-22
359. Homburg R, Eshel A, Armar NA, Tucker M, Mason PW, Adams J, Kilborn J, Sutherland IA, Jacobs HS. One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. BMJ (Clinical research ed) 1989; 298:809-812
360. Messinis IE. Ovulation induction: a mini review. Hum Reprod 2005; 20:2688-2697
361. Couzinet B, Lestrat N, Brailly S, Forest M, Schaison G. Stimulation of ovarian follicular maturation with pure follicle-stimulating hormone in women with gonadotropin deficiency. J Clin Endocrinol Metab 1988; 66:552-556
362. Shimoda M, Iwayama H, Ishiyama M, Nakatani A, Yamashita M. Successful pregnancy by vitrified-warmed embryo transfer for a woman with Kallmann syndrome. Reprod Med Biol 2016; 15:45-49
363. Kuroda K, Ezoe K, Kato K, Yabuuchi A, Segawa T, Kobayashi T, Ochiai A, Katoh N, Takeda S. Infertility treatment strategy involving combined freeze-all embryos and single vitrified-warmed embryo transfer during hormonal replacement cycle for in vitro fertilization of women with hypogonadotropic hypogonadism. J Obstet Gynaecol Res 2018;
364. Hoffman AR, Crowley WF, Jr. Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. The New England journal of medicine 1982; 307:1237-1241

365. Spratt DI, Finkelstein JS, O'Dea LS, Badger TM, Rao PN, Campbell JD, Crowley WF, Jr. Long-term administration of gonadotropin-releasing hormone in men with idiopathic hypogonadotropic hypogonadism. A model for studies of the hormone's physiologic effects. Ann Intern Med 1986; 105:848-855
366. Aulitzky W, Frick J, Galvan G. Pulsatile luteinizing hormone-releasing hormone treatment of male hypogonadotropic hypogonadism. Fertil Steril 1988; 50:480-486
367. Whitcomb RW, Crowley WF, Jr. Clinical review 4: Diagnosis and treatment of isolated gonadotropin-releasing hormone deficiency in men. J Clin Endocrinol Metab 1990; 70:3-7
368. Gayral MN, Millet D, Mandelbaum J, Serfaty D, Netter A. [Male hypogonadotrophic hypogonadism: successful treatment of infertility with HMG + HCG (author's transl)]. Ann Endocrinol (Paris) 1975; 36:227-241
369. Burger HG, Baker HW. Therapeutic considerations and results of gonadotropin treatment in male hypogonadotropic hypogonadism. Ann N Y Acad Sci 1984; 438:447-453
370. Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. The New England journal of medicine 1985; 313:651-655
371. Ley SB, Leonard JM. Male hypogonadotropic hypogonadism: factors influencing response to human chorionic gonadotropin and human menopausal gonadotropin, including prior exogenous androgens. J Clin Endocrinol Metab 1985; 61:746-752
372. Okuyama A, Nakamura M, Namiki M, Aono T, Matsumoto K, Utsunomiya M, Yoshioka T, Itoh H, Itatani H, Mizutani S, et al. Testicular responsiveness to long-term administration of hCG and hMG in patients with hypogonadotrophic hypogonadism. Hormone research 1986; 23:21-30
373. Liu L, Banks SM, Barnes KM, Sherins RJ. Two-year comparison of testicular responses to pulsatile gonadotropin-releasing hormone and exogenous gonadotropins from the inception of therapy in men with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1988; 67:1140-1145
374. Schopohl J, Mehltretter G, von Zumbusch R, Eversmann T, von Werder K. Comparison of gonadotropin-releasing hormone and gonadotropin therapy in male patients with idiopathic hypothalamic hypogonadism. Fertil Steril 1991; 56:1143-1150
375. Saal W, Happ J, Cordes U, Baum RP, Schmidt M. Subcutaneous gonadotropin therapy in male patients with hypogonadotropic hypogonadism. Fertil Steril 1991; 56:319-324
376. Vicari E, Mongioi A, Calogero AE, Moncada ML, Sidoti G, Polosa P, D'Agata R. Therapy with human chorionic gonadotrophin alone induces spermatogenesis in men with isolated hypogonadotrophic hypogonadism--long-term follow-up. Int J Androl 1992; 15:320-329
377. Schaison G, Young J, Pholsena M, Nahoul K, Couzinet B. Failure of combined follicle-stimulating hormone-testosterone administration to initiate and/or maintain spermatogenesis in men with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1993; 77:1545-1549
378. Jones TH, Darne JF. Self-administered subcutaneous human menopausal gonadotrophin for the stimulation of testicular growth and the initiation of spermatogenesis in hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf) 1993; 38:203-208
379. Kung AW, Zhong YY, Lam KS, Wang C. Induction of spermatogenesis with gonadotrophins in Chinese men with hypogonadotrophic hypogonadism. Int J Androl 1994; 17:241-247

380. Kirk JM, Savage MO, Grant DB, Bouloux PM, Besser GM. Gonadal function and response to human chorionic and menopausal gonadotrophin therapy in male patients with idiopathic hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf) 1994; 41:57-63
381. Burgues S, Calderon MD. Subcutaneous self-administration of highly purified follicle stimulating hormone and human chorionic gonadotrophin for the treatment of male hypogonadotrophic hypogonadism. Spanish Collaborative Group on Male Hypogonadotropic Hypogonadism. Hum Reprod 1997; 12:980-986
382. Efficacy and safety of highly purified urinary follicle-stimulating hormone with human chorionic gonadotropin for treating men with isolated hypogonadotropic hypogonadism. European Metrodin HP Study Group. Fertil Steril 1998; 70:256-262
383. Buchter D, Behre HM, Kliesch S, Nieschlag E. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. Eur J Endocrinol 1998; 139:298-303
384. Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, Handelsman DJ. Efficacy and safety of recombinant human follicle stimulating hormone (Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. Hum Reprod 1999; 14:1540-1545
385. Bouloux P, Warne DW, Loumaye E, Infertility FSHSGiMs. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. Fertil Steril 2002; 77:270-273
386. Liu PY, Gebski VJ, Turner L, Conway AJ, Wishart SM, Handelsman DJ. Predicting pregnancy and spermatogenesis by survival analysis during gonadotrophin treatment of gonadotrophin-deficient infertile men. Hum Reprod 2002; 17:625-633
387. Depenbusch M, von Eckardstein S, Simoni M, Nieschlag E. Maintenance of spermatogenesis in hypogonadotropic hypogonadal men with human chorionic gonadotropin alone. Eur J Endocrinol 2002; 147:617-624
388. Bouloux PM, Nieschlag E, Burger HG, Skakkebaek NE, Wu FC, Handelsman DJ, Baker GH, Ochsenkuehn R, Syska A, McLachlan RI, Giwercman A, Conway AJ, Turner L, van Kuijk JH, Voortman G. Induction of spermatogenesis by recombinant follicle-stimulating hormone (puregon) in hypogonadotropic azoospermic men who failed to respond to human chorionic gonadotropin alone. J Androl 2003; 24:604-611
389. Miyagawa Y, Tsujimura A, Matsumiya K, Takao T, Tohda A, Koga M, Takeyama M, Fujioka H, Takada S, Koide T, Okuyama A. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. J Urol 2005; 173:2072-2075
390. Zorn B, Pfeifer M, Virant-Klun I, Meden-Vrtovec H. Intracytoplasmic sperm injection as a complement to gonadotrophin treatment in infertile men with hypogonadotrophic hypogonadism. Int J Androl 2005; 28:202-207
391. Matsumoto AM, Snyder PJ, Bhasin S, Martin K, Weber T, Winters S, Spratt D, Brentzel J, O'Dea L. Stimulation of spermatogenesis with recombinant human follicle-stimulating hormone (follitropin alfa; GONAL-f): long-term treatment in azoospermic men with hypogonadotropic hypogonadism. Fertil Steril 2009; 92:979-990
392. Warne DW, Decosterd G, Okada H, Yano Y, Koide N, Howles CM. A combined analysis of data to identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin. Fertil Steril 2009; 92:594-604
393. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab 2009; 94:801-808

394. Oldereid NB, Abyholm T, Tanbo TG. Spermatogenesis and fertility outcome in male hypogonadotrophic hypogonadism. Hum Fertil (Camb) 2010; 13:83-89
395. Sinisi AA, Esposito D, Bellastella G, Maione L, Palumbo V, Gandini L, Lombardo F, De Bellis A, Lenzi A, Bellastella A. Efficacy of recombinant human follicle stimulating hormone at low doses in inducing spermatogenesis and fertility in hypogonadotropic hypogonadism. J Endocrinol Invest 2010; 33:618-623
396. Rohayem J, Sinthofen N, Nieschlag E, Kliesch S, Zitzmann M. Causes of hypogonadotropic hypogonadism predict response to gonadotropin substitution in adults. Andrology 2016; 4:87-94
397. Liu Z, Mao J, Wu X, Xu H, Wang X, Huang B, Zheng J, Nie M, Zhang H. Efficacy and Outcome Predictors of Gonadotropin Treatment for Male Congenital Hypogonadotropic Hypogonadism: A Retrospective Study of 223 Patients. Medicine (Baltimore) 2016; 95:e2867
398. Morris DV, Adeniyi-Jones R, Wheeler M, Sonksen P, Jacobs HS. The treatment of hypogonadotrophic hypogonadism in men by the pulsatile infusion of luteinising hormone-releasing hormone. Clin Endocrinol (Oxf) 1984; 21:189-200
399. Shargil AA. Treatment of idiopathic hypogonadotropic hypogonadism in men with luteinizing hormone-releasing hormone: a comparison of treatment with daily injections and with the pulsatile infusion pump. Fertil Steril 1987; 47:492-501
400. Delemarre-Van de Waal HA. Induction of testicular growth and spermatogenesis by pulsatile, intravenous administration of gonadotrophin-releasing hormone in patients with hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf) 1993; 38:473-480
401. Gong C, Liu Y, Qin M, Wu D, Wang X. Pulsatile GnRH Is Superior to hCG in Therapeutic Efficacy in Adolescent Boys With Hypogonadotropic Hypogonadodism. J Clin Endocrinol Metab 2015; 100:2793-2799
402. Mao JF, Liu ZX, Nie M, Wang X, Xu HL, Huang BK, Zheng JJ, Min L, Kaiser UB, Wu XY. Pulsatile gonadotropin-releasing hormone therapy is associated with earlier spermatogenesis compared to combined gonadotropin therapy in patients with congenital hypogonadotropic hypogonadism. Asian J Androl 2017; 19:680-685
403. Heller CG, Nelson WO. Classification of male hypogonadism and a discussion of the pathologic physiology, diagnosis and treatment. J Clin Endocrinol Metab 1948; 8:345-366
404. Lytton B, Kase N. Effects of human menopausal gonadotrophin on a eunuchoidal male. The New England journal of medicine 1966; 274:1061-1064
405. Johnsen SG. Maintenance of spermatogenesis induced by HMG treatment by means of continuous HCG treatment in hypogonadotrophic men. Acta Endocrinol (Copenh) 1978; 89:763-769
406. Li R, Thorup J, Sun C, Cortes D, Southwell B, Hutson J. Immunofluorescent analysis of testicular biopsies with germ cell and Sertoli cell markers shows significant MVH negative germ cell depletion with older age at orchiopexy. J Urol 2014; 191:458-464
407. Kollin C, Granholm T, Nordenskjold A, Ritzen EM. Growth of spontaneously descended and surgically treated testes during early childhood. Pediatrics 2013; 131:e1174-1180
408. Burger HG, de Kretser DM, Hudson B, Wilson JD. Effects of preceding androgen therapy on testicular response to human pituitary gonadotropin in hypogonadotropic hypogonadism: a study of three patients. Fertil Steril 1981; 35:64-68
409. Handelsman DJ, Goebel C, Idan A, Jimenez M, Trout G, Kazlauskas R. Effects of recombinant human LH and hCG on serum and urine LH and androgens in men. Clin Endocrinol (Oxf) 2009; 71:417-428
410. McCormack SE, Cousminer DL, Chesi A, Mitchell JA, Roy SM, Kalkwarf HJ, Lappe JM, Gilsanz V, Oberfield SE, Shepherd JA, Winer KK, Kelly A, Grant SFA, Zemel BS.

Association Between Linear Growth and Bone Accrual in a Diverse Cohort of Children and Adolescents. JAMA Pediatr 2017; 171:e171769
411. Finkelstein JS, Lee H, Leder BZ, Burnett-Bowie SA, Goldstein DW, Hahn CW, Hirsch SC, Linker A, Perros N, Servais AB, Taylor AP, Webb ML, Youngner JM, Yu EW. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. The Journal of clinical investigation 2016; 126:1114-1125
412. Maione L, Colao A, Young J. Bone mineral density in older patients with never-treated congenital hypogonadotropic hypogonadism. Endocrine 2018; 59:231-233
413. Finkelstein JS, Klibanski A, Neer RM, Doppelt SH, Rosenthal DI, Segre GV, Crowley WF, Jr. Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1989; 69:776-783
414. Laitinen EM, Hero M, Vaaralahti K, Tommiska J, Raivio T. Bone mineral density, body composition and bone turnover in patients with congenital hypogonadotropic hypogonadism. Int J Androl 2012; 35:534-540
415. Iolascon G, Frizzi L, Bianco M, Gimigliano F, Palumbo V, Sinisi AM, Sinisi AA. Bone involvement in males with Kallmann disease. Aging Clin Exp Res 2015; 27 Suppl 1:S31-36
416. Irwig MS. Male hypogonadism and skeletal health. Current opinion in endocrinology, diabetes, and obesity 2013; 20:517-522
417. Guo CY, Jones TH, Eastell R. Treatment of isolated hypogonadotropic hypogonadism effect on bone mineral density and bone turnover. J Clin Endocrinol Metab 1997; 82:658-665
418. Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997; 82:2386-2390
419. Leifke E, Korner HC, Link TM, Behre HM, Peters PE, Nieschlag E. Effects of testosterone replacement therapy on cortical and trabecular bone mineral density, vertebral body area and paraspinal muscle area in hypogonadal men. Eur J Endocrinol 1998; 138:51-58
420. Canale D, Vignali E, Golia F, Martino E, Pinchera A, Marcocci C. Effects of hormonal replacement treatment on bone mineral density and metabolism in hypogonadal patients. Mol Cell Endocrinol 2000; 161:47-51
421. De Rosa M, Paesano L, Nuzzo V, Zarrilli S, Del Puente A, Oriente P, Lupoli G. Bone mineral density and bone markers in hypogonadotropic and hypergonadotropic hypogonadal men after prolonged testosterone treatment. J Endocrinol Invest 2001; 24:246-252
422. Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. Endocrine reviews 2004; 25:389-425
423. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. The Journal of clinical endocrinology and metabolism 2004; 89:2085-2098
424. Hayashi M, Nakashima T, Taniguchi M, Kodama T, Kumanogoh A, Takayanagi H. Osteoprotection by semaphorin 3A. Nature 2012; 485:69-74
425. Gioia A, Ceccoli L, Ronconi V, Turchi F, Marcheggiani M, Boscaro M, Giacchetti G, Balercia G. Vitamin D levels and bone mineral density: are LH levels involved in the pathogenesis of bone impairment in hypogonadal men? J Endocrinol Invest 2014; 37:1225-1231
426. Meric C, Sonmez A, Aydogdu A, Tapan S, Haymana C, Basaran Y, Baskoy K, Sertoglu E, Taslipinar A, Bolu E, Azal O. Osteoprotegerin, fibroblast growth factor 23, and vitamin D3 levels in male patients with hypogonadism. Horm Metab Res 2014; 46:955-958

427. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2007; 92:4254-4259
428. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384:766-781
429. Sonmez A, Haymana C, Bolu E, Aydogdu A, Tapan S, Serdar M, Altun B, Barcin C, Taslipinar A, Meric C, Uckaya G, Kutlu M. Metabolic syndrome and the effect of testosterone treatment in young men with congenital hypogonadotropic hypogonadism. Eur J Endocrinol 2011; 164:759-764
430. Wu XY, Mao JF, Lu SY, Zhang Q, Shi YF. Testosterone replacement therapy improves insulin sensitivity and decreases high sensitivity C-reactive protein levels in hypogonadotropic hypogonadal young male patients. Chin Med J (Engl) 2009; 122:2846-2850
431. Naharci MI, Pinar M, Bolu E, Olgun A. Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. Endocr Pract 2007; 13:629-635
432. Tripathy D, Shah P, Lakshmy R, Reddy KS. Effect of testosterone replacement on whole body glucose utilisation and other cardiovascular risk factors in males with idiopathic hypogonadotrophic hypogonadism. Horm Metab Res 1998; 30:642-645
433. Bayram F, Elbuken G, Korkmaz C, Aydogdu A, Karaca Z, Cakir I. The Effects of Gonadotropin Replacement Therapy on Metabolic Parameters and Body Composition in Men with Idiopathic Hypogonadotropic Hypogonadism. Horm Metab Res 2016; 48:112-117
434. Chehab FF. 20 years of leptin: leptin and reproduction: past milestones, present undertakings, and future endeavors. J Endocrinol 2014; 223:T37-48

Figure 1. Pubertal progression in two male patients with delayed puberty. Testicular volume (TV) was plotted on the age-matched puberty normogram. **(A)** Patient 1 was diagnosed with delayed puberty at age 14 (TV 3mL) and completed pubertal development at age 18 (TV 16mL) confirming CDGP diagnosis. **(B)** Patient 2 was diagnosed at age 15 (TV 3mL) and discharged at age 17 (TV 8mL), despite the fact that his progression is still abnormal (< -2SD) 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/.

Figure 2: Non-reproductive, non-olfactory signs associated with Kallmann syndrome. **(A)** Coronal CT scan showing the normal palatine bone in a normal subject (yellow circle). **(B)** Cleft palate (yellow arrow) in a patient with Kallmann syndrome carrying a heterozygous *FGFR1* mutation (adapted from (161). **(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 Kallmann syndrome and a heterozygous *CHD7* mutation (adapted from (162). **(E)** Ear pavilion abnormality suggesting CHARGE syndrome in a male CHH patient initially referred for Kallmann syndrome. **(F)** Inner ear CT scan showing patient's semicircular canals hypoplasia in a male patient with Kallmann syndrome and deafness resulting from a heterozygous *SOX10* mutation (adapted from (163) and (164)). **(G)** Post-natal 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). (C and F) 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.

Figure 3. Hormone levels and ultrasound features in female CHH patients compared with healthy controls. Serum FSH and LH (panel A), estradiol (E2) (panel B) and serum ovarian peptides inhibin B (panel C), and AMH (panel D) levels in in untreated women with CHH (n = 68, aged from 18 to 34 years) and age-matched healthy young women (controls, n = 52). Mean ovarian volume (panel E), total mean antral follicle (AF) number /ovary (panel F) in untreated women with CHH (n = 39) and in healthy women (n = 41). 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.

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. CHH, congenital hypogonadotropic hypogonadism.

Figure 5. Pedigrees and gene mutations in CHH and KS patients. 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 ACMG recommendations (258). **Pedigree 1**: X-Linked Kallmann syndrome 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; and squares denote males; arrows mark probands. A diagonal slash through a symbol means the subject is deceased. Regarding the gene mutations, + represents wild-type (reference) sequence, and a 0 is present in hemizygous male subjects for genes on the X chromosome. NA, not available.

Figure 6. Practical algorithm of clinical management for patients with delayed puberty. SD, standard deviation; E2, estradiol; TV, testicular volume; T, testosterone; FSH, follicule stimulating hormone; LH, luteinizing hormone; INB, inhibin B; CHH, congenital hypogonadotropic hypogonadism; HH, hypogonadotropic hypogonadism; CDGP,

constitutional delay of growth and puberty. * TV increase under testosterone treatment or after therapeutic window highly indicate CDGP.

Table 1. The prevalence of main non-reproductive phenotypes in CHH versus general population.

Phenotypes	All CHH		KS		General population
	Waldstreicher et al. (n = 106) (157)	Quinton et al. (n = 215) (158)	Quinton et al. (n = 112) (158)	Costa-Barbosa et al. (n = 219) (160)	
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)

NA: not assessed; [a] only sensorineural hearing loss is included. Prevalence in the general population: anosmia data from NIH 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 NIH Genetics Home Reference (https://ghr.nlm.nih.gov, accessed in January 2018); unilateral renal agenesis data is from Orphanet (http://www.orpha.net/consor/cgi-bin/index.php, accessed in January 2018).

Table 2. Complex syndromes with clinical & genetic overlap with CHH.

Syndrome	Major signs	Minor signs	Genetic overlap with CHH *
CHARGE syndrome	coloboma, choanal atresia, semi-circular 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	**hypogonadotropic hypogonadism**, **anosmia with OB aplasia/hypoplasia,** facial dysmorphism, megacolon, semi-circular 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	**hypogonadotropic hypogonadism,** adrenal hypoplasia	-	*NR0B1 (DAX1)* (183,184)
4H syndrome	**hypogonadotropic hypogonadism, hypodontia,** hypomyelination	-	*POLR3B* (185,186)
Septo-optic dysplasia	optic nerve hypoplasia, **hypothalamic-pituitary defect, midline brain defect**	-	*HESX1* (187,188) *SOX2* (189-191)

Phenotypes which overlap between these syndromes and CHH are highlighted in bold. OB, olfactory bulb; 4H syndrome: hypomyelination, hypogonadotropic hypogonadism and hypodontia. * Genetic overlap with CHH: list of genes mutated in both syndromic and non-syndromic forms of CHH, with landmark studies cited as references.

Table 3. Clinical and biochemical characteristics of neonatal CHH males reported in literature

Case No.	Clinical signs		Hormonal testing				Diagnosis	Neonatal treatment	References
	Neonatal signs	Family history	Age (months)	T (nmol/L)	LH (IU/L)	FSH (IU/L)			
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-	CHH	rFSH + rLH,	(203)

						0.17		T	
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	

T, testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; n.r., not reported; CLP, cleft lip palate; hCG, human chorionic gonadotropin; rFSH, recombinant FSH; rLH, recominant LH; n.d., not detectable.

Table 4. Medical treatment for puberty induction, hypogonadism and infertility in female CHH patients.

Treatment	Dosing & administration	Advantage	Disadvantages
Induction of puberty in girls			
17b-estradiol (tablets)	Initial dose: 5 μg/kg daily P.O. ↑ 5 μg/kg increments every 6-12 months Up to 1-2 mg daily	Natural estrogen	Less preferable than transdermal route
17b-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 25ug/24h
	↑ to 0.08 - 0.12 μg/kg every 6 months	No hepatic passage (decrease thromboembolic risk)	
	Up to 50 - 100 μg/24 h		
Progesterone	Added after full breast development or break-through bleeding, during the last 14 days of menstrual cycle		
Treatment of hypogonadism in adult females			
Estroprogestin therapy (tablets)	17β-estradiol 1 or 2 mg Progestin: during the last 14 days of the months micronized progestin 200mg P.O. daily, or dydrogesterone 10 mg P.O. daily	Mimic the physiological hormone changes	
Estroprogesin therapy (patch or gel)	17β-estradiol patch 50-100 ug/24h daily, OR 17β-estradiol gel 7.5 - 15 mg daily Progestin: during the last 14 days of the months micronized progestin 200mg P.O. daily, or dydrogesterone 10 mg P.O. daily	Mimic the physiological hormone changes	
Treatment of fertility in adult females			
Pulsatile GnRH	**I.V. pump**: 75 ng/kg per pulse every 90 min	Most physiological treatment	Not available in many countries
	Dose adaped based on response, up to 500 ng/kg per pulse	Possibility to adjust pulse frequency in I.V. pump	Require centers with expertise
	S.C. pump: 15 μg per pulse every 90 min	High success rate	Risk of phlebitis for I.V. 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 days for 3 times		
Gonadotropins	hMG (FSH + LH) 75 - 150 IU S.C. daily, dose adapted based on follicular growth	Available around the world	More expensive
	Induction of ovulation by hCG 6500 IU S.C. injection	Self-injection	Higher risk of overstimulation
	Luteal phase:		Requires close monitoring of E2 & US
	hCG 1500 U every 3 days for 3 times		Higher risk of multiple pregnancy
	Progesterone 200mg intravaginal daily		

Table 5. Medical treatment for puberty induction, hypogonadism and infertility in male CHH patients.

Treatment	Dosing & administration	Advantage	Disadvantages
Induction of puberty in boys			
Testosterone enanthate (TE)	Initial dose: 50 mg I.M. monthly	Standard care with long clinical experience	Premature epiphyseal closure (high dose)
	↑ 50 mg increments every 6 - 12 months,	Aromatizable to E2: promote bone maturation	Could inhibit TV & spermatogenesis
	Up to 250 mg monthly		Impact on future fertility: unknown
Gonadotropin	hCG: initial dose 250 IU twice weekly, S.C.	Stimulate TV growth & spermatogenesis	Not standard treatment
	↑ 250 - 500 IU increments every 6 months	Pre-FSH treatment can be beneficial in patients with TV < 4ml or history cryptorchidism	Need good compliance in adolescent patients
	Up to 1500 IU 3 times weekly		Need studies in larger cohorts
	rFSH: dose 75-150 IU 3 times weekly, S.C.		
Hypogonadism treatment in adult males			
Testosterone enanthate (TE)	250 mg I.M. every 2-4 weeks	Cost effective	Relative frequent I.M. injection
	Interval adjusted based on trough T	Available around the world	S.C. route is under investigation (302)
		Self injection	
Testosterone undecanoate (TU)	1000 mg I.M. every 10-14 weeks	Cost effective	Interval of treatment is highly variable, follow-up of trough T is important
	Interval adjusted based on trough T	Infrequent injection	Injections by nurses
Testosterone gel	50-80 mg transdermal daily	Non invasive	Risk of transmission by skin contact
		Self-administrated	
Treatment of infertility in adult males			
Pulsatile GnRH	S.C. 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 3 times weekly, S.C.	Available around the world	Relative expensive for rFSH
	Dose adjusted based on trough T	For patients with absent puberty (TV < 4ml):	Frequent injections
	rFSH: dose 75-150 IU 3 times weekly, S.C.	pre-rFSH treatment increases fertilty prognosis	
	Dose adjusted based on serum FSH, sperm count		

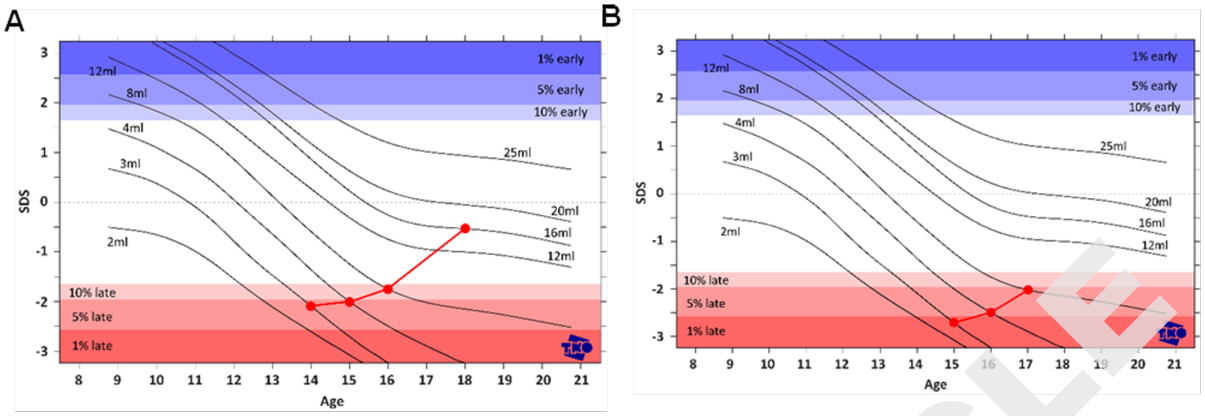
Table 6. Fertility outcomes in male patients with congenital hypogonadotropic hypogonadism: summary of 44 published studies.

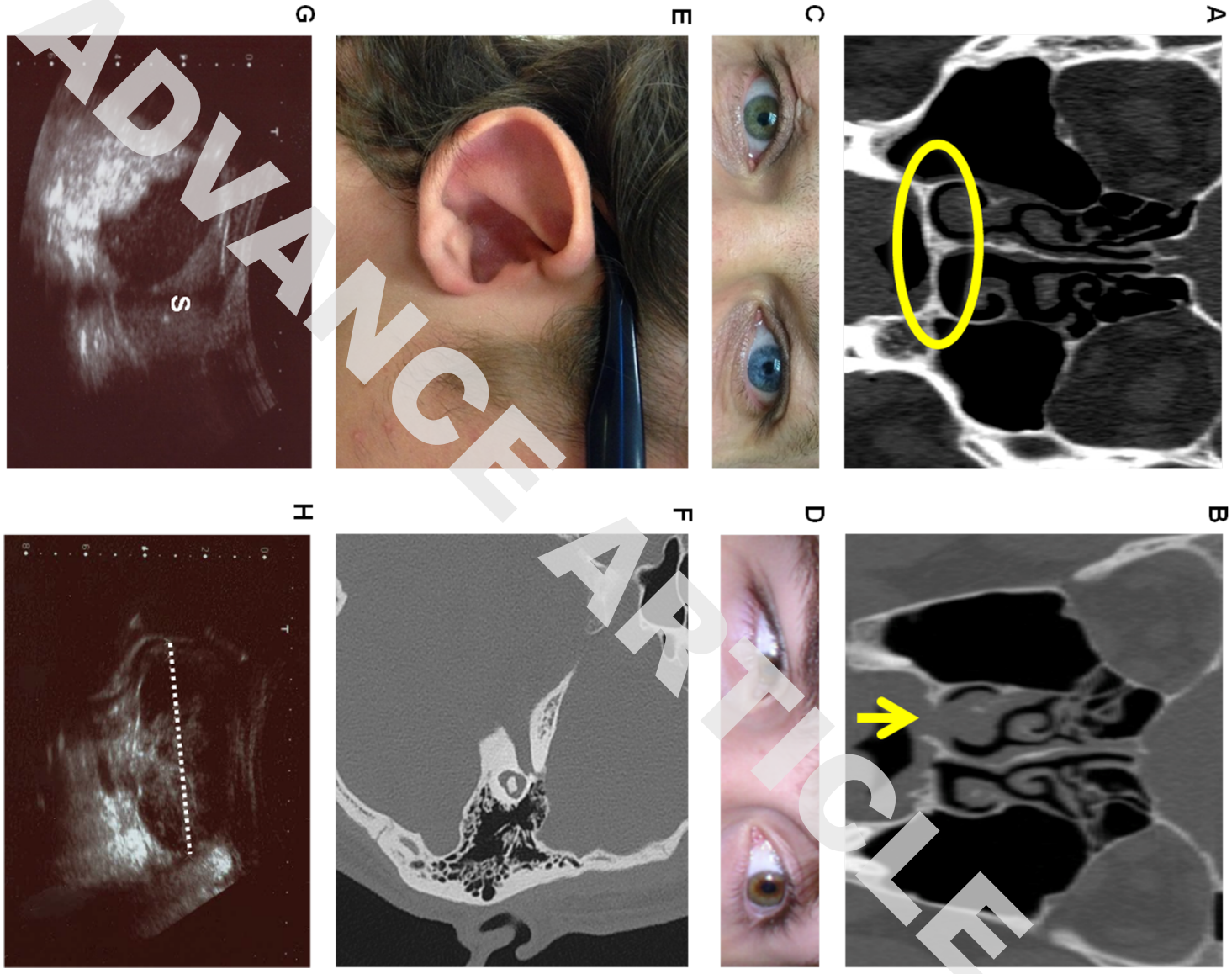
Study #	CHH (n)	nCHH (n)	KS (n)	CHH with cryptorchi-dism (n)	Median Basal TV (mL)	Median Maximal TV (mL)	Median Max. Sperm Count (10^6/mL)	Median TTS (months)	Therapy failure (persistent azoospermia) (n)	Therapies used	Pregnancies* (n)	Reference
Combined gonadotropin therapy												
1	10	8	2	NA	NA	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	Exclude	4	12	18.5	24	NA	hMG+hCG	3 (4)	(377)

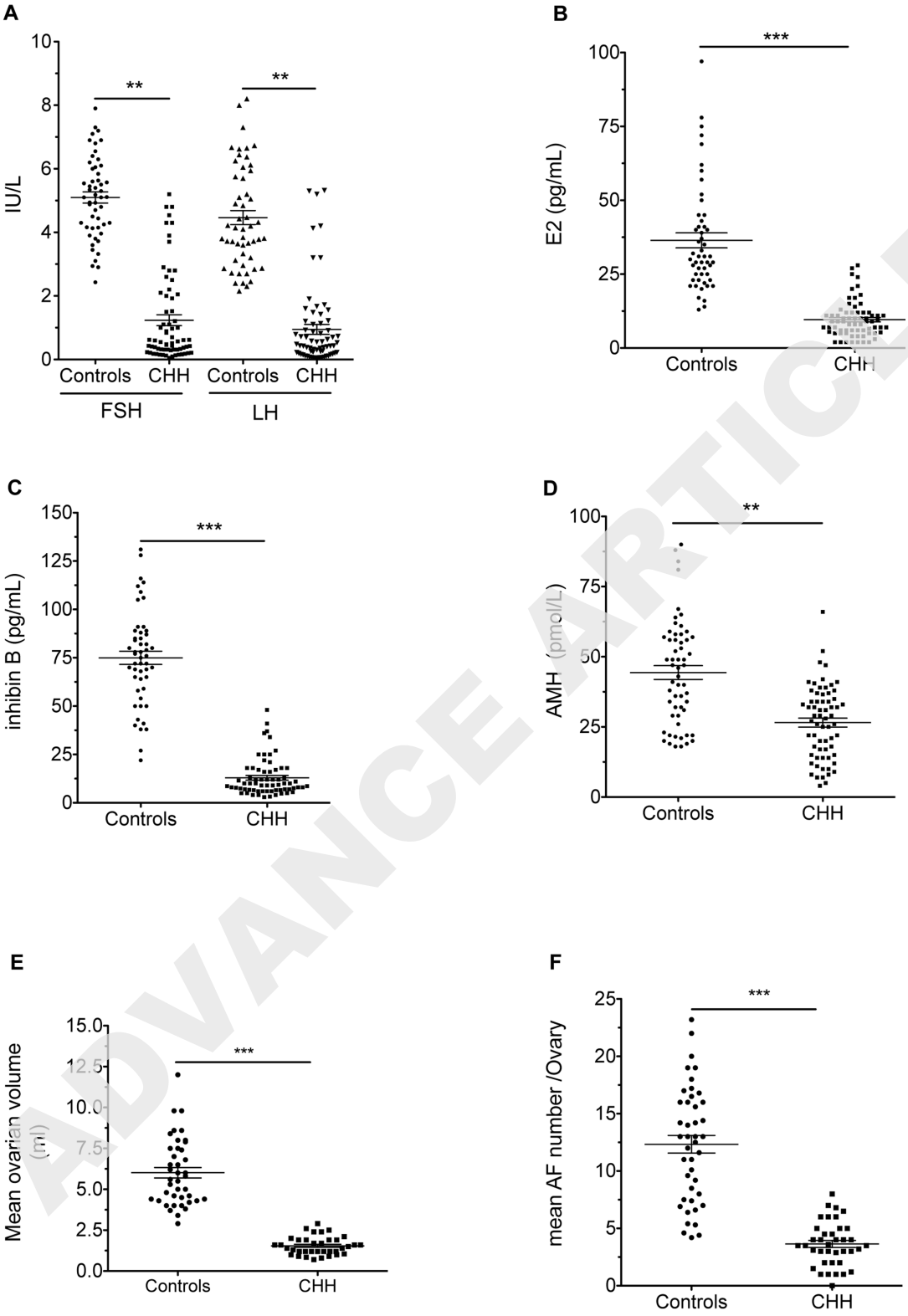
				d								
12	7	6	1	6	1.2	9	10.0	11.8	1	hMG+hCG	3	(378)
13	9	7	2	0	2.2	8	8.0	14	2	hMG+hCG	4	(379)
14	26	12	14	13	1.5	3.8	2.2	12.2	12	hMG+hCG	3	(380)
15	35	19	16	Excluded	4.3	11.1	14.0	5	12	uFSH+hCG	1 (4)	(381)
16	27	16	11	Excluded	3.6	10.5	16.5	9	3	uFSH+hCG	2 (10)	(382)
17	18	9	9	8	4.4	15.3	1.2	6	2	hMG+hCG	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)
33	38	18	20	19	2.5	16.5	15.0	55	3	rhFSH+hCG	0	(325)
Sub-Total	**899**	**515**	**358**	**158**					**190**		**181***	
Pulsatile GnRH therapy												
34	5	3	2	NA	3	4.5	4.1	3	3	GnRH	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)
Sub-Total	**219**	**95**	**89**	**55**					**38**		**36***	
Total, n	**1118**	**610**	**447**	**213**					**228**		**217***	
Mean					**3.4**	**9.8**	**7.59**	**15.3**				
Weighted mean**					**3.51**	**10.8**	**9.83**	**15.2**				

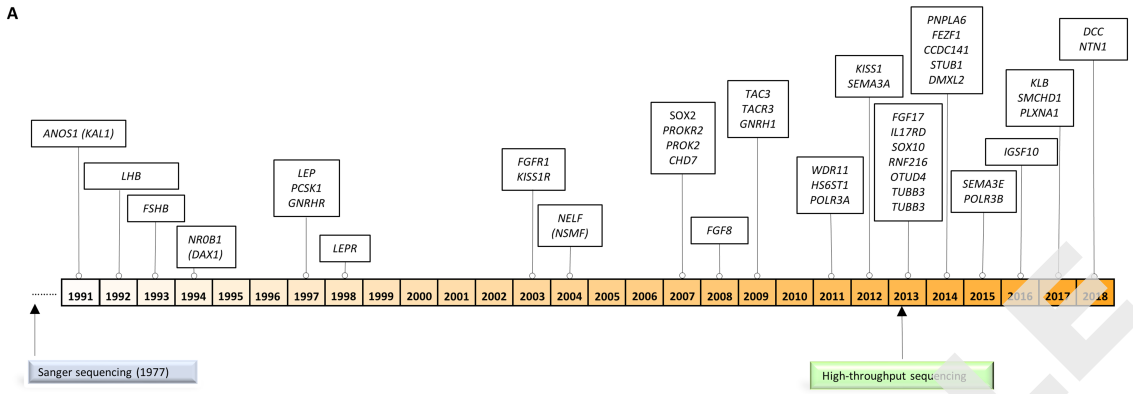
CHH: congenital hypogonadotropic hypogonadism; n= number of male CHH patients; nCHH: CHH without reported Kallmann syndrome features; KS: patients with Kallmann syndrome;
TV: mean testicular volume; TTS: time to induce sperm appearance in ejaculate (months);
Therapies used: FSH-preparations used in combination with chorionic gonadotropin (hCG): hMG: human menopausal gonadotropin (FSH+LH); uFSH: urinary highly purified FSH; rhFSH: recombinant human FSH; hPG: human pituitary gonadotropin (mixture of FSH and LH); GnRH: gonadorelin (pulsatile administration via a pump).
Excluded: CHH/KS patients with cryptorchidism excluded from the study design.
NA: not available; NC: non calculable

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.
*Pregnancies obtained (number in parentheses indicate the total number of patients treated who wished paternity).
** To underline the importance of the populations' size, we also calculate the weighted means of these medians (i.e. we calculated weighted means of 8,489.9 10^6/mL (patients x sperm count), and 10,341.4 mL (patients x testicular volumes)). The weighted means are then divided on the total number of patients whom these numbers refer (respectively 864 for the sperm count and 956 for the testicular volumes).
+, ++ and +++: data from the same study.









B

GnRH neuron fate specification

FGF8 / FGFR1
SOX2
CHD7
FGF17
IL17RD

Olfactory axon guidance GnRH neuron migration / axon projection

ANOS1 (KAL1)
PROK2 / PROKR2
SEMA3A / PLXNA1
SEMA3E
NSMF (NELF)
HS6ST1
WDR11
SOX10
FEZF1
IGSF10
DCC / NTN1
TUBB3
SMCHD1

GnRH neuron homeostasis

GNRH1
KISS1 / KISS1R
TAC3 / TACR3
LEP / LEPR
PCSK1
DXML2
KLB

Gonadotrope defect

GNRHR
NR0B1 (DAX1)
PNPLA6
POLR3B

Unclear

OTUD4
RNF216