Diagnosis and treatment options for hypogonadotropic hypogonadism in adolescents, men and women – Review of an expert meeting

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ABSTRACT

Hypogonadotropic hypogonadism (HH) may be caused in most cases by deficient production or deficient function of gonadotropin-releasing hormone (GnRH). This hormone is secreted in a pulsatile manner by hypothalamic neurons, stimulating the release of gonadotropins – luteinizing hormone (LH) and follicle stimulating hormone (FSH) – from the pituitary. Both FSH and LH activate gonadal maturation in ado-lescents and regulate fertility in adults.

In this paper we summarize the results of the presentations given and discussions held during an inter-national meeting in June 2018 in which all the authors participated. The paper discusses the physiology of the hypothalamus-pituitary-gonadal axis, induction of puberty and sexual development in adolescents with HH, and the diagnosis and treatment of HH in adult men and women.

Hypogonadotropic hypogonadism is a rare disorder with major clinical implications such as pubertal failure and infertility. Adolescents with HH should be treated with hormonal replacement therapy to allow pubertal development. Treatment with gonadotropins or pulsatile GnRH is proposed for testicular maturation in boys/men and fertility, whereas gonadotropins or pulsatile GnRH may be given to fe-males only for fertility purposes.

GnRH, administered subcutaneously in a pulsatile fashion with the aid of a portable infusion pump, is a safe and effective treatment for restoring fertility in men and women with HH. In women with polycystic ovarian syndrome (PCOS) pulsatile GnRH is less effective, but in women with hypothalamic amenorrhoea with underlying PCOS, some studies have shown that pulsatile GnRH therapy is a more successful and safer treatment for ovulation induction than gonadotropins and should therefore be the first-line therapy in these women.

Randomized controlled studies are still awaited to examine the cost-effectiveness of gonadotropins compared with pulsatile GnRH in infertile patients with HH.

KEYWORDS

Hypogonadotropic hypogonadism, Induction of puberty, Sexual development, Infertility, PCOS, GnRH, Pulsatile GnRH, Gonadotropins.

Introduction

An international meeting on hypogonadotropic hypogonadism (HH), in which all the authors participated, was held in June 2018 in Amsterdam. The meeting focused on the prevalence and clinical picture of HH, the latest treatment options, and practical experiences with respect to the treatment of HH in different patient subgroups and situations.

This paper reports the physiology of the HPG axis, the induction of puberty in adolescents with HH, and the prevalence and treatment of infertility caused by HH in men and women.

Article history

Received 14 Jan 2020 - Accepted 17 Mar 2020

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Physiology of the HPG axis

The term hypothalamic-pituitary-gonadal axis (HPG axis) refers to the hypothalamus, pituitary gland, and gonads (Figure 1). Gonadorelin or gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus by specialized hypothalamic neurons in a pulsatile manner, stimulating the release of gonadotropins — luteinizing hormone (LH) and follicle stimulating

hormone (FSH) —from the pituitary. These hormones activate gonadal function and therefore fertility [1,2,3].

During puberty, activation of the HPG axis triggers the development of secondary sex characteristics, both in boys and in girls. Interestingly, elevated levels of FSH and LH are already observed during the first six months after birth. This period is known as mini puberty. After this period, FSH and LH levels decrease and then remain low throughout childhood until puberty (Figure 2) [1,4].

In women, the most important functions of the HPG axis are the secretion of steroids, such as estradiol and progesterone, and the regulation of reproduction, through control of the ovarian and therefore uterine cycles. During most of the menstrual cycle, the ovarian hormones estradiol and progesterone act as a negative feedback loop, inhibiting the production of GnRH in the hypothalamus. Only during the preovulatory peak does estradiol exert a positive feedback loop on GnRH secretion [1,2].

In addition to changing pattern of FSH and LH secretion during life (Figure 2), there is also variation along the menstrual cycle, and even hourly episodic fluctuation. The frequency of LH pulses differs throughout the ovulatory cycle, ranging from once every 90 minutes during the early follicular phase to once per hour before ovulation and once per two/three hours after ovulation. In 1982, Clarke and Cummings demonstrated that this pulsatile secretion of FSH and LH has its origin in the pulsatile secretion of GnRH by the hypothalamus [5]. This pulsatile secretion of GnRH is essential for the normal functioning of the HPG axis [2]. Conversely, continuous, non-pulsatile stimulation of the pituitary gland prevents the normal production and secretion of gonadotropins [1,6].

Although GnRH is the key regulator of the reproductive axis, it is not the only neuronal mediator involved. It has been shown that GnRH neurons do not express the estrogen receptor alpha, which is required for sex steroid-mediated control of gonadotropin secretion [7]. The discovery of kisspeptin neurons has transformed our understanding of the neuroendocrine signals controlling the reproductive axis. Kisspeptin neurons mediate gonadal steroid negative and positive feedback.

Figure 1 The hypothalamic-pituitary-gonadal axis. The gonadotropin-releasing hormone (GnRH) neurons are shown with their intertwined and back-projecting dendrons passing to the median eminence where they form many small axon terminals that release GnRH into the median eminence portal system. The dendrons receive synaptic input all along their course to the median eminence, as represented schematically by the small synaptic spines. The GnRH decapeptide then acts on anterior pituitary gonadotrophs to control the pulsatile and, in females, surge release of gonadotropins that regulate gonadal function. In turn, gonadal steroid hormones exert feedback on the brain and pituitary gland. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Reprinted and adapted and from Herbison AE. Control of puberty onset and fertility by gonadotropin-releasing hormone neurons. Nat Rev Endocrinol. 2016; 12:454).

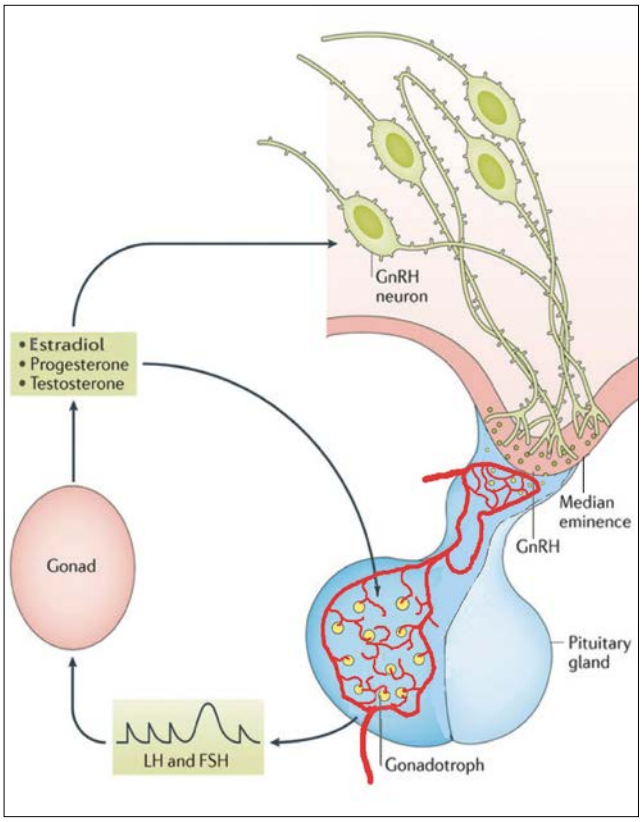
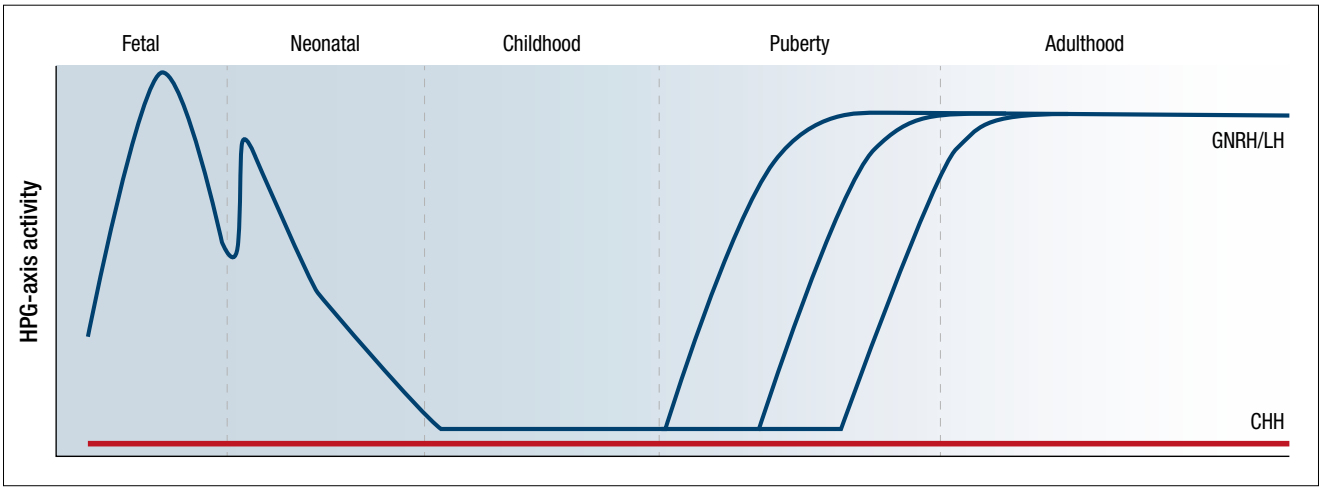


Figure 2 Activity of the HPG axis across the lifespan. Normal GnRH and LH secretion from fetal life to adulthood (blue line) compared with non-reversible CHH (red line). Abbreviations: CHH, congenital hypogonadotropic hypogonadism; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone. (Reprinted from Boehm U, Bouloux PM, Dattani MT, et al. European consensus statement on congenital hypogonadotropic hypogonadism - pathogenesis, diagnosis and treatment. Nat Rev Endocrinol. 2015;11:550).

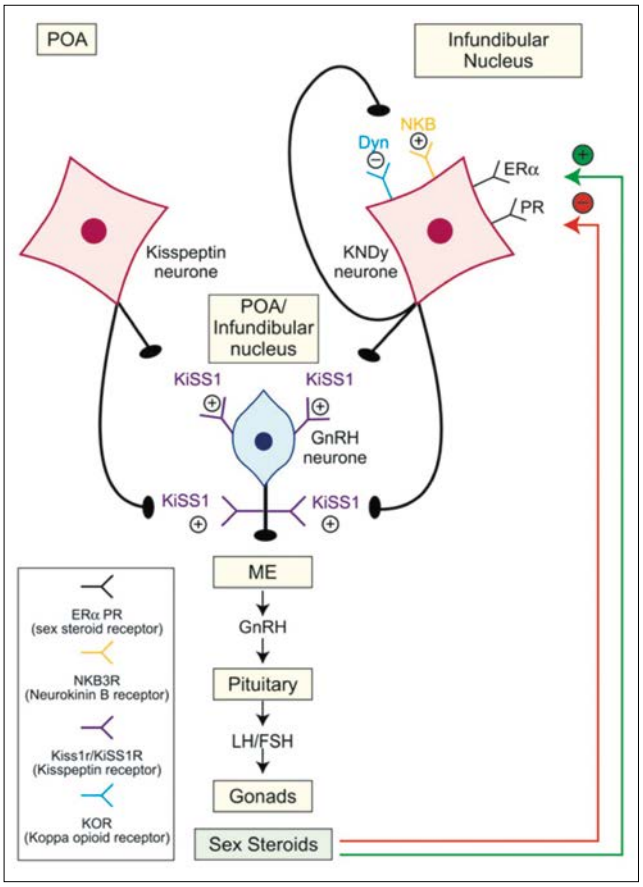


Furthermore, studies have shown that it controls the onset of puberty, and relays information regarding lipids and therefore the body's energy stores. The related discovery of the kisspeptin-neurokinin B-dynorphin (KNDy) pathway has further strengthened understanding of the modulation of GnRH secretion by endocrine, metabolic and environmental inputs [8].

Kisspeptin neurons secrete Kiss; it binds on the membrane of the GnRH neurons, which express the kisspeptin receptor KiSS1R (Figure 3). In humans, the kisspeptin neurons reside within the preoptic area (POA) and the infundibular nucleus. The kisspeptin neurons in the infundibular nucleus coexpress neurokinin B and dynorphin (KNDy neurons), which via neurokinin B receptor and kappa opioid peptide receptors autosynaptically regulate pulsatile kisspeptin secretion. Through the stimulatory effect of neurokinin B and kisspeptin, and the inhibitory action of dynorphin, these neuropeptides coordinate pulsatile GnRH and LH secretion. Negative and positive sex steroid feedback is mediated via the KNDy neurons in the infundibular nucleus (Figure 3) [8]. The role of the POA kisspeptin neurons in mediating sex steroid feedback in humans is not yet clear. Manipulation of kisspeptin signaling has the potential for novel therapies in patients with pathologically low or high LH pulsatility [8].

The functioning of the HPG axis in men is quite similar to that of the female axis. The main difference is that FSH and LH have different targets, with LH stimulating testosterone production in Leydig cells and FSH supporting spermatogenesis by stimulating Sertoli cells, which also express the androgen receptor. Although testosterone levels rise during mini puberty, no spermatogenesis occurs since, in this period of life, the androgen receptors are not yet present in Sertoli cells [9].

Figure 3 Schematic diagram showing the neuroanatomy of the kisspeptin-GnRH pathway and the control of the HPG axis in humans. ME: median eminence; +: stimulatory; -: inhibitory; ERα: estrogen receptor alpha; PR: progesterone receptor; Kiss1/KiSS1: kisspeptin; NKB: neurokinin B; Dyn: dynorphin; POA: preoptic area. (Reprinted from Skorupskaite K, George JT, Anderson RA. The kisspeptin-GnRH pathway in human reproductive health and disease. Hum Reprod Update. 2014;20:487).



Induction of puberty and sexual development in adolescents with HH

The onset of puberty is triggered by the pulsatile production of GnRH in the hypothalamus and subsequent HPG activity [10]. Clinically, pubertal onset is defined by Tanner II breast development in girls and testicular growth (volume > 3 ml) in boys. Within the European population, delayed puberty is defined either by absent pubertal onset at 13 (girls) or 14 (boys) years of age, or by absent menarche at the age of 15 years in adolescent girls, or absent growth spurt at the age of 16 in boys [11]. There are four main causes of delayed puberty [12]:

- constitutional delay of growth and puberty (CDGP), which is the most common cause both in boys (63%) and in girls (30%);
- hypergonadotropic hypogonadism, characterized by elevated levels of LH and FSH secondary to gonadal failure;
- congenital hypogonadotropic hypogonadism (CHH), characterized by low levels of LH and FSH caused by hypothalamic and/or pituitary disorders;
- transient or functional hypogonadotropic hypogonadism (FHH), in which pubertal delay is caused by delayed maturation of the HPG axis secondary to an underlying condition.

Distinguishing between CHH and CDGP remains a challenge, because there is, as yet, no gold standard test to differentiate between the two. CDGP can be considered as the extreme end of the spectrum of normal pubertal timing and it is characterized by very delayed spontaneous onset of puberty. CDGP is a diagnosis by exclusion, which can be made after exclusion of pathological causes of delayed puberty. Family history is a critical part of the evaluation, because it can provide clues for the correct diagnosis [11,12].

In most cases of CHH there is no GnRH production and consequently both mini puberty and full puberty fail to occur (Figure 2). Clinically, a micropenis and bilateral cryptorchidism are symptomatic for CHH. The absence of GnRH during adolescence leads to lack of virilization in boys, resulting in small testicular volume, azoospermia and very low levels of testosterone and gonadotropins.

Diagnosis and treatment of newborn boys is becoming an increasingly important issue, the aim being to treat the lack of mini puberty as soon as possible. Neonatal treatment corrects genital hypotrophy and improves testicular endocrine function, which might improve the response to treatments intended to induce post-pubertal virilization and to restore fertility in men with CHH.

Long-term studies are needed to assess the effect of this approach on sexuality and fertility before recommending its routine use [13].

In girls, the absence of GnRH during adolescence leads to absent breast development and primary amenorrhea. Estradiol levels are low, with low or normal but inappropriate gonadotropin levels, and normal prolactin. About 25% of CHH patients have a partial GnRH deficiency with some pubertal development, which sometimes makes the condition difficult to diagnose [4].

- In both boys and girls, early diagnosis is important to allow timely initiation of treatment in order to promote the development of secondary sexual characteristics and growth, but also in order to induce gonadal maturation for future fertility [4,10].
- In boys, testosterone is an effective treatment to initiate virilization, psychological maturation, growth spurt, and increasing bone mass, but for the induction of testicular maturation pulsatile GnRH or gonadotropin treatment is needed [10,13].
- It is probably important to induce testicular maturation as early as during adolescence in order to improve future spermatogenesis. This type of treatment will take an average of two years and can be challenging for these patients during adolescence [4,10]. As soon as maturation of the testis is accomplished, one may switch back to testosterone replacement therapy until the patient wishes to become fertile.
- In CHH girls, hormonal replacement therapy during puberty should be prescribed in order to induce feminization (i.e. breast development), to stimulate the development of the uterus for future pregnancy, to increase final height and promote bone health, and to improve psychological and overall well-being [10]. At the meeting it was recommended that these girls could have one or two treatment cycles with pulsatile GnRH during puberty, just for reassurance to show them that they are capable of ovulating with proper treatment (Oral communication N. Pitteloud, June 12, 2018). When the patient desires to become pregnant later on, treatment with GnRH pump or second-line gonadotropin therapy should be given in order to stimulate the ovarian follicles and induce ovulation [10].

Diagnosis and treatment of hypogonadotropic hypogonadism in men

In adults, HH is less frequently congenital and most cases are acquired. Two types of CHH can be distinguished: anosmic HH (Kallmann syndrome) and normosmic isolated or idiopathic HH. The prevalence of CHH in men is approximately 1:10,000, of which 2/3 cases are caused by Kallmann syndrome and 1/3 by idiopathic hypogonadotropic hypogonadism (IHH). Acquired HH can be caused by tumors of the hypothalamic-pituitary region, infiltrative or infectious pituitary lesions, hyperprolactinemia, brain trauma or brain radiation. Both IHH and Kallmann syndrome are very heterogeneous disorders.

- During the diagnostic work-up of HH, it is necessary to exclude pituitary diseases with magnetic resonance imaging. In cases of CHH, genetic counseling should be performed before starting fertility treatment.
- Hypogonadism as such can be treated with testosterone to achieve virilization. However, for achieving fertility, temporary treatment with gonadotropins or pulsatile GnRH is required [14].

In a retrospective study carried out in 2013, it was shown that in patients with a pituitary disorder spermatogenesis is achieved in 100% of cases through the administration of gonadotropins, while treatment with either gonadotropins or GnRH in patients diagnosed with a hypothalamic disorder will induce spermatogenesis in only 80% of all cases [15]. This difference is explained by the increased history of maldescensus testis (MT) or cryptorchidism among patients with a hypothalamic disorder; in fact, MT has a negative impact on spermatogenesis and – as a consequence – on the achievement of pregnancy [14]. Another finding in this study was that treatment with gonadotropins given in adolescence increases the success rate of treatment later in life. This is presumably related to testis volume [14]. In comparison with gonadotropins, treatment with pulsatile GnRH is a more physiological approach and it is speculated that the consequential pulsatility of LH and FSH is essential to achieve secretion of testosterone and production of sperm. In a cohort study by Mao et al., it was demonstrated that pulsatile GnRH treatment was associated with earlier spermatogenesis than gonadotropin treatment.

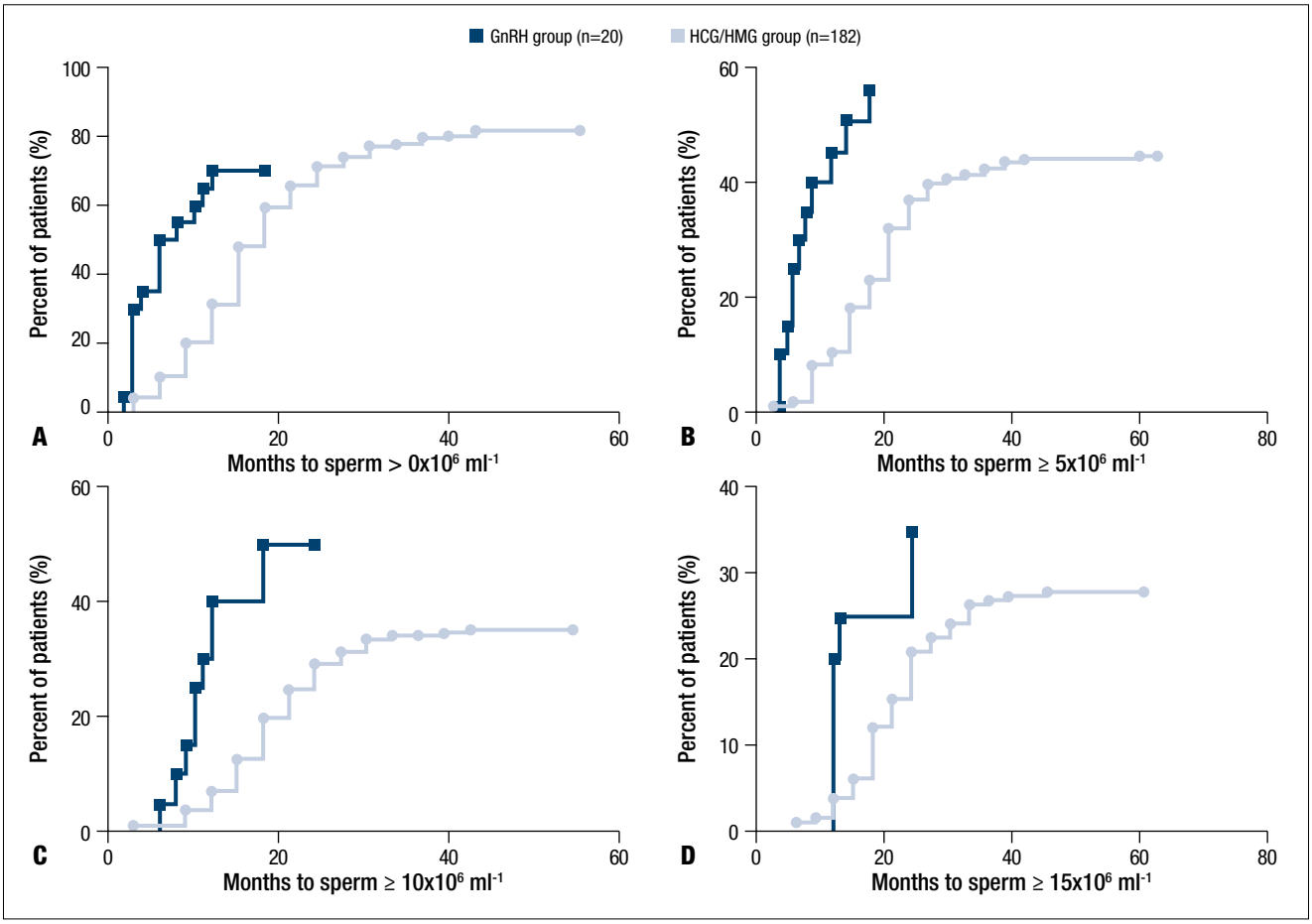
Furthermore, patients with pulsatile GnRH took less time to achieve higher sperm concentrations and had a larger testicular size. In this study, the median time until the first sperm detection was 6 months in the GnRH group versus 18 months in the human chorionic gonadotropin/human menopausal gonadotropin (hCG/hMG) group ($P < 0.001$) (Figure 4a). The delay to achieve sperm concentrations $\geq 5 \times 10^6$ ml^{-1} was 14 months (95% CI: 5.8-22.2) in the GnRH group versus 27 months (95% CI: 18.9-35.1) ($P < 0.001$) in the hCG/hMG group (Figure 4b) [16]. Further (randomized) research is needed to explore whether these findings lead to shorter times to pregnancy and higher pregnancy rates.

In current clinical practice treatment usually starts with a dose of 5-10 µg per pulse per 90-120 minutes and is then adapted according to LH and FSH serum levels (target value: 5-10 IU/l), testosterone levels, testicular growth, and initiation of spermatogenesis. If it is necessary to increase the dose, this needs to be done by steps of 5-10 µg up to a maximum of 25 µg/pulse/90 minutes, and if this still is not sufficient, the interval may be shortened to 60 minutes [16]. In CHH patients with severe GnRH deficiency, fertility outcome can be enhanced by pre-treatment with recombinant FSH (rFSH) for two months [10]. In fact, this could have the effect of compensating for the lack of mini puberty, a period during which FSH prepares the Sertoli cells for spermatogenesis later on in life.

CHH may be reversible. Indeed, discontinuation of androgen replacement therapy, in 10% of patients, may lead to a sustained reversal of HH [17]. This phenomenon can be masked by continuous hormonal replacement therapy [10].

- It is recommended to explore reversibility in every patient by withdrawing the hormonal treatment when patients achieve full virilization, and to repeat this every two years [10].

Figure 4 Time to achieve sperm concentration thresholds > 0, ≥ 5, ≥ 10 and ≥ 15 × 10^6 ml^{-1} (Kaplan–Meier analysis). (a) Percentage of patients in each group (GnRH group, n = 20; and HCG/HMG group, n = 182) to achieve sperm concentration > 0 × 10^6 ml^{-1} (P < 0.001). (b) Percentage of patients in each group to achieve sperm concentration ≥ 5 × 10^6 ml^{-1} (P < 0.001). (c) Percentage of patients in each group to achieve sperm concentration ≥ 10 × 10^6 ml^{-1}. (d) Percentage of patients in each group to achieve sperm concentration ≥ 15 × 10^6 ml^{-1}; GnRH, gonadotropin-releasing hormone; HCG/HMG, human chorionic gonadotropin/human menopausal gonadotropin. (Reprinted from Mao J, Liu Z, Nie M, et al. Pulsatile gonadotropin-releasing hormone therapy is associated with earlier spermatogenesis compared to com-bined gonadotropin therapy in patients with congenital hypogonadotropic hypogonadism. Asian J Androl. 2017;19:682).



Prevalence and treatment of infertility in women with HH

In women, one important function of the HPG axis is the regulation of reproduction, through control of ovulation and endometrial proliferation and differentiation.

Ovulatory disorders are classified in three groups (WHO classification) [18]:

- **Group I** anovulatory condition (10%) includes HH, which is characterized by low estradiol and low gonadotropins.
- **Group II** ovulation disorders (80%). FSH, LH and estradiol levels are normal. Most type II anovulation disorders are polycystic ovary syndrome (PCOS).
- **Group III** ovulation disorders (10%) are caused by ovarian failure. FSH and LH levels are higher than 25 IU/L and estradiol levels are low [19].

Typically, women in group I present with amenorrhea (primary or secondary). Functional hypothalamic amenorrhea (FHA) is characterized by hormonal dysregulation without any organic cause identified. It may be due to stress and/or low energy availability as a result of decreased caloric intake, excessive exercise, or both. FHA accounts for 14% of primary amenorrhea and 34% of secondary amenorrhea [20]. A recent systematic review of 35 articles (including 1,002 patients) dealing with the results of GnRH in ovulation induction showed that treatment with GnRH resulted in 80-100% ovulation, with an average of 85%. The birth rate was between 20 and 40% per cycle. There was no substantial difference in ovulation rate between women with primary or secondary amenorrhea [21].

One of the advantages of treatment with pulsatile GnRH compared with gonadotropins is the lower risk of multiple pregnancies (Table 1) [22]. In the above-mentioned systematic review, the risk of multiple pregnancies in patients treated with pulsatile GnRH was 0% in most of the studies, with an average of 3-4% [21]. Other advantages of treatment with pulsatile GnRH are a lower risk of ovarian hyperstimulation syndrome, the fact that it is not necessary to trigger an LH surge, and the fact that it requires only once-a-month monitoring of the patient [22]. The luteal phase needs to be supported by progesterone, hCG or GnRH pump treatment.

These findings were confirmed in a large multicenter retro-

Table 1 Summary of published studies evaluating pulsatile GnRH in patients with World Health Organization (WHO) type 1 anovulatory disorders.

Authors	Patients	Cycles	Ovulation/cycle	Pregnancy/cycle	Multiple pregnancy	Cumulative
Berg et al., 1983	27	40	80%	28%	0%	Not reported
Liu & Yen, 1984	17	22	86%	41%	Not reported	Not reported
Santoro et al., 1986	7	20	100%	93%	16.7%	Not reported
Blunt & Butt	28	84	100%	33%	10%	57% median of three cycles
Jansen et al., 1987	27	79	97%	34%	16.7%	88%/six cycles
Homburg et al., 1989	118	434	70%	23%	8.8%	93%/6 months
Filicori et al., 1991	63	105	91%	25%	11%	Not reported
Braat et al., 1991	34	112	90%	26%	14%	100%/12 months
Martin et al., 1993	41	118	93%	29%	8.3%	96%/6 months
Filicori et al., 1994	140	168	81%	20%	5.5%	Not reported
Skarin et al., 1994	30	96	90%	30%	4.5%	Not reported
Kesrouani et al., 2001	24	44	100%	46%	0%	83%/18 months
Christin-Maitre et al., 2007	248	829	Not reported	25%	8.8%	71%/3 years' time span evaluation
Total	**804**	**2151**	**70-100%**	**20-93%**	**0-16.7%**	

Data from table 14.3 in: Lambalk CB. Treatment of WHO 1: GnRH or gonadotropins? In: Cohlen B, Van Santbrink E, Laven J, eds. Ovulation Induction – Evidence based guidelines for daily practice. Boca Raton: CRC Press; 2017:83. doi.org/10.1201/9781315381459 (references to the publications listed in this table can be found in the original article) Reprinted and adapted

spective study in France. The pregnancy rate per cycle was 25% and the mean number of cycles to get pregnant was 2.8, which is of interest from a cost-effectiveness perspective. The cumulative pregnancy rate was 71.4%. The rate of miscarriages was low (8.2%), as was the rate of multiple pregnancies (8.8%) [23].

- In women with HA, pulsatile GnRH therapy is an effective treatment to induce ovulation and pregnancy [23].

Standard pulsatile GnRH pump treatment starts with a dose of 10 µg GnRH/pulse/90 minutes. According to follicle growth, the dose can be increased by steps of 5 µg up to a maximum of 20 µg. If necessary, the interval may be lengthened to 120 minutes. Every treatment cycle takes 2-4 weeks, depending on the ovarian response and the choice of luteal support.

Subgroup of women with FHA and underlying PCOS

Polycystic ovary syndrome is the most common cause of chronic anovulation, infertility and hyperandrogenism and it affects 6-20% of women of reproductive age. In some cases, FHA can occur in women with PCOS. A negative energy balance may negatively affect GnRH release and reduce the insulin and IGF-1 concentrations. As a consequence, ovarian hyperandrogenism may be masked, giving rise to a new subgroup of anovulatory women with FHA and underlying PCOS. FHA-PCOS women form a significant subgroup (33%) of women with FHA. Over time, these patients may fluctuate between symptoms of FHA and of PCOS, depending on the status of their hypothalamic function and their body weight [24,25].

The diagnosis of FHA-PCOS is essentially based on a good anamnestic investigation as well as a thorough assessment of weight, body mass index, clinical hypometabolism symptoms, and clinical hyper-androgenism. The clinical history often reveals clinical and/or biological hyperandrogenism before the appearance of the FHA gonadotropin deficiency.

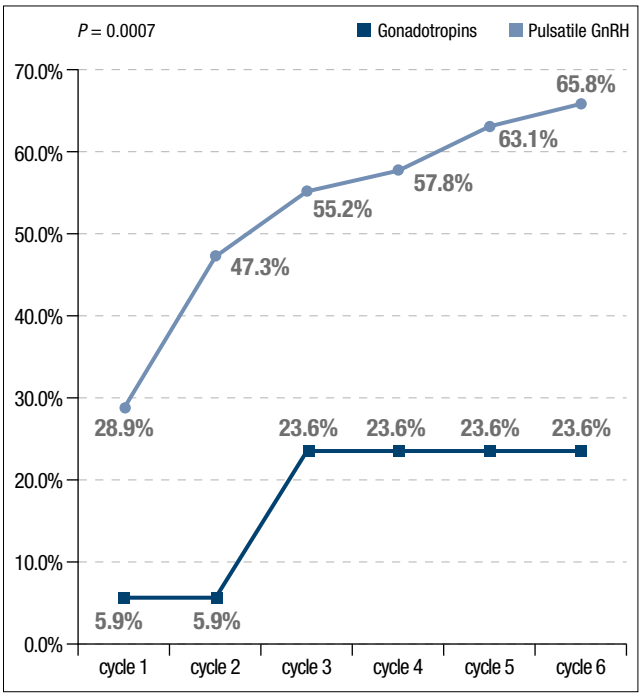
Although the diagnostic criteria of PCOS have been defined by the Rotterdam criteria [26], additional typical findings in these women are normal FSH serum levels together with fluctuating LH serum levels, ranging from low to slightly elevated, depending on the degree of GnRH suppression. Other

findings are low to normal levels of estradiol and normal levels of androgens and prolactin. The most useful diagnostic tool is the serum level of anti-Müllerian hormone (AMH). AMH is strongly correlated with the ovarian antral follicle count and therefore a marker of PCOS: FHA-PCOS women show a higher AMH level compared with women affected by FHA alone. Assessment of ovarian morphology with ultrasound is also a very good tool for differentiating between FHA and FHA-PCOS [27,28]. FHA-PCOS women have a higher baseline ovarian volume compared with women with FHA and normal ovaries. Moreover, on ultrasound FHA-PCOS women have more than 10 small-sized (2-9 mm) follicles per ovary [29].

In a prospective randomized comparison between treatment with pulsatile GnRH and treatment with gonadotropins in FHA-PCOS women with a history of failed ovulation induction with clomiphene citrate, letrozole or gonadotropins, a clinical ongoing pregnancy rate of 46.6% was shown in the GnRH group versus 0.0% in the gonadotropins group. There were no multiple pregnancies and no miscarriages in the GnRH group. The authors also concluded that the starting dose in GnRH treatment should be reduced (5 µg/pulse is recommended) in order to prevent multiple follicular growth in such patients [30].

In a retrospective study by Dumont and coworkers, it was shown that pulsatile GnRH therapy is a more successful and safer treatment for ovulation induction than gonadotropins in this subgroup of patients. Although this was not a randomized study, the ovulation rate was higher with GnRH than with gonadotropins, respectively 78.6% versus 56.6% (p=0.005); furthermore, the pregnancy rates were higher with the GnRH therapy, i.e. both the pregnancy rate per initiated cycle (26.9% versus 7.6%, p=0.005) and the pregnancy rate per patient (65.8% versus 23.6%, p=0.007) (Figure 5) [28].

Figure 5 Cumulative ongoing pregnancy rates per patient. Comparison between pulsatile GnRH therapy and gonadotropins for ovulation induction in women with both functional hypothalamic amenorrhea and polycystic ovarian morphology. (Reprinted from Dumont A, Dewailly D, Plouvier P, Catteau-Jonard S, Robin G. Comparison between pulsatile GnRH therapy and gonadotropins for ovulation induction in women with both functional hypothalamic amenorrhea and polycystic ovarian morphology. Gynecol Endocrinol. 2016;32:1002).



- In selecting the best ovulation induction treatment for women with FHA and underlying PCOS, the status of their hypothalamic function is decisive, rather than their ovarian status [30].
- In women with PCOS, the first-line treatment for ovulation induction is clomiphene citrate or letrozole (off-label). The recommended second-line treatment is gonadotropins using the chronic low-dose step-up protocol to prevent multiple follicle recruitment.
- In women with FHA and PCOS, pulsatile GnRH therapy is a more successful and safer treatment for ovulation induction than gonadotropins, and should therefore be the first-line therapy in FHA-PCOS women [28,30].

Conclusions

Hypogonadotropic hypogonadism is not a frequent disorder but it is one that may have major implications for the patient, such as absence of puberty and infertility. Various treatment options are available.

Adolescents with HH should be treated with hormonal replacement therapy to initiate puberty. Treatment with gonadotropins or pulsatile GnRH is proposed for testicular maturation in boys/men, whereas gonadotropins or pulsatile GnRH may be given to females only to reverse infertility.

GnRH administered subcutaneously in a pulsatile fashion with the aid of a portable pump is a safe and effective treatment in adolescents and adult men and women with HH.

In women with PCOS pulsatile GnRH is less effective, but in women with hypothalamic amenorrhoea associated with PCOS, pulsatile GnRH therapy is a more successful and a safer treatment for ovulation induction than gonadotropins and should therefore be the first-line therapy in these women.

Randomized controlled studies should be performed to compare the cost-effectiveness of treatment with pulsatile GnRH and with gonadotropins in infertile women diagnosed with HH.

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Conflict of interest: *The authors SC-M, MZ, CL, NP, SD, TH and HJO all gave a presentation during the European masterclass on hypogonadotropic hypogonadism, organized by Ferring B.V. (EC) on June 12th, 2018. CDG chaired the meeting. EC and HJO are employees of Ferring.*

Acknowledgements: *Joep Paulides, MSc, took minutes of the expert meeting and is the medical writer of the review. He received financial compensation from Ferring B.V. for his medical writing activities involved in this publication.*