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REVIEW ARTICLE

Gonadotropin Treatment for the Male Hypogonadotropic Hypogonadism

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Abstract: Hypogonadotropic hypogonadism (HH) is caused by a dysfunction in the hypothalamus and/or the pituitary gland and it can be congenital or acquired. This condition is biochemically characterized by low or inappropriately normal gonadotropin levels along with low total testosterone levels. If fertility is not an issue, testosterone therapy is the treatment of choice to induce and maintain secondary sexual characteristics and sexual function. Spermatogenesis is frequently impaired in patients with HH, but usually responsive to hormonal therapy such as gonadotropin therapy or GnRH supplementary/replacement therapy. When gonadotropins are the choice of treatment, conventional therapy includes human chorionic gonadotropin (hCG) along with different FSH formulations: human menopausal gonadotropins (hMG), highly purified urinary FSH preparations (hpFSH) (e.g., urofollitropin) or recombinant FSH (rFSH). The combination of FSH and hCG demonstrated to be associated with better outcomes than single compounds, whereas similar results were obtained with different FSH preparations in male individuals; both regarding the ability to stimulate spermatogenesis and eventually inducing physiology pregnancy. Gonadotropins can be administered either subcutaneously or intramuscularly. The combination therapy with hCG and FSH for a period of 12-24 months was found to promote testicular growth in almost all patients, spermatogenesis in approximately 80% and pregnancy rates in the range of 50%. Gynecomastia is the most common side effect of gonadotropin therapy and is due to hCG stimulation of aromatase causing increased secretion of estradiol. The therapeutic success is higher in patients with post-pubertal HH, in those without previously undescended testes, in patients with higher baseline testicular volume, who underwent repeated cycles of therapy and in patients with higher baseline inhibin B serum concentrations. Reversal of hypogonadism can occur in up to 10% of patients but its physiopathologic mechanism has yet to be elucidated. In conclusion, gonadotropin therapy is effective in promoting puberty and in supporting spermatogenesis onset and preservation in HH patients with either hypothalamic or pituitary conditions.

Keywords: Gonadotropin, male hypogonadotropic hypogonadism, infertility, FSH, hCG.

1. INTRODUCTION AND BACKGROUND

The hypothalamic–pituitary–gonadal (HPG) axis is essential in a number of processes related to the development, maturation and aging of the male [1]. Through a pulsatile secretion of gonadotropin-releasing hormone (GnRH), the hypothalamus stimulates the biosynthesis of gonadotropins — namely, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) — which is controlled by extremely sophisticated positive and negative feedbacks. Of gonadotropins, LH stimulates testicular endocrine function by activating Leydig cells hosted in the interstitial space of the testicle, with a consequent activity in terms of male genital development and differentiation, throughout human sexual determination [2]. Instead, FSH sustains testicular exocrine function led by Sertoli cells through spermatogenesis. Both testosterone synthesis and male fertility result from the delicate coordination throughout the HPG axis, thus assuring normal testicular function. In this context, congenital or acquired disturbances at any level of the HPG axis can lead to an impairment of reproductive function and the clinical syndrome of hypogonadism.

Hypogonadism can be caused by a primary testicular pathology (i.e., primary hypogonadism, otherwise known as hypergonadotropic hypogonadism) resulting from a malfunction at the level of the testes themselves. On the contrary, hypothalamic and/or pituitary failures are responsible for secondary hypogonadism (also called central hypogonadism or hypogonadotropic hypogonadism), which is most often caused by genetic defects, neoplasm or infiltrative disorders [3]. More recently, Grossmann & Matsumoto [4] proposed a classification of male hypogonadism based on the distinction between functional and organic hypogonadism. Accordingly, functional hypogonadism relies on the absence of any recognized organic alterations in the HPG axis and should be treated, firstly, just by resolving or improving the associated comorbidities. On the contrary, organic hypogonadism is characterized by any proven pathology affecting the HPG axis and should be treated with conventional medications (i.e., gonadotropins or testosterone, accordingly) [4].

This narrative review is devoted to discussing the topic of gonadotropin treatment for infertile males with hypogonadotropic hypogonadism (HH).

2. METHODS

2.1. Search Strategy

A literature search for English-language original and review articles either published or e-published up to May 2019 was performed using Google and the National Library of Medicine's PubMed database. The Mesh terms used for the search were: hypogonadotropic hypogonadism; gonadotropin; testosterone; therapy;

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treatment. The retrieved articles were gathered and examined. Reference lists of retrieved articles as well as relevant review articles were also studied.

2.2. Exclusion Criteria

The exclusion criteria were as follows: 1) reviews or editor letters and single case report; 2) non-English language publications; 3) studies with insufficient or unconfirmed information; and, 4) studies not involving infertile men.

3. RESULTS

The first section of the review focuses on a clinical evaluation of the different categories of male HH. Effectiveness of different gonadotropin preparations for HH was the focus of the second part of the manuscript, principally reporting key aspects/differences among human chorionic gonadotropin (hCG) along with different FSH formulations, including human menopausal gonadotropins; highly purified urinary FSH preparations; and, recombinant FSH as for published data. The third section of the manuscript discusses factors influencing treatment efficacy and hypogonadism reversal. Gonadotropin treatment for male idiopathic infertility is the key issue discussed throughout the last section of the review.

3.1. Evidence Synthesis

Male Hypogonadotropic Hypogonadism. As detailed, HH is a condition caused by a dysfunction in the hypothalamus and/or the pituitary gland; as an epiphenomenon, HH is biochemically characterized by low or inappropriately normal gonadotropin levels along with low total testosterone levels. Moreover, spermatogenesis is impaired, but usually responsive to hormonal therapy.

Hypogonadotropic hypogonadism can be either congenital or acquired (Table **1**). Congenital forms typically present with low GnRH and/or gonadotropin levels with the rest of the HPG axis intact. Congenital forms of HH may occur throughout the life of male individuals, but they are rare; isolated congenital HH, for instance, has a global prevalence of 1 case per 4,000–10,000 boys [5], and represents about 10% of delayed puberty cases [3].

The Kallmann syndrome is a paradigmatic example of the congenital forms of HH and accounts for almost 60% of these forms. Kallmann syndrome has been recognized to be familial (X-linked, autosomal dominant or autosomal recessive) or sporadic [6]. Along with HH, patients with Kallmann syndrome may also present with hypo-anosmia and potentially a number of phenotypic malformations, including midline defects, unilateral renal agenesis, bimanual synkinesia, syndactyly and dental agenesis [5]. Overall, most patients with HH/Kallmann syndrome respond to exogenous GnRH, pointing to a deficiency of endogenous GnRH as the important feature of their pathology [7]. Combined congenital HH may result from a wide variety of genetic conditions, with characteristics of other deficiencies of multiple pituitary hormones resulting from mutations of rare genes that encode proteins involved in the HPG axis (e.g., HESX1, PROP1, LHX3 and LHX4) [3].

Conversely, acquired HH could result from infrequent conditions, thus including intracranial masses (e.g., craniopharyngioma) or infiltrative diseases (such as Langerhans cell histiocytosis), with a reported incidence of <5.0 per 1,000,000 per year; of clinical relevance, this condition has a twofold higher prevalence during childhood than adulthood [8], mostly delaying normal pubertal onset or progression. Other causes of acquired HH are more typical in adults (Table **1**).

Infertility is a relatively common condition, affecting nearly 15% of couples worldwide [9-11]; overall, male factors account for approximately half of the cases. Regardless of the underlying etiology, HH is one of the few causes of male infertility that eventually can effectively benefit from medical therapy. Indeed, either gonadotropin therapy or GnRH supplementary/replacement therapy actually improves spermatogenesis and androgenization [3,11-13].

Table 1. Causes of hypogonadotropic hypogonadism.

Congenital causes

- Kallman syndrome
- Idiopathic secondary hypogonadism

Acquired causes

- Hyperprolactinaemia
- Pituitary dysfunction (e.g., tumour, surgery, trauma, infections or infiltrative diseases)
- Hypothalamic dysfunction (e.g., tumours or intracranial masses**)**
- Chronic conditions (e.g., type 2 diabetes mellitus, haemochromatosis, hepatic steatosis and cirrhosis or coronary artery disease)
- Drug use (i.e., glucocorticoid, opioids, androgen, progestins, oestrogens or gonadotropin-releasing hormone analogs)
- Obesity
- Eating disorders (e.g., malnutrition, wasting or anorexia nervosa)
- Excessive exercise
- Older age (with associated comorbidities)

3.2. Treatment

In general, HH is characterized by low or inappropriately normal gonadotropin levels, and, therefore, the rationale is to substitute the gonadotropin deficiency with FSH and LH, if fertility is desired. In adulthood, fertility can also be induced using GnRH administered in a pulsatile manner, but this treatment is not widely available. Conversely, the use of antiestrogens is useless and even contraindicated in these subjects [3].

If fertility is not an issue, testosterone therapy (TTh) is advised. In this context, TTh for congenital forms of hypogonadism must be life-long, and management of acquired causes depends on whether the condition is permanent or can be resolved. In contrast to TTh for congenital forms of hypogonadism, TTh of LOH is still controversial, because of unclear indications for replacement and potential risks in older individuals, which have been widely and often harshly debated, without a definitive conclusion.

Overall, although the therapy is effective, as well as "on label" and scientifically recommended by most scientific societies, including the European Association of Urology (EAU) [14], the choice about the most appropriate treatment at a specific time in individuals with HH should be based upon an informed and comprehensive discussion between the patient and the physician. In this context, androgen therapy, in the form of exogenous testosterone replacement or induction of endogenous testosterone production by human chorionic gonadotropin (hCG) is necessary for all HH patients. Indeed, androgens are responsible for virilization and sexual functioning in men, but no data would suggest a role even for adequate maintenance of muscle and bone mass, and even for normal mood and cognition [3][15][16][17]. In adolescence and adulthood, male patients with HH typically seek medical attention for absent or minimal virilization, low libido, and erectile dysfunction [18]. Male patients with HH reported a higher incidence of sexual dysfunction, anxiety, depression, and a poorer quality of life, as compared to eugonadal controls [19].

Testosterone is the first choice of treatment to induce and maintain secondary sexual characteristics and sexual function in men with hypogonadism [3]. Testosterone therapy can improve not only the sexual function but also the mental health and quality of life of patients with HH [19]. Studies have also looked at the role of hCG therapy in men with HH, and it has been shown to improve

hypogonadal symptoms and have favorable effects on body composition (increased fat-free mass and lower fat mass), lipid profile (lower total cholesterol, low-density lipoprotein cholesterol, and triglycerides) and bone formation [20]. Conversely, other authors failed to find any significant improvements in erectile function after hCG treatment for HH [21,22].

Of primary clinical importance, TTh is not indicated to restore fertility. Therefore, induction of gonadotropin secretion by pulsatile GnRH or exogenous gonadotropins is necessary for patients, for whom fertility is the treatment goal [18].

3.3. Induction of Spermatogenesis

From the early 1970s, several studies dealing with fertility promotion and preservation in HH patients have been published. As discussed, irrespective of etiology, HH is one of the few causes of male infertility effectively treatable with hormone replacement; in that aim, both gonadotropin therapy and GnRH may induce the appearance of sperm in the ejaculate [23,24] and ultimately restore fertility in men with HH [18]. Overall, the vast majority of patients (>80%) have been treated with subcutaneous combined gonadotropin injections [18,11,25]. Indeed, although pulsatile GnRH is an effective therapy to induce spermatogenesis in the absence of pituitary defect, the preferential use of gonadotropins may indicate that GnRH therapy is not available in every country, and that this therapy is expensive and likely less comfortable than gonadotropin injections given the long period (i.e., 1 to 3 years) needed to promote testicular maturation [18]. When gonadotropins are the choice of treatment, FSH preparations along with a pharmacological compound to stimulate intratesticular testosterone production by the Leydig cells are usually required. Since there is a lack of LH preparations currently approved for male HH, generally patients are treated with hCG preparations which have similar, but not identical, bioactivity [26]. In this context, some studies also showed that hCG treatment without FSH may stimulate spermatogenesis, particularly in patients with a large testicular volume (>4 ml) and no history of cryptorchidism [27].

Conventional therapy uses hCG along with different FSH formulations: human menopausal gonadotropins (hMG), highly purified urinary FSH (hpFSH) preparations (e.g., urofollitropin [28]) or recombinant FSH (rFSH) [23]. Human menopausal gonadotropins had been the first preparation developed to treat HH. They are produced from the urine of postmenopausal women and have both FSH and LH activity. More in-depth, FSH activity is predominant and LH activity is so low that a combination with hCG is almost mandatory to achieve fertility. Subsequently, hpFSH compounds were developed, showing greater specific activity compared to hMG. Lastly, in the early 1990s, rFSH formulations were launched on the market, with even greater purity and specific activity than any of the urinary preparations and no intrinsic LH activity [29-31].

In everyday clinical practice, traditional treatment includes the administration of hCG (1000–1500 IU) and FSH (75–150 IU) 2 to 3 times per week [23] (Figs. **1** and **2**). Unfortunately, no large, randomized controlled trials (RCTs) have ever been conducted to compare the efficacy of recombinant (any) or hpFSH with the urinary hMG preparations in males. Therefore the efficacy of the various FSH preparations in men with HH is "arbitrarily" considered to be comparable, both regarding the ability to stimulate spermatogenesis and eventually inducing physiology pregnancy [32-37]. Likewise, no ideal pharmaceutical dosage for HH treatment has been clearly established, as well as the success rate of treatment and its influencing factors [24,38,25].

3.4. Human Menopausal Gonadotropins

MacLeod et al. reported the first experience of FSH treatment in HH patients using hMG in a 37-year-old patient who underwent complete hypophysectomy in 1963 [39,40]. Since then, hMG plus hCG have been extensively proposed to several HH patients to stimulate spermatogenesis and restore fertility. Büchter et al. [41] analysed data from 21 patients with HH due to pituitary disorders and treated with 30 courses of hMG in combination with hCG. They found that gonadotropin therapy induced spermatogenesis in 90% of treatment courses in patients with the hypothalamic disor-

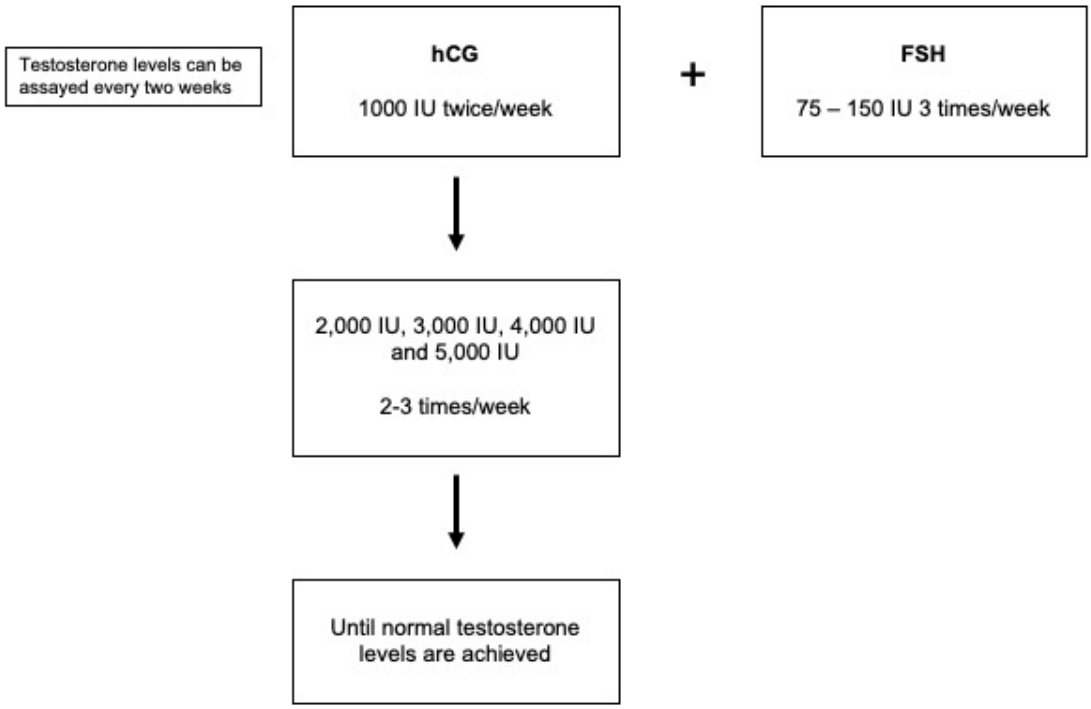

Fig. (1). Induction of spermatogenesis in males with pre-pubertal onset hypogonadotropic hypogonadism.

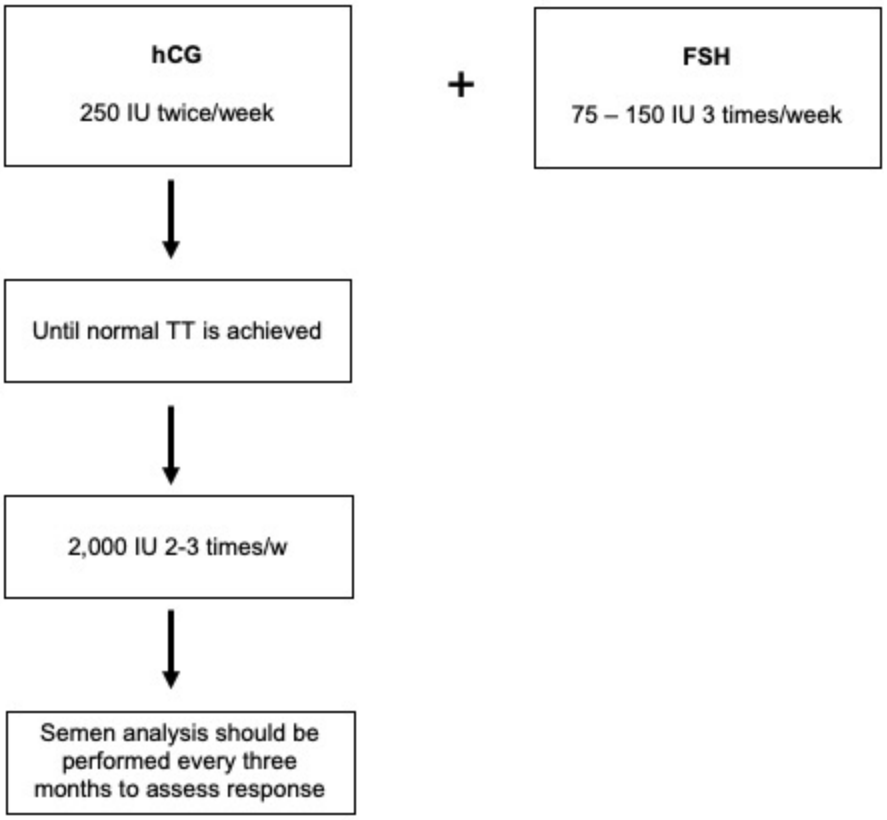

Fig. (2). Induction of spermatogenesis in males with post-pubertal onset hypogonadotropic hypogonadism.

der. In such a case, the timing for sperm detection in the ejaculate while on treatment was quite variable, with an average treatment time of 4 months and 6 months in patients with pituitary and hypothalamic disorder, respectively. Similarly, the duration of time until the induction of pregnancy of the female partner in patients with pituitary disorders was 10 months, whereas of 8 months in men with hypothalamic disorders [41,42].

3.5. FSH in Combination with Recombinant hCG or LH

So far, no adequate studies have been published comparing these preparations with hMG in men. A combination of rFSH with either recombinant LH (rLH) or hCG in one injection pen would allow easier self-administration, more fine-tuning of individual therapy, higher compliance and maybe higher treatment efficacy. In addition, it could be speculated that LH instead of hCG therapy in combination with FSH could lead to much better clinical efficacy in terms of spermatogenesis stimulation and pregnancy rate in HH males [26,43]. Thereof, injection pens with recombinant LH are still only approved to treat female patients.

3.6. Long-acting FSH

In a recent phase III multicenter clinical trial of corifollitropin alfa in azoospermic men with HH, it was demonstrated that administration of 150 μg of a long-acting FSH preparation, given every second week, leads to a significant increase of testicular volume and induction of spermatogenesis, comparable to the effects seen with short-acting rFSH preparations [37,44].

3.7. Routes of Administration

Gonadotropins can be administered either subcutaneously or intramuscularly. The subcutaneous route of administration is as effective as the intramuscular one but significantly increases patient compliance. Some HH patients can restore sperm production and fertility even using hCG alone, with a standard dosage of 500 - 2500 IU injection 2 to 3 times weekly [23]. The dose of hCG can be reduced over time as the testicular size eventually increases. However, when sperm concentration in the ejaculate is lower than 10 million/ml or once there is a plateau in the response to hCG, which typically occurs at 6 months, FSH therapy (in one of the three forms described above) should be added at a dose of 75 IU on alternate days. If sperm production and testicular growth remain suboptimal, the dose of FSH can be gradually increased up to 150 IU daily. A number of evidences have shown that adding FSH (any forms) to hCG was associated with a significantly better outcome as compared with hCG alone [24] (Fig. **2**). The use of this combined therapy for a period of 12-24 months induces testicular growth in almost all patients, spermatogenesis in approximately 80% and pregnancy rates in the range of 50% [24,41,32,45].

Furthermore, it has also been shown that induction of spermatogenesis achieved by FSH plus hCG treatment in HH can be maintained qualitatively, but not quantitatively in most of the patients with hCG alone [46]. Along this line, a sequential therapy with 3 months of treatment with FSH plus hCG alternated by hCG therapy alone for another 3 months has been proposed to reduce the relatively high costs of gonadotropin therapy [28]. However, it is still not known if this dosing regimen has the same high efficacy on the primary outcome i.e. clinical pregnancy rate.

The dose and injection interval of FSH might be adapted on an individual basis to achieve the best treatment outcome. As a whole, the testicular volume increase, the stimulation of spermatogenesis, the serum levels of FSH and testosterone achieved, and other factors can monitor the efficacy of the treatment. Unfortunately, large randomized comparative studies with different FSH preparations, different doses and different injection intervals are still missing in HH men [47,36]. Interestingly enough, a retrospective study suggested that lower weekly FSH doses are sufficient to stimulate

spermatogenesis and allow induction of the desired pregnancy in the female partner [36].

In terms of efficacy, a quite recent meta-analysis evaluating the available longitudinal studies dealing with the achievement of spermatogenesis after gonadotropin therapy in azoospermic HH individuals showed an overall successful outcome in 75% of patients, with a mean sperm concentration achieved of almost 6 million/mL [48]. Better results were obtained in patients with a post-pubertal onset of HH and in those with lower endogenous LH and FSH levels before initiating therapy [48]. In an Australian study of 75 men with HH treated with gonadotropins, the median time for sperm to appear in the ejaculate was 7.1 months and for conception, it was approximately 28 months [32]. Similar data were reported in a compilation of clinical trial data from Asian, European, Australian and American patients [45].

On a practical level, most HH patients treated with gonadotropins achieved a sperm density below the normal range. However, failure to achieve a normal sperm density does not seem to preclude fertility. Indeed, the median sperm concentrations reported at conception range from 5-8 million/mL [49,32]. While spermatogenesis can be obtained even in patients with very small testes [50,49], a longer duration of therapy is typically required and it may take up to 24 months for spermatogenesis to be induced. Therefore, it is compulsory to comprehensively discuss the issue of infertility treatment with patients, thus including an extensive explanation about medical treatment duration: it is important to plan a treatment at least 6 to 12 months prior to the time at which fertility is desired. In this context, it appears to be that a vast majority of HH patients require long-term hormone treatment for fertility preservation. For many chronic conditions, adhering to treatment and medical care can be problematic. A recent report showed that men with HH often struggle with long-term adherence to treatment, and have an increased incidence of depressive symptoms and significant physical, psychological and social consequences related to their GnRH deficiency. Indeed, according to that specific data, only about one-quarter of patients with HH would have shown high levels of adherence to the prescribed treatment [51]. A fortiori, it is really important that in everyday clinical practice, the andrologist spends adequate time with his HH patient, and the infertile couple, in order to allow him/them to understand the physiological relevance of the duration of medical therapy.

Once pregnancy is achieved, gonadotropin therapy should be continued until at least the second trimester. If the couple plans to have another child in the near future, then hCG monotherapy should be continued. However, if a long interval is expected to elapse before the next pregnancy, it may be more convenient for HH patients to resume testosterone replacement therapy. Storing sperm for subsequent use in intrauterine insemination or intracytoplasmic sperm injection should be always offered to every HH patient who had eventually succeeded in retrieving sperm in the ejaculate.

Gynecomastia is the most common side effect of gonadotropin therapy and is due to hCG stimulation of aromatase causing increased secretion of estradiol. This undesirable side effect can be prevented by using the lowest dose of hCG capable of maintaining serum testosterone levels towards the lower end of the normal range [52].

3.8. Factors Influencing the Efficacy of Treatment

Human Menopausal Gonadotropins plus hCG therapy of infertile HH men is quite successful in stimulating spermatogenesis and promoting clinical pregnancy in the female partner, but the treatment might last quite long [24]. As detailed above, patients have to be informed that hormonal therapy might last for several months and even years before the desired pregnancy can be achieved. Therefore, it is important to identify predictive factors influencing treatment efficacy.

Concerning the site of origin of the disease, both hypothalamic and pituitary HH achieved spermatogenesis, without any apparent difference between these groups [24]. A recent study with 51 adult HH patients who underwent FSH (urinary or rFSH) plus hCG therapy showed that those patients who had HH acquired after puberty or had a pubertal arrest showed significantly better treatment outcomes [53]. Testicular volume and sperm concentrations were higher in these groups compared to patients with HH manifesting before the normal onset of puberty. Most relevant, the pregnancy rate of 62% was higher in patients with post-pubertally acquired HH as compared to patients with pre-pubertally acquired hypogonadism (42%). Similarly, conception occurred significantly earlier in the female partners of patients with post-pubertally acquired HH than in the cohort of female partners of patients with pre-pubertally acquired hypogonadism. The therapeutic success was also higher in patients without previously undescended testes, in patients with higher baseline testicular volume, in those who underwent repeated cycles of therapy and in patients with higher baseline inhibin B serum concentrations [32,5325]. The latter identified predictive factors that are in line with various clinical studies by other study groups [26,54,32,45,33,34].

Since normal testicular function is an essential part of a functional HPG axis in healthy adult men, the relationship between testicular development and sperm restoration is expected [55]. It was proposed that mean testicular volumes >4 ml define an important threshold in terms of successful spermatogenesis restoration [56]. Miyagawa et al. [54] showed that 71% of HH patients with a testicular size of ≥4 ml responded to gonadotrophin treatment, whereas this rate was only 36% in patients with a testicular size <4 ml.

Finally, previous TTh has been reported as a negative prognostic factor, associated with a slower achievement of spermatogenesis [32]. No difference in spermatogenesis restoration was seen according to the type of FSH preparation [24].

Among potential negative prognostic factors, the anabolic-androgenic steroids (AAS) should also be considered - including, for instance, testosterone, its 17α-alkyl-derivates (e.g., oxandrolone, stanozolol), its 17β-ester-derivates (e.g., nandrolone, testosterone esters), and its precursors (androstenedione, dehydroepiandrosterone) – which emerge to be the most used drugs to improve sports performance and/or physical appearance; a global lifetime prevalence rate of their use is 6.4% for males [57]. The detrimental effect of AAS on both endogenous androgens production and spermatogenesis is widely known, eventually leading to an AAS-induced HH [58]. Therefore, while during AAS administration, abusers may exhibit high androgen levels, they suffer from a prolonged HH following AAS discontinuation, especially after prolonged drugs use [59]. The recovery of the HPG axis can take from a few weeks to over a year after AAS withdrawal, but recent data also indicated cases of persistent hypogonadism [60]. Similarly, AAS abuse leads to severe oligozoospermia up to azoospermia because the elevated levels of exogenous androgens inhibit gonadotropin and testosterone production, along with a marked reduction of intratesticular testosterone, of which adequate concentrations are required to maintain normal spermatogenesis [61]. Furthermore, the lack of FSH due to AAS-induced suppression thus aggravates the intratesticular hypotestosteronemia and its consequences on spermatogenesis. As a consequence, men using AAS have been extensively demonstrated to have a reduced sperm concentration and a higher prevalence of azoospermia compared to controls [62]. Of clinical relevance, as for AAS-induced HH, the alterations of spermatogenesis are usually transient, with a variably and heterogeneously long time frame required to recover spermatogenesis. In this context, gonadotropin therapy could be eventually considered.

3.9. Induction of Androgenization

Treatment with gonadotropins, as an alternative to testosterone, is also widely used for inducing androgenization of phenotype in subjects with prepubertal onset of HH [27]. Administration of hCG induces the development of secondary sexual characteristics, favors testicular growth and, differently from TTh, it allows the occurrence of spermatogenesis [3].

3.10. Reversal

Congenital HH (CHH) has been thought to be a lifelong disorder, but the recent demonstration of reversal of hypogonadism suggests that this may not always be the case [63-65]. In practical terms, the definition of reversal from idiopathic HH has not been clearly determined. One study defined it as endogenous total testosterone levels were seen above 270 ng/dl after discontinuation of all hormonal therapy for 6 months [64]. Another study defined the reversal based on spontaneous testicular growth and normal reproductive hormone levels without any symptoms of hypogonadism [66].

The prevalence of HH reversal is variable. In a study of a large cohort of men with CHH, 10% of cases demonstrated a sustained reversal after discontinuation of treatment. A recent study showed that 5.1% of HH patients acquired normal reproductive function during treatment [67]. They also suggest that reversible patients may retain partially active reproductive axis function at initial diagnosis [67].

Reversal occurred across a spectrum of phenotypes, thus including patients with and without anosmia and those with absent or partial spontaneous puberty [64]. Clinical findings that can predict reversal are spontaneous testicular enlargement on testosterone therapy and patients with higher baseline and stimulated LH [64,65,67]. Reversal has been documented in patients with a variety of genetic defects – e.g., GNRHR, FGFR1 and CHD – but has been shown to be particularly common in those with defects in the neurokinin pathway [63]. While the mechanism of reversal in CHH is not properly understood, it is possible that the dynamic changes in the sensitivity of the GnRH neuronal network to kisspeptin and the exposure to sex steroids may be responsible for this reversal [68]. In light of these studies, it seems reasonable to recommend that a brief discontinuation of hormonal therapy has to be considered in patients with CHH to assess for reversibility.

4. GONADOTROPIN TREATMENT FOR IDIOPATHIC MALE INFERTILITY

Idiopathic infertility represents the most commonly observed form of infertility in clinical practice [69–71]; unfortunately, a reliable and rational therapy from the pathophysiological point of view is lacking [72-74]. Since gonadotropins are needed for testis physiology and represent a successful treatment in HH, they have been also offered to men with idiopathic infertility based on the hypothesis that spermatogenesis could be eventually stimulated by increasing gonadotropin levels.

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 – 8 mIU/ml) [75], despite the fact that results in this setting are still controversial. A meta-analysis including 15 controlled clinical studies (614 men treated with FSH and 661 treated with placebo or untreated) showed a significant improvement of sperm concentration after FSH administration (mean improvement of 2.66×10^6/ml, $p = 0.02$) and a non-significant improvement in sperm progressive motility (mean raise of 1.22×10^6/ml, p=0.06) [48]. Of clinical importance, the efficacy of FSH treatment has been associated with FSH dose and duration of the treatment [76,77]. Concerning the dosage, differences in treatment outcomes have been associated with the type of FSH prescribed. Several studies reported the efficacy of hpFSH administered at weekly cumulative doses ≤ 450 IU (e.g. 150 IU three times a week, 75 IU on alternate days, etc.) for 3 months [77]. A significant improvement of the sperm concentration was shown in all the studies and most of them reported a beneficial effect on sperm motility as well. On the contrary, rhFSH administered at a weekly cumulative dose ≤ 450 IU, was found to be less effective [77]. Few studies reported the effects of rhFSH and hpFSH administered at a weekly cumulative dose > 450 IU on conventional sperm parameters. Data from RCTs showed that high dose FSH treatment was highly effective in improving sperm concentration and motility compared to placebo [76,77].

In terms of duration of FSH therapy, most of the available studies analysed FSH administration for 3 months. Only a few studies evaluated the effects on conventional sperm parameters after 4-month-long therapies, and all of them have reported a significant improvement in terms of sperm concentration [77]. Furthermore, 4-month-long therapies did not improve sperm morphology, whereas it was significantly increased in the fifth month [76]. As a whole, since human spermatogenesis takes about 72 days, positive effects on all conventional sperm parameters are likely to be observed in ≥4-month-long therapies, particularly with a high weekly cumulative dosage of FSH [77].

Previous authors have also reported that FSH treatment was associated with sperm DNA fragmentation improvement, particularly in patients with high baseline DNA fragmentation impairment [77,78].

As far as pregnancy rate is concerned, a Cochrane Database Systemic Review including 6 RCTs with 456 participants, different treatment protocols and follow-up periods reported that FSH treatment resulted in a higher live birth and pregnancy rates compared to either placebo or no treatment [79]. No significant difference among groups was observed when intracytoplasmic sperm injection (ICSI) or intrauterine insemination (IUI) were considered [79]. In a more recent meta-analysis, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies (OR 4.5, 95% CI 2.17-9.33) and pregnancies after assisted-reproductive techniques (ART) (OR 1.6, 95% CI 1.08-2.37) [48]. Of clinical relevance, the significant increase in pregnancy rate was confirmed regardless of FSH preparation (either rFSH or hpFSH) [48].

Lastly, only a few reports have studied the role of FSH treatment in azoospermic men undergoing TESE-ICSI. Cocci et al., for instance, analysed outcomes of 25 azoospermic patients treated with hpFSH for three months prior to TESE as compared with 25 controls. Their findings suggested improved sperm retrieval rates and higher pregnancy and fertilisation rates in men treated with FSH compared to non-treated subjects [80]. The combination of hCG/FSH therapy has in only one study been shown to increase sperm retrieval rates [81].

In conclusion, current evidence suggested a significant positive effect of FSH therapy on sperm parameters and pregnancy rate in men with altered sperm parameters and normal FSH levels. However, studies are heterogeneous in terms of patient selection, dosage and duration of treatment. Future large studies are needed to better define to whom, at which doses and for how long we should prescribe FSH in this specific setting.

4.1. Gonadotropins for Late-Onset Hypogonadism

The effectiveness of gonadotropin therapy has been extensively studied in prepubertal onset HH, while their role in adulthood for the treatment of late-onset hypogonadism (LOH) has been scarcely investigated [3]. In an RCT involving 40 LOH subjects, Liu et al. [82,21] showed that, compared to the placebo-treated arm, body weight and lean mass significantly increased in the rhCG-treated patients, whereas fat mass decreased [82,21]. Besides body composition, lipid profile also improved, with a significant decrease in total and low-density lipoprotein (LDL) cholesterol as well as triglycerides [21]. No concomitant improvement of sexual function

was observed [21]. Concerning bone metabolism, the treatment arm had a higher level of neo-formation markers, without differences in bone resorption markers [83]. Similar results were reported by Tsujimura et al. [22], who evaluated the effects of hCG in 77 HH men, aged 50-79 years, complaining of consistent sexual, physical or psychological symptoms. During follow-up, a significant improvement in sexual, physical and psychological symptoms was observed. However, no actual improvement of erectile functioning was detected. In addition, no difference in total or high-density lipoprotein (HDL) cholesterol, as well as triglycerides, was shown after hCG treatment [22]. Accordingly, total and calculated free testosterone levels, measured after therapy, although significantly higher compared to baseline levels, were barely above the lower limit of the normal range. Hence, data on hCG treatment of LOH are still scanty and studies effectively comparing TTh and gonadotropin therapy are not yet available.

CONCLUSION

Gonadotropin therapy is effective in inducing spermatogenesis in HH patients with either hypothalamic or pituitary conditions. This approach is effective both in promoting puberty and in supporting spermatogenesis onset and preservation. The combination of FSH and hCG demonstrated to be associated with better outcomes, whereas similar results were obtained with different FSH preparations (hpFSH or rFSH) in male individuals. Several positive and negative predictors of treatment outcomes have been identified but not with a unanimous agreement between studies. Reversal of hypogonadism can occur in up to 10% of patients but its physiopathologic mechanism has yet to be elucidated. FSH therapy has shown positive effects on sperm parameters and pregnancy rate in men with altered sperm parameters and normal FSH levels, but data is too heterogeneous to draw definitive conclusions. If fertility is not an issue, TTh is advised. In contrast to TTh for congenital forms of HH, TTh of LOH is still controversial, because of unclear indications for replacement and potential risks in older individuals that have been widely and often harshly debated, without a definitive conclusion.

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The authors declare no conflict of interest, financial or otherwise.

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