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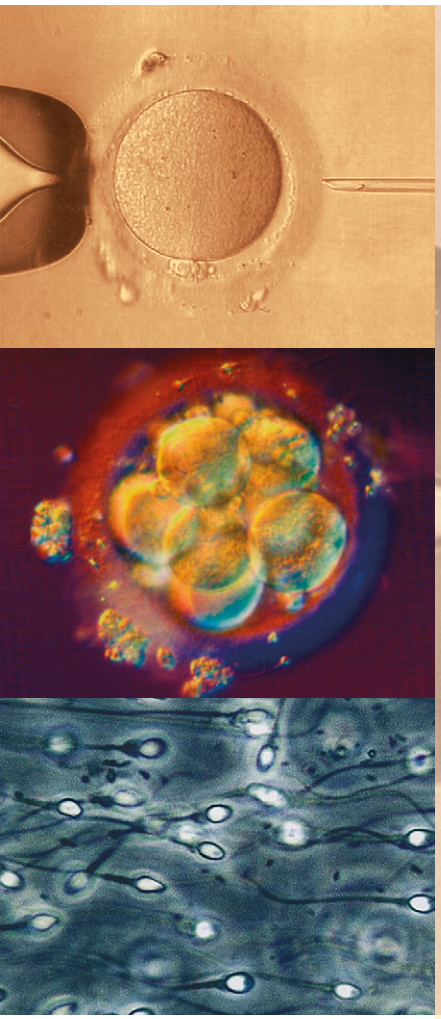

Gonadotropin Treatment in Male Infertility

Zitzmann M, Behre HM, Kliesch S

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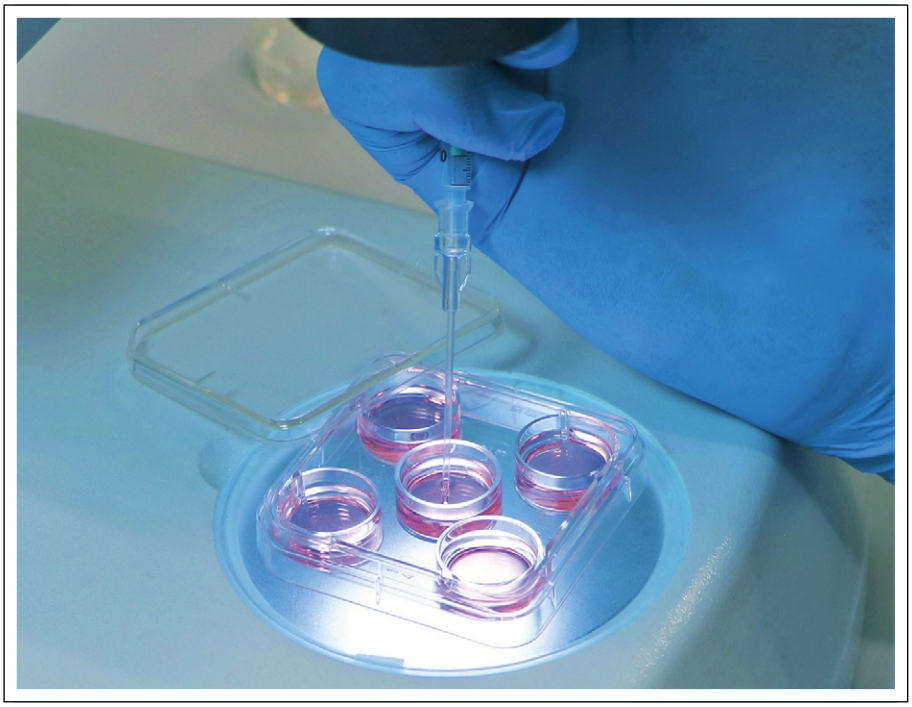

Abbildung 1: Die breiten Wells der Minitüb-Schale erleichtern Pipettierarbeiten – ein nicht zu unterschätzender Vorteil.

Abbildung 2: Nahaufnahme des Schalenunterteils – die abgerundeten Innenkanten der Wells und die hohen Außenränder sind gut erkennbar.

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Gonadotropin Treatment in Male Infertility

M. Zitzmann[1], H. M. Behre[2], S. Kliesch[1]

Male hypogonadism is often associated with impaired fertility. In special cases, treatment with gonadotropins can induce, maintain or augment spermatogenesis. Patients responsive to such regimens are men with secondary hypogonadism, lacking gonadotropin secretion due to pituitary disorders or hypothalamic insufficiency. Such diseases may be inherited or acquired. Available substances are recombinant follicle-stimulating hormone and human chorionic gonadotropin (substituting activity of luteinizing hormone). Recommendation based on current research is that treatment should last at least 2 years. Successful induction of spermatogenesis is more likely in men with pituitary disorders than in those lacking hypothalamic GnRH secretion (e.g. patients with Kallman Syndrome). **J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 23–8.**

Key words: hypogonadism, gonadotropins, spermatogenesis, Kallmann Syndrome, male fertility

Introduction

Testicular dysfunction often comprises both production of testosterone and spermatogenesis. These functions are dependent on gonadotropin action in men, with LH stimulating testosterone production in Leydig cells and FSH supporting spermatogenesis by stimulating Sertoli cell function.

While hypogonadism as such is usually treated with testosterone applied by various methods, for achieving fertility – possible in the hypogonadotropic forms – temporary treatment with gonadotropins or their clinical substitutes is required, i.e. human chorionic gonadotropin (hCG) in combination with human menopausal gonadotropin (hMG) or purified urinary follicle stimulating hormone (FSH) or recombinant human FSH (rhFSH) or, alternatively to gonadotropins, pulsatile GnRH application. Once paternity has been achieved, the treatment scheme should switch back to the more convenient and cost-effective testosterone substitution. Information about the state of the art of gonadotropin treatment in infertile men with hypogonadotropic hypogonadism will be given in the following.

Hormone Replacement by Pulsatile GnRH Application or Gonadotropin Substitution in General

In hypogonadotropic hypogonadism the origin of the disease influences the choice of treatment to achieve fertility. GnRH substitution is only effective in hypothalamic disorders; a pituitary insufficiency always requires administration of gonadotropins (either the conventional choice of human chorionic gonadotropin and human menopausal gonadotropin, or purified urinary FSH, or more recently, recombinant human FSH) [1]. FSH plays a pivotal role in the initiation and maintenance of spermatogenesis. The induction of proliferation of Sertoli cells and spermatogonia depends on this gonadotropin [2].

Concerning maintenance of spermatogenesis by FSH, several experiments in monkeys with long-term immuni sation against FSH induced testicular regression and oligo- or azoospermia [3]. In the cases of oligozoospermia the few sperm left were probably functionally impaired, as these monkeys were infertile in mating tests. Similarly, a study conducted in India with human volunteers receiving an FSH vaccine showed altered parameters of sperm quality such as acrosome content and chromatin condensation. A marginal suppression of sperm counts was achieved (around 30–65%) after the short duration of four spermatogenic cycles, indicating that elimination of FSH not only causes quantitative, but possibly also qualitative damage of spermatogenesis [4].

In the setting of a contraceptive trial using a testosterone ester, complete azoospermia was reached only in those subjects whose serum FSH levels were suppressed below the lower limit of the normal range [5]. The role of FSH is demonstrated impressively by the example of a hypophysectomised patient, who had full spermatogenesis and was still fertile due to an activating mutation of the FSH receptor which was able to induce receptor activity (cAMP production) without FSH stimulation [6].

For completely normal spermatogenesis, FSH and testosterone are important, and the intratesticular location/action of testosterone is pivotal. Thus for treating infertility in hypogonadal men, there is a need for high intratesticular testosterone levels to initiate spermatogenesis. This was demonstrated by treating men with hypogonadotropic hypogonadism with purified FSH and testosterone and comparing its effectiveness to hCG/hMG therapy [1]. The latter was able to induce spermatogenesis while the FSH/testosterone regimen failed [7].

During the course of hormonal treatment to achieve fertility in hypogonadotropic hypogonadal men, usually sperm counts below the lower limit of the normal range are seen. This does not preclude fertility, as has been demonstrated in 24 men with IHH who proved fertile after gonadotropin therapy. Seventy-one percent of a total of 40 initiated pregnancies were conceived with sperm concentrations ranging from 1 to 20 [8]. Confirming results were seen in 42 cases of fertility treatment in hypogonadotropic hypogonadal men using pulsatile GnRH therapy or the hCG/hMG regimen [9, 10].

Initial testicular volume allows prediction of the necessary duration of therapy

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until sperm first appear in the ejaculate. Spermatogenesis can be induced even in patients with a very small testicular volume (of less than 3 ml), but this may require treatment for 18–24 months [9–11]. During therapy, testicular volume can be monitored carefully by ultrasound sonography, in order to detect subtle increases, which precede the first appearance of sperm [1].

A review of 42 patients showed that previous maldescent (uni- or bilateral) hampers spermatogenesis and requires a longer course of treatment, but does not preclude patients from gaining fertility. This is especially the case in unilateral maldescent, but there are also reports of patients with bilateral cryptorchidism having been treated successfully. The group comprising all patients with unilateral maldescent required 5 months of treatment until induction of spermatogenesis (1–16 months); 13 months (12–22 months) was the average time for patients with bilateral maldescent. In comparison all patients with no history of maldescent needed 4.5 months of treatment (2–18 months; [10]).

This is in agreement with other trials [12–14]. Since treatment may be required up to for 2 years or longer, it is recommended that patients with hypogonadotropic hypogonadism try to induce spermatogenesis even prior to the immediate desire for paternity. In repeatedly treated patients, stimulation of spermatogenesis tended to be faster, leading to a reduced time to pregnancy [10].

This was later confirmed by another large study [15]: A total of 75 men, with 72 desiring fertility, was treated at two academic andrology centers for a total of 116 courses of therapy from 1981–2008, semen analysis and testicular examination were performed every 3 months. A total of 38 men became fathers, including five through assisted reproduction. The median time to achieve first sperm was 7.1 months [95%-CI: 6.3–10.1]) and for conception was 28.2 months (95%-CI: 21.6–38.5). The median sperm concentration at conception for unassisted pregnancies was 8.0 m/ml (95%-CI: 0.2–59.5). Multivariate correlated time-to-event analyses showed that larger testis volume, previous treatment with gonadotropins, and no previous androgen use each independently predicted faster

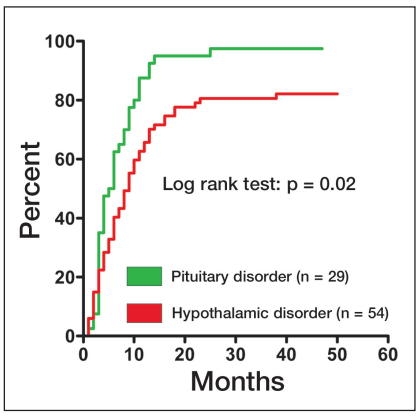

Figure 1: Effects of gonadotropin therapy (see Table 1 for modalities) on spermatogenesis in secondary hypogonadism. Induction of spermatogenesis – time until appearance of first sperm in ejaculate.

induction of spermatogenesis and unassisted pregnancy. In conclusion a larger testis volume is a useful prognostic indicator of response. The association of slower responses after prior androgen therapy suggested that faster pregnancy rates might be achieved by substituting gonadotropin for androgen therapy for pubertal induction.

Confounders of fertility induction were also described in 83 men with secondary hypogonadism [Zitzmann et al., unpublished data] since a marked amount of uncertainty exists in regard to factors influencing fertility induction in men with secondary hypogonadism. 83 men (Kallmann syndrome: n = 20, idiopathic hypogonadotropic hypogonadism: n = 34, postpubertal pituitary disorder: n = 29) were treated in 107 stimulation cycles with hCG/hMG (n = 100) or pulsatily application of GnRH (n = 7); 53/83 men desired paternity. Spermatogenesis was induced in 72/83 patients. 43/74 treatment cycles to achieve pregnancies were successful using spontaneous fertilisation (n = 36) or ICSI (n = 7). Maximum durations to induce appearance of sperm in the ejaculate or pregnancy were 38 and 50 months, respectively. Regression models revealed age ($p = 0.03$), hypothalamic disorder (0.05) and maldescension of at least one testis (0.03) to exert negative influence on successful induction of spermatogenesis, while serum testosterone concentrations under therapy had a positive effect ($p = 0.002$). Subsequent sperm concentrations were then positively dependent on FSH levels ($p = 0.03$) and bitesticular volume ($p < 0.001$). Also see Figure 1.

Induction of pregnancies was negatively influenced by maldescension ($p = 0.009$), while ejaculate volume ($p = 0.005$), sperm concentration ($p = 0.02$) and morphology ($p = 0.001$) were positive predictors. Similarly, the time until pregnancy was dependent on these factors; in addition, progressive sperm motility (positive, $p = 0.001$) and body mass index (negative, $p = 0.01$) exerted influence. The odds ratio for men with a pituitary disorder in comparison to those with hypothalamic disorders to induce a pregnancy was 1.65 (95%-CI: 1.01–2.67; $p = 0.04$) and men with no history of maldescension had an odds ratio of 1.41 (95%-CI: 1.08–1.83; $p = 0.01$) compared to those patients with maldescension. The induction of fertility in men with secondary hypogonadism is highly effective but obviously needs patience in subgroups with unfavorable confounders [1].

Pulsatile GnRH Therapy

Treatment with GnRH requires subcutaneous pulsatile application using a portable pump and a butterfly needle placed in the abdominal wall and changed every 2 days. The dose ranges from 5 to 20 µg/120 min, or 100–400 ng/kg body weight per 120 min. Low-dose pulsatile GnRH therapy (2 µg/150 min) may not elicit a sufficient pituitary response, reflecting different degrees of central maturation [16]. In most cases the induction of spermatogenesis is evidenced by the appearance of sperm in the ejaculate. Therapy lasts on average 4 months, as shown in six of seven GnRH therapy cycles in patients with idiopathic hypogonadotropic hypogonadism or Kallman syndrome [10]. Sperm counts were below the normal range 1.2–15.3 mill/ml.

Similar results have been demonstrated in other studies [13, 17, 18]. Despite low sperm counts, pregnancies can be achieved, the duration until conception being on average 6–7 months. Under treatment testicular size will increase significantly, as demonstrated in the above mentioned patients where the initial mean size of 6.8 ± 2.2 ml rose to 14.9 ± 3.2 ml after 5–12 months of treatment with pulsatile GnRH [10].

When pulsatile GnRH treatment fails, mutation of the GnRH receptor gene can be the cause. These defects have been

Table 1: Modern modalities of gonadotropin substitution therapy in men to achieve spermatogenesis and maintain androgenicity.

Substance	Form of Application	Dosage
GnRH pulsatile	Subcutaneous by minipump	5–20 mg/pulse every 2 h
	or alternatively	
Human Chorion-Gonadotropin (hCG)	Subcutaneous or intramuscular	1500–3000 IU 2 2 to 3 times per week depending on testosterone levels achieved
	in combination with	
Highly purified or recombinant FSH	Subcutaneous or intramuscular	150 IU 3ml 3 times per week

PHCG preparations are only approved for i. m. application, however, it long clinical experience that a s. c. administration of hCG-preparations is therapeutically very effective and safe. But this is, strictly speaking, an off-label use.

described and are probably transmitted as an autosomal recessive trait. A variable degree of hypogonadism in an affected kindred was seen: a male showed no response to pulsatile administration of GnRH, which was effective in his two sisters, all showing clinical patterns of hypogonadotropic hypogonadism [19].

Another cause for failure of pulsatile GnRH treatment was observed in a patient who formed anti-GnRH antibodies during intravenous administration. This was associated with deterioration of testosterone and gonadotropin levels [20].

In an elegant approach using only pulsatile GnRH therapy in patients with hypogonadotropic hypogonadism, GnRH treatment was successful in inducing virilization and spermatogenesis in men with hypothalamically associated idiopathic hypogonadotropic hypogonadism (IHH) [21]. A small subset of IHH men, poorly characterized to date, fail to reach a normal testicular volume (TV) and produce sperm on this therapy. To determine predictors of outcome in terms of TV and sperm count, authors studied 76 IHH men (38% with anosmia) undergoing GnRH therapy for 12–24 months. The population was stratified according to the baseline degree of prior pubertal development: absent (group 1, n = 52), partial (group 2, n = 18), or complete (adult onset HH; group 3, n = 6). Cryptorchidism was recorded in 40% of group 1, 5% of group 2, and none in group 3. Pulsatile GnRH therapy was initiated at 5–25 ng/kg per pulse sc and titrated to attain normal adult male testosterone (T) levels. LH, FSH, T, and inhibin B (I[B]) levels were measured serially, and maximum sperm count was recorded. A longitudinal mixed effects model was used to determine predictors of final TV. LH (97%) and T (93%) levels were normalized in the majority of IHH men. Groups 2 and 3 achieved a normal adult testicular size (92%), FSH (96%), I(B) levels (93%), and sperm in their ejaculate (100%). However, given their prior complete puberty and thus primed gonadotropin producing cells and testes; group 3 responded faster, normalizing androgen production by 2 months and completing spermatogenesis by 6 months.

In contrast, group 1 failed to normalize TV (11 ± 0.4 ml) and I(B) levels (92 ± 6 pg/ml) by 24 months, despite normalization of their FSH levels (11 ± 2 IU/l). Similarly, sperm counts of group 1 plateaued well below the normal range with 18% remaining azoospermic. The independent predictors of outcome of long-term GnRH therapy were: 1.) the presence of some prior pubertal development (positive predictor; p = 0.003); 2.) a baseline I(B) < 60 pg/ml (negative predictor; p = 0.009); and 3.) prior cryptorchidism (negative predictor; p = 0.05). Conclusion were: a) pulsatile GnRH therapy in IHH men is very successful in inducing androgen production and spermatogenesis; b) normalization of the LH-Leydig cell-T axis is achieved more uniformly than the FSH-Sertoli cell-I(B) axis during GnRH therapy; and c) favorable predictors for achieving an adult testicular size and consequently optimizing spermatogenesis are prior history of sexual maturation, a baseline I(B) greater than 60 pg/ml, and absence of cryptorchidism.

Gonadotropin Therapy

In order to achieve fertility in cases of pituitary lesions or GnRH receptor gene defects, the regimens using gonadotropins must be applied, but they are also a useful option in hypothalamic disorders. Historical therapy used hCG and hMG, both purified extractions from urine. In recent years, however, purified urinary FSH and recombinant human FSH have replaced hMG in most countries for various reasons [1].

Treatment with hCG/hMG

As the subunits of hCG and LH are structurally very similar, they act on the same receptor located on Leydig cells. This effect is used to substitute LH by purified urinary hCG or recombinant hCG. Human menopausal gonadotropin contains both LH- and FSH-activity. However, a dose that provides adequate FSH-activity does not maintain Leydig cell function because the LH-activity is low. Thus a combination with hCG is required to achieve fertility.

95% of hMG consists of co-purified proteins that lack LH or FSH activity and is believed to cause the hypersensitivity reactions occasionally observed under hMG therapy, but not under highly purified FSH or recombinant FSH [22–24].

HCG may also induce antibody formation [25], which may neutralise hCG bioactivity [26–28]. Contraceptive trials in women using the effect of antibody formation against hCG after vaccination (with preparations based on the beta-subunit of hCG; [29]) have shown that pregnancies can be prevented at and above 50 ng/ml antibody titers [30]).

Therapy in men is initiated by administration of hCG alone, which is given intramuscularly or subcutaneously. The usual dose is 1500–3000 IU applied twice per week (Monday and Friday) for a period of 8–12 weeks; adjustments have to be made to achieve testosterone levels within the normal range. In some cases sperm can be found in the ejaculate by then, due to residual FSH secretion [11, 31, 32].

Following the induction phase, hMG or rhFSH is administered intramuscularly at a dose of 75–150 IU thrice weekly (Mon-

day, Wednesday, Friday). Sometimes it may be necessary to reduce the hCG dose due to increasing testosterone levels or development of gynecomastia caused by increased levels of testosterone which are aromatized to estradiol. A review of 9 patients with IHH, 9 patients with Kallmann syndrome (group A) and 21 patients with hypopituitarism (group B) treated with this regimen showed appearance of first sperm in the ejaculate after an average period of 6 months (1–18 months) in group A, and 4 months (2–16 months) in group B. Sperm concentrations were 1.2 mill/ml (0.1–9.0 mill/ml) in group A, and 8.1 mill/ml (0.1–180 mill/ml) in group B [10].

As mentioned above, duration of therapy depends on the initial testicular size and the patients' history of uni- or bilateral maldescensus. Pregnancies were induced in 5 of 10 patients belonging to group A (time to pregnancy on average 8 months), and in 17 of 21 patients of group B (time to pregnancy on average 10 months). Testicular size increased from 4.4 ± 2.86 to 15.3 ± 7.4 ml (group A), and from 14.0 ± 8.7 to 28.3 ± 10.9 ml (group B; [10]).

Treatment with hCG/Highly Purified Urinary Human FSH (Urinary-hFSH)

Improved purification methods have provided highly purified urinary FSH with enhanced specific activity in comparison to hMG (10,000 IU/mg of protein vs. 150 IU: mg of protein for hMG). A study including 28 men with hypogonadotropic hypogonadism examined the effects of hCG 2000 IU twice weekly for 3–6 months followed by 18 months of additional subcutaneous administration of highly purified urinary FSH. Twenty-five patients achieved spermatogenesis, 18 of them with a sperm density of more than 1.5 mill/ml. The median time to initiation of spermatogenesis (appearance of sperm in the ejaculate) was 9 months. Mean testicular volume increased from 3.6 ± 1.7 to 10.5 ± 4.1 ml. The partner of one patient seeking fertility conceived a child. The effectiveness was comparable to regimens using hCG and hMG [33].

Corroborating results were seen in 14 prepubertal males with isolated hypogonadotropic hypogonadism or panhypopituitarism; complete virilisation was achieved in all patients; in 7 of 8 patients willing to provide ejaculates spermatogenesis was achieved [34]. The subcutaneous form of application makes self-administration feasible: in 60 men with different forms of hypogonadotropic hypogonadism (16 with Kallmann syndrome, 19 with IHH, 25 with hypopituitarism) highly purified urinary FSH (150 IU thrice/week) and hCG (2500 IU twice/week) were tested for at least 6 months in such a regimen. Results were comparable to other studies and the treatment was well tolerated [1, 35].

Treatment with hCG/Recombinant Human FSH (r-hFSH)

rhFSH has advantages over urinary preparations in terms of purity, specific activity, consistent composition and constant supply. Multiple dose pharmacokinetics showed an elimination half-life of 48 ± 5 h and proved that serum FSH is increased in a dose-proportional fashion. No intrinsic LH activity was detected [36].

Nevertheless, and interestingly, it has been demonstrated that rhFSH increases testosterone concentrations in spermatic venous blood. The testosterone production described in Leydig cells is assumed to be increased by a Sertoli cell-released nonsteroidal factor [37]. Early case reports suggested its effectiveness in inducing spermatogenesis in hypogonadotropic hypogonadism [38]. A study including ten men with such a diagnosis due to hypothalamic or pituitary disorders provided data concerning the combined therapy with recombinant FSH (150 IU s.c. thrice/week) and hCG (2000 IU 2–3 times/week). Eight men commenced rhFSH treatment and seven of these initiated spermatogenesis at a median of 6 months. Five achieved a sperm output of more than 1.5 mill/ml. Mean testicular volume increased by 4.2 ml. Three pregnancies were achieved during FSH treatment. Its efficacy is comparable to urinary FSH in restoring normal fertility in men with gonadotropin deficiency [1, 39].

A combined analysis of data from 4 studies using rFSH/hCG to induce spermatogenesis in men with hypogonadotropic hypogonadism (n = 100) revealed that spermatogenesis could be achieved in 68 men after a maximal duration of treatment of 18 months [40].

Use of Recombinant Human LH (rhLH)

Recombinant hLH is available for stimulation purposes in cycles of assisted reproduction and used in women to induce ovulation [41]. Whilst hCG is effective for 36 hours, rhLH would have to be administered daily for substitution in men. Its use may therefore be limited, but longer comparative studies in men are lacking. A recent in vitro study suggests that, although human luteinizing hormone (hLH) and chorionic gonadotropin (hCG) act on the same receptor, they may nevertheless elicit a different cellular and molecular response in COS-7 and hGL5 cells [42].

Comparison of GnRH and Gonadotropin Therapy

There is still some degree of uncertainty regarding the optimal treatment modality in patients with hypogonadotropic hypogonadism caused by disorders at the hypothalamic level. Our group reported 42 cases of men with hypogonadotropic hypogonadism treated for infertility, comprising 24 patients with IHH or Kallmann syndrome. Six of these received pulsatile GnRH treatment, the other 18 the conventional hCG/hMG regimen. No statistically significant differences in terms of first appearance of sperm in the ejaculate or time to pregnancy were seen, nor was the increment of testicular size significantly different [10].

Another study with 36 patients with disorders at the hypothalamic level (IHH or Kallmann syndrome), divided into groups of 18, reported no significant difference in effectiveness with respect to sperm counts. With GnRH therapy increment of testicular volume occurred more rapidly and was significantly more pronounced than under a gonadotropin regimen. Five patients with the latter therapy developed gynecomastia, probably due to the significantly higher testosterone concentrations in that group [18]. A 2-year comparison including 16 patients showed no advantage of either therapy concerning acceleration and/or enhancement of testicular growth, onset of spermatogenesis or increment of sperm output [17].

Hormonal Treatment of Normogonadotropic Oligoasthenotheratozoospermia

Since GnRH and the different gonadotropins have proven their benefit in induction of spermatogenesis in hypogonadotropic hypogonadism, the application of these substances was also tested in idiopathic male infertility. While the application of pulsatile GnRH resulted in a decrease in FSH levels, no effect on reproductive parameters was seen. There was no evidence for a benefit of this treatment modality [43]. One randomised, controlled study using an hCG/hMG regimen for treatment of normogonadotropic oligoasthenoteratozoospermia showed no significant improvement of sperm parameters or pregnancy rates [44].

A randomised, double-blind, placebo-controlled clinical trial using recombinant human FSH (daily subcutaneous injections of 150 IU rhFSH) for treatment of idiopathic male infertility in 67 patients showed significant increases in sperm motility in the placebo group and improved sperm DNA condensation in the FSH-treated group. Testicular volume increased significantly in the FSH-treated group compared to the placebo group. No significant increase in pregnancy rate over placebo could be detected [45].

However, the 2007 meta-analysis of the Cochrane Collaboration including all truly randomized controlled clinical trials where FSH or hMG were administered for the treatment of idiopathic male infertility with reporting of pregnancy rates demonstrated that the gonadotropin therapy resulted in a significantly higher pregnancy rate per couple randomized within 3 months of completing therapy (OR 3.03, 95%-CI: 1.30 to 7.09) [46]. The pregnancy rate was 13.4% (19/142) in the gonadotropin group and 4.4% (6/136) in the control group. These data indicate that FSH or hMG therapy might cause improvements of sperm function leading to higher pregnancy rates that might not be detected by classical variables of ejaculate analysis. Currently, a prospective clinical study is being performed to select those infertile men on the basis of the FSH receptor polymorphism p.N680S who might benefit best from this kind of hormonal therapy of male infertility.

Outlook: Pharmacogenetic Implications

Recent reports demonstrate that a polymorphism in the follicle-stimulating hormone beta-subunit promoter (TT-genotype vs G/T- or GG-genotype) can be associated with inadequately low FSH levels and, consequently, lower sperm counts [47]. This may present a novel type of partial hypogonadism, selectively regarding spermatogenesis and, hence, an indication for treatment with rFSH in those men with a TT-genotype. A first trial with rFSH induced a significantly higher improvement in sperm count and quality in TT homozygotes regarding carriers of the G allele [48].

Conclusion

Gonadotropin substitution therapy is highly effective in men with hypogonadotropic hypogonadism to achieve both androgenisation and fertility. Up to now, the use of gonadotropins, especially FSH, in normogonadotropic infertile men cannot be recommended generally. However, clearly predefined patients might benefit from this therapy.

Relevancy to Practice

- Secondary hypogonadism can be due to pituitary or hypothalamic disorders.
- In men with secondary hypogonadism, fertility can be achieved.
- Gonadotropin substitution is a well-established procedure to achieve this goal.
- Treatment effects are highly variable and substitution demands expertise and patience.

Conflict of Interest

No potential conflict of interest to this article was reported.

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