Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases

Dorothee Büchter, Hermann M Behre, Sabine Kliesch and Eberhard Nieschlag
Institute of Reproductive Medicine of the University, D-48149 Münster, Germany
(Correspondence should be addressed to E Nieschlag, Institute of Reproductive Medicine of the University, Domagkstrasse 11, D-48149 Münster, Germany)

Abstract
Stimulatory therapy with either GnRH or gonadotropins is an effective treatment to induce spermatogenesis and achieve paternity in men with secondary hypogonadism. However, there is still uncertainty about the optimal treatment modality and schedule, the duration of treatment necessary and the influence of interfering factors such as maldescended testes. We have extended our previous series of men treated for secondary hypogonadism and now present our therapeutic experience with 42 cases. Twenty-one patients with hypothalamic disorders (11 with idiopathic hypogonadotropic hypogonadism (IHH) and 10 with Kallmann syndrome (KalS)) were treated with GnRH (group Ia) or human chorionic gonadotropin (hCG)/human menopausal gonadotropin (hMG) (group Ib), and 21 patients with hypopituitarism (group II) were treated with hCG/hMG. A total of 57 treatment courses were initiated for induction of spermatogenesis. 36 of these for the purpose of induction of pregnancy in the female partner. Bilateral testicular volumes doubled within 5–12 months of therapy. Spermatogenesis as evidenced by the appearance of sperm in the ejaculate was induced in 54/57 courses. Pregnancies occurred in 26/36 courses. Unilaterally maldescended testes did not preclude patients with IHH or KalS from gaining fertility under therapy and spermatogenesis could be successfully initiated even in some individuals with bilateral maldescended testes. In general there was a tendency for a longer duration of therapy until induction of spermatogenesis in patients with a history of bilateral cryptorchidism. However, this did not reach statistical significance. In patients with IHH or KalS treated with either hCG/hMG or GnRH there were no statistically significant differences in terms of duration to appearance of sperm or pregnancy rates. Even in KalS patients as old as 43 years spermatogenesis could be induced. In repeatedly treated patients stimulation of spermatogenesis tended to be faster while time until induction of pregnancy was significantly shorter in the second treatment course. In conclusion, GnRH or hCG/hMG are effective therapeutic modalities for patients with IHH or KalS. It remains to be determined whether highly purified urinary gonadotropin preparations or recombinant LH and FSH will provide therapeutic advantages.

Introduction
It is well known that in men with secondary hypogonadism spermatogenesis and fertility can be induced by gonadotropin or gonadotropin-releasing hormone (GnRH) therapy. In hypothalamic disorders (idiopathic hypogonadotropic hypogonadism (IHH) or Kallmann syndrome (KalS)) pulsatile GnRH or gonadotropins can be used alternatively, while male patients with pituitary insufficiency can only be treated with gonadotropins. However, there is still uncertainty with regard to the optimal treatment modality and schedule, the necessary duration of treatment and the influence of interfering factors such as maldescended testes.

As treatment with urinary human menopausal gonadotropin (hMG) may be replaced by highly purified urinary preparations or by recombinant follicle-stimulating hormone (FSH) in the near future we found it timely to summarize our experience with the conventional treatment in order to provide a basis of standard therapy. We have therefore extended our previous series and now present our therapeutic experience with 42 cases, including the previously published 26 cases (1).

Subjects and methods
Patients
Forty-two adult hypogonadal men received 57 courses of GnRH or gonadotropin treatment in order to induce spermatogenesis. From the total of 57 courses, 36 were initiated with the intention of inducing a pregnancy in the female partner. These patients formed three groups according to diagnosis and/or treatment.
The patients with hypothalamic disorders (group I) chose either GnRH or human chorionic gonadotropin (hCG)/hMG therapy according to their own predilection and formed groups Ia or Ib: group Ia consisted of six patients with IHH (n = 4) or KalS (n = 2) and was given pulsatile GnRH treatment (Lutrelle, Ferring, Kiel, Germany) in seven courses. Group Ib consisted of 18 patients with IHH (n = 9) and KalS (n = 9) and received hCG (Pregnesin, Serono, Unterschleissheim, Germany) and hMG (Pergonal, Serono) in combination in 20 courses. Group II consisted of 21 patients with hypopituitarism treated with hCG/hMG in 30 therapy cycles.

Some patients were treated with more than one treatment course (five of the patients of groups Ia and Ib, and six of group II). Each cycle was considered separately. Three patients with IHH/KalS changed their treatment regimen from one cycle to another and are therefore represented in group Ia and in group Ib. Again each course was considered separately.

Treatment continued until sperm appeared in the ejaculate, until pregnancy occurred or until the patient opted for termination of therapy. For the analysis of the pregnancy rates only those patients who had been treated for at least 12 months and had not terminated therapy early were included.

Some patients had a history of treated unilateral or bilateral maldescended testes: three patients of group Ia, eight of group Ib and one of group II. One of these patients had a unilateral maldescended testis located in the inguinal canal. One patient had experienced testicular torsion with consecutive testicular atrophy of the right testis at the age of 18 years (1). Two patients had bilateral cryptorchidism until adolescence (age 17 and 22 years).

At the beginning of treatment, mean age of the patients of group Ia was 30.1 ± 5.0 years (19–35 years), in group Ib mean age was 29.1 ± 7.2 years (21–43 years), while in group II patients had a mean age of 34.1 ± 6.1 years (23–48 years). Testosterone substitution was terminated at least 4 weeks before GnRH or hCG/hMG treatment. It consisted of either testosterone enanthate (250 mg/14–21 days intramuscularly) (Testoviron Depot 250 mg, Schering, Berlin, Germany), transdermal testosterone (10–15 mg/day perscrotal) (Testoderm, Alza, Palo Alto, CA, USA) or testosterone undecanoate (2–3 × 40 mg/day orally) (Andriol, Organon, Oberschleissheim, Germany).

Previous GnRH or gonadotropin treatment had been terminated at least 6 months before initiation of a new GnRH or hCG/hMG treatment. It consisted of either testosterone enanthate (250 mg/14–21 days intramuscularly) (Testoviron Depot 250 mg, Schering, Berlin, Germany), transdermal testosterone (10–15 mg/day perscrotal) (Testoderm, Alza, Palo Alto, CA, USA) or testosterone undecanoate (2–3 × 40 mg/day orally) (Andriol, Organon, Oberschleissheim, Germany).

Previous GnRH or gonadotropin treatment had been terminated at least 6 months before initiation of a new GnRH or hCG/hMG treatment with the exception of one patient (patient number 8, see results), whose gonadotropin pretreatment was immediately followed by GnRH therapy (1).

Methods

Treatment of patients with hypopituitarism or with hypothalamic disorders consisted of a combination of intramuscular or subcutaneous doses of 1000–2500 IU hCG applied twice a week (Monday and Friday) and 75–150 IU hMG applied three times a week (Monday, Wednesday and Friday) (2). Alternatively, patients with hypothalamic disorders were administered 5–20 μg GnRH every 120 min subcutaneously using a Zyklomat pulse pump (Ferring). The butterfly needle was placed in the abdominal wall subcutaneously and changed every second day.

During the course of treatment control examinations were performed every 3 to 6 months between 0800 h and 1200 h at which time a physical and clinical examination was performed. Blood samples were drawn for hormone measurements as well as hematology and clinical chemistry (data not shown). Testicular volume was measured regularly by palpation or ultrasonography (3). Results are recorded as total testicular volume of right and left testes. Semen parameters were analyzed according to WHO guidelines (4).

Statistics

Regression analysis was applied where appropriate. Results are given as mean ± s.d. or as median and range. Differences between groups were tested by Student’s t-test, Mann–Whitney rank sum test or Kruskal–Wallis test. Contingency tables were tested by Chi-square test and Fisher exact test where appropriate. P values <0.05 were considered significant. Computations were performed using the statistical software package Sigma Stat 2.0 (Jandel, Erkrath, Germany).

Results

The treatment was tolerated well by all patients and none discontinued treatment because of medical reasons.

Testicular size

After 5–12 months of therapy bilateral testicular volumes increased from an initial mean of 6.8 ± 2.2 ml (group Ia), 4.4 ± 2.86 ml (group Ib) and 14.0 ± 8.7 ml (group II) to 14.9 ± 3.2 (Ia), 15.3 ± 7.4 (Ib) and 28.3 ± 10.9 ml (II) respectively. In patients with maldescended testes an increase of testicular volumes also occurred (Fig. 1). There was a clear relation between the initial testicular volume and the duration of therapy until first appearance of sperm in the ejaculate (Fig. 2).

Induction of spermatogenesis

Spermatogenesis as evidenced by the appearance of sperm in the ejaculate was induced in 54/57 therapy cycles. In group Ia sperm appeared in six of seven GnRH therapy cycles (85.7%). In group Ib gonadotropin therapy led to achievement of sperm in 18/20 therapy cycles (90%). In patients of group II 30 therapy cycles...
with hCG/hMG were initiated and all were successful in induction of spermatogenesis.

Duration of therapy until first appearance of sperm in the ejaculate lasted on average 4 months (2–22 months) for patients of group Ia, 6 months (1–18 months) for group Ib and 4 months (2–16 months) for group II. Furthermore the duration of time until induction of pregnancy was on average 6.5 months (3–21 months) for group Ia, 8.0 (1–15 months) for group Ib and 10 months (2–46 months) for patients with hypopituitarism (group II) (Fig. 3).

In the subgroup of patients treated by more than one treatment course mean duration until appearance of sperm was 5.5 ± 6.4 months in the first and 3.3 ± 1.34 months for the second course. This difference is not statistically significant (P = 0.256). Duration until induction of pregnancy was significantly shorter in the second than in the first treatment course (6.4 ± 3.6 vs 12.9 ± 7.2 months, P = 0.038).

Most pregnancies occurred with sperm counts far below the normal range: group Ia median $1.65 \times 10^6$/ml (1.2–15.3 $\times 10^6$/ml); group Ib $1.2 \times 10^6$/ml (0.1–9.0 $\times 10^6$/ml) and group II $8.1 \times 10^6$/ml (0.1–180 $\times 10^6$/ml) (Fig. 4).

**Pregnancy rates**

Thirty-six of 57 cycles (24 different patients) had been initiated for the induction of pregnancy in the female partner. Pregnancies occurred in 26/36 cycles (72%) (16 different patients).

In group Ia four out of five therapy cycles (80%) led to a pregnancy (three patients), in group Ib five out of ten (50%) cycles led to a pregnancy (three patients) and in group II the pregnancy rate per therapy cycle was 17/21 (81%) (12 patients). (Two patients achieved paternity both after gonadotropin and after GnRH therapy). In each group there were patients with successful induction of pregnancy who were older than 30 years or, in single cases, even older than 40 years at the beginning of therapy. Fig. 5 shows the efficacy of induction of spermatogenesis and induction of pregnancy per therapy cycle. Four of the 16 described pregnancies were achieved with the aid of techniques of assisted reproduction (one by intrauterine insemination, three by intracytoplasmic sperm injection (ICSI)). Altogether one of these ICSI pregnancies and three naturally achieved pregnancies ended prematurely in an abortion.

Seven patients had a history of unilateral maldescent: one of group Ia (IHH), five of group Ib (two IHH, three KalS) and one of group II (pituitary malformation). Spermatogenesis could be successfully induced in all seven of them. Four of these patients desired offspring and pregnancy occurred in two of their wives. Five patients had a history of bilaterally maldescended testes: two of group Ia (one IHH, one KalS) and three of group Ib (one IHH, two KalS). Spermatogenesis could be initiated in three of these five cases. Two failed, of whom one had had bilateral cryptorchidism up until the age of 22 years and the other until the age of 17 years. (The last one was patient number 8 who changed from gonadotropin therapy directly to therapy with the GnRH pump but both therapy regimens failed.) Two of five patients with a history of bilateral maldescent intended to achieve paternity, but no pregnancy occurred.

Duration until induction of spermatogenesis was 5 months (1–16 months) in the group of all patients with unilateral maldescent and 13 months (12–22 months)
in the patients with bilateral maldescent. In comparison to that a group of all patients without uni- or bilateral maldescent needed 4.5 months (2–18 months). The differences between these three conditions were not statistically significant. Duration until induction of pregnancy was 9 months (1–21 months) for patients with a history of unilateral cryptorchidism. Neither of the two patients with a history of bilateral cryptorchidism who wanted to father a child was successful in this goal. Duration until pregnancy for all patients without history of uni- or bilateral cryptorchidism (independent of diagnosis and treatment regimen) was 8 months (2–46 months). This difference was not statistically significant.

Discussion

Treatment of hypogonadotropic hypogonadism may be initiated for two purposes, androgenization and fertility. While the first goal can be reached by testosterone substitution, the second can only be achieved by gonadotropins or with pulsatile GnRH treatment.

Several trials have been performed using only one of the pituitary gonadotropins to assess the initiation and maintenance of spermatogenesis. Burris et al. (5) classified their IHH patients according to testicular volume and considered volumes of less than 4 ml as a sign of complete gonadotropin deficiency and a volume above 4 ml as a sign of partial gonadotropin deficiency. When treatment consisted of hCG only they failed to induce spermatogenesis in 5/11 men in the small testis group but could successfully achieve fertility by hCG alone in 9/11 patients in the large testis group. Vicari et al. (6) were able to initiate spermatogenesis in patients with IHH by administration of hCG alone, but found an increasing testicular volume and a higher sperm output in some patients after additional treatment with hMG and concluded that the combined treatment with hCG/hMG should be the method of choice for patients with the wish for pregnancy.

When comparing the administration of FSH in combination with testosterone to hCG/hMG therapy Schaison et al. (7) concluded that the combined treatment is necessary since neither testosterone alone nor testosterone...
in the presence of FSH could bring about or maintain spermatogenesis.

The question of interfering factors such as previous maldescent has been discussed controversially. A history of maldesced testes is generally considered a negative prognostic factor (8, 9). In contrast, other authors found that maldesced testes do not necessarily preclude fertility (10–12). We were able to initiate spermatogenesis in all of our patients with a history of unilateral maldescent and achieved a pregnancy rate of 50% (of patients) in those who had a wish for children. Spermatogenesis could also be induced in patients with a history of bilateral maldescent. However, two of this subgroup failed to develop spermatogenesis. One of the two patients was patient number 8, who changed therapy regimen directly (gonadotropin to GnRH pump), but both regimens failed. Because there are only few patients with bilateral cryptorchidism treated with these therapies we found it useful and necessary to include this patient in this evaluation although he had changed therapy directly. Altogether we can conclude that unilateral maldescent does not preclude fertility under gonadotropin or GnRH therapy, and spermatogenesis can even be successfully induced in some patients with previous bilateral cryptorchidism. Nevertheless there is a tendency for a longer duration of therapy until induction of spermatogenesis in patients with a history of bilateral maldescent, but differences did not reach statistical significance. This might be due to the small number of patients but this observation should be borne in mind when counseling patients.

Our data clearly show that testicular volume at the beginning of therapy is a good predictor for the necessary length of treatment and confirm earlier observations (13). Even in patients with very small initial testicular volume successful therapy is possible. Testicular volume should be monitored very carefully, preferably by ultrasonography. Less meticulous assessments may be the reason why others did not find these correlations (12).

In our patients we could not find a statistically significant difference between the two treatment forms, GnRH or gonadotropin administration, either concerning duration of therapy or with regard to efficacy of induction of spermatogenesis or pregnancy. In our patients with IHH or Kallmann there is a tendency for higher success in achieving paternity with the GnRH pump than with hCG/hMG. However, our group of patients treated with this therapy form is too small to allow a valid answer and differences are not statistically significant. Previously more rapid initiation of spermatogenesis and higher testicular volumes were seen with GnRH therapy compared with gonadotropins (14, 15) and patients who had failed to respond to gonadotropin treatment achieved adequate testicular stimulation by intravenous administration of GnRH (10). However, in a 2-year comparison of pulsatile GnRH and hCG/hMG in patients with IHH Liu et al. (16) showed that GnRH therapy ‘does not accelerate or enhance testicular growth, hasten the onset of sperm production or increase sperm output significantly’. Thus even after three decades of hCG/hMG treatment and two decades of pulsatile GnRH no preference can be given to either therapy and the patient can decide which modality he may prefer.

In comparison to the first treatment course, time until sperm appeared in semen and pregnancies occurred was shorter in the consecutive treatment courses. This has important implications for the counseling of the patients. We now advise patients to induce spermatogenesis even if there is no immediate desire for paternity.
since this first course of treatment will assure the patient (and the physician) that paternity is possible and if required, time to induction of pregnancy will be shorter. In our experience the information that fertility can be achieved brings high psychological benefit for the patients with respect to self-confidence and quality of life.

Currently, highly purified urinary hMG preparations and recombinant FSH are being tested for the treatment of hypogonadotropic hypogonadism. It appears that these preparations are at least as effective as conventional hCG/hMG treatment (17, 18). However, a direct comparison between old and new gonadotropin treatments will be impossible since the current clinical trials – as far as we know – are testing only the new substances and are not designed as comparative trials in terms of efficacy. This would also be desirable for its economic aspects as the new FSH preparations are considerably more expensive than conventional hMG. Hence, clinical experience with conventional treatment, as summarized here, may serve as a basis for future comparisons with more advanced modalities.

**Addendum in proof**

Since acceptance of this paper two further patients have induced pregnancies in their wives (without assisted fertilisation), so that the total pregnancy rate increased from 72 to 78% (28/36 cycles). One patient suffered from IHH (group lb) and was treated with hCG/hMG for 48 months; the other suffered from hypopituitarism (group II) and was treated with hCG/hMG for 42 months.

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**References**


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