Subcutaneous self-administration of highly purified follicle stimulating hormone and human chorionic gonadotrophin for the treatment of male hypogonadotrophic hypogonadism

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The efficacy and safety of highly purified follicle stimulating hormone (FSH) associated with human chorionic gonadotrophin (HCG) was studied in 60 men with hypogonadotrophic hypogonadism. Of these men, 16 suffered from Kallmann’s syndrome, 19 from idiopathic hypogonadotropic hypogonadism and 25 from hypopituitarism. Basal testosterone concentrations were found to be far below the normal range. At baseline, 26 patients were able to ejaculate and all of them showed azoospermia, while the remaining patients were aspermic. All patients self-administered s.c. injections of FSH (150 IU × three/week) and HCG (2500 IU × two/week) for at least 6 months and underwent periodic assessments of testicular function. Testosterone concentrations increased rapidly during treatment and all but one patient reached normal values. Testicular volume showed a sustained increase reaching almost 3-fold its baseline value. At the end of treatment, 48 patients (80.0%) had achieved a positive sperm count. The maximum sperm concentration during treatment was 24.5 ± 8.1 × 10⁶/ml (mean ± SEM). The median time to induce spermatogenesis was 5 months. Eleven patients reported adverse events, generally not related to treatment. Three patients experienced gynaecomastia. No local reactions at injection site were observed. In conclusion, the s.c. self-administration of highly purified FSH + HCG was well tolerated and effective in stimulating spermatogenesis and steroidogenesis in these patients.

Key words: highly purified FSH/male hypogonadotrophic hypogonadism/spermatogenesis/subcutaneous self-administration/testicular size

Introduction

Male hypogonadotrophic hypogonadism (HH) has been successfully treated for several decades by administration of gonadotrophins (Finkel et al., 1985; Ley and Leonard, 1985; Okuyama et al., 1986), which allows the restoration of testicular steroidogenesis and spermatogenesis. Human chorionic gonadotrophin (HCG) is normally used as the source of luteinizing hormone (LH) activity to stimulate testosterone secretion by Leydig cells, whereas human menopausal gonadotrophin (HMG) has been generally used as the follicle stimulating hormone (FSH) source to stimulate proliferation and maturation of germinal cells.

Since spermatogenesis is a time-consuming process, any attempt aimed at its restoration must rely on a long-term treatment; normally, thrice-weekly intramuscular (i.m.) HMG injections have been administered for several months. The i.m. administration involves various inconveniences, such as local pain or need to visit a health centre for injections, which are particularly relevant in the case of a chronic treatment, thus decreasing compliance and often leading to the interruption of treatment before spermatogenesis has been achieved (Saal et al., 1991). Thus, the availability of a treatment which could be given s.c. is especially advantageous since it would be less painful and could be done by the patient himself, with a better cost-benefit ratio. On the other hand, the s.c. route has been shown to produce more sustained and less fluctuating FSH concentrations as compared to those obtained by the i.m. route (Handelsman et al., 1995).

Recently, a new FSH preparation, highly purified FSH (FSH-HP), has been made commercially available by Serono. Like HMG, FSH-HP is a gonadotrophin obtained from the urine of menopausal women but it is purified by specific anti-FSH monoclonal antibodies, giving a purer product that can be self-administered s.c. by the patient (Le Cotonnec et al., 1993; Howles et al., 1994).

The purpose of this study was to assess the efficacy and safety of combined treatment with highly purified FSH and HCG, both administered s.c., to stimulate testicular spermatogenesis and steroidogenesis in males suffering from HH with azoospermia or aspermia.

Materials and methods

Study design

The study was designed as a prospective, phase II–III, open, non-comparative, multicentre trial with patients serving as their own controls.
controls. The study was conducted between February 1992 and April 1996 in 14 Spanish centres. A total of 60 male patients with HH were planned to be included in the study, assigned to a single group treated with FSH-HP plus HCG.

The clinical trial was approved by the Ethics Committee of each participating centre as well as by the Directorate General of Pharmacy and Health Products of the Ministry of Health. The study was conducted in accordance with the Declaration of Helsinki and in compliance with good clinical practice. Each patient gave written informed consent before entering the study.

**Patient selection**

The study population consisted of males suffering from HH with azoospermia or aspermia, aged between 18 and 45 years, with low plasma testosterone concentrations (<200 ng/dl) which responded to HCG stimulation, and plasma LH/FSH concentrations below or at the lower normal limit; a washout period of at least 2 months for previous treatment with testosterone/HCG and 6 months for gonadotrophin releasing hormone (GnRH) or HMG was established. Exclusion criteria were: relevant systemic diseases or treatments which might influence the study results or drug pharmacokinetics; body mass index (BMI) >28.3; existence of other non-treated pituitary deficiencies; hyperresponse to the GnRH stimulation test; infection of genital tract; bilateral anorchia; mechanical abnormalities impairing sperm collection; hyperprolactinaemia; varicocele; cryptorchidism; intellectual deficiency or inability to comply with the study procedures.

**Study drugs**

FSH-HP (Metrodin HP®, Serono, Madrid, Spain) was supplied as lyophilized powder in ampoules, each containing 75 or 150 IU FSH (batch nos 0615/s, 17501042, 17504082, 17521123 and 17502035). HCG (Profasi HP®, Serono) was supplied as a lyophilized powder in ampoules, each containing 2500 IU HCG (batch nos P-5371, I-5 and J-2).

**Treatment schedule**

Before starting combined gonadotrophin treatment, written informed consent was obtained from each patient and compliance with eligibility criteria was verified; this included a positive testosterone response to HCG administration (2500 IU, twice a week) over 4 weeks. Then, all eligible patients self-administered s.c. injections of FSH-HP (150 IU, three times a week) and HCG (2500 IU, twice a week). The HCG dose was reduced in three patients due to abnormal testosterone responses or gynaecomastia. Combined treatment needed to be carried out for at least 6 months; at the end of this period, if no adequate spermatogenic response had been obtained, treatment was to be extended for at least 3 additional months.

**End points**

The primary efficacy end point was the spermatogenic response in terms of sperm concentration. The response was defined as complete if a sperm concentration of at least $1 \times 10^6$/ml was achieved during treatment, whereas it was considered as partial in the case of sperm appearance in the ejaculate with a concentration $<1 \times 10^6$/ml. Secondary end points for efficacy included total sperm count, sperm quality in terms of motility, morphology and viability, ejaculate volume, plasma testosterone concentrations, testicular size and secondary sexual characteristics.

Safety was assessed in terms of adverse events, physical examination (including injection site) and routine laboratory tests, including haematological parameters (red blood cell count, haemoglobin, haematocrit, leukocyte numbers and differential count and platelets), blood chemistry [glucose, creatinine, total proteins, bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), alkaline phosphatase, cholesterol and uric acid] and urinalysis (proteinuria, glucosuria, ketonuria, pH and density).

**Evaluation methods**

At screening, a medical history was obtained and a physical examination was performed. In addition to routine laboratory parameters, baseline hormonal concentrations of prolactin, thyroid stimulating hormone (TSH), thyroid hormones, and cortisol were determined. LH and FSH concentrations were measured basally and after GnRH stimulation, and plasma testosterone concentrations were estimated also basally and after HCG stimulation, as follows: after a basal plasma sample was collected, 2500 IU HCG were administered s.c. twice a week for 4 consecutive weeks. Three days after the last HCG injection, blood was obtained again, spun and the plasma used to measure post-stimulation testosterone concentrations. At all time-points at least two blood samples were collected with a $\geq 20$ min interval and were assayed either separately or as a pool. In the case of independent assay, testosterone concentration was defined as the mean of values obtained in each aliquot. Testosterone concentrations were measured in plasma obtained from heparin- or EDTA-treated blood. Measurements were performed using a commercially available radioimmunoassay method. Testosterone measurements were repeated after 1, 3, 6 or 9 months of treatment.

Spermograms were performed under basal conditions (two spermograms at least 7 days apart within 3 months before entering the study), and then monthly from the third month of treatment onwards. Seminal fluid was collected by masturbation after 3–5 days of abstinence using glass or plastic containers, avoiding the use of condoms. Sperm samples were immediately transported to the laboratory, avoiding delays of $>1$ h or exposure to extremes of temperature. Spermograms were assessed according to the World Health Organization (WHO, 1992) criteria, using a haemocytometer to measure sperm concentration.

To assess testicular size, the short and long axis of each testis was measured with a caliper. Testicular volume was calculated according to the following formula (Ley and Leonard, 1985):

$$V = \frac{4}{3} \pi \left(\frac{a}{2}\right)^2 \left(\frac{b}{2}\right)^2$$

where $a$ represents the short testicular axis and $b$ the long testicular axis (in cm). Volumes ($V$) are expressed in ml, as the average of both testicles.

Penis length was measured at the beginning of the study and at each subsequent visit using a caliper. Pubic hair was assessed initially and at each subsequent visit using Tanner’s classification. At the end of the treatment period, testicular biopsy samples were taken in some of the patients who had not responded.

Adverse events and physical examination results were recorded at each visit. Routine laboratory tests were performed basally and periodically during treatment.

**Statistical methods**

The protocol aimed for the inclusion of at least 60 evaluable patients, since this sample size was considered to be representative of the studied population, taking into account the low incidence of HH. To assess treatment efficacy, the proportion of patients achieving a spermatogenic response and the corresponding 95% confidence interval (CI) were calculated. Basal values of sperm concentration and total sperm count were compared with maximum values obtained after treatment, using Wilcoxon’s matched pairs signed-ranks test. Testosterone plasma concentrations at the different time-points were
analysed by Friedman’s test and the evolution of ejaculate volume, testicular volume and penis size were analysed using analysis of variance (ANOVA) for repeated measures. Concerning pubic hair, baseline status was compared with that reached at the end of treatment, using Wilcoxon’s matched pairs signed-ranks test.

To assess the influence of several prognostic factors, the response to treatment was compared in different diagnostic groups, as well as in terms of previous treatments, testicular volume, and pre- or post-pubertal onset of hypogonadism. Correlation between different variables was analysed using the Pearson $r$ coefficient.

To assess treatment safety, further to calculating the incidence of adverse events and physical examination or laboratory findings, the evolution of laboratory parameters from baseline throughout the treatment was assessed by ANOVA for repeated measures.

Statistical significance was defined as a $P$ value <0.05.

Results

Study population

Treatment was initiated in 63 patients, but three of them were withdrawn from the study because of ineligibility, severe headache and personal reasons respectively, before any efficacy assessment could be performed. Thus, 60 patients could be assessed for efficacy while 63 patients were considered for the safety analysis.

Treatment compliance was correct in the vast majority of patients, with only three patients being considered as poor compliants.

Demographic and other baseline characteristics

Demographic, epidemiological and baseline characteristics of the 60 patients included in the efficacy analysis are summarized in Table I. The study sample consisted of relatively young patients, 35 showing isolated HH (Kallmann’s syndrome or idiopathic HH) and 25 with hypopituitarism. The disease started before puberty in 52 patients. Most patients had been previously treated with testosterone, either as a single treatment or preceded by gonadotrophin administration, while three patients had never been treated.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SEM</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>26.3 ± 0.85</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 0.38</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>18.1 ± 0.8</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Kallmann’s syndrome</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>idiopathic HH</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>multiple pituitary deficiency</td>
<td>25 (41.7)</td>
</tr>
<tr>
<td>Onset of hypogonadism (%)</td>
<td></td>
</tr>
<tr>
<td>prepubertal</td>
<td>52 (86.7)</td>
</tr>
<tr>
<td>postpubertal</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Previous treatment (%)</td>
<td></td>
</tr>
<tr>
<td>testosterone</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td>gonadotrophins</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>testosterone + gonadotrophins</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td>none</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Testicular volume (ml)</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>Baseline spermiogram (%)</td>
<td></td>
</tr>
<tr>
<td>azoospermia</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td>aspermia</td>
<td>34 (56.7)</td>
</tr>
</tbody>
</table>

Table I. Demographic and epidemiological characteristics ($n = 60$)

Testosterone plasma concentrations

At the beginning of the study, all patients had testosterone concentrations far below the normal range (0.4 ± 0.1 ng/ml, mean ± SEM). As shown in Figure 1, testosterone plasma concentrations increased considerably in response to the HCG test and continued increasing during combined treatment with HCG and FSH-HP reaching a value of 8.8 ± 0.9 ng/ml (mean ± SEM) after 6 months of treatment ($P <0.001$). All patients achieved testosterone concentrations within the normal range (>3 ng/ml), with the exception of one patient with a minimal testicular volume (0.4 ml), whose testicular biopsy after 9 months of treatment revealed interstitial fibrosis and absence of Leydig’s cells in both testes.

Testicular volume

Figure 2 shows the evolution of testicular volume, which experienced a sustained and significant increase with the treatment from 4.3 ± 0.5 ml at baseline to 11.1 ± 1.0 after 6 months ($P <0.001$). All but one patient experienced an increase during treatment and 14 achieved a normal testicular volume.
Highly purified FSH for male hypogonadotrophic hypogonadism

Table II. Patients showing spermatogenic response to gonadotrophin treatment (n = 60)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (&gt;1 \times 10^6/ml)</td>
<td>39</td>
<td>65.0</td>
<td>51.5–76.5</td>
</tr>
<tr>
<td>Partial response (0 and &lt;1 \times 10^6/ml)</td>
<td>9</td>
<td>15.0</td>
<td>7.5–27.1</td>
</tr>
<tr>
<td>Overall response (positive sperm count)</td>
<td>48</td>
<td>80.0</td>
<td>67.3–88.8</td>
</tr>
<tr>
<td>No response</td>
<td>12</td>
<td>20.0</td>
<td>11.2–32.7</td>
</tr>
</tbody>
</table>

for a healthy adult (>16 ml). The testicular volume at 6 months of treatment was significantly correlated with that shown at baseline (r = 0.5; P <0.01).

Spermatogenic response

At the beginning of the study, only 26 patients (43.3%) were able to ejaculate and all of them showed azoospermia, while the rest of patients were aspermic. After 6 months of treatment, 28 patients (46.7%) had achieved a sperm concentration >1 \times 10^6/ml and all of them finished the study at this point except four patients who were willing to continue therapy.

The remaining 32 patients who had not achieved an adequate response were asked to extend treatment for at least 3 additional months. Three of these patients refused to continue therapy for personal reasons and another one was withdrawn from the study because of an adverse event, so 28 out of 32 patients with no adequate response continued treatment beyond 6 months.

Table II shows the proportion of patients who achieved a spermatogenic response during the study period. At the end of treatment, an adequate response was observed in 39 (65%) patients while another nine patients showed a positive sperm count with a sperm concentration <1 \times 10^6/ml. Thus, the overall response rate was 48/60 (80.0%) (95% CI: 67.3–88.8%). Testicular specimens were obtained in those non-responders who accepted biopsies; their examination generally revealed testicular fibrosis and/or spermatogenesis arrested at early stages.

A survival analysis of time required to induce spermatogenesis is shown in Figure 3. The median time to achieve a positive sperm count was 5 months (95% CI: 3.31–6.69 months).

The evolution of sperm concentration throughout the study period is shown in Figure 4. All patients who were able to ejaculate basally (n = 26) showed azoospermia. Sperm concentration increased progressively over the treatment period achieving an average maximum value of 24.5 \pm 8.1 \times 10^6/ml (mean \pm SEM), significantly higher (P <0.001) than the pre-treatment value. In all, 14 patients reached a sperm concentration within the normal range (>20 \times 10^6/ml, according to WHO criteria). Total sperm count showed a similar pattern, increasing from a 0 value at baseline up to a maximum of 59.8 \pm 19.7 \times 10^6 spermatozoa per ejaculate (mean \pm SEM) during treatment (P <0.001).

Sperm motility, morphology and viability could not be assessed at baseline since all the patients capable of ejaculating presented with azoospermia. After 3 months of treatment, motility was observed in 44.1 \pm 4.0% (mean \pm SEM) of spermatozoa, with a normal morphology in 56.4 \pm 8.5% and viability in 64.3 \pm 4.9% of spermatozoa. These values did not show significant changes at subsequent assessments throughout the treatment period.

Ejaculate volume

Prior to the beginning of treatment, the ejaculate volume in those patients who produced sperm samples was 1.2 \pm 0.2 ml (mean \pm SEM). Ejaculate volume was promptly and significantly (P <0.001) increased by gonadotrophin treatment so that a normal volume was achieved, on average, at 3 months (2.4 \pm 0.2 ml, mean \pm SEM) and was maintained over the treatment period.

Out of 34 patients who were not able to ejaculate at the beginning, 30 started to do so during treatment and reached normal volumes.
Secondary sexual characteristics
Penis length increased significantly ($P < 0.001$) over the treatment period from $6.0 \pm 0.3$ cm (mean $\pm$ SEM) at baseline to $8.1 \pm 0.3$ cm at 6 months. Regarding pubic hair, prior to starting treatment 20% of patients were prepubertal (Tanner’s stage I–II). However, after 5 months of treatment all patients had reached Tanner’s stage III–V ($P < 0.01$).

Pregnancies
Most patients included in the study were not interested in immediate procreation. Only four patients manifested their desire to father children and the partner of one of them became pregnant during the study and gave birth to a normal child. Pregnancy was achieved in the fourth month of treatment when the sperm concentration was $4.9 \times 10^6$/ml.

Prognostic factors
No significant differences were observed in the spermatogenic response between the different diagnostic groups. The rate of complete responses in patients with isolated HH (63%) was quite similar to that observed in patients with multiple pituitary deficiencies (68%). Treatment efficacy was significantly related to the onset of hypogonadism. Thus, in patients diagnosed of hypogonadism before puberty the response rate at the end of treatment was of 59.6%, whereas 100% of the eight patients with hypogonadism of postpubertal onset showed an adequate response at 6 months ($P < 0.01$). Likewise, maximum sperm concentration in patients with postpubertal onset hypogonadism ($37.9 \pm 14.5 \times 10^6$/ml) was significantly higher ($P = 0.04$) than that observed in the rest of patients ($22.3 \pm 8.5 \times 10^6$/ml, mean $\pm$ SEM).

The spermatogenic response was not significantly related to previous treatments received by patients, although there was a trend to a better response in patients treated with gonadotrophins. Thus, nine out of 10 (90%) patients who were receiving gonadotrophins before entering the study achieved spermatogenesis as compared to 78% of the rest of patients ($P = 0.3$). Likewise, the overall response rate in patients who had received FSH preparations was slightly higher than in the rest of patients (84.2 versus 77.5%) but the difference was not significant.

Neither the response rate nor maximum sperm concentration showed a significant association with basal or post-treatment testicular size. Finally, the response rate in those patients who were able to ejaculate at the beginning of the study (overall response of 88.5%, 95% CI: 68.7–96.9%) was not significantly different from that observed in the subgroup of patients that could not ejaculate at baseline (overall response of 73.5%, 95% CI: 55.3–86.5%).

Safety
Safety was assessed in a total of 63 patients who received at least one dose of FSH-HP. Only 11 patients (17.5%) reported some adverse event which, in most cases, was not serious and not considered as related to treatment. These included acute hepatitis B, trauma, chest pain, dizziness, traumatic orchitis and biochemical abnormalities (increase in bilirubin, cholesterol or uric acid). Six patients (9.5%) suffered from adverse events which could be related to the combined treatment with FSH-HP + HCG. One of them presented with intense headache leading him to withdraw from the study. Three patients showed mild or moderate bilateral gynaecomastia, which improved in one case after HCG dose reduction. One patient suffered from acne, probably related to HCG administration. Only two serious adverse events were observed during treatment, both occurring in the same patient; the first event was a surgical intervention due to coxa vara, not related to the study drugs; then, after 6 months of treatment, the patient presented with an episode of benign intracranial hypertension, considered as possibly related to treatment, which caused the patient’s withdrawal from the study and improved after corticosteroid administration.

Most patients showed some abnormalities in haematological or biochemical parameters, either before or during treatment, which in general were not clinically relevant. Nine patients had a low basal red blood cell count, frequently accompanied by a decrease in haemoglobin and/or haematocrit values, which generally improved during treatment. ANOVA showed a significant increase in mean red blood cell count (from $4.64 \pm 0.4$ at pre-treatment to $5.0 \pm 0.4 \times 10^6$/μl at 6 months), haemoglobin (from $13.8 \pm 1.1$ to $15.0 \pm 1.3$ g/dl) and haematocrit (from $40.5 \pm 3.2$ to $44.3 \pm 3.4$%) over the treatment period. There was also a significant increase in creatinine, uric acid and alkaline phosphatase, whereas mean concentrations of cholesterol, SGOT and SGPT were significantly decreased by treatment. Physical examination, heart rate and blood pressure were always normal. At all visits the injection site was carefully examined with no local reactions observed in any patient.

Discussion
To the best of our knowledge, the present study represents the largest therapeutic trial in men with HH ever reported in the literature.

Regarding the testicular steroidogenic response, testosterone reached normal values in nearly all patients, which is consistent with the data published by other authors (Finkel et al., 1985; Ley and Leonard, 1985; Saal et al., 1991; Mastrogiacomo et al., 1991). These figures are higher than those obtained by Okuyama et al. (1986) in patients with HH whose mean testosterone concentrations were still below the normal range after 6 months of treatment with HCG and HMG. Likewise, the response rate of the present study is higher than that obtained by Kirk et al. (1994) in patients with HH treated with slightly lower HCG doses.

The testicular volume experienced a dramatic, almost 3-fold increase during treatment, although most patients did not reach normal values, which agrees with the results obtained by others (Ley and Leonard, 1985; Liu et al., 1988; Saal et al., 1991; Kliesch et al., 1994) in patients treated with HMG + HCG.

The spermatogenic response observed with the new preparation of highly purified FSH was comparable or even better than that reported in patients treated with HMG + HCG (Saal et al., 1991; Schopohl et al., 1991; Kirk et al., 1994).

Although most patients did not reach a normal sperm concentration ($\geq 20 \times 10^6$/ml), normal values are currently
thought not to be absolutely necessary to achieve fertility (Van Zyl et al., 1975; Zukerman et al., 1977; Sheriff, 1983; Ley and Leonard, 1985; Sokol and Sparkes, 1987; Kiesch et al., 1994). This is particularly true in patients with HH who, after treatment with gonadotrophins, usually become fertile with sperm concentrations far below $20 \times 10^6$/ml (Burris et al., 1988).

On the other hand, and taking into account the spermatogenic process, treatment duration in the present study was too short to normalize sperm concentration, since most of the enrolled patients were not seeking fertility at that time and the aim of the study was just to assess the ability of the treatment to induce spermatogenesis. A longer treatment period would certainly have been required to normalize sperm concentrations, as shown by Okuyama et al. (1986) who only achieved it in 10 out of 18 patients with HH after 24–48 months of HMG + HCG treatment.

The time required to obtain a positive sperm count was shorter in the present clinical trial (median of 5 months) than in other studies. Kiesch et al. (1994) described a mean time of 8.7 ± 4.8 months to induce spermatogenesis in patients with isolated HH and of 6.7 ± 4.8 months in those with hypopituitarism.

The response rate was quite similar in patients with hypopituitarism and in those with isolated HH. Literature reports are not consistent on this issue, since some authors found a better response in patients with multiple pituitary deficiencies (Okuyama et al., 1986; Kiesch et al., 1994) while others (Ley and Leonard, 1985) observed a poorer sperm response in these patients.

The spermatogenic response was not significantly dependent on the previous treatments, which is consistent with data from others (Ley and Leonard, 1985; Kiesch et al., 1994). The response rate was slightly higher in patients who were receiving gonadotrophins before their inclusion in the study and particularly in those who had received FSH preparations, but the difference was not significant, possibly due to the relatively small number of patients in this situation.

The response was better in patients with postpubertal HH than in those with a prepubertal onset, as shown by other authors (Finkel et al., 1985; Ley and Leonard, 1985; Mastrogiacomo et al., 1991).

Concerning sperm quality, the rate of motile, normal and viable forms observed during treatment with FSH-HP was similar to that observed with HMG (Kiesch et al., 1994).

As far as safety is concerned, treatment was well tolerated with a low incidence of adverse events, most of which were not related to the study drug. In the present study only three cases of gynaecomastia were observed; this incidence is lower than that described by others (Schopohl et al., 1991; Kiesch et al., 1994; Kirk et al., 1994) in patients treated with HMG + HCG and corresponds to the physiological gynaecomastia observed during puberty.

Treatment with gonadotrophins caused a significant increase in red blood cell count, haemoglobin and haematocrit, which is consistent with an improvement of the discrete anaemia presented by various patients prior to treatment. This phenomenon could be due to the stimulating effect of testosterone on erythropoiesis (Wilson, 1991). The increase in uric acid and creatinine could be related to anabolic effects of treatment. Alkaline phosphatase increase was probably associated with body growth.

Local tolerance to s.c. injections was excellent with no reactions at the injection site.

Treatment compliance was good with a very low rate of drop-outs, in spite of repeated injections administered for months. This confirms the great advantage of s.c. self-administration, allowed by the high purity of FSH.

In conclusion, combined treatment with FSH-HP + HCG is effective and safe to stimulate spermatogenesis, steroidogenesis and testicular growth in patients suffering from HH.

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References
S. Burgués et al.


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