Treatment of the male with follicle-stimulating hormone in intrauterine insemination with husband’s spermatozoa: a randomized study

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We have examined the potential of follicle-stimulating hormone (FSH) therapy for the male to improve pregnancy rates in intrauterine insemination (IUI) with husband’s spermatozoa. A prospective randomized trial was performed in 148 couples undergoing IUI because of male subfertility. In the treatment group, 150 IU FSH were administered to the husbands, either i.m. or s.c., three times a week, starting 3 months before the beginning of IUI cycles and maintained until the fifth IUI cycle. In the control group no treatment was given. FSH therapy did not change semen parameters. The pregnancy rate per cycle was 13.47% in the FSH group versus 10.07% in the non-FSH group; the pregnancy rate per woman was 44.38% in the FSH group versus 37.18% in the non-FSH group. Although the pregnancy rate increase was >30% per cycle and >20% per woman, statistical significance was not achieved. The cumulative pregnancy rate was 59.20% in the FSH group versus 42.91% in the non-FSH group. The pregnancy rate outside the IUI cycle was 14.70% (10/68) in the FSH group versus 2.5% (2/80) in the non-FSH group, the difference being statistically significant. In conclusion, a non-significant trend towards higher pregnancy rates in IUI was observed in the FSH group.

Key words: FSH/husband’s spermatozoa/intrauterine insemination/male therapy/pregnancy rates/randomized study

Introduction

Intrauterine insemination (IUI) with husband’s spermatozoa is a controversial technique. The pregnancy rates differ widely depending on the population analysed and the methodology employed (Matorras et al., 1995).

A number of works highlight the role of follicle-stimulating hormone (FSH) in human spermatogenesis (Steinberger, 1971; Bremner et al., 1984). On the other hand, different gonadotrophin regimes have been empirically employed in male infertility. FSH therapy may cause an improvement in sperm ultramorphology (Bartoov et al., 1994). In recent years it has been reported that in in-vitro fertilization (IVF) performed because of severe male subfertility, the fertilization rate could be increased with FSH male therapy (Acosta et al., 1991, 1992).

The aim of this study was to analyse if FSH male therapy causes an increase in the pregnancy rate in IUI.

Materials and methods

General management

The population of the study consisted of 148 consecutive couples subjected to IUI with husband’s spermatozoa because of male subfertility, between January 1991 and December 1994. In all cases there was an infertility history >2 years. The female study included at least a pelvic and systemic examination, blood chemistry, an endometrial biopsy, plasma progesterone and prolactin measurement, a postcoital test, a hysterosalpingography (HSG) and a pelvic ultrasound examination. Laparoscopy was performed when any minimal anomaly was detected during a HSG, ultrasound or pelvic examination. Women were considered eligible for IUI when aged <40 years and there was at least one patent Fallopian tube.

The following pathologies were detected in the women: 14.9% tubal factor, 12.2% endometriosis, 14.9% ovulatory disorders, 2.0% hyperprolactinaemia and 6.0% mixed causes.

Semen samples were obtained after 4 days of sexual abstinence. The first semen study included World Health Organization (WHO, 1987) standards, an eosine test (Eliasson, 1977), a hypo-osmotic swelling test (Jeyendran et al., 1984) and strict morphology criteria (Kruger et al., 1987). At least two sperm samples were studied, taken at an interval >30 days.

A semen evaluation was performed by the same observers, who were unaware of the identity of the patient or the treatment. The male factor was considered to be susceptible to IUI when, although not change semen parameters. The pregnancy rate per cycle can be increased with FSH male therapy (Acosta et al., 1991, 1992).

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A semen evaluation was performed by the same observers, who were unaware of the identity of the patient or the treatment. The male factor was considered to be susceptible to IUI when, although some of the parameters of the semenogram were subnormal following WHO (1987) standards, it was possible after semen preparation with Percoll to obtain at least 2×106 motile spermatozoa/ml. An endocrine evaluation of the male included radioimmunoassays of serum FSH, luteinizing hormone, prolactin and testosterone. Cases with low concentrations of FSH (being the lower cut-off of normality of our laboratory, i.e. 5 IU/ml) were excluded from the study. The main categories of semen classification were: asthenoteratozoospermia (73.6%), oligoasthenozoospermia (12.8%), asthenozoospermia (6.1%), teratozoospermia (2.0%) and oligoteratozoospermia (5.4%).

The IUI method has been reported previously (Matorras et al., 1994, 1995). Ovarian stimulation started on day 2 of the menstrual cycle, with two ampoules human menopausal gonadotrophin (HMG; Pergonal 500; Laboratorios Serono, Madrid, Spain) during the first 2 years of the study, or with 150 IU FSH (Laboratorios Serono) during the subsequent 2 years. Ovarian monitoring was carried out by vaginal ultrasound and oestradiol monitoring, starting on day 8 of the menstrual cycle, and adjusting the dose of gonadotrophins according to response. Human chorionic gonadotrophin (HCG; 5000 IU; Profasi; Laboratorios Serono) was administered on the day when there were two or more follicles >17 mm in diameter, with an oestradiol concentration >1468.4 IU. If there were more than six follicles >17 mm in diameter and/ or oestradiol concentrations >7342 IU, then the cycle was cancelled because of the risk of hyperstimulation.
A single insemination per cycle was performed with 0.3–0.5 ml of prepared spermatozoa, 36 h after the administration of HCG. Sperm preparation was performed with Percoll (Pardo et al., 1988). In all cases the luteal phase was supplemented as reported previously (Matorras et al., 1993), i.e. with HCG in cases where oestradiol concentrations were >5006.5 IU (2500 IU on days +1, +3, +5 and +7 following IUI) or with vaginal micronized progesterone in cases where oestradiol concentrations were >1500 pg/ml (Utrogestan, Laboratoires Besins-Iscovesco, Paris, France; 100 mg/12 h during non-FSH group the two women who conceived without IUI had received 16 IUI cycles, while in the non-FSH group the two women who conceived without IUI had received no IUI cycles. The pregnancy rates concerning the whole initial population are reported as ‘crude pregnancy rates’ (68 and 80 women, 209 and 288 cycles respectively).

Table I. Characteristics of the follicle-stimulating hormone (FSH) group and the non-FSH group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FSH group (n = 68)</th>
<th>Non-FSH group (n = 80)</th>
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<tbody>
<tr>
<td>Demographic parameters</td>
<td></td>
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<tr>
<td>Infertility duration (years)</td>
<td>5.53 ± 3.27</td>
<td>5.59 ± 3.01</td>
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<tr>
<td>Women’s age (years)</td>
<td>32.16 ± 2.98</td>
<td>32.61 ± 3.35</td>
</tr>
<tr>
<td>Men’s age (years)</td>
<td>34.06 ± 3.16</td>
<td>34.63 ± 4.28</td>
</tr>
<tr>
<td>Raw specimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejaculate volume (ml)</td>
<td>3.03 ± 1.78</td>
<td>3.09 ± 2.02</td>
</tr>
<tr>
<td>Total number of spermatozoa (×10⁶)</td>
<td>210.64 ± 121.78</td>
<td>223.48 ± 125.80</td>
</tr>
<tr>
<td>Concentration of spermatozoa (×10⁶/ml)</td>
<td>69.52 ± 40.68</td>
<td>72.31 ± 43.19</td>
</tr>
<tr>
<td>Percentage of motile forms (%)</td>
<td>27.49 ± 11.84</td>
<td>30.33 ± 12.27</td>
</tr>
<tr>
<td>Concentration of motile forms (×10⁶/ml)</td>
<td>19.11 ± 8.92</td>
<td>21.93 ± 9.21</td>
</tr>
<tr>
<td>Percentage of normal forms (%)</td>
<td>33.43 ± 14.28</td>
<td>30.74 ± 14.40</td>
</tr>
<tr>
<td>Percentage of strict normal forms (%)</td>
<td>2.98 ± 3.97</td>
<td>3.80 ± 4.94</td>
</tr>
<tr>
<td>Positive eosine test (%)</td>
<td>48.91 ± 13.94</td>
<td>47.09 ± 17.86</td>
</tr>
<tr>
<td>Prepared specimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sperm concentration (×10⁶/ml)</td>
<td>48.54 ± 15.06</td>
<td>47.46 ± 14.52</td>
</tr>
<tr>
<td>Percentage of motile forms (%)</td>
<td>68.21 ± 19.24</td>
<td>71.35 ± 21.49</td>
</tr>
<tr>
<td>Concentration of motile forms (×10⁶/ml)</td>
<td>33.04 ± 15.42</td>
<td>33.38 ± 18.70</td>
</tr>
<tr>
<td>Cycle characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ampoules of FSH or HMG</td>
<td>24.68 ± 9.95</td>
<td>26.60 ± 11.10</td>
</tr>
<tr>
<td>Oestradiol concentration on the day of HCG (IU)</td>
<td>3340 ± 1817</td>
<td>3190 ± 1769</td>
</tr>
<tr>
<td>No. of follicles ≥17 mm in diameter</td>
<td>3.07 ± 1.47</td>
<td>2.96 ± 1.72</td>
</tr>
</tbody>
</table>

Values are means ± SD. Non-significant differences. HCG = human choric gonadotrophin; HMG = human menopausal gonadotrophin. Sperm data correspond to the last sperm analysis before randomization.

Characteristics of both groups

Both groups were comparable regarding the duration of infertility, the proportion of secondary infertility (26.47 versus 21.25%), the proportion of normal women (30/68 = 44.12% and 39/80 = 48.75%) and other infertility parameters (Table I). There were no differences regarding female diagnoses: 17.6 and 12.5% ovulatory disorders, 19.1 and 11.2% tubal factor, 8.8 and 15.0% endometriosis, 2.9% and 1.2% hyperprolactinaemia, and 7.4 and 5.0% mixed causes. The main categories of semen classification were similar in both groups: 77.94 and 70.00% of cases with asthenoteratozoospermia, 13.23 and 12.50% with oligoasthenozoospermia, 4.4 and 7.5% with asthenozoospermia, 0.00 and 3.75% with teratozoospermia and 4.40 and 6.25% with oligoteratozoospermia.

The FSH and non-FSH groups were comparable regarding sperm characteristics in the raw and prepared specimens (Table I). The characteristics of the ovarian cycle were also similar in both groups (Table I). The number of ovarian cycles not receiving IUI (because of cancellation or for non-medical reasons) after IUI was scheduled was also similar in both populations (2.05 ± 2.59 versus 2.13 ± 2.21 months).

There were no differences between the aforementioned characteristics regarding the FSH and non-FSH groups after excluding the cases of pregnancy without IUI.
Table II. Sperm parameters post-follicle-stimulating hormone (FSH) therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before FSH (n = 63)</th>
<th>3 months after FSH (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculate volume (ml)</td>
<td>3.01 ± 2.28</td>
<td>3.06 ± 1.12</td>
</tr>
<tr>
<td>Concentration of spermatozoa (×10⁹/ml)</td>
<td>62.50 ± 25.6</td>
<td>61.09 ± 28.52</td>
</tr>
<tr>
<td>Percentage of motile forms (%)</td>
<td>29.54 ± 10.21</td>
<td>31.20 ± 11.15</td>
</tr>
<tr>
<td>Percentage of normal forms (%)</td>
<td>32.78 ± 13.72</td>
<td>31.86 ± 15.28</td>
</tr>
<tr>
<td>Percentage of strict normal forms (%)</td>
<td>1.87 ± 1.36</td>
<td>2.40 ± 2.51</td>
</tr>
<tr>
<td>Post-preparation volume (ml)</td>
<td>0.47 ± 0.15</td>
<td>0.52 ± 0.18</td>
</tr>
<tr>
<td>Sperm concentration (×10⁹/ml)</td>
<td>35.97 ± 17.37</td>
<td>43.81 ± 22.6</td>
</tr>
<tr>
<td>Percentage of motile forms (%)</td>
<td>70.02 ± 26.02</td>
<td>74.27 ± 17.32</td>
</tr>
<tr>
<td>Concentration of motile forms (×10⁹/ml)</td>
<td>25.18 ± 11.23</td>
<td>31.93 ± 13.78</td>
</tr>
</tbody>
</table>

No significant differences.

Statistical analysis

A statistical analysis was performed using the χ² test, the Mann–Whitney U-test, two-tailed Fisher’s test and Student’s t-test following the standard criteria of applicability. Each parameter was tested by the odds ratio (OR) and its 95% confidence interval (CI) (Lilienfeld and Lilienfeld, 1980). Cumulative pregnancy rates were calculated following a lifetable analysis (Cramer et al., 1979). The limit of statistical significance was defined as α = 0.05.

Results

Semen parameters post-FSH treatment

A second sperm analysis was performed 3 months after the first, immediately before the commencement of IUI, i.e. after 3 months of therapy in the FSH group and after 3 months of no treatment in the non-FSH group. There were no differences between the FSH group and the non-FSH group in the different parameters analysed in the raw and prepared specimens. FSH therapy did not change the sperm parameters (Table II).

Pregnancy rates

There were 12 pregnancies achieved without IUI. Of these, six occurred before the beginning of IUI: five in the FSH group (after 15 days, 1 month, 2 months and two cases after 3 months of treatment) and one in the non-FSH group (two-tailed Fisher’s test, P = 0.09). The remaining six pregnancies corresponded to two cases in cycles that were cancelled because of a risk of hyperstimulation (one in the FSH group and one in the non-FSH group), one in a cycle cancelled because of insufficient response (FSH group), one in a spontaneous cycle without IUI because of vacations (FSH group) and two after concluding the last IUI (both in the FSH group).

The pregnancy rates per woman (excluding those women who achieved pregnancy without IUI) were 44.83% (26/58) in the FSH group versus 37.18% (29/78) in the non-FSH group (P = 0.47, χ² = 0.47), with the OR being 1.37 (95% CI = 0.76–2.53) (Table III).

When normal women only were considered, the pregnancy rates per woman were 58.33% (14/24) in the FSH group and 43.25% (16/37) in the non-FSH group (P = 0.37, χ² = 0.79; OR = 1.84, 95% CI = 0.57–5.95) and per cycle were 18.91% (14/74) and 11.94% (16/134) respectively (P = 0.24, χ² = 1.36; OR = 1.72, 95% CI = 0.73–4.02).

If the patients who were initially excluded because of becoming pregnant without IUI were considered, crude pregnancy rates were 52.94% (36/68) in the FSH group and 38.75% (31/80) in the non-FSH group (P = 0.12, χ² = 2.44). The OR was 1.78 (95% CI = 0.88–3.61). The proportions of couples who achieved pregnancy without IUI were 14.7% (10/68) in the FSH group versus 2.5% (2/80) in the non-FSH group (P = 0.02, χ² = 5.80), with the OR being 6.72 (95% CI = 1.3–31.7) (Table III).

Adverse effects

No adverse effects were reported among males in the FSH group. A control male (no FSH) suffered an intracranial haemorrhage during the period of study.
With a similar study design (one case/one control), to demonstrate that the pregnancy rates per woman found were statistically different (should that be the case), with a power of 90% and an α of 0.05 would require 878 study couples and 878 control couples. Similarly, under the same methodological conditions, to achieve the statistical significance regarding our pregnancy rates per cycle would require 3736 study cycles and 3736 control cycles (or 1886 and 1886 if those corresponding to women achieving pregnancy without IUI were excluded).

Sample size estimation

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Discussion

IUI with husband’s spermatozoa is a widely employed, although controversial, technique. Early works reported low pregnancy rates, but present pregnancy rates are much higher. This improvement in pregnancy rate is mainly a result of the use of advances in IVF methodology (semen preparation, ovarian stimulation, cycle monitoring) in IUI. At present, IUI is being used even in artificial insemination by donor (Matorras et al., 1996).

FSH plays an important role in spermatogenesis in humans (Steinberger, 1971; Brenner et al., 1984) and primates (VanAalphen et al., 1988). The regulation of FSH secretion in normal and infertile patients and its clinical significance have been revised recently (Carreau, 1995; Comhaire, 1995; Martin-du-Pan and Bischof, 1995; Wu, 1995). Recently it has been reported that the administration of FSH in normal fertile men increases circulating inhibin (Comhaire et al., 1995). A beneficial effect of FSH therapy has been reported in infertile males (Conte et al., 1990). In uncontrolled studies, a dramatic increase in fertilization and pregnancy rates has been reported after FSH therapy of infertile males undergoing IVF (Acosta et al., 1991, 1992). Thus, the combination of IUI and FSH male therapy seems a rational alternative for improving IUI results in male factor infertility.

Regarding semen characteristics after FSH therapy, there were no differences after FSH therapy in comparison with the initial semen (before FSH) in any of the classic parameters analysed (motility, classic or strict morphology, sperm concentration) in the raw specimens. This finding is in agreement with other works which failed to report changes in semen parameters after FSH therapy in raw specimens (Acosta et al., 1992; Bartoov et al., 1994) following routine light microscopic analysis. In addition, we observed no changes in the prepared specimen characteristics. However, an improvement in some ultramorphological characteristics has been reported following FSH therapy in infertile males (Bartoov et al., 1994).

The dose of pure FSH used was determined empirically, based on the dose of gonadotrophins employed in the treatment of clinical male infertility (Conte et al., 1990) and of male infertility in IVF (Acosta et al., 1992). However, some experiences in primates (VanAalphen et al., 1988) and humans (Jockenhovel et al., 1990) suggest that this dose may be insufficient, particularly considering the relatively short half-life of bio-FSH (13.4 h) (Jockenhovel et al., 1990; Acosta et al., 1992).

Pregnancy without insemination in IUI with husband’s sperm programmes is well known, although rarely reported. In a previous work we found a 0.8% pregnancy rate per cycle in non-IUI cycles as opposed to a 6.6% pregnancy rate per cycle in IUI cycles (Matorras et al., 1991). Thus the non-IUI pregnancy rate in the non-FSH group is consistent with our previous experience (Matorras et al., 1991). The non-IUI pregnancy rate was five times higher in the FSH group than in the non-FSH group (P = 0.02). Although it is tempting to attribute this increase in pregnancy rate to the FSH treatment, this hypothesis is merely speculative. In fact, the aim of our study was not to test this hypothesis, and the distribution of pregnancies in the study period was quite heterogeneous. On the other hand, the study was not double blind. Although couples were not encouraged to have a special coitus frequency, one cannot discard the fact that in the FSH group pregnancy was more actively sought.

Regarding pregnancy rates in IUI, the pregnancy rate per cycle was 13.47% in the FSH group compared with 10.07% in the control group. Although the pregnancy rate per cycle was 33% higher, no significant differences were observed. Similarly the pregnancy rates per woman were 44.83% in the FSH group and 37.18% in the control group (difference not statistically significant). It must be highlighted that differences were much less than suggested in IVF with male FSH reports.

Crude pregnancy rates per woman, although also 36% higher in the FSH group (52.94 versus 38.75%), did not differ significantly between the two groups. The cumulative pregnancy rates were 59.20% in the FSH group and 42.91% in the non-FSH group, the differences being of marginal significance (P = 0.08). The interpretation of results was jeopardized by the unexpectedly high pregnancy rate achieved without IUI in the FSH group. All the same, the differences found were considerably less than suggested in IVF programmes with male FSH therapy. It is possible that the discrepancy stems from the fact that FSH is presumed to act on the ultrastructural morphology of spermatozoa (Bartoov et al., 1994). However, whereas IVF prognosis is closely related to strict morphology (Kruger et al., 1988), IUI prognosis does not depend on strict morphology (Matorras et al., 1995), probably reflecting the influence of a number of factors, especially sperm motility. On the other hand, FSH therapy could have a less beneficial effect in the IUI cases because they are less severe than the IVF cases.

Thus, from our study a non-significant increase in IUI

| Table IV. Pregnancy rates per cycle and cumulative pregnancy rates in the follicle-stimulating hormone (FSH) and non-FSH groups* |
|-----------------|-----------------|-----------------|-----------------|
|                  | FSH group (%)   | Non-FSH group (%) |
| First cycle      | 13.79 (8/58)    | 11.54 (9/78)    |
| Second cycle     | 13.04 (6/46)    | 18.18 (12/66)   |
| Third cycle      | 5.71 (2/35)     | 8.51 (4/47)     |
| Fourth cycle     | 23.07 (6/26)    | 2.56 (1/39)     |
| Fifth cycle      | 25.0 (4/16)     | 0 (0/32)        |
| Sixth cycle      | 0.00 (0/12)     | 11.54 (3/26)    |
| Cumulative pregnancy rate* | 59.20 | 42.91 |

Values in parentheses are number of cases. *P = 0.08.

Women obtaining pregnancy without IUI are not included.
pregnancy rates was obtained when males were treated with FSH. However, because a 33% increase in the pregnancy rate per cycle is clinically relevant, we think it would be interesting to discard a β error by studying a much larger population in a multicentric trial.

References


Received on February 26, 1996; accepted on September 24, 1996