Treatment with the GnRH antagonist ganirelix prevents premature LH rises and luteinization in stimulated intrauterine insemination: results of a double-blind, placebo-controlled, multicentre trial*

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BACKGROUND: This study was designed to assess whether the use of ganirelix in women undergoing stimulated IUI could prevent the occurrence of premature LH rises and luteinization (LH + progesterone rises). METHODS: Women of infertile couples, diagnosed with unexplained or male factor infertility, were randomized to receive either ganirelix (n = 103) or placebo (n = 100) in a double-blind design. All women were treated with an individualized, low-dose rFSH regimen started on day 2–3 of cycle. Ganirelix (0.25 mg/day) was started if one or more follicles ≥11 mm were visualized. Ovulation was triggered by HCG injection when at least one follicle ≥18 mm was observed and a single IUI was performed 34–42 h later. The primary efficacy outcome was the incidence of premature LH rises (± progesterone rise). RESULTS: In the ganirelix group, four subjects had a premature LH rise (value ≥10 IU/l), one LH rise prior to the start of ganirelix and three LH rises during ganirelix treatment, whereas in the placebo group 28 subjects had a premature LH rise, six subjects prior to the start of placebo and 22 subjects during placebo treatment. The incidence of LH rises was significantly lower in ganirelix cycles compared to placebo cycles (3.9 versus 28.0%; P = 0.003 for ITT analysis). When excluding subjects with an LH value ≥10 IU/l before the start of ganirelix/placebo the incidence of LH rises was also significantly lower in ganirelix cycles compared to placebo cycles (2.9 versus 23.4%; P = 0.003 for ITT analysis). Premature luteinization (LH rise with concomitant progesterone rise ≥1 ng/ml) was observed in one subject in the ganirelix group and in 17 subjects in the placebo group of which three subjects had a premature spontaneous ovulation. Ongoing pregnancy rates per attempt were 12.6 and 12.0% for the ganirelix and placebo groups respectively. CONCLUSIONS: Treatment with ganirelix effectively prevents premature LH rises, luteinization in subjects undergoing stimulated IUI. Low-dose rFSH regimen combined with a GnRH antagonist may be an alternative treatment option for subjects with previous proven luteinization or in subjects who would otherwise require insemination when staff are not working.

Key words: male factor infertility/mild stimulation/premature LH rises/recombinant FSH/unexplained infertility

Introduction

At present, controlled ovarian stimulation (COS) treatment combined with intrauterine insemination (IUI) is widely used in unexplained or male factor infertility. The use of IUI with COS (as compared to COS alone) may result in improved cycle fecundity (Dodson and Haney, 1991; Cohlen et al., 2000). In several studies comparing the results of IUI with or without COS, it became evident that the use of COS with IUI may result in higher success rates (Hannoun et al., 1998; Guzick et al., 1999), but this improvement should be weighed against the increased risk for complications. The combination of IUI with gonadotrophin treatment also resulted in higher pregnancy
rates when compared to IUI cycles with clomiphene citrate stimulation (Hannoun et al., 1998; Matorras et al., 2002). In comparison with the more expensive and invasive IVF, COS with IUI appears to have a similar cumulative pregnancy rate (Goverde et al., 2000; Hughes, 2003; Pandian et al., 2003). Therefore, the balance between benefits and costs often favours COS. However, the use of COS for IUI is associated with an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Therefore, new low-dose treatments with recombinant FSH (rFSH) combined with IUI have been studied for treatment of unexplained or male factor infertility (Hughes et al., 1998; Sengoku et al., 1999; Ragni et al., 2004). The results of these studies indicate that a daily low dose of FSH (50 or 75 IU) could reduce the incidence of OHSS and multiple pregnancy rates while retaining comparable pregnancy rates (Sengoku et al., 1999; Ragni et al., 2004).

The main drawback of COS regimens is the frequent occurrence of premature LH rises and luteinization (Loumaye, 1990). This may interfere with the adequate timing of IUI or result in cycle cancellation, thus impairing the pregnancy rate. In IVF it is well known that the combination of GnRH agonist (Barlow, 1998) or antagonist (Shapiro and Mitchell-Leef, 2003) with COS treatment improves the reproductive outcome by preventing premature LH surges and synchronizing the development of follicles. Some previous studies on COS/IUI treatment in unexplained infertility have demonstrated that the addition of a GnRH agonist suppresses the occurrence of premature luteinization (Dodson et al., 1991; Sengoku et al., 1994). However, these studies did not find an enhanced cycle fecundity with the addition of a GnRH agonist.

Ganirelix (Orgalutran®) is a GnRH antagonist developed for the prevention of an endogenous LH surge in women undergoing COS for assisted reproduction techniques. Studies have demonstrated the benefits of ganirelix treatment in IVF regimens (Out and Mannaerts, 2002).

Recently one small open-labelled, randomized study (Gomez-Palomares et al., 2005) showed more mature follicles and clinical pregnancies in IUI patients treated with rFSH and ganirelix than in patients treated with rFSH alone (clinical pregnancy rate 38 versus 14%); however, this improved clinical outcome was thought to be related to the longer stimulation resulting in more mature ovulatory follicles, which also increases the risk of multiple gestations.

In another small controlled IUI study, no significant differences for these parameters (Williams et al., 2004) were found and clinical pregnancy rates were 12% in the ganirelix group versus 7% in the control group. However, neither of these two studies basically investigated the potential of combining these treatments to inhibit premature LH and progesterone rises.

To date, no placebo-controlled data are available on the use of a GnRH antagonist in COS combined with IUI. Therefore, the present study was designed to assess whether the use of ganirelix (as compared to a placebo) in women undergoing treatment with recombinant FSH (rFSH) for IUI could reduce the incidence of premature LH rises and luteinization.

Materials and methods

Subjects
A total of 204 women, scheduled for stimulated IUI, were randomly assigned (described below) to receive ganirelix (n = 104) or placebo (n = 100). They were recruited from 10 centres in four European countries and in Canada. The number of selected subjects per centre ranged from three to 44. Selection criteria were: healthy females of infertile couples diagnosed with unexplained infertility or mild male-factor infertility, aged 18–39 years at screening, a body mass index (BMI) of 18–29 kg/m², a body weight of 50–90 kg, a menstrual cycle with a range of 24–35 days, bilateral tubal patency confirmed by a laparoscopy or hysterosalpingogram, a total motile sperm count ≥10x10⁶/ml, no history of endocrine abnormality, no serum FSH and/or LH >10 IU/l during the early follicular phase (cycle days 2–7), no abnormal cervical smear, not more than three previous IUI attempts, no use of hormonal preparations within 1 month prior to treatment and willing to give written informed consent.

Study design
This was a randomized, double-blind, placebo-controlled, comparative, multicentre trial designed to assess whether the use of ganirelix would reduce the incidence of LH rises during ovarian stimulation treatment. Subjects who complied with all selection criteria were randomly assigned to one of two treatment groups by giving them a code number from a randomization list in the order of enrolment. Recombinant (r) FSH treatment ( follitropin beta, Puregon®/Follistim®; NV Organon, The Netherlands) was started from day 2 or 3 of the menstrual cycle (equals day 1 of the treatment cycle) onwards by a once-daily s.c. injection in the abdominal wall, injected by the patient using Puregon Pen (Follistim AQ Cartridge). The rFSH starting dose was determined by the investigator based on patient’s characteristics and history. On day 6, the dose of rFSH could be adjusted, depending on the individual ovarian response as assessed by ultrasound. The dose increments of rFSH were not predefined. Ganirelix (0.25 mg per day, Orgalutran®; NV Organon, The Netherlands) or placebo treatment was given by a daily s.c. injection as soon as one or more follicles ≥14 mm were seen on transvaginal ultrasound. Unlike the rFSH, the ganirelix or placebo was administered by the investigator or a nurse. Both the rFSH and the ganirelix/placebo treatments were continued until (and including) the day of ovulation induction. On the day when at least one follicle ≥18 mm was observed by ultrasound, ovulation was triggered by means of a single i.m. injection of 5000 or 10 000 IU HCG (Pregnyl®, NV Organon, The Netherlands). A single IUI was performed 34–42 h after HCG administration, and luteal phase support was started in all patients according to the preference of the treatment centre. The cycle was cancelled if more than three follicles ≥21 mm were observed on ultrasound. In such cases, the cycle could be converted into an IVF cycle. All subjects gave written informed consent. The study was approved by the Ethics Committee of each participating centre and performed according to the Declaration of Helsinki, the ICH guidelines, and Good Clinical Practice.

Assessments
Prior to the treatment cycle, a pregnancy test was performed, ultrasoundography of the ovaries was assessed and a blood sample was taken for hormone assessments (by the local laboratory). From day 1 of rFSH treatment, the subjects returned to the clinic at least every 2 days for ultrasonography. When one or more follicles ≥21 mm were seen by ultrasound until and including the day of ovulation induction, blood samples were taken daily for hormone assessments. All blood samples were drawn prior to daily drug administration. Serum LH, FSH, estradiol (E₂) and progesterone values were determined by a
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A pregnancy (HCG) test was performed in the second week after the day of IUI. If the HCG test result was positive, ultrasonography was performed at 5–6 weeks after IUI to confirm intrauterine pregnancy. To establish ongoing pregnancy, ultrasonography was done 12–16 weeks after IUI.

**Statistical analysis**

This study was designed to test whether ganirelix is superior to placebo in preventing premature LH rises in women undergoing mild COS for IUI. For this purpose, a double-blind, placebo-controlled design was chosen. Given a premature LH rise in 3% of the ganirelix group (European Ganirelix Study Group, 2000) versus 15% of the placebo group (Sengoku et al., 1994), 89 evaluable subjects per treatment group gave a power of 80% to detect a difference at \( P < 0.05 \). To allow for a 10% rate of premature discontinuation, ~100 subjects per treatment group were considered to be sufficient.

The primary efficacy outcome measure was the incidence of premature LH rises (with or without a progesterone rise). A premature LH rise was defined as a serum LH value \( \geq 10 \) IU/l during the period of ganirelix or placebo treatment, but not within 4 h after the first administration of the investigational product. Premature luteinization was defined as a premature LH rise, as defined above, with a serum progesterone value \( \geq 1 \) ng/ml (\( \geq 3.18 \) nmol/l). To establish a significant treatment difference in incidence of premature LH rises, the exact method of Berger and Boos (1994) was used, with \( P < 0.05 \). All tests were two-sided. The other main efficacy outcome measures were serum LH values, treatment failure rate, and ongoing pregnancy rate. A treatment failure was recorded if the subject did not have HCG injection or did receive an HCG injection after switching to IVF. For all of these main outcome measures, summary statistics were calculated for the intent-to-treat (ITT) group defined as all randomized subjects who received one dose of rFSH.

**Results**

**Patients**

Figure 1 presents the subject disposition, including the number of subjects who discontinued in each stage of the study and the reasons for discontinuation. Of 204 patients randomized, one subject did not start treatment because of a spontaneous pregnancy. As a result, in total 203 women started rFSH treatment (ITT group). Of these, 193 subjects received treatment with either ganirelix (n = 98) or placebo (n = 95). The main reasons for discontinuation before HCG injection were too many follicles (n = 8) and an insufficient ovarian response (n = 5). Among the HCG-treated patients (n = 187), nine women (three in the ganirelix group and six in the placebo group) had more than three follicles \( \geq 14 \) mm and were converted to IVF. In total, 93 subjects in the ganirelix group and 85 in the placebo group underwent an IUI. None of the patients discontinued because of an adverse event or serious adverse event.

Table 1 shows a summary of baseline characteristics of all women who started treatment. No clinically relevant differences were observed between the two groups.

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**Figure 1.** Disposition of subjects.
Table I. Subject characteristics (intention to treat)

<table>
<thead>
<tr>
<th></th>
<th>Ganirelix (n = 103)</th>
<th>Placebo (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>32.7 ± 3.3</td>
<td>32.5 ± 3.9</td>
</tr>
<tr>
<td>Body height (cm)*</td>
<td>166.1 ± 6.0</td>
<td>166.4 ± 6.9</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>63.1 ± 9.3</td>
<td>64.6 ± 10.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>22.9 ± 3.0</td>
<td>23.3 ± 3.1</td>
</tr>
<tr>
<td>Duration of infertility (years)*</td>
<td>3.1 ± 1.7</td>
<td>3.4 ± 1.8</td>
</tr>
<tr>
<td>Cause of infertility [%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>78 (75.7)</td>
<td>71 (71.0)</td>
</tr>
<tr>
<td>Mild male factor</td>
<td>21 (20.4)</td>
<td>26 (26.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.9)</td>
<td>3 (3.0)</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.

Table II. Duration of treatment and exposure (intention-to-treat groups)

<table>
<thead>
<tr>
<th></th>
<th>Ganirelix (n = 103)</th>
<th>Placebo (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First day of ganirelix/placebo treatment</td>
<td>6 (4–11)</td>
<td>6 (4–12)</td>
</tr>
<tr>
<td>Duration of ganirelix/placebo treatment (days)</td>
<td>3 (0–6)</td>
<td>3 (0–6)</td>
</tr>
<tr>
<td>Duration of rFSH stimulation (days)</td>
<td>8 (5–14)</td>
<td>8 (5–13)</td>
</tr>
<tr>
<td>Total dose of rFSH (IU)</td>
<td>550 (125–2075)</td>
<td>600 (225–1350)</td>
</tr>
<tr>
<td>Starting dose of rFSH [no. of subjects (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 IU</td>
<td>4 (4.1)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>50 IU</td>
<td>27 (27.8)</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>75 IU</td>
<td>44 (45.4)</td>
<td>43 (44.8)</td>
</tr>
<tr>
<td>100 IU</td>
<td>16 (16.5)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>&gt;100 IU</td>
<td>4 (4.1)</td>
<td>5 (5.2)</td>
</tr>
</tbody>
</table>

Values are medians (range), unless otherwise indicated.

Table III. Number of subjects with LH values ≥10 IU/l prior to or during ganirelix/placebo treatment and the difference between the treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Ganirelix</th>
<th>Placebo</th>
<th>Difference between treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior</td>
<td>During</td>
<td>Prior</td>
</tr>
<tr>
<td>LH rise</td>
<td>–</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>LH + progesterone rise</td>
<td>1</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>3/102 (2.9)*</td>
<td>22/94 (23.4)</td>
<td>4/103 (3.9)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

*Excluding subjects with LH values ≥10 IU/l before the start of ganirelix/placebo treatment.
incidence of LH rises and the incidence of LH + premature LH rises and luteinization rises was significantly lower in the ganirelix group. No cases of premature luteinization occurred during ganirelix treatment whereas 13% of the subjects showed premature luteinization during placebo treatment.

**Serum LH, FSH, E₂, and progesterone values**
Figure 3 shows the serum hormone profiles during stimulation in women who received HCG. Both treatment groups had a similar decrease in the median LH serum values during the first 6 days of stimulation: from 4.7 and 4.2 IU/l respectively to 2.0 and 2.2 IU/l respectively. After day 6, LH values remained low in subjects treated with ganirelix, whereas those treated with placebo showed an increase to 4.7 IU/l on the day of HCG. The profiles for the median values for serum levels of FSH, E₂ and progesterone profiles were similar between treatment groups. However, the placebo group tended to a slightly higher E₂ level at day 8 and to a higher progesterone level at the end of stimulation.

**Follicle growth**
In the patients who received HCG, the number of follicles ≥11, ≥14 and ≥18 mm on the last ultrasonography before HCG injection was comparable between treatment groups. The mean ± SD number of follicles ≥11, ≥14 and ≥18 mm was respectively 4.0 ± 2.4 versus 3.8 ± 3.5, 2.6 ± 1.3 versus 2.5 ± 2.0 and 1.3 ± 0.6 versus 1.2 ± 1.0 in the ganirelix group and placebo group.

**Ongoing pregnancies**
There were in total 15 biochemical pregnancies and two miscarriages in the ganirelix group and 16 biochemical pregnancies and four miscarriages in the placebo group. The clinical pregnancy rate (with heart activity) per started cycle was 13.6% (95% CI: 7.6–21.8) and 13.0% (7.1–21.2) and the ongoing pregnancy rate per started cycle was 12.6% (6.9–20.6) and 12.0% (6.4–12.0) in the ganirelix and placebo groups respectively. The ongoing pregnancy rate of subjects with IUI was 14.0% in the ganirelix group and 14.1% in the placebo group. In each group, two patients carried twins, thus the incidence of twin pregnancies was 15.4 and 16.7% in the ganirelix and placebo groups respectively. There were no higher-order multiple pregnancies.

**Discussion**
This study demonstrates that treatment with ganirelix during mild stimulation with rFSH for IUI significantly reduces the number of premature LH rises and premature luteinization (LH rises + progesterone rises) that may result in spontaneous ovulation, from 17% in the placebo group to 1% in the ganirelix group and 13 and 0% respectively after exclusion of the subjects with elevations before ganirelix or placebo had been given. The incidence of premature LH rises prior to the start of ganirelix or placebo treatment was 1 and 6% respectively, which difference is mainly caused by chance. When excluding
Ganirelix effectively prevents premature LH surges in stimulated IUI subjects with a premature LH rise prior to the start of drug administration, the difference in the incidence of LH rises and the incidence of LH + progesterone rises was still substantially lower in the ganirelix group. No cases of premature luteinization occurred during ganirelix treatment whereas 13% of the subjects showed premature luteinization during placebo treatment.

These differences in number of LH and progesterone rises are reflected in the median serum LH and progesterone values, which reached higher values in the placebo group at the end of the stimulation period. In studies investigating the effects of GnRH agonist treatment in HMG/IUI (Dodson et al., 1991; Sengoku et al., 1994), a similar suppressive effect of the GnRH analogue on premature luteinization has been observed.

In a study comparing daily versus alternate day administration of FSH in IUI in which all patients received ganirelix, no cases of progesterone and/or LH rise on the day of HCG were found (Ragni et al., 2004).

In the current double-blind study the applied treatment regimen was flexible with respect to the FSH starting dose and its dose increments, allowing investigators to keep close to their own routine practice. Regardless of this flexibility, the duration of stimulation, the total dose of rFSH and the number of follicles at the day of HCG was the same in the two treatment groups.

Our observed higher incidence of premature LH surges in the placebo group did not result in a higher treatment failure rate in this group of subjects. The occurrence of a premature LH surge resulted in treatment cancellation in only three subjects (3% in placebo group), because of spontaneous ovulation. In this trial serum LH and progesterone were measured by central laboratory and, as in routine practice, treating physicians were not aware that premature luteinization occurred unless follicles arrested their growth or ruptured. Three subjects with LH and progesterone rises showed follicular rupture of the largest follicle(s) as observed by ultrasound. These cases were recorded as spontaneous ovulation. Apart from cycle cancellation due to premature ovulation, premature luteinization may impair the overall success rates and typically in the current trial none of the subjects with premature luteinization

Figure 3. Median serum hormone levels (5th to 95th percentile) on days 1, 6 and 8 of rFSH stimulation and on the day of HCG injection. Restricted to subjects with HCG injection. Number of observations per median value varied between 90 (day of HCG) and 38 (day 8) in the ganirelix group and between 85 (day of HCG) and 26 (day 8) in the placebo group. P = progesterone; E2 = estradiol.
became pregnant. This favours the idea that premature luteinization may have less favourable effects on oocyte quality, fertilization and implantation (Loumaye, 1990). However, in this study the considerably reduced incidence of premature luteinization in the ganirelix group did not increase the pregnancy rate in this group. Similar results have been reported in previous IUI studies on the effect of GnRH agonist/HMG treatment compared to HMG alone (Dodson et al., 1991; Sengoku et al., 1994). These studies also observed that the addition of GnRH agonist treatment did not result in an increased pregnancy rate, despite an effective reduction of premature luteinization. These results suggest that the success rates of IUI are only modestly affected by premature luteinization in comparison to other factors, such as the timing of triggering of ovulation and insemination.

Nevertheless, depending on the stimulation protocol applied, GnRH antagonist treatment may be considered for each patient undergoing IUI, especially for those with previous proven luteinization or spontaneous ovulation. In the current study, the duration of ganirelix treatment was only 3 days and the amount of rFSH needed to reach the same criteria for HCG was not increased by the GnRH antagonist. Because a low-dose, individualized rFSH treatment was used in this study, the median total rFSH dose was \(\sim 550\) IU over a period of 8 days only. This rFSH amount is less than half of the amount needed with the conventional and more aggressive gonadotrophin protocols in IUI treatment (Dodson et al., 1991; Sengoku et al., 1994, 1999).

In the current study, the ongoing pregnancy rates per initiated cycle were similar in both treatment groups: 12.6 and 12.0% for the ganirelix and placebo groups respectively. Importantly, the low-dose rFSH regimen was not associated with any high-order multiple gestations. The pregnancy rates are within the range of success rates reported for conventional COS/IUI studies per stimulated cycle, i.e. 8–18% (Dodson et al., 1991; Sengoku et al., 1994; Hannoun et al., 1998; Guizck et al., 1999; Gouverde et al., 2000; Matorras et al., 2002) and those of one recent open-label assessor-blind study comparing ganirelix versus no GnRH antagonist in IUI, i.e. 7–12% (Williams et al., 2004); but the rates are markedly lower than those reported by others, i.e. 34–38% (Ragni et al., 2004; Gomez-Palomares et al., 2005). Each of these studies was relatively small, but the current larger study was also not designed to assess a possible clinical relevant difference in pregnancy rates. Whether GnRH antagonist treatment indeed improves success rates by preventing premature luteinization and ovulation should be assessed in a much larger trial, in which the criteria for giving HCG are strict, to prevent advanced stimulation in the GnRH antagonist treatment group resulting in more ovulatory follicles and therefore in a higher (multiple) pregnancy rate.

Nevertheless, to improve the convenience for clinics in daily practice, less-restrictive demands for timing of insemination may be desired. Prevention of premature luteinization could reduce the strict requirements for timing of HCG injection and insemination, thus making the demands for extensive monitoring superfluous. Treatment with a GnRH antagonist at the end of stimulation prior to IUI may lower the cancellation risk for patients and provides more flexibility for the timing of HCG administration and insemination, thus avoiding the need for IUI during weekends.

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