

Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome

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BACKGROUND: During IVF or ICSI cycles, ovarian hyperstimulation syndrome (OHSS) is a major problem. The aim of this prospective, multicentre, comparative study (using historical controls) was to assess the efficacy of a GnRH antagonist protocol in preventing OHSS in selected patients who had experienced OHSS or had been at risk of OHSS in their previous IVF/ICSI attempt. **METHODS AND RESULTS:** Patients underwent a new cycle where the same gonadotrophin protocol was used [same dose of recombinant FSH (rFSH)] but a different protocol was used for pituitary desensitization: cetrorelix 0.25 mg multiple-dose antagonist instead of GnRH agonist long protocol. Cetrorelix 0.25 mg was administered daily, starting when the leading follicle reached a diameter of 14 mm. In other words, rFSH was administered in the new cycle according to the dosage and the step-up or step-down modalities used during the previous cycle, independently of ultrasound findings and serum estradiol (E₂) levels. Eighty-seven patients entered the study. Out of the 87 cycles involving GnRH agonists, 49 (56.3%) were cancelled and out of the 87 involving GnRH antagonists 28 (32.2%) were cancelled [McNemar's test; 95% confidence interval (CI) –35.8% to –11.2%; $P < 0.001$]. After GnRH agonist cycles, we recorded 24 cases of OHSS (18 moderate and six severe; 27.6%), whereas after the GnRH antagonist cycles there were 10 cases of OHSS (nine moderate and one severe; 11.5%) (95% CI –26.4% to –5.7%; $P = 0.006$). There was a statistically significant reduction in the total number of follicles with a diameter >10 mm (Wilcoxon's test; $Z = 6.1$; $P < 0.001$) and of E₂ levels on the day of HCG administration (2538 versus 4322.4 pg/ml; $P < 0.001$) in the GnRH antagonist cycles versus GnRH agonist cycles. Twenty-nine patients had an embryo transfer in the first cycle (76.3% of oocyte retrievals) and 57 in the cycle using GnRH antagonist (96.6%). This 20.3% difference was also significant (Z-test; 95% CI 6.8–36.0%; $P = 0.003$). After the antagonist cycles, 18 pregnancies (20.7 per initiated cycle; 31.6% per embryo transfer) were obtained. **CONCLUSIONS:** Although this study presents some limitations owing to the use of historical controls, our data show a favourable effect of GnRH antagonists in reducing the incidence of OHSS and the number of assisted fertilization cycles cancelled because of the risk of OHSS in high responder patients. As a consequence, GnRH antagonist plus gonadotrophin administration could also increase the percentage of oocyte retrievals and embryo transfers in this high risk group of patients.

Key words: GnRH antagonist/ICSI/IVF/ovarian hyperstimulation syndrome/recombinant FSH

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the major problems of ovarian stimulation during cycles of IVF or ICSI. OHSS occurs after triggering ovulation by HCG and is worsened by an ensuing pregnancy. Given its potentially fatal outcome, all efforts should be made to identify patients who are at high risk of developing OHSS and to minimize this risk by using appropriate ovarian stimulation therapy.

Although the incidence of the severe form of OHSS is low (0.5–5%) (Delvigne and Rozenberg, 2002), the large number of IVF/ICSI cycles performed every year throughout the

world means that a considerable number of patients are affected. Factors influencing the incidence of OHSS include age (Enskog *et al.*, 1999), body mass index (BMI) (Navot *et al.*, 1988), polycystic ovary syndrome (PCOS) (MacDougall *et al.*, 1992; Delvigne *et al.*, 1993), use of exogenous HCG to induce ovulation (Segal and Casper, 1992; Kulikowski *et al.*, 1995; Shalev *et al.*, 1995), luteal phase supplementation with HCG (Penzias, 2002) and, more importantly, the stimulation regimen. The incidence of OHSS is lower when clomiphene citrate is used for ovarian stimulation and increases when urinary or recombinant gonadotrophins are administered.

Moreover, the introduction of GnRH agonists in 1986 led to a large increase (six-fold) in the incidence of OHSS (Forman *et al.*, 1990; Asch *et al.*, 1991). More recently, there have been reports that the incidence of OHSS is lower when GnRH antagonists are used (Ludwig *et al.*, 2000; Olivennes *et al.*, 2000), although a systematic review of five randomized trials failed to demonstrate a significant reduction in the incidence of OHSS using GnRH antagonists instead of GnRH agonists in gonadotrophin regimens for ovarian stimulation (Al-Inany and Aboulghar, 2002). However, it should be said that the main focus of these five studies was pregnancy rate, and not OHSS prevention.

In contrast, another meta-analysis from Ludwig *et al.* (2001), in which more studies were included, showed a reduction in OHSS risk using the GnRH antagonist cetrorelix. Therefore, the available studies are insufficient to draw definitive conclusions on the advantage of using a GnRH antagonist instead of a GnRH agonist for patients at risk for OHSS.

The aim of this prospective, multicentre, comparative study with historical controls was to assess the efficacy of a GnRH antagonist protocol in preventing OHSS, used in selected patients found to have experienced OHSS or to have been at risk of OHSS in their previous IVF/ICSI attempt, using a GnRH agonist mid-luteal long protocol.

Materials and methods

This was a prospective, multicentre, comparative study with historical controls conducted in three different infertility centres in Italy. From January 2002 to December 2003, patients who were found to have experienced OHSS or to have been at risk of OHSS during their first IVF/ICSI cycle with a mid-luteal long GnRH agonist plus a gonadotrophin stimulation protocol were recruited. Each of the following findings, which occurred during the previous IVF/ICSI cycle (agonist cycle), was considered a risk factor for OHSS: estradiol (E₂) levels >4000 pg/ml on the day of HCG administration/cycle cancellation, >20 follicles with a mean diameter >10 mm on the day of HCG administration/cycle cancellation and development of moderate or severe OHSS after HCG administration. Other inclusion criteria were age <40 years, BMI between 19 and 30 kg/m² and basal FSH concentration (day 3 of the cycle) <12 IU/l. Exclusion criteria were the presence of systemic diseases or other conditions contraindicating pregnancy, previous breast or genital cancer, a previous cycle without GnRH agonist desensitization or more than one previous IVF/ICSI cycle.

All couples gave written informed consent to ovarian stimulation and IVF/ICSI protocol. After a washout period of 2–6 months after the previous IVF/ICSI cycle, the patients underwent a new cycle where the same gonadotrophin protocol was used [same dose of recombinant FSH (rFSH); β-follitropin: Puregon, Organon, The Netherlands; or α-follitropin: Gonal-F, Serono, Switzerland], but a different protocol was used for pituitary desensitization: cetrorelix 0.25 mg (Cetrotide; Serono) multiple-dose antagonist instead of GnRH agonist long protocol. Cetrorelix 0.25 mg was administered daily, starting when the leading follicle reached a diameter of 14 mm. In other words, rFSH was administered in the new cycle according to the dosage and the step-up or step-down modalities used during the previous cycle, independently of ultrasound findings and serum E₂ levels. If a patient required a rFSH dose reduction

because of OHSS risk, rFSH dosage was reduced and the cycle continued, but for final evaluation the patient was included among the number of stopped cycles. Urinary HCG (Profasi; Serono) was administered 36 h before oocyte pick-up, when the diameter of the leading follicle was at least 18 mm. The results obtained in each patient with GnRH antagonist were retrospectively compared with those obtained in the previous cycle using GnRH agonist.

The primary aim of this study was to compare the percentage of cycles stopped due to OHSS risk and the incidence of moderate or severe OHSS/initiated cycles. Secondary aims were to evaluate and compare outcomes of IVF/ICSI cycles in terms of E₂ levels on the day of HCG administration, number of follicles on the day of HCG administration, implantation rate and pregnancy rate.

Statistical methods

Data were analysed using paired analyses with comparison of proportions (McNemar’s test); 95% confidence intervals (CIs) were calculated. Wilcoxon’s test for rank comparison was applied for the number of follicles. Stating a 50% reduction in cancelled cycles and OHSS cases as being clinically relevant, and setting type I and type II error of 0.05 and 0.20, respectively, we calculated that the sample size should be 85 patients (Machin *et al.*, 1997).

Results

Eighty-seven patients entered the study. The baseline characteristics of the patients are shown in Table I. Seventy-one patients suffered from primary infertility and 16 from secondary infertility. The causes of infertility were male factors (54 couples; 62.1%), tubal factors (14 couples; 16.1%), mixed infertility (10 couples; 11.5%), unexplained infertility (six couples; 6.9%) and endometriosis (three couples; 3.4%).

Out of the 87 cycles involving GnRH agonists, 49 (56.3%) were cancelled and out of the 87 involving GnRH antagonists 28 (32.2%) were cancelled. This 24.1% difference was statistically significant (McNemar’s test; 95% CI–35.8% to –11.2%; *P* < 0.001) (Figure 1). After the GnRH agonist cycles we recorded 24 cases of OHSS (18 moderate and six severe; 27.6%), whereas after the GnRH antagonist cycles there were 10 cases of OHSS (nine moderate and one severe; 11.5%). The 16.1% difference in the incidence of OHSS was statistically significant (95% CI–26.4% to –5.7%; *P* = 0.006) (Figure 1).

Duration of gonadotrophin stimulation was 10.7 ± 12 days in GnRH agonist cycles versus 8.6 ± 2.0 days in GnRH antagonist cycles (*P* < 0.001; paired *t*-test). The amount of rFSH administered was 1572 ± 363 IU versus 1450 ± 282 IU in GnRH agonist and GnRH antagonist cycles, respectively (*P* = not significant; paired *t*-test). The mean duration of GnRH agonist was 25.7 ± 1.2 days, whereas the mean

Table I. Baseline characteristics of the 87 patients enrolled in the study

	Mean (SD)	Median (range)
Age (years)	32.3 (3.5)	32 (21–40)
Height (cm)	166.1 (5.6)	165 (150–180)
Weight (kg)	59.4 (8.2)	58 (48–86)
BMI (kg/m ²)	21.5 (2.4)	21.2 (16.6–31.6)
Age at menarche (years)	12.4 (1.4)	12 (9–16)
Duration of infertility (years)	4.6 (2.8)	4 (1–19)

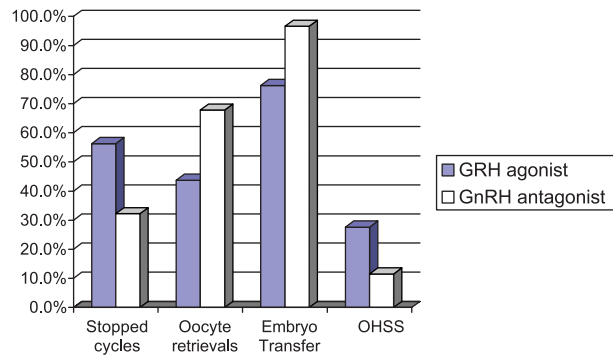


Figure 1. Comparison of stopped cycles, oocyte retrieval, embryo transfer and incidence of OHSS between the two treatment cycles (filled bars, GnRH agonist; empty bars, GnRH antagonist). Values are expressed in percentages; differences were statistically significant for stopped cycles and oocyte retrieval (both $P < 0.001$), embryo transfer ($P < 0.003$) and OHSS ($P < 0.006$).

duration of GnRH antagonist administration was 2.7 ± 1.2 days.

The mean number of follicles with a diameter > 10 mm, > 15 mm or > 18 mm on the day of HCG day administration after GnRH agonist or antagonist use are detailed in Table II. The only statistically significant difference was a reduction of the total number of follicles with a diameter > 10 mm in the GnRH antagonist cycles versus GnRH agonist cycles (Wilcoxon's test; $Z = 6.1$; $P < 0.001$).

The comparison of E_2 levels on the day of HCG administration of patients who underwent oocyte pick-up showed a lower value in GnRH antagonist cycles compared with GnRH agonist cycles (2538 versus 4322.4 pg/ml; $P < 0.001$).

Oocyte retrieval was obtained in 38 patients in the cycle with the GnRH agonist (43.7% per initiated cycle) and in 59 patients in the cycle with the GnRH antagonist (67.8% per initiated cycle). This 24.1% increase was statistically significant (McNemar's test; 95% CI 12.2–35.8%; $P < 0.001$) (Figure 1).

Twenty-nine patients had an embryo transfer in the first cycle (76.3% of retrievals) and 57 in the cycle using GnRH antagonist (96.6% of retrievals). The 20.3% difference was significant (Z-test; 95% CI 6.8–36.0%; $P = 0.003$) (Figure 1).

After the antagonist cycles, 18 pregnancies (20.7 per initiated cycle; 31.6% per embryo transfer) were obtained: 10 clinical pregnancies (one twin and nine singleton pregnancies), one first trimester miscarriage, two ectopic pregnancies and five biochemical pregnancies. The implantation rate in this cycle was 9.3%.

Discussion

GnRH agonists have been widely used since the mid-1980s in order to prevent the surge of LH in IVF/ICSI cycles. Since their introduction in 1986, the incidence of severe OHSS has been reported to have increased six-fold compared with the incidence in IVF cycles stimulated by clomiphene/HMG only (Delvigne and Rozenberg, 2002). GnRH agonist use leads to an increase in the number of oocytes retrieved, in E_2 levels, in the number of corpora lutea and in the incidence of OHSS (MacDougall *et al.*, 1992; Rizk and Smits, 1992; Mordel and Schenker, 1993).

In the late 1990s, a third generation of GnRH antagonists became available: these compounds suppress gonadotrophin release by competitive receptor binding resulting in an immediate suppression and blockage of gonadotrophin secretion rather than pituitary desensitization. The safety and efficacy of GnRH antagonists and agonists in IVF and ICSI cycles have been reported to be similar (Albano *et al.*, 2000; European Orgalutran Study Group, 2000; Olivennes *et al.*, 2000; European-Middle East Orgalutran Study Group, 2001; Fluker *et al.*, 2001). GnRH antagonists are now part of the therapeutic options of infertility units worldwide.

In the study by Albano *et al.* (2000), stimulation with cetrorelix plus HMG was compared with buserelin plus HMG: in the cetrorelix-treated patients a shorter duration of stimulation and a lower number of ampoules of HMG were described. In the antagonist group a significantly lower incidence of OHSS was also observed (1.1% versus 6.5% in the buserelin group; $P < 0.03$). These data were confirmed when the other GnRH antagonist on the market, ganirelix, was tested in another multicentre study (European Orgalutran Study Group, 2000). In this latter study a reduced duration of stimulation and a lower amount of rFSH ampoules were needed in the ganirelix-treated patients compared with patients treated with buserelin. The incidence of OHSS was also reduced in the antagonist group (2.4% versus 5.9% in the buserelin group). Therefore, the results seem to be related to the antagonist protocol rather than to a particular antagonist choice (cetrorelix or ganirelix), at least when compared with buserelin. Results seem also to be independent of the use of HMG or rFSH. In other two clinical trials, the incidence of OHSS was reported to be reduced using GnRH antagonists rather than the GnRH agonist long luteal protocol (Ludwig *et al.*, 2000; Olivennes *et al.*, 2000), although a systematic review and meta-analysis including five randomized trials failed to confirm this finding (Al-Inany and Aboulghar,

Table II. Number of follicles after ovarian stimulation in GnRH agonist and antagonist cycles on the day of HCG administration, divided according to mean diameter

Number of follicles of:	GnRH agonist cycle	GnRH antagonist cycle	<i>P</i> -value
> 10 mm mean diameter	27.0 ± 7.1	19.6 ± 9.7	< 0.001
> 15 mm mean diameter	12.5 ± 9.6	10.6 ± 8.5	NS
> 18 mm mean diameter	6.0 ± 6.8	4.7 ± 5.1	NS

NS = not significant.

2002). However, it should be noted that, with the exception of the study by Ludwig *et al.* (2000), none of the above-mentioned studies was specifically designed to determine differences in OHSS incidence between the two treatment protocols. Moreover, the patients studied were usually normo-responders, and in two of these studies, PCOS patients were excluded (Albano *et al.*, 2000; Olivennes *et al.*, 2000); therefore, they recorded a low total incidence of OHSS. Another meta-analysis published in 2001 showed a reduction in OHSS risk for the antagonist cetrorelix only (Ludwig *et al.*, 2001).

Since OHSS incidence seems to be related to the stimulation regimen used, and in particular to the amount of gonadotrophin administered, a comparison between agonist and antagonist use should be carried out, comparing cycles using the same FSH treatment protocol (the same FSH product and the same timing for dose adjustments). This is the reason for our study design, where each patient was compared with her own previous cycle (historical control). In the new cycle, the same amount of rFSH that was used during the first cycle was administered. The only difference between the two cycles was that a GnRH antagonist was used in the new cycle (multiple dose protocol) instead of a GnRH agonist used in the previous cycle (long luteal protocol). We included patients considered at high risk of OHSS because they had experienced OHSS in the first treatment cycle or because their first cycle had been stopped due to high E_2 serum levels or a high number of follicles, factors that are both generally considered as risk factors for OHSS (Cooke, 1970; Haning *et al.*, 1983; Navot *et al.*, 1988; Asch *et al.*, 1991; Enskog *et al.*, 1999; Marthur *et al.*, 2000).

This study design presents some inconveniences: pregnant patients are excluded from the second treatment cycle and ovarian response could be reduced over time. To minimize the possibility of the latter bias, we performed the second cycle as soon as possible after the first cycle (2–6 months).

In our study, ovarian stimulation with a GnRH antagonist proved to be more frequently successful, and oocyte retrieval could be performed significantly more frequently and with a reduced risk compared with cycles using GnRH agonists. The incidence of OHSS was significantly reduced in the GnRH antagonist cycles. This result was probably due to the shorter stimulation in the antagonist cycles, to the lower number of follicles and the lower E_2 levels on the day of HCG administration found in this group. Data on reduction of the ovarian stimulation duration and of the gonadotrophin amount needed for each patient are consistent with findings reported by other studies comparing mid-luteal GnRH agonist and GnRH antagonist protocols (Albano *et al.*, 2000; Olivennes *et al.*, 2000; Al-Inany and Aboulghar, 2002). Patients treated with GnRH antagonist reached oocyte retrieval more promptly, with a reduced amount of gonadotrophin administered.

The data show that ovarian stimulation using a GnRH antagonist could produce a more physiological follicular selection than the long luteal GnRH agonist protocol, recruiting a smaller number of follicles and thus reducing OHSS risk.

Raga *et al.* (2002) proposed an interesting hypothesis regarding the lower OHSS rates observed in antagonist cycles. In a recent prospective, randomized study, higher vascular endothelial growth factor mRNA and protein levels in IVF patients treated with GnRH agonists were found than in patients treated with GnRH antagonists, providing a hypothetical biological explanation for our findings.

In conclusion, our data show a favourable effect of GnRH antagonists in reducing the incidence of OHSS and the number of assisted fertilization cycles cancelled because of the risk of OHSS in high responder patients. As a consequence, GnRH antagonist plus gonadotrophin administration could also increase the percentage of oocyte retrievals and embryo transfers in this high risk group of patients. Further prospective randomized controlled trials focusing on this issue should be conducted to confirm our findings and support our belief that a GnRH antagonist regimen is more suitable in patients at risk of OHSS.

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