Article

Comparative efficacy and safety of cetrorelix with or without mid-cycle recombinant LH and leuprolide acetate for inhibition of premature LH surges in assisted reproduction

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Abstract

An open label, randomized, multi-centre study was performed to compare cetrorelix and leuprolide acetate for prevention of premature LH surge and to assess whether patients treated with cetrorelix benefit from addition of recombinant human (r-h)LH. Normo-ovulatory women (n = 74) undergoing ovarian stimulation prior to intracytoplasmic sperm injection were treated with leuprolide acetate (n = 25) before ovarian stimulation with recombinant human FSH (r-hFSH) or with cetrorelix 3 mg on stimulation day 7 (with (n = 25) or without (n = 24) r-hLH 150 IU on days 7–10). The main outcome measures were the number of metaphase II (MII) oocytes retrieved; secondary efficacy end-points; adverse events (AE) and other safety measures. There were no significant differences between groups for MII oocytes retrieved, duration of stimulation, total r-hFSH dose and pregnancy rates. The group treated with cetrorelix alone had a significantly lower concentration of oestradiol per follicle compared with the other groups. The majority of AE were mild to moderate in severity. Cetrorelix and leuprolide acetate appear to have comparable efficacy and safety, although cetrorelix has the advantage of typically requiring only one injection.

Keywords: *cetrorelix, clinical trials, leuprolide acetate, ovarian stimulation, pituitary down-regulation, recombinant human LH*

Introduction

Ovulation follows a surge in the release of LH from the pituitary in response to rising concentrations of oestradiol produced by the maturing ovarian follicle (Zeleznik and Hillier, 1984; Hillier, 1994). However, the development of multiple follicles in infertile women receiving gonadotrophin therapy as part of an assisted reproductive technology programme typically result in supraphysiological high oestradiol concentrations in the early follicular phase. This in turn can induce a premature LH surge, causing luteinization of immature follicles, developmental arrest and cancellation of IVF cycles (Stanger and Yovich, 1985; Devroey *et al*., 1994).

Premature LH surges can be controlled by the desensitization of the pituitary to gonadotrophin-releasing hormone (GnRH) through exposure to exogenous GnRH agonists. These long-acting GnRH analogues initially stimulate the pituitary, but continued use results in receptor down-regulation and suppression of LH release (Macnamee and Brinsden, 1992). This effect has been successfully exploited in assisted

reproduction, leading to a significant increase in pregnancy rate per IVF cycle initiated (Barbieri and Hornstein, 1999).

Suppression of endogenous LH release may also be achieved by the use of GnRH antagonists such as cetrorelix (Cetrotide®; Serono Inc., Rockland, MA, USA). These agents cause an immediate suppression of LH release without transient stimulation, and so require a shorter exposure, the mean duration of treatment being 5 days. Moreover, GnRH antagonists may be initially administered during the follicular phase of a treatment cycle, permitting a more rapid therapeutic response to rising patient oestrogen concentrations and great flexibility in cycle control (Diedrich *et al*., 1994; Olivennes *et al*., 1995). Cetrorelix has been reported to be a safe and effective treatment for the prevention of premature ovulation in clinical trials (Felberbaum *et al*., 2000; Elter and Nelson, 2001).

The combination of GnRH agonist treatment with oral contraceptive pill (OCP) programming is a common practice in assisted reproduction centres and has been associated with a reduced incidence of residual cysts produced by the traditional long luteal protocol for GnRH agonists. Preliminary studies have shown the combination of GnRH antagonists with OCP programming to be effective, well tolerated, convenient and patient friendly (O'Brien *et al*., 2000). However, further data are required to elucidate the best programming protocol.

FSH stimulates the development of oocyte-bearing ovarian follicles, and exogenous FSH alone is clinically effective in stimulating follicle development (Shoham *et al*., 1993a). FSH is used for the treatment of WHO group II anovulatory women and for the recruitment of multiple follicles in cycles for assisted reproduction. However, since LH activity is required for maturation of the follicle and ovulation induction (Berger and Taymor, 1971; Filicori *et al*., 1999), the concomitant suppression of LH concentrations through co-administration of a GnRH antagonist might be expected to disrupt follicle development, as reported in some GnRH agonist cycles (Fleming *et al*., 1998). As cetrorelix strongly suppresses LH, the use of recombinant human LH (r-hLH) at mid-cycle in IVF cycles with GnRH antagonists might provide 'add-back' benefits in terms of follicle development and oocyte maturity.

The present study was performed to compare the safety and efficacy of the GnRH antagonist cetrorelix and the agonist leuprolide acetate (Lupron®; TAP Pharmaceuticals, Chicago, IL, USA) for the inhibition of a premature LH surge in normo-ovulatory women undergoing ovarian stimulation with recombinant human FSH (r-hFSH) prior to intracytoplasmic sperm injection (ICSI). An additional objective was to assess the necessity of adding r-hLH mid-cycle to an r-hFSH stimulatory cycle for follicle development in conjunction with the administration of cetrorelix. OCP programming was used for all cycles.

Materials and methods

Study design

This was an open label, randomized, multi-centre study. All patients provided written informed consent. The study was approved by the relevant Institutional Review Board or Independent Ethics Committee at each participating centre.

Patients

A total of 74 infertile women (aged 18–39 years) who were planning to undergo ICSI on their physician's recommendation were recruited and randomized equally into three treatment groups. Women were eligible for inclusion if all of the following criteria were satisfied within three menstrual cycles prior to randomization: regular menstrual cycles, body mass index (BMI) <35 kg/m^2, both ovaries present, no clinical signs of pelvic or uterine abnormalities, normal cervical cytology, wash-out period completed for any previous IVF drug protocols and FSH concentrations in the normal range. All women were also required to be willing and able to comply with the study protocol.

The principal exclusion criteria included clinically significant systemic disease, infection with human immunodeficiency virus, hepatitis C or B viruses, the presence of endometriosis or medical conditions likely to interfere with the study drug. Women were also excluded if previous assisted reproduction cycles had failed through insufficient response to gonadotrophin stimulation or absence of motile spermatozoa, or if they had undergone three or more consecutive assisted reproduction cycles without a clinical pregnancy, or had a history of extrauterine pregnancy or abnormal gynaecological bleeding.

Drugs and treatment protocols

Patients were randomly assigned to three treatment groups using a computer-generated, Internet-based system (**Figure 1**). Group A received leuprolide acetate (Lupron®; TAP Pharmaceuticals) for pituitary down-regulation and r-hFSH (Gonal-f® in multi-dose vials of 450 IU or 1050 IU; Serono Inc.) for ovarian stimulation. Group B received cetrorelix (Cetrotide®; Serono Inc.) for down-regulation and r-hFSH for ovarian stimulation. Group C was treated with cetrorelix and r-hFSH together with mid-cycle r-hLH (Luveris®; Serono).

All patients took an oral contraceptive (Orthocept® 21, Ortho-McNeil, Raritan, NJ, USA; 0.15 mg desogestrel and 0.03 mg ethinyl oestradiol) from the first day of menses for 14–28 days. Women in groups B and C received an injection of cetrorelix, 3 mg subcutaneously (s.c.), on day 7 of the FSH stimulation cycle (day S7). If the patient did not achieve follicle maturation and receive recombinant human chorionic gonadotrophin (r-HCG) by day S11, an injection of cetrorelix, 0.25 mg s.c., was administered on day S11 and on each proceeding day up to, but not including, the day of r-HCG administration. Women in group A received daily injections of leuprolide acetate, 0.5 mg s.c., starting during the mid-luteal phase of the cycle, with a low-dose, long luteal phase protocol, which overlapped OCP treatment for at least 7 days. Following evidence of pituitary desensitization (ultrasound confirmation of lack of pre-existing cysts or follicles >25 mm and oestradiol <50 pg/ml), the dose was reduced to 0.25 mg s.c. daily. Leuprolide therapy was continued for a maximum of 25 days for down-regulation, following which time the patient was withdrawn from the study if there was no evidence of menses or pituitary desensitization.

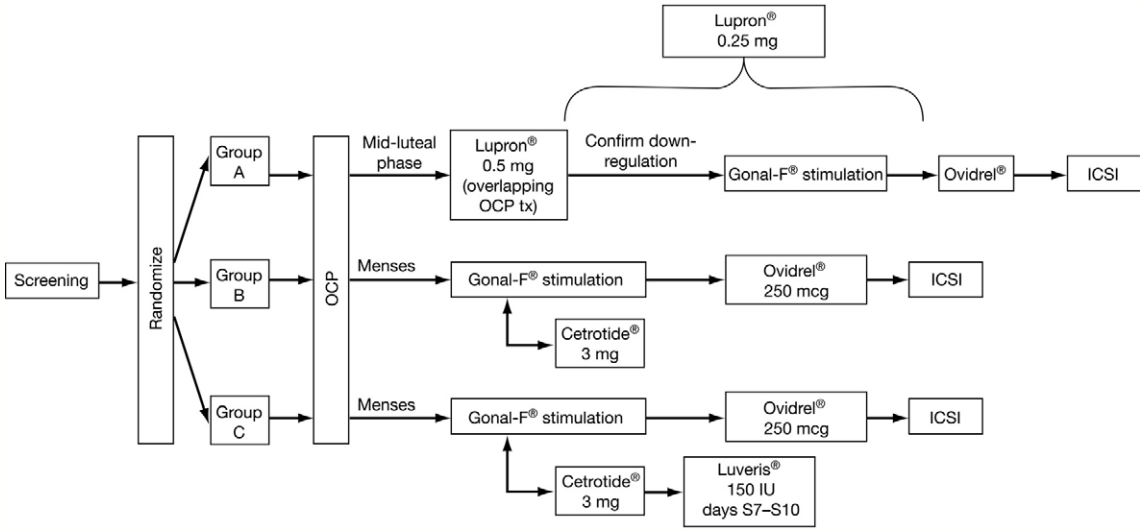

Figure 1. Summary of treatment regimens. If a patient receiving cetrorelix (Cetrotide®) 3 mg did not achieve follicle maturation and receive recombinant human chorionic gonadotrophin (r-HCG) by 4 days after treatment (stimulation day 11), an injection of cetrorelix, 0.25 mg s.c., was administered on that day and on each proceeding day up to, but not including, the day of r-HCG administration. OCP = oral contraceptive pill.

r-hFSH, 225 IU s.c., was administered to group A patients on confirmation of down-regulation and 5 days after the last OCP, while patients in groups B and C started this regimen 5 days after the last OCP. From day S6, the dose was individualized according to patient response, with doses in the range of 75–450 IU daily. Women in group C received r-hLH, 150 IU s.c., on days S7–S10 following the cetrorelix injection and at the same time as the r-hFSH injection.

To induce final follicle maturation before patients underwent the ICSI procedure, r-HCG (Ovidrel®; Serono Inc.), 250 µg s.c., was administered within 36 h of the last r-hFSH injection. Criteria for r-HCG administration were: presence of at least one follicle with a mean diameter ≥18 mm, at least two other follicles with a mean diameter ≥16 mm and a serum oestradiol concentration within an acceptable range, according to the centre's standard practice (approximately 150 pg/ml per mature follicle). Serum LH, oestradiol and progesterone were measured on the day of HCG administration.

Progesterone could be administered for luteal phase support according to the standard practice at each of the study centres involved. Following ICSI, no more than three embryos were to be replaced; two if transferred at blastocyst stage.

End-points

The primary efficacy end-point was defined as the number of metaphase II oocytes retrieved per patient. Secondary efficacy end-points were the duration and total dose of r-hFSH therapy, the total number of follicles ≥14 mm on the day of r-HCG administration, oocyte and embryo quality and development, the number of patients with at least one embryo considered viable for cryopreservation, oestradiol concentration per follicle >10 mm, total number of oocytes fertilized, implantation rates per embryos transferred and pregnancy rates (biochemical and clinical).

Safety

Safety assessments included recording via a patient diary of the incidence and severity of adverse events (AE), the incidence and severity of symptoms related to the ovarian hyperstimulation syndrome (OHSS), the local tolerability of study drugs and the extent of exposure to study drugs.

Statistical methods

Approximately 72 patients were to be randomized to this study. The sample size was not based on statistical considerations, since the study was intended to provide preliminary information on the objectives stated previously.

Statistical analyses were performed using Statistical Analysis System® Version 6.12 software. The primary efficacy end-point, the number of metaphase II oocytes retrieved, was analysed by two-way analysis of variance (ANOVA). Continuous secondary end-points were analysed by ANOVA, while dichotomous parameters were analysed using logistic regression. Nominal- and ordinal-scaled parameters with >2 levels were analysed using the Cochran–Mantel–Haenszel (CMH) general association test and row means score test, respectively.

All patients receiving at least one injection of r-hFSH were included in the intent-to-treat (ITT) population. Efficacy analyses were also performed on a secondary data set (the evaluable population), which included those patients who received at least one injection of r-hFSH, and who completed the assessments for the primary study end-point with no major deviation from eligibility criteria or treatment plan. Analysis of safety was performed on all patients who received at least one dose of OCP (all treated patients set).

Results

Demographic and baseline characteristics

The all-treated-patients population comprised 74 women, of whom 73 formed the ITT population. Mean age (±SD) of the ITT population was 32.6 ± 4.0 years. The age range was broad (22–39 years) and there were no significant differences between the three treatment groups. Mean BMI was 24.2 ± 4.5 kg/m^2, again with no significant differences between groups. Fifty-one of the 73 women in the ITT population (69.9%) were Caucasian and the proportion of Caucasians did not differ between treatment groups.

Forty women (54.8%) had primary infertility and 33 (45.2%) had secondary infertility. These proportions were similar across the three treatment groups. For all patients in the study, the main cause of infertility was male infertility (76.7%, 56/73), followed by tubal factor (24.7%, 18/73).

Efficacy results

Concerning the primary end-point of the study, the median number of metaphase II oocytes retrieved was 11 for the leuprolide and cetrorelix groups and 10 for the cetrorelix + r-hLH group (not significant). Similarly, no significant differences were found between the three treatment groups with respect to the majority of secondary efficacy end-points in those who received r-HCG (**Table 1**). The mean oestradiol concentration per follicle >10 mm on the day of r-HCG administration was significantly lower in group B (cetrorelix) than in the other two groups ($P < 0.001$ versus leuprolide; $P = 0.022$ versus cetrorelix + r-hLH). Serum concentrations of LH and oestradiol on the day of HCG administration were slightly lower in the cetrorelix group compared with the other two groups, while mean serum progesterone was slightly higher (**Table 2**). Pregnancy rates were similar for the three treatment groups (**Table 1**).

Safety

Of 74 patients, 17 (23.0%) reported AE. The most-frequently reported events were headache, nausea, abdominal pain, abdominal distension, and OHSS. Overall, the three treatment groups were similar with regard to the incidence of AE (group A: seven patients, 20 events; group B: four patients, nine events; group C: six patients, 12 events). The majority of events in each group were judged unlikely to be related to the study medication. The majority of AE were judged to be mild (31 events) or moderate (nine events) in severity. One severe event (injection-site pain on the day of r-HCG administration) was reported in group A.

One patient in each treatment group reported moderate OHSS. All three patients were pregnant: the group A patient had three fetal sacs, the group B patient was clinically pregnant with one fetal sac, and the patient from group C had a multiple pregnancy with two fetal sacs, which was considered a serious AE requiring hospitalization; the case was resolved after 7 days of intravenous rehydration.

Discussion

In this study, cetrorelix showed comparable safety and efficacy to leuprolide acetate in normo-ovulatory women undergoing ovarian stimulation with r-hFSH prior to ICSI. The results must, however, be considered preliminary in view of the small sample size and lack of a statistical power calculation.

Oestradiol concentrations were decreased in the cetrorelix group, an observation reported by other investigators (Olivennes *et al.*, 1998). The risk of OHSS has been linked to elevated oestradiol concentrations and, therefore, would be expected to decrease with the faster action of cetrorelix in comparison with GnRH agonists (Rizk and Smitz, 1992), although no such effects were observed in this study. However, the initial 'flare up' response to GnRH agonists has been associated with oestrogen withdrawal syndrome symptoms, causing side-effects such as hot flashes, headaches and premature bleeding (Frydman *et al.*, 1988). It is notable that there appeared to be a trend toward a reduced frequency of AEs among patients who received cetrorelix compared with those who received leuprolide acetate. Furthermore, cetrorelix has the advantage of potentially requiring only a single injection in comparison with the low-dose, long luteal phase protocol of leuprolide acetate, which comprises daily injections over 7–25 days. In this study, the use of cetrorelix was confirmed as effective, well tolerated, convenient and patient friendly.

The addition of r-hLH to the ovulation stimulation regimen in normo-ovulatory women receiving cetrorelix did not provide a clinically significant improvement in treatment outcomes in this study. Cédrin-Durnerin and colleagues have recently reported similar results from a prospective randomized study in which women received r-hLH 75 IU or no supplementary LH from GnRH antagonist (cetrorelix 3 mg) initiation to the day of HCG administration (Cédrin-Durnerin *et al.*, 2004). The present findings are also in line with the recent study by Marrs and colleagues (Marrs *et al.*, 2004), who reported that women aged <35 years did not benefit from supplementation with r-hLH (150 IU daily from stimulation day 6). However, low endogenous LH concentrations in the late follicular phase of an IVF cycle have been associated with significantly lower fertilization rates and a trend toward early pregnancy loss (Westergaard *et al.*, 2000; Esposito *et al.*, 2001). LH concentrations in this study were comparably low in all three treatment groups, although considerable individual variation was recorded (leuprolide group: mean 2.0 IU/l, range 0.8–3.6; cetrorelix group: mean 0.8 IU/l, range 0.1–4.0; cetrorelix + r-hLH group: mean 2.1 IU/l, range 0.2–12.5). Van Loenen and colleagues also reported low concentrations of LH during stimulation in patients treated with cetrorelix combined with OCP programming (van Loenen *et al.*, 2002) and suggested the addition of recombinant LH to prevent excessive LH depletion. However, these authors did not provide any data on the effects of treatment on pregnancy rates. Since LH is responsible for reinstating meiosis I in the pre-ovulatory follicle (Shoham *et al.*, 1993b) and plays a primary role in the complete maturation of the follicle, resulting in oocytes capable of fertilization (Balasch *et al.*, 1995), the patient's endogenous concentrations of LH are likely to be a critical factor in the success of treatment.

Table 1. Summary of end-points (for patients in the ITT population who received r-HCG). r-hFSH = recombinant human FSH.

	Statistics	*Leuprolide acetate (P-value[a])*	*Cetrorelix (3 mg)*	*Cetrorelix (3 mg) + r-hLH (P-value[b])*
Duration (days) of stimulation required	No. of patients	23	21	21
	Mean (SD)	9.7 (1.7)	9.3 (1.1)	9.4 (1.7)
	Median	9.0	9.0	9.0
	Range	5.0–13.0	8.0–11.0	6.0–13.0
	P-value	0.282[c]		0.974[c]
Total dose (IU) of r-hFSH used	No. of patients	23	21	21
	Mean (SD)	2230.4 (629.6)	2228.6 (359.8)	2214.2 (612.0)
	Median	2025	2250.0	2025.0
	Range	1125.0–3525.0	1725.0–3000.0	1275.0–3600.0
	P-value	0.679[d]		0.323[d]
Number of follicles ≥14 mm on day of HCG administration	Number of patients	23	21	21
	Mean (SD)	13.2 (5.7)	13.7 (8.1)	14.1 (8.6)
	Median	13.0	12.0	11.0
	Range	3.0–26.0	4.0–41.0	6.0–42.0
	P-value	0.971[c]		0.974[c]
Oestradiol concentration (pg/ml) per follicle >10 mm on day of hCG administration	Number of patients	17	17	20
	Mean (SD)	204.7 (105.2)	110.1 (69.1)	158.4 (79.8)
	Median	205.6	99.4	127.6
	Range	58.6–429.5	10.4–305.5	66.7–330.2
	P-value	<0.001[e]		0.022[e]
Number of 2PN fertilized oocytes per patient	Number of patients	23	21	21
	Mean (SD)	9.5 (5.0)	9.3 (5.4)	10.1 (7.6)
	Median	8.0	8.0	7.0
	Range	1.0–19.0	2.0–19.0	4.0–32.0
	P-value	0.880[c]		0.0753[c]
Number of 2PN cleaved embryos	Number of patients	22	21	20
	Mean (SD)	9.8 (5.0)	9.2 (5.3)	9.2 (6.9)
	Median	9.5	8.0	6.5
	Range	1.0–19.0	2.0–19.0	0.0–29.0
	P-value	0.699[c]		0.634[c]
Implantation rate (%) per embryo transferred	Number of patients	23	21	21
	Mean (SD)	30.4 (38.8)	23.8 (25.6)	29.7 (37.3)
	Median	0.0	33.3	0.0
	Range	0.0–100.0	0.0–66.7	0.0–100.0
	P-value	0.874[d]		0.855[d]
Number of transferred/ cryopreserved embryos	Number of patients	23	21	21
	Mean (SD)	6.0 (4.1)	4.5 (2.4)	5.1 (5.1)
	Median	4.0	3.0	3.0
	Range	1.0–15.0	2.0–10.0	2.0–25.0
	P-value	0.253[c]		0.802[c]
Number of patients with at least one embryo considered viable for cryopreservation	Number of patients			
	23	21	21	
	Yes, *n* (%)	11 (47.8)	9 (42.9)	9 (42.9)
	No, *n* (%)	12 (52.2)	12 (57.1)	12 (57.1)
	P-value	0.738[f]		>0.999[f]
Pregnancies, *n* (%)	Number of patients	23	21	21
	Total pregnancies	11 (47.8)	12 (57.1)	11 (52.4)
	Biochemical	0	1 (4.8)	1 (4.8)
	Clinical	11 (47.8)	11 (52.4)	10 (47.6)

[a]Cetrorelix versus leuprolide acetate.
[b]Cetrorelix versus cetrorelix + r-hLH.
[c]*P*-value from an ANOVA model on ranked data with effects for treatment and centre.
[d]*P*-value from an ANOVA model on ranked data with effects for treatment, centre and interaction.
[e]*P*-value from an ANOVA model on raw data with effects for treatment and centre.
[f]Logistic regression.

Table 2. Serum hormone concentrations on the day of HCG administration (ITT population who received HCG).

Serum hormone	*Statistics*	*Leuprolide acetate*	*Cetrorelix (3 mg)*	*Cetrorelix (3 mg) + r-hLH*	*All patients*
LH (IU/l)	*n*	18	18	20	56
	Mean (SD)	2.0 (0.8)	0.8 (0.9)	2.1 (2.6)	1.6 (1.8)
	Median	1.9	0.5	1.6	1.3
	Range	0.8–3.6	0.1–4.0	0.2–12.5	0.1–12.5
Oestradiol (pg/ml)	*n*	17	17	20	54
	Mean (SD)	2931.2 (1603.3)	1540.0 (951.2)	2440.5 (1181.7)	2311.5 (1367.5)
	Median	2915.0	1193.0	2351.5	2061.5
	Range	505.0–6443.0	435.0–3971.0	734.0–4536.0	435.0–6443.0
Progesterone (ng/ml)	*n*	17	17	20	54
	Mean (SD)	1.7 (1.0)	1.9 (1.0)	1.7 (0.9)	1.8 (0.9)
	Median	1.5	1.7	1.4	1.6
	Range	0.4–4.8	0.5–4.3	0.9–4.1	0.4–4.8

It is well established that patient sensitivity to GnRH agonists is variable (Butt, 1988), requiring titration against oestradiol to determine the appropriate dose. The use of extensive monitoring of the ovarian response to GnRH therapy, including frequent ultrasonography to determine follicle maturity, results in improved pregnancy rates (March, 1987) and forms a central element in providing a therapeutic regimen tailored to individual patient needs. Studies in women with WHO group I (hypogonadotrophic hypogonadal, HH) infertility have revealed a dose threshold of r-hLH for effective promotion of follicle development (European Recombinant Human LH Study Group, 1998). In conjunction with the LH 'ceiling' described by the Recombinant LH Study Group (Loumaye *et al.*, 2003), in which excessively high concentrations of LH caused a spectrum of effects, including complete or selective arrest of follicle growth and impaired ability to luteinize, this clinical threshold delineates a therapeutic window for LH to ensure effective follicle maturation and viable oocytes in the late follicular phase. It would appear critical, therefore, that the administration of GnRH analogues for the suppression of premature LH surges should not decrease the concentrations of endogenous LH below this therapeutic window. Consequently, protocols for ovarian stimulation should include close monitoring of responses to therapy to enable the regimen to be tailored to the varying requirements of individual patients, as is already employed in the management of HH women (ESHRE Capri Workshop Group, 1995; American Society for Reproductive Medicine, 1998; Burgues and Spanish Collaborative Group on Female Hypogonadotrophic Hypogonadism, 2001). The addition of r-hLH to the ovarian stimulation regimen should be considered when periovulatory serum LH concentrations are low (Esposito *et al.*, 2001).

In this study, cetrorelix was administered on day 7 of stimulation in all patients. However, the rapid onset of action of cetrorelix, and the availability of two different doses, means that treatment can potentially be given on an individual basis during the follicular phase of the cycle. The potential to further improve outcomes for patients by using variable rather than fixed start dates for GnRH antagonist treatment deserves investigation.

In conclusion, a single 3 mg administration of the GnRH antagonist cetrorelix combined with r-hFSH for ovarian stimulation seems to be comparable with a long GnRH agonist protocol in terms of number of MII oocytes retrieved. Other outcome parameters also appeared to be similar between the groups. Further prospective studies are required to substantiate these findings. The results were not different whether r-hFSH alone or r-hFSH + r-hLH was used. In addition, the immediate action of cetrorelix means that it only needs to be administered for a short period, so improving the patient's acceptance of the treatment.

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