Application of GnRH antagonist in combination with clomiphene citrate and hMG for patients with exaggerated ovarian response in previous IVF/ICSI cycles

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Abstract

Purpose To investigate if the combination of clomiphene citrate, hMG, and cetrorelix (CC/hMG/cetrorelix protocol) can be applied to patients who had excessive response to GnRHa long protocol.

Methods Fifty patients who coasted and failed to conceive in their first cycles stimulated with GnRHa long protocol were stimulated with CC/hMG/cetrorelix protocol. The peak serum estradiol levels, the need of coasting and prolonged coasting (≥ 4 days), and the incidences of OHSS were compared.

Results The peak estradiol level was significantly lower with CC/hMG/cetrorelix protocol compared to GnRHa long protocol. With CC/hMG/cetrorelix protocol, only four patients (8%) needed coasting and no one coasted ≥ 4 days. In contrast, in the first cycles, 11 patients (22%) needed coasting ≥ 4 days. The incidence of moderate OHSS was significantly lower with CC/hMG/cetrorelix protocol.

Conclusions The CC/hMG/cetrorelix protocol is an acceptable alternative protocol for patients who had excessive response to GnRHa long protocol.

Keywords Cetrorelix · Coasting · GnRH agonist · GnRH antagonist · Ovarian hyperstimulation syndrome

Clomiphene citrate/hMG/cetrorelix protocol is a good alternative for patients who had excessive response to GnRHa long protocol.

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Introduction

Obtaining multifollicular growth is the goal of ovarian stimulation for assisted reproductive technologies. One of the most severe and potentially life-threatening complications of ovarian stimulation, however, is ovarian hyperstimulation syndrome (OHSS), which occurs in 1–10% of IVF cycles [1]. The risk factors associated with OHSS are younger age, asthenic habitus, rapidly increasing estradiol (E2) levels, high preovulatory serum E2 levels, large number of follicles during ovarian stimulation, polycystic ovary syndrome (PCOS), and the presence of ultrasound-detected polycystic ovaries [1–3]. Moreover, after the introduction of gonadotropin-releasing hormone agonist (GnRHa), a sixfold increase in the incidence of severe OHSS has been observed relative to the clomiphene citrate (CC)/human menopausal gonadotropin (hMG) protocol [3].

Since GnRHa prevents LH surge, more follicles will develop to full or near maturation, with a consequent rise in E2 levels and an increased risk of OHSS.

Several strategies have been used to prevent severe OHSS, including coasting, cancellation of oocyte retrieval, elective freezing of all the embryos, and intravenous albumin infusion [2, 4]. Among those, coasting appears to be the most frequently used for the prevention of OHSS [5]. This approach is based on the assumption that serum E2 levels on the day of hCG injection are predictive of the risk of OHSS [3]. Coasting involves cessation of exogenous gonadotropin stimulation when serum E2 and the number and size of growing follicles reach a certain threshold. GnRHa is maintained and the administration of hCG is postponed until serum E2 levels decrease to a safer range [3, 6]. Although coasting results in satisfactory pregnancy rate (36.5–63%) and low incidence of severe OHSS (<2%) [6], it increases patients' inconvenience and cost. Besides, coasting ≥ 4 days has been reported to reduce the implantation and pregnancy rates [6–8].

Among the different stimulation protocols available, GnRHa long protocol is the most commonly used and is generally considered the most effective [9]. Some women, however, develop excessive ovarian response or even OHSS despite coasting. Since GnRHa suppression confers a risk for OHSS [2, 3] and patients who have a history of excessive ovarian response or OHSS are prone to develop it again in subsequent cycles [2, 4], some modification of the stimulation protocol must be made in next cycle.

Recently, there has been a trend to use mild or “soft” stimulation protocol to reduce multiple pregnancies and the complications association with ovarian stimulation. The introduction of GnRH antagonists makes soft stimulation possible. The stimulation protocol of CC/gonadotropin, once abandoned after the advent of GnRHa, has regained attention after the introduction of GnRH antagonist. In our previous study, we have proposed a CC/hMG/cetrorelix protocol for male-factor infertility and a 40% pregnancy rate was achieved [10]. Since CC/hMG resulted in a significantly lower incidence of severe OHSS compared to GnRHa long protocol [11] and GnRH antagonist results in lower E2 on the day of hCG [12], it is plausible to apply the CC/hMG/cetrorelix protocol to patients who have excessive response to GnRHa long protocol. Therefore we conducted a study to see if the CC/hMG/cetrorelix protocol could be applied to women who had excessive ovarian response in their first cycles.

Materials and methods

This is a prospective observational study. The study was approved by the Ethics Committee of the hospital. The

subjects included 50 patients who had excessive ovarian response and required coasting in their first IVF/ICSI cycles but failed to conceive. Exclusion criteria were patient age over 38 years and day 3 FSH > 15 mIU/ml.

The stimulation protocol for the first cycles was GnRHa long protocol. The women were down regulated by 0.5 mg/day of buserelin acetate (Supremon, Hoechst, Frankfurt, Germany) for at least 2 weeks, starting from day 2 after progestin-induced withdrawal bleeding in PCOS patients, or 7 days before expected menstruation in ovulatory women. The dose was decreased to 0.25 mg/day upon hMG stimulation until the day of hCG (Pregnyl; NY Organon, Oss, The Netherlands) administration. After pituitary desensitization, two to three ampoules of hMG (Pregonal; Serono, Geneva, Switzerland) were administered for 5 days, and were adjusted according to follicular growth and serum E2 levels. The criterion of coasting at our institute was the fulfillment of all three conditions: serum E2 > 3,600 pg/ml, > 20 growing follicles (with diameter > 10 mm), and 25% follicles > 15 mm [13]. During coasting, hMG was withheld but buserelin was continued at 0.25 mg/day. Administration of 10,000 IU hCG was withheld until serum E2 levels fell below 3,600 pg/ml, and two leading follicles > 18 mm. Oocyte retrieval was cancelled if serum E2 levels decreased by more than 20% after hCG injection, as suggested by Benadiva et al. [14]. Transvaginal oocyte retrieval was performed 36 h later, and fertilization was achieved by IVF or intracytoplasmic sperm injection (ICSI). Only follicles > 10 mm in diameter were punctured. Following fertilization, each oocyte was transferred into a 20 μ l droplet of P-1 medium (Preimplantation Stage One; Irvine Scientific, Santa Ana, CA, USA) in a tissue culture dish (35 $\times$ 10 mm; Falcon, Becton Dickinson, Lincoln Park, NJ, USA) under mineral oil. Fertilization was assessed 16 to 18 h later by the appearance of 2 pronuclei (2PN). Embryo transfer was performed 2 days after fertilization. All patients received luteal phase support with 600 mg of micronized progesterone (Utrogestan; Piette, Brussels, Belgium) daily per vagina starting from the day after oocyte retrieval. Clinical pregnancy was defined as a visible fetal heart beat on ultrasonography at 7 weeks' gestation. Assessment of the severity of OHSS was based on the classification of Golan et al. [15].

CC/hMG/cetrorelix protocol

The interval between the first and second IVF/ICSI cycles was 3–6 months. No hormonal treatment was given during this period, except cyclic progestin in PCOS patients. The CC/hMG/cetrorelix protocol has been described previously [10]. In brief, clomiphene citrate (Clomid; Shionogi, Tokyo, Japan) at 100 mg per day was given from cycle days 3–7. hMG (Pregonal; Serono) was given on days 4, 6 and 8 at

Table 1 Serum E2 levels and incidences of coasting

Characteristics	GnRHa long protocol	CC/hMG/cetrorelix protocol	<i>P</i> value
No. of patients treated	50	50	
No. of cycles	50	50	
Peak serum E2 (pg/ml)	5,041±1,027	2,569±774	<0.05
Serum E2 on day of hCG(pg/ml)	3,106±415	2,515±702	<0.05
No. of coasting patients	50(100%)	4(8%)	<0.05
Duration of coasting (days)	2.8±1.2	1.3±0.5 ^a	
No. patients with coasting ≥ 4 days	11(22%)	0	<0.05
No. of cycles cancelled ^b	8(16%)	1(2%)	<0.05
Days of hMG treatment	9.3±1.3	7.1±1.4	<0.05
Ampoules of hMG used	25.7±5.2	17.9±4.1	<0.05
No. of oocytes retrieved per cycle	17.1±5.7	13.3±5.1	<0.05
Oocyte recovery rate ^c	65.4%	75.4%	<0.05
Fertilization rate	78.8%	80.1%	NS
No. of OHSS	9(18%)	1(2%)	<0.05
No. of moderate OHSS	8(16%)	1(2%)	<0.05
No. of severe OHSS	1(2%)	0	NS

NS Not significant

^a Mean duration of the four patients with coasting^b Cancellation indicated all terminated cycles before embryo transfer^c Percentage of oocytes collected relative to number of follicles punctured

two to three ampoules (the same dose as in the patient's previous cycle), and was adjusted from day 9 according to the follicular response. Cetrorelix acetate (Cetrotide; Serono) at 2.5 mg was given when the leading follicle had reached 14 mm. If hCG was not given 4 days after cetrorelix injection, 0.25 mg cetrorelix was given every day until the day of hCG injection. HCG at 10,000 IU was given when at least two follicles had reached 18 mm with E2 level ≥ 200 pg/ml per follicle. Oocyte retrieval was performed 36 h later. The procedures of fertilization, embryo culture, and luteal support were identical to those in the first cycles.

The primary outcome measures of this study were the incidence of OHSS, peak serum E2 levels and the need of coasting. Secondary outcome measures were the rate of cancellation, amount of hMG used, number of oocytes retrieved, oocyte recovery rate, fertilization rate, and incidence of OHSS. An LH surge is defined as LH ≥ 10 mIU/ml and progesterone ≥ 1.0 ng/ml. A premature LH surge means that LH surge occurs before the administration of hCG.

Statistical analysis

Values are expressed as mean±SD. Chi-square test, Fisher's exact test, and paired *t* test was used for statistical analysis, as appropriate. A *p*<0.05 was considered statistically significant. Analysis was performed using the SPSS statistical package for Windows (version 12.0; SPSS Inc., Chicago, IL, USA).

Results

The mean age of the 50 patients was 31.3(±4.3) years. The etiologies of infertility were polycystic ovarian syndrome (PCOS, *n*=18), male factor (*n*=14), tubal factor (*n*=12), endometriosis (*n*=2), and unexplained (*n*=4).

The outcomes of the 50 patients with the two protocols are shown in Table 1. The peak serum E2 level and the E2 level on the day of hCG injection were significantly lower with the CC/hMG/cetrorelix protocol compared to the GnRHa long protocol. The duration of coasting was 2.8±

Table 2 Outcomes of 18 PCOS patients with the two stimulation protocols

Characteristics	GnRHa long protocol	CC/hMG/cetrorelix protocol	<i>P</i> value
Peak serum E2 (pg/ml)	5,438±1,014	2,484±870	<0.05
Serum E2 on day of hCG(pg/ml)	3,025±422	2,389±743	<0.05
Days of hMG treatment	9.2±1.5	6.9±1.6	<0.05
Ampoules of hMG used	26.9±3.8	17.2±4.8	<0.05
No. of oocytes retrieved per cycle	16.6±5.0	12.6±4.3	<0.05
Oocyte recovery rate	63.9%	75.1%	0.05
No. of OHSS	4(22.2%)	1(5.6%)	<0.05
No. of moderate OHSS	3(16.7%)	1(5.6%)	<0.05
No. of severe OHSS	1(5.6%)	0	<0.05

Table 3 Outcomes of fresh and frozen ET

Outcome parameters	GnRHa long protocol (<i>n</i> =50)	CC/hMG/cetrorelix protocol (<i>n</i> =50)	<i>P</i> value
Fresh ET			
No. of ET	42	49	
No. of embryos per transfer	2.7±0.5	2.5±0.6	NS
Clinical pregnancy rate (per started cycle)	6% (3/50)	42% (21/50)	<0.05
Implantation rate	2.7% (3/112)	23.8% (29/122)	<0.05
Miscarriage rate	100% (3/3)	9.5% (2/21)	<0.05
No. of deliveries and ongoing pregnancies	0	19	
Frozen ET			
No. of cycles	14	8	
No. of embryos per transfer	2.9±0.5	2.8±0.7	NS
Clinical pregnancy rate (per ET)	7.1% (1/14)	37.5% (3/8)	NS
Implantation rate	2.5% (1/40)	18.1% (4/22)	<0.05
Miscarriage rate	100% (1/1)	33.3% (1/3)	NS
No. of deliveries and ongoing pregnancies	0	2	

NS Not significant

1.2 days (range: 1–6 days) with GnRHa long protocol, and was ≥ 4 days in 11 women (22%). On the contrary, with CC/hMG/cetrorelix protocol, only four women (8%) needed coasting (mean: 1.3 ± 0.5 days, range: 1–2 days) to lower the serum E2 levels and no one coasted for ≥ 4 days.

More cycles were cancelled with the GnRHa long protocol. Six cycles were cancelled because of a fall in serum E2 $>20\%$ on the day after hCG injection, and two cycles due to fertilization failure. With the CC/hMG/cetrorelix protocol only one cycle was cancelled because of fertilization failure. Although more oocytes were obtained with the GnRHa long protocol, the duration of GnRHa and hMG administration was longer, and more hMG was used. The oocyte recovery rate was significantly higher with the CC/hMG/cetrorelix protocol, but the fertilization rates for the two stimulation protocols were similar. The incidence of moderate OHSS was significantly lower with the CC/hMG/cetrorelix protocol. There was no significant difference in the incidence of severe OHSS. No premature LH surge occurred with the CC/hMG/cetrorelix protocol.

The outcomes of the 18 PCOS patients with the two stimulation protocols are shown in Table 2. E2 levels at peak and on the day of hCG injection were lower with the CC/hMG/cetrorelix protocol. Although fewer oocytes were obtained with the CC/hMG/cetrorelix protocol, the difference in oocyte recovery rates was borderline significant ($p=0.05$). Seven pregnancies were achieved with the CC/hMG/cetrorelix protocol. With the CC/hMG/cetrorelix protocol, only two patients needed coasting (1 and 3 days, respectively), and the incidence of OHSS was lower.

Table 3 lists the outcomes of fresh and frozen embryo transfer (ET) with the two protocols. In the first cycles, the pregnancy rate was 6% (3/50) per started cycle or 7.1% (3/42) per ET, and the implantation rate was 2.7%. All three pregnancies ended up as miscarriage. The implantation rate was much higher with the CC/hMG/cetrorelix protocol. Twenty-one clinical pregnancies (42%) were obtained after CC/hMG/cetrorelix protocol. Fourteen were delivered successfully (five twin pregnancy and nine singleton pregnancy), five were ongoing at the time of writing (one twin pregnancy and four singleton pregnancy), and two were aborted before 12 week.

After the first cycles, 14 patients underwent frozen ET. The clinical pregnancy rate was 7.1% (1/14) per ET, and the implantation rate was 2.5%. With CC/hMG/cetrorelix protocol, eight patients received frozen ET. The clinical pregnancy rate and the implantation rate were 37.5% (3/8) and 18.1%, respectively. The pregnancy rates were similar, but the implantation rate was higher with the CC/hMG/cetrorelix protocol.

Discussion

Among the several strategies to prevent OHSS, coasting is the most popular and is appealing to the physicians and the patients. This study showed that the CC/hMG/cetrorelix protocol reduced peak E2 levels and the need of coasting and prolonged coasting (≥ 4 days) in women who had excessive ovarian response to the GnRHa long protocol. Coasting increases the duration of GnRHa administration

and hormonal and ultrasound monitoring, thus increases cost and inconvenience. Besides, several studies have demonstrated that long coasting reduces the implantation and pregnancy rates [7, 8, 16–20]. Although the cut-off point varied from 4 to 5 days, most studies set at 4 days. The mechanism of the adverse effect of prolonged coasting might be due to impaired endometrial receptivity [7, 19] or probably oocyte quality [18]. In the present study the peak E2 levels were significantly lower with the CC/hMG/cetrorelix protocol, which might explain why coasting was required only for a small proportion (8%) of patients. The duration of coasting was also relatively short and no patient coasted for ≥ 4 days. In contrast, with the GnRHa long protocol, 11 patients (22%) coasted for ≥ 4 days.

Another way to prevent OHSS is to use milder stimulation. Decreasing the dose of gonadotropin would result in less follicular recruitment and lower E2 levels, hence lower risk of OHSS. This fact was reflected in the present study in that E2 levels at peak and on the day of hCG injection were lower, and oocytes obtained were fewer, with the CC/hMG/cetrorelix protocol. In contrast, with GnRHa long protocol, more gonadotropins are usually needed, resulting in more follicular recruitment and higher risk of OHSS. Although some researchers proposed that GnRHa suppression confers a risk for OHSS [2], it has never been proved.

We found that oocyte recovery rate was significantly lower with the GnRHa long protocol compared to the CC/hMG/cetrorelix protocol. Reduced oocyte recovery rate after coasting has also been described by other authors [21, 22]. Removing FSH stimulation from granulosa cells during coasting inhibits their proliferation and reduces the number of granulosa cells. A decline in FSH level also causes apoptosis of granulosa cells and atresia of small follicles [16]. Coasting has also been reported to lead to a reduced number of recovered oocytes and reduced oocyte quality [4, 16, 17, 23].

Most studies reported low incidences ($< 2\%$) of severe OHSS after coasting except 20% in two studies [21, 24]. The discrepancy in results may be due to different coasting regimens and different patient groups. The present study demonstrates that coasting is an effective way to prevent OHSS; only one case (2%) of severe OHSS developed in the first cycles. The incidences of severe OHSS were similar with the two protocols, but the incidence of moderate OHSS was lower with the CC/hMG/cetrorelix protocol. The benefit of the CC/hMG/cetrorelix protocol is more obvious in PCOS women, since it reduced the incidences of moderate and severe OHSS in PCOS women. Although moderate OHSS may not represent real threat to the patients, it still causes discomfort and inconvenience to the patients. Reduced incidence of OHSS with the CC/hMG/cetrorelix protocol may be due to lower serum E2 and fewer oocytes.

Exposure to high serum E2 concentrations not only increases the risk of OHSS, but also impairs uterine receptivity [25]. Other benefits of the CC/hMG/cetrorelix protocol include fewer injections of GnRHa and hMG.

Other stimulation protocols have been proposed for patients who have excessive response to GnRHa long protocol. Marci et al. [26] proposed a low-dose stimulation protocol (starting at 75 IU FSH, increased by 37.5 IU every 4 days) and they obtained a high implantation (21.8%) and pregnancy (38.4%) rates without cycle cancellation. Damario et al. [27] proposed dual suppression with oral contraceptives and GnRHa, and 150 IU gonadotropin was initiated from day 3. Although a 46.5% pregnancy rate was achieved, 13 cycles (13.1%) were cancelled before embryo transfer. These protocols, however, have the drawback of prolonged stimulation besides prolonged pituitary desensitization by GnRHa. The average days of gonadotropin stimulation were 15 in the study of Marci et al. and 9.5 in the study of Damario et al., but only 7.1 days in our study. Similarly, Fielder and Ludwig [28] used CC, gonadotropin, in conjunction with multiple-dose GnRH antagonist in normal cycling women and obtained satisfactory oocyte-pickup and pregnancy rates (91.9 and 31.3% per started cycle, respectively). Severe OHSS occurred only in 0.8% of cycles. They suggested that the protocol might be applied to patients at high risk of OHSS. The incidence of premature LH surge was not mentioned in that study, but several studies showed that multiple-dose GnRH antagonist in combination with CC and gonadotropin was associated with high rate of premature LH surge [29, 30]. In the present study, no premature LH surge occurred with the CC/hMG/cetrorelix protocol. Higher dose of GnRH antagonist may be needed to prevent the LH surges in cycles stimulated with CC and gonadotropin.

In summary, this study indicates that the CC/hMG/cetrorelix protocol can be an alternative stimulation protocol for patients who had excessive response to GnRHa long protocol. This protocol produced favorable outcome compared to the GnRHa long protocol, while reducing the use of hMG. We think the CC/hMG/cetrorelix protocol can be used as the first-line stimulation protocol for patients at risk of OHSS. A prospective randomized study is necessary to prove its efficacy.

References

1. Brinsden PR, Wada I, Tan SL, Balen A, Jacobs HS. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. *Br J Obstet Gynaecol* 1995;102:767–72.
2. Whelan JG, Vlahos NF. The ovarian hyperstimulation syndrome. *Fertil Steril* 2000;73:883–96.

3. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Hum Reprod Update* 2002;8:559–77.
4. Chen D, Burmeister L, Goldschlag D, Rosenwaks Z. Ovarian hyperstimulation syndrome: strategies for prevention. *Reprod Biomed Online* 2003;7:43–9.
5. Delvigne A, Rozenberg S. Preventive attitude of physicians to avoid OHSS in IVF patients. *Hum Reprod* 2001;16:2491–5.
6. Levinsohn-Tavor O, Friedler S, Schachter M, Raziel A, Strassburger D, Ron-El R. Coasting—what is the best formula? *Hum Reprod* 2003;18:937–40.
7. Ulug U, Bahceci M, Erden HF, Shalev E, Ben-Shlomo I. The significance of coasting duration during ovarian stimulation for conception in assisted fertilization cycles. *Hum Reprod* 2002;17:310–3.
8. Mansour R, Aboulghar M, Serour G, Amin Y, Abou-Setta AM. Criteria of a successful coasting protocol for the prevention of severe ovarian hyperstimulation syndrome. *Hum Reprod* 2005;20:3167–72.
9. Biljan MM, Tan SL. GnRH agonists in gonadotrophin ovulation induction: characteristics of long regimens. In: Filicori M, Flamigani C, editors. *Ovulation induction: update 98*. New York: Parthenon; 1998. p. 75–82.
10. Hwang JL, Huang LW, Hsieh BC, Tsai YL, Huang SC, Chen CY, et al. Ovarian stimulation by clomiphene citrate and hMG in combination with cetrorelix acetate for ICSI cycles. *Hum Reprod* 2003;18:45–9.
11. MacDougall MJ, Tan SL, Jacobs HS. In-vitro fertilization and the ovarian hyperstimulation syndrome. *Hum Reprod* 1992;7:597–600.
12. Olivennes F, Belaisch-Allart J, Emperaire JC, Dechaud H, Alvarez S, Moreau L, et al. Prospective, randomized, controlled study of in vitro fertilization-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (cetrorelix) or a depot formula of an LH-RH agonist (triptorelin). *Fertil Steril* 2000;73:314–20.
13. Chen CD, Wu MY, Chao KH, Chen SU, Ho HN, Yang YS. Serum estradiol level and oocyte number in predicting severe ovarian hyperstimulation syndrome. *J Formos Med Assoc* 1997;96:829–34.
14. Benadiva CA, Davis O, Kligman I, Moomjy M, Liu HC, Rosenwaks Z. Withholding gonadotrophin administration is an effective alternative for the prevention of ovarian hyperstimulation syndrome. *Fertil Steril* 1997;67:724–7.
15. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. *Obstet Gynecol Surv* 1989;44:430–40.
16. Tortoriello DV, McGovern PG, Colon JM, Skumick JH, Lipetz K, Santoro N. “Coasting” does not adversely affect cycle outcome in a subset of highly responsive in vitro fertilization patients. *Fertil Steril* 1998;69:454–60.
17. Waldenstrom U, Kahn J, Marsk L, Nilsson S. High pregnancy rates and successful prevention of severe ovarian hyperstimulation syndrome by ‘prolonged coasting’ of very hyperstimulated patients: a multicentre study. *Hum Reprod* 1999;14:294–7.
18. Isaza V, Garcia-Velasco JA, Aragonés M, Remohi J, Simon C, Pellicer A. Oocyte and embryo quality after coasting: the experience from oocyte donation. *Hum Reprod* 2002;17:1777–82.
19. Moreno L, Diaz I, Pacheco A, Zuniga A, Requene A, Garcia-Velasco JA. Extended coasting duration exerts a negative impact on IVF cycle outcome due to premature luteinization. *Reprod Biomed Online* 2004;9:500–4.
20. Ulug U, Ben-Shlomo I, Bahceci M. Predictors of success during the coasting period in high-responder patients undergoing controlled ovarian stimulation for assisted conception. *Fertil Steril* 2004;82:338–42.
21. Egbase PE, Sharhan MA, Grudzinskas JG. Early unilateral follicular aspiration compared with coasting for the prevention of severe ovarian hyperstimulation syndrome: a prospective randomized study. *Hum Reprod* 1999;14:1421–5.
22. Delvigne A, Kostyla K, Murillo D, Van Hoeck J, Rozenberg S. Oocyte quality and IVF outcome after coasting to prevent ovarian hyperstimulation syndrome. *Int J Fertil Womens Med* 2003;48:25–31.
23. Dhont M, Van der Streten F, De Sutter P. Prevention of severe ovarian hyperstimulation by coasting. *Fertil Steril* 1998;70:847–50.
24. Lee C, Tummon I, Martin J, Nisker J, Power S, Tekpetey F. Does withholding gonadotrophin administration prevent severe ovarian hyperstimulation? *Hum Reprod* 1998;13:1157–8.
25. Valbuena D, Jasper M, Remohi J, Pellicer A, Simon C. Ovarian stimulation and endometrial receptivity. *Hum Reprod* 1999;14 Suppl 2:107–11.
26. Marci R, Senn A, Dessole S, Chanson A, Loumaye E, De Grandi P, et al. A low-dose stimulation protocol using highly purified follicle-stimulating hormone can lead to high pregnancy rates in in vitro fertilization patients with polycystic ovaries who are at risk of a high ovarian response to gonadotrophins. *Fertil Steril* 2001;75:1131–5.
27. Damario MA, Barmat L, Liu HC, Davis OK, Rosenwaks Z. Dual suppression with oral contraceptives and gonadotrophin releasing-hormone agonists improves in-vitro fertilization outcome in high responder patients. *Hum Reprod* 1997;12:2359–65.
28. Fiedler K, Ludwig M. Use of clomiphene citrate in in vitro fertilization (IVF) and IVF/intracytoplasmic sperm injection cycles. *Fertil Steril* 2003;80:1521–3.
29. Engel JB, Ludwig M, Felberbaum R, Albano C, Devroey P, Diedrich K. Use of cetrorelix in combination with clomiphene citrate and gonadotrophins: a suitable approach to ‘friendly IVF’? *Hum Reprod* 2002;17:2022–6.
30. Tavanitoutou A, Albano C, Van Steirteghem A, Devroey P. The impact of LH serum concentration on the clinical outcome of IVF cycles in patients receiving two regimens of clomiphene citrate/gonadotrophin/0.25 mg cetrorelix. *Reprod Biomed Online* 2003;6:421–6.