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SHORT COMMUNICATION

Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: preliminary report

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A new treatment option for patients undergoing ovarian stimulation is the gonadotrophin-releasing hormone (GnRH) antagonist protocol, with the possibility to trigger a mid-cycle LH surge using a single bolus of GnRH agonist, reducing the risk of developing ovarian hyperstimulation syndrome (OHSS) in high responders and the chance of cycle cancellation. This report describes the use of 0.2 mg triptorelin (Decapeptyl®) to trigger ovulation in eight patients who underwent controlled ovarian hyperstimulation with recombinant FSH (rFSH, Puregon®) and concomitant treatment with the GnRH antagonist ganirelix (Orgalutran®) for the prevention of premature LH surges. All patients were considered to have an increased risk for developing OHSS (at least 20 follicles ≥11 mm and/or serum oestradiol at least 3000 pg/ml). On the day of triggering the LH surge, the mean number of follicles ≥11 mm was 25.1 ± 4.5 and the median serum oestradiol concentration was 3675 (range 2980–7670) pg/ml. After GnRH agonist injection, endogenous serum LH and FSH surges were observed with median peak values of 219 and 19 IU/l respectively, measured 4 h after injection. The mean number of oocytes obtained was 23.4 ± 15.4, of which 83% were mature (metaphase II). None of the patients developed any signs or symptoms of OHSS. So far, four clinical pregnancies have been achieved from the embryos obtained during these cycles, including the first birth following this approach. It is concluded that GnRH agonist effectively triggers an endogenous LH surge for final oocyte maturation after ganirelix treatment in stimulated cycles. Our preliminary results suggest that this regimen may prove effective in triggering ovulation and could be said to prevent OHSS in high responders. The efficacy and safety of such new treatment regimen needs to be established in comparative randomized studies.

Key words: GnRH agonist/GnRH antagonist/ovarian hyperstimulation syndrome/recombinant FSH/triggering ovulation

Introduction

Since their introduction in the early 1960s, human menopausal gonadotrophins (HMG) have been used in ovulation induction cycles, particularly during the last 2 decades in IVF programmes. Typically, human chorionic gonadotrophin (HCG) is used as a surrogate to luteinizing hormone (LH) for oocyte maturation and induction of ovulation. Given its significantly longer half-life [>24 h versus 60 min for LH (Yen *et al.*, 1968; Damewood *et al.*, 1989)], HCG administration results in a prolonged luteotrophic effect, characterized by the development of multiple corpora lutea and supraphysiological levels of oestradiol and progesterone. This sustained luteotrophic effect may result in the development of ovarian hyperstimulation syndrome (OHSS), the most frequent and severe complication of HMG treatment (Golan *et al.*, 1989). The threat of OHSS often leads to cycle cancellation.

An alternative to HCG-induced ovulation triggering, is the use of gonadotrophin releasing hormone (GnRH) agonists. These compounds induce a sustained (>24 h) release of LH (and FSH) from the pituitary, that effectively induces oocyte maturation and ovulation. Importantly, they also provide a means by which OHSS is effectively prevented (Itskovitz *et al.*, 1988, 1991; Gonen *et al.*, 1990; Emperaire *et al.*, 1991; Imoedemhe *et al.*, 1991; Segal *et al.*, 1992; Lanzone *et al.*, 1994; Lewit *et al.*, 1995, 1996).

The major limitation of the use of GnRH agonist to trigger ovulation is that GnRH agonists are ineffective in women with a low gonadotrophin reserve or after pituitary down-regulation with a GnRH agonist. In these situations, the pituitary is unresponsive for inducing an endogenous LH surge. Since GnRH agonist-based protocols are routinely used in most IVF programmes, the application of GnRH agonist for induction of ovulation has been limited.

The recent introduction of GnRH antagonist protocols (Albano *et al.*, 1997; Ganirelix Dose Finding Group, 1998; Itskovitz-Eldor *et al.*; 1998) has offered new opportunities of using GnRH agonist to trigger ovulation and preventing OHSS due to the mechanism of action of GnRH antagonists, i.e. competitive inhibition and relatively short duration of action. Studies in monkeys (Chillik *et al.*, 1987) have clearly demonstrated that although tonic gonadotrophins remain suppressed under GnRH antagonist treatment, acute LH release can be elicited in a GnRH challenge test. In small scale studies in humans, it was demonstrated (Felberbaum *et al.*, 1995) that under GnRH antagonist treatment the pituitary retains its

Table I. Stimulation characteristics of 8 women with increased risk for developing OHSS and who received 0.2 mg triptorelin for triggering ovulation

Subject	Total dose of rFSH (IU)	Follicles ⩾11 mm	Serum oestradiol[a] (pg/ml)	Number of oocytes	Mature oocytes (%)
7	1350	22	2980	29	100
33	1500	21	3660	14	100
39	1950	24	3350	30	90
108[b]	1875	22	6410	1	100
109	1275	28	7670	52	54
112	1575	34	4050	30	93
126	2175	22	3690	15	67
158	1575	28	3020	16	56

[a]On the day of the LH surge triggering.
[b]Subject with empty follicle syndrome.

Table II. Median (range) values of serum hormones after ovulation induction by means of a single bolus of 0.2 mg triptorelin

Time after Injection	Serum LH (IU/l)	Serum FSH (IU/l)	Serum progesterone (ng/ml)	Serum oestradiol (pg/ml)
Pre-dose	2.4	5.4	1.0	4775
$n = 8$	(1.1–5.7)	(3.9–6.7)	(0.5–2.6)	(3410–9870)
0.5 h	12.7	5.6	1.2	4630
$n = 8$	(7.6–33.7)	(4.2–6.9)	(0.7–3.2)	(3400–10000)
1 h	14.3	5.7	1.4	4505
$n = 8$	(8.9–47.5)	(4.1–6.9)	(0.9–3.9)	(3630–9180)
2 h	73.7	8.1	2.2	5080
$n = 8$	(32.7–118)	(4.9–8.7)	(1.3–4.4)	(3890–9830)
4 h	219	18.6	4.5	5540
$n = 8$	(152–235)	(9.2–28.8)	(2.4–6.2)	(3850–10.500)
10–12 h	71.0	16.4	8.7	6000
$n = 8$	(59–117)	(7.6–18.3)	(6.8–15.6)	(3010–10.800)
Day of OPU	7.9	5.7	9.7	2375
	(3.1–11.7)	(3.4–7.3)	(3.8–16.7)	(1070–5920)
Day of embryo transfer	0.8	1.6	27.5	963
	(<0.6–2.6)	(1.4–2.5)	(14.2–36.4)	(598–1890)
First week post-embryo transfer	1.0	<1.0	25.3	145
	(<0.6–3.2)	(<1.0–1.7)	(11.5–40.8)	(68–196)
Second week post-embryo transfer	1.2	<1.0	16.2	69
	(<0.6–2.8)	(<1.0–<1.0)	(11.7–40.9)	(51–126)

responsiveness to GnRH, while others (Olivennes *et al.*, 1996) showed in stimulation cycles for intrauterine insemination that ovulation can be triggered by GnRH agonist after GnRH antagonist treatment. From these preliminary reports, it can be deduced that the pituitary response to GnRH or GnRH agonist is preserved during stimulation protocols including GnRH antagonists. The extent of pituitary suppression in this type of protocol is GnRH antagonist dose dependent. Under the reported minimal effective dose of GnRH antagonists (0.25 mg, daily; Ganirelix Dose Finding Group, 1998), it is most probable that ovulation can be safely and effectively triggered with a GnRH agonist.

In this communication, data are presented on the safety and efficacy of triggering final oocyte maturation with 0.2 mg triptorelin in patients with increased risk of developing OHSS after ovarian stimulation with rFSH for intracytoplasmic sperm injection (ICSI) and treatment with the GnRH antagonist ganirelix for the prevention of premature LH surges.

Materials and methods

A single-centre, open label study to assess the safety of a GnRH antagonist (ganirelix, Orgalutran®; NV Organon, Oss, The Netherlands) in women undergoing multiple stimulation cycles for IVF or ICSI (for male infertility) was conducted in our centre. The hospital and national health authorities review boards approved the study. Ovarian stimulation with recombinant FSH (Puregon®; NV Organon) was initiated on day 2 or 3 of the cycle with 150 IU or 225 IU daily. From stimulation day 6, daily injection of ganirelix (0.25 mg, s.c.) was added, until at least three follicles with a diameter of ⩾17 mm were observed by ultrasound. Ovulation was routinely triggered with 10 000 IU HCG.

HCG was withheld in eight women considered at risk of developing OHSS, since more then 20 follicles of >11 mm and/or oestradiol concentrations >3000 pg/ml were observed on the last stimulation day. In these patients, final oocyte maturation was triggered with a single injection of triptorelin 0.2 mg s.c. (Decapeptyl®; Ferring, Malmo, Sweden) at ~30 h after the last injection of ganirelix, and 35 h before oocyte retrieval. Repeated blood samples were taken to

document the hormonal changes (oestradiol, progesterone, LH, FSH) 0, 0.5, 1, 2, 4, 12 h following triptorelin. Luteal support was initiated on the day of embryo transfer with daily injections of 50 mg progesterone in oil (Gestone®; Paines and Byrne, UK) and 2 mg oestradiol orally (Estrofem®; Novo Nordisk, Denmark).

Results

The mean age and weight of the eight women were 26 years (range 22–36 years) and 62 kg (range 50–83 kg) respectively. All patients were scheduled for ICSI. The main causes of infertility were male factor in five couples, oligomenorrhoea in one patient, amenorrhoea with polycystic ovary syndrome in one patient, and unknown in one couple.

Table I presents the stimulation characteristics of each patient including the total amount of rFSH administered, the number of follicles, serum oestradiol levels and the number and maturity of recovered oocytes. On the day of triggering ovulation the mean number of follicles ⩾11 mm was 25.1 ± 4.5 and the median serum oestradiol concentration was 3675 (range 2980–7670) pg/ml. The mean (±SD) number of oocyte retrieved was 23.4 (±15.4), of which 83% were metaphase II oocytes. In one patient (108, see Table I) one oocyte was recovered, whereas 22 follicles ⩾11 mm were observed by ultrasound. This patient had repeated unsuccessful treatment with a long protocol of GnRH agonist and HCG for triggering ovulation and was diagnosed as suffering from an empty follicle syndrome. In the other seven patients the total mean (±SD) number of embryos obtained was 15.4 ± 6.6 per patient. There were 88 good quality embryos and seven fresh embryo transfers and for six patients, surplus embryos were frozen (in total 83).

Table II depicts median serum LH, FSH, progesterone and oestradiol concentrations after the bolus injection of 0.2 mg triptorelin. Serum LH concentrations rose rapidly from 2.4 IU/l just prior to triptorelin administration to peak values of 219 IU/l at 4 h after injection. Median LH concentrations were 71 and 7.9 IU/l at 10–12 h and 34–36 h (at oocyte retrieval) respectively. Serum FSH started to increase only at 2 h after triptorelin injection and a median peak value of 18.6 IU/l was measured at 4 h. By the day of oocyte retrieval, serum FSH had returned to its pre-dose value (5.4 IU/l).

Median serum oestradiol concentrations remained high during the first 12 h after triptorelin injection (4775–6000 pg/ml), but rapidly decreased thereafter to 2375, 963 and 69 pg/ml at the day of oocyte retrieval, day of embryo transfer, and the end of the luteal phase respectively. A mid-luteal oestradiol peak was not observed. None of the patients developed signs or symptoms of OHSS. Importantly, none of the patients had free pelvic fluid when assessed by vaginal ultrasound during the luteal phase.

Fresh transfers resulted in one positive HCG test. Seventeen frozen–thawed cycles with embryos obtained during these cycles resulted in four clinical pregnancies (fetal heart activity assessed by ultrasound) so far. Of these four clinical pregnancies, three ended in early abortions and one in normal vaginal delivery of a healthy newborn.

Discussion

This is the first report suggesting the feasibility of prevention of OHSS in patients at risk undergoing controlled ovarian stimulation using a GnRH antagonist protocol, in which a single GnRH agonist injection was given to induce final oocyte maturation prior to retrieval. An adequate pituitary response to GnRH agonist given 30 h after the last injection of ganirelix was documented by the occurrence of endogenous LH and FSH surges, which were comparable to those described nearly a decade ago in patients undergoing ovulation induction without pituitary suppression (Itskovitz *et al.*, 1991). Our findings are in line with previous studies (Chillik *et al.*, 1987; Felberbaum *et al.*, 1995; Olivennes *et al.*, 1996), which demonstrated that an effective LH surge can be elicited with a GnRH agonist when pituitary suppression is established by GnRH antagonist-induced competitive inhibition of native GnRH.

The fact that 83% of the oocytes retrieved were mature clearly documents the adequacy of the gonadotrophin surges in initiating the final oocyte maturation process.

The limited clinical experience presented here supports a major advantage of GnRH antagonist protocols in allowing the use of GnRH agonist to trigger and prevent OHSS (Itskovitz *et al.*, 1988, 1991; Lewit *et al.*, 1995, 1996). The rapid fall of oestrogen concentrations after embryo transfer, the lack of mid-luteal oestradiol peak, as well as the absence of free pelvic fluid suggest that triggering of final oocyte maturation with GnRH agonist may lead to a more physiological luteal phase oestradiol and progesterone concentrations. This moderate response is in sharp contrast with the exaggerated luteotrophic effect often seen after ovulation triggering with HCG (Itskovitz-Eldor *et al.*, 1993). The introduction of the GnRH agonist induced triggering of ovulation in GnRH antagonist protocols would offer additional benefits to all patients, i.e. both high and normal responders, though the efficacy and safety of such new treatment regimen needs to be established in comparative, randomized studies. The relatively low pregnancy rate in our limited series should be assessed in larger scale clinical studies.

In summary, we have demonstrated the ability of a single bolus of 0.2 mg triptorelin to trigger an adequate LH surge in stimulation cycles using a GnRH antagonist protocol. Our results suggest that this regimen may prove highly effective in terms of OHSS prevention, though further studies are needed to establish this potential advantage.

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