

CASE REPORT

First established pregnancy after controlled ovarian hyperstimulation with recombinant follicle stimulating hormone and the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462)

J.Itskovitz-Eldor^{1,3}, S.Kol¹, B.Mannaerts² and H.Coelingh Bennink²

¹Department of Obstetrics and Gynecology, Rambam Medical Center, Faculty of Medicine, Technion–Israel Institute of Technology, PO Box 9602, Haifa 31096, Israel and ²Medical R&D Unit, Organon International, PO Box 20, 5340 BH, Oss, The Netherlands

³To whom correspondence should be addressed

This case report describes the first established pregnancy after the use of gonadotrophin-releasing hormone (GnRH) antagonist, ganirelix (Org 37462; Organon), to prevent a premature luteinizing hormone surge during ovarian hyperstimulation with recombinant human follicle stimulating hormone (rhFSH). The pregnancy progressed normally and ended with the birth of a healthy boy and a girl after an elective Caesarean section at gestational age of 37 weeks. This case illustrates, for the first time, the use of a GnRH antagonist in combination with a pure FSH preparation for ovarian stimulation.

Key words: ganirelix/GnRH antagonist/ovarian stimulation/pregnancy/recombinant human FSH

Case report

A 32 year old patient and her 30 year old husband had been infertile for 3 years due to severe male infertility. Sperm count ranged from 0.5 to 1×10^6 /ml on repeated tests. Because of the very low sperm count the couple was referred to our in-vitro fertilization (IVF) programme. The first treatment cycle was initiated following pituitary down-regulation with mid-luteal gonadotrophin releasing hormone (GnRH) agonist (Decapeptyl[®] CR, 3.75 mg; Ferring, Malmo, Sweden). Ovarian stimulation was achieved with daily injections of urinary human menopausal gonadotrophin (HMG; Pergonal[®] and Metrodin[®]; Teva, Petach–Tikva, Israel). A total of 34 ampoules was given in 10 treatment days. Ovulation was triggered with 10 000 IU human chorionic gonadotrophin (HCG, Chorigon[®], Teva), followed by transvaginal oocyte retrieval 36 h later. Nineteen oocytes were retrieved, resulting in seven embryos, of which three were transferred and four were frozen. Since pregnancy was not achieved, four thawed embryos were transferred 3 months later, but again, unsuccessfully.

The couple gave informed consent to participate in a double-blind, dose-finding study to assess the minimal effective dose of the GnRH antagonist ganirelix (Org 37462; Organon, Oss,

The Netherlands), to prevent premature luteinizing hormone (LH) rises in women undergoing ovarian stimulation with recombinant human follicle stimulating hormone (rhFSH). Ovarian stimulation was initiated on day 2 of the cycle with daily s.c. injection of 150 IU rFSH (Puregon[®]; Organon). Serum concentrations of hormones and follicular growth during treatment are summarized in Table I. Due to rising oestradiol concentrations endogenous LH levels decreased from 7.6 to 1.6 IU/l from rhFSH treatment day 1 to day 5. From treatment day 6 onwards a daily s.c. injection of 0.125 mg ganirelix (injection volume of 0.5 ml) was added. The immediate effect induced by ganirelix was apparent by a decrease in endogenous LH levels from 2.8 IU/l in the morning prior to injection, to 1.4 IU/l in the afternoon, i.e. 8 h after the administration. In parallel, a small decrease of serum oestradiol was noted. On treatment day 7, ultrasonography revealed the development of seven pre-ovulatory follicles (≥ 15 mm), of which four follicles were ≥ 17 mm in diameter. Serum oestradiol and LH were 2178 pmol/l and 4.7 IU/l, respectively. In accordance with the protocol, the patient received that morning her last rhFSH and ganirelix injections. Overall, s.c. administration of ganirelix was very well-tolerated and no adverse effects, either locally or systemically, were observed. Ovulation was triggered with 10 000 IU HCG (Pregnyl[®]; Organon) administered in that evening. Thirty-six hours later, six mature (metaphase II) oocytes were retrieved transvaginally, all of which were inseminated by intracytoplasmic sperm injection. Sperm parameters on the day of retrieval were as follows: volume 2.4 ml, 1600 motile spermatozoa/ml (44% of which were abnormal), 900 immotile spermatozoa/ml (88% of which were abnormal). Three embryos were transferred to the uterus 2 days after oocyte retrieval. The luteal phase was supplemented with progesterone (50 mg i.m. daily). The pregnancy test was positive (501 IU HCG/ml) 12 days after embryo transfer. Thirty-seven days after embryo transfer, ultrasonography revealed three gestational sacs, all of which proved to contain embryos with heart activity. However, repeated assessment 12 days later revealed that one of the embryos was not viable. An ongoing twin pregnancy progressed normally, with the first fetus in the breech presentation. A Caesarean section was performed at a gestational age of 37 weeks and 3 days and a healthy boy weighing 2940 g (Apgar score 9/10) and a healthy girl weighing 2550 g (Apgar score 9/10) were born.

Discussion

Although the first reported birth after IVF was achieved during a natural cycle, early in IVF evolution (Steptoe and Edwards,

Table I. Follicular growth and serum hormone concentrations during recombinant follicle stimulating hormone (rhFSH) and ganirelix treatment up to and including the day of human chorionic gonadotrophin (HCG)

Day	Treatment		No. follicles			FSH (IU/l)	LH (IU/l)	Oestradiol (nmol/l)	Progesterone (pmol/l)
	FSH (IU)	Ganirelix (mg)	12–14 mm	15–16 mm	≥17 mm				
1 (a.m.)	150	–	0	0	0	6.3	7.6	<183	3.1
2 (a.m.)	150	–					3.7	233	2.6
3 (a.m.)	150	–					2.8	509	1.7
4 (a.m.)	150	–	1	0	0		1.9	594	1.4
5 (a.m.)	150	–	3	1	0		1.6	1195	1.7
6 (a.m.)	150	0.125	5	3	0	8.3	2.8	1637	1.2
6 (p.m.)	–	–					1.4	1446	0.8
7 (a.m.)	150	0.125	4	3	4	8.1	4.0	2178	1.6
7 (p.m.)	10 000 IU HCG								

LH = luteinizing hormone.

1978) it became apparent that retrieval of a single oocyte is inefficient, hence the adoption of ovarian stimulation. A major caveat of different stimulation strategies is the threat of premature LH rise (Glasier *et al.*, 1988). To avoid premature LH surge most, if not all, IVF programmes currently use GnRH analogues. These compounds make use of the pituitary down-regulation mechanism, under which pituitary quiescence is achieved following a transient gonadotrophin 'flare' effect. Although allowing for a more convenient organization of the IVF service (mainly by avoiding weekend work), this strategy is not without disadvantages. Specifically, the need for a significantly longer duration of ovarian stimulation, with the resultant excessive consumption of HMG ampoules imposes therapeutic as well as economic burden on the patients and IVF programmes.

A more rational approach is to use GnRH antagonists, which act directly on the pituitary GnRH receptors, leading to immediate suppression of the pituitary–gonadal axis (Nelson *et al.*, 1995). Early efforts at this direction were hampered by intolerable side-effects, namely, histamine-releasing activity and anaphylactoid-like cutaneous effects. Continuous efforts have resulted in the introduction of several compounds which are currently under clinical investigation. These third generation GnRH antagonists have the potential to replace the agonists in routine assisted reproductive technology stimulation cycles (Bouchard *et al.*, 1994), while the advantage of rhFSH compared to urinary products has been suggested (Out *et al.*, 1995). A typical approach to their combined use is described in this case report. Comparison of the two cycles undertaken by our patient suggests a shorter duration of treatment with GnRH antagonist (7 versus 10 stimulation days), as well as the lower number of rhFSH/HMG ampoules consumed (14 versus 30). In addition, judicious use of a GnRH antagonist may combine satisfactory baseline LH levels (necessary to drive the follicular oestradiol production machinery), while preventing LH surge, as described in this report. The full scope of the therapeutic effects of this regimen is currently under investigation.

Given the fluctuations in LH levels during the follicular phase, follicular steroidogenesis might be affected, i.e. progesterone levels may rise (Ubaldi *et al.*, 1996) or drop (Albano

et al., 1996), and oestradiol levels may plateau transiently during stimulation (Albano *et al.* 1996). Furthermore, the use of GnRH antagonist during the follicular phase may also affect the luteal phase, particularly if high doses are used (Fraser *et al.*, 1997).

Information gained from the multicentre, dose-finding study and future large scale studies will allow for an objective assessment of this new approach.

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