Short communication

Recombinant gonadotrophin-based, ovarian hyperstimulation syndrome-free stimulation of the high responder: suggested protocol for further research

Shahar Kol[1], Mira Muchtar
IVF Unit, Elisha Hospital, POB 6518, Haifa 31064, Israel
[1]Correspondence: Tel: +972 4 8300087; Fax: +972 4 8300086; e-mail: sk@ivf.co.il

Abstract

Ovarian stimulation of the high responder remains controversial. The narrow margin between a too-low gonadotrophin dose (and abnormal oestradiol rise) and excessive stimulation (risk of OHSS) is a challenging situation. This study describes an OHSS-free protocol, based on the use of recombinant gonadotrophins for stimulation and gonadotrophin-releasing hormone (GnRH) antagonist to prevent premature LH surge. In six patients with a previous history of excessive response, stimulation was started on day 3 of cycle with recombinant FSH. When follicular diameter reached 13–14 mm, a daily injection of GnRH antagonist was added, together with a daily dose of 75 IU of recombinant LH. When the leading follicles reached 17 mm in diameter, ovulation was triggered with a single dose of 0.2 mg triptorelin. Luteal support with vaginal oestradiol and progesterone was started on the day of oocyte retrieval. None of the patients developed clinically significant OHSS. Mean maximal oestradiol concentration was 23,209 pmol/l, and mean number of embryos obtained per patient was 20.5. Fresh embryo transfer resulted in one ongoing pregnancy and two chemical pregnancies. Thaw cycles have resulted so far in two additional ongoing pregnancies. This protocol removes the risk of OHSS and has a good clinical outcome, and therefore merits further research.

Keywords: *GnRH agonist, GnRH antagonist, OHSS, ovarian stimulation, ovulation triggering, recombinant gonadotrophins*

Introduction

Ovarian stimulation of high responders remains controversial. A high responder can be defined as a patient with a history of ovarian hyperstimulation syndrome (OHSS), or aborted cycles due to OHSS risk. The narrow margin between a too-low gonadotrophin dose (and abnormal oestradiol rise) and excessive stimulation (OHSS) is a challenging situation. A too-low stimulation dose may result in only one follicle developing, leading, ironically, to cycle cancellation for low response. Curtailing stimulation dose in mid-stimulation often results in decreased oestradiol concentrations, follicular growth arrest and poor oocyte quality. On the other hand, excessive ovarian stimulation with these patients is common, leading to therapeutic manoeuvres to prevent OHSS, such as freezing all embryos, coasting, or albumin administration. Unfortunately, these therapeutic measures do not completely prevent OHSS. A second long-lasting controversy is the question of optimal LH concentrations during the follicular phase. Based on available data, an 'LH window' was formulated to reflect the 'ideal' serum LH concentration range (Shoham, 2002; Tesarik and Mendoza, 2002). In gonadotrophin-releasing hormone (GnRH) antagonist-based protocols excessive pituitary response to the antagonist may lead to very low LH concentrations during the late follicular phase, outside of the desired range. A sharp decrease in LH concentrations was shown to have a detrimental effect on cycle outcome, as was clearly demonstrated when high doses of antagonist were used (Ganirelix Dose-Finding Study Group, 1998). Recently, Acevedo *et al.* (2004) have elegantly shown the benefit of supplemented LH in GnRH antagonist cycles. To neutralize the uterine factor, they included young oocyte donors in their study. Embryos originating from donors who received LH supplementation had significantly higher implantation rate compared with control (35 versus 15%).

The current communication describes an ovarian stimulation protocol, which may give satisfactory solutions to both problems: complete prevention of OHSS, and adequate follicular phase LH concentrations. The proposed protocol uses recombinant gonadotrophins, avoiding urinary-derived products.

Materials and methods

Six patients attending the IVF clinic, with a history of OHSS in previous stimulation cycles, sought further treatment. Stimulation was started on day 3 of the cycle with 225 IU recombinant FSH (GONAL-f®; Serono, Geneva, Switzerland). When follicular diameter reached 13–14 mm, a daily injection of GnRH antagonist (Cetrotide®; Serono) was added, together with a daily dose of 75 IU recombinant LH (Luveris®; Serono). When at least three follicles reached 17

Table 1. Relevant clinical details of six patients. Oestradiol in pmol/l, LH in IU/l.

Subject of	*No. of ampoules of Gonal F*	*No. of ampoules Luveris*	*Oestradiol max*	*Last LH*[a]	*No. of oocytes retrieved*	*No. of embryos*	*Mid-luteal LH*
1	34	3	14,211	2.0	9	4	0
2	24	4	24,669	1.5	18	8	0
3	27	4	33,769	1.7	31	20	1.9
4	32	5	12,177	1.0	38	23	1.6
5	24	3	36,560	4.6	71	52	0.9
6	28	3	17,868	1.8	29	16	1.4
Mean	28	3.67	23,209	2.1	32.7	20.5	0.97
SD	3.85	0.82	10,228	1.27	21.4	17.5	0.82

[a]On the day ovulation was triggered with decapeptyl.

mm in diameter, ovulation was triggered with a single dose of 0.2 mg triptorelin (Decapeptyl®; Ferring, Copenhagen, Denmark). Oestradiol concentrations were not taken as limiting criteria for triggering ovulation. Luteal support with vaginal oestradiol (Estrofen® 4 mg daily; Novo Nordisk, Malmö, Sweden) and micronized progesterone (Utrogestan® 600 mg daily; Besins Iscovesco, Paris, France) was started on the day of oocyte retrieval. Such support is needed because of the resultant complete luteolysis. Embryos (two or three) were transferred to the uterus on day 2 post-retrieval.

Results

None of the patients developed clinically significant (signs or symptoms leading to hospitalization) OHSS. **Table 1** describes the main outcome measures. Mid-luteal mean ovarian diameters were 4–5 cm on vaginal ultrasound. Fresh embryo transfer resulted in one ongoing pregnancy and two chemical pregnancies. Thaw cycles have resulted so far in two additional ongoing pregnancies.

Discussion

The prevalence of OHSS varies considerably between IVF units. A World Health Organization report states that the worldwide incidence of severe OHSS is 0.2–1% of all assisted reproduction cycles, with a 1:4500–1:50,000 mortality per infertile woman receiving gonadotrophins. Following IVF, the overall incidence is estimated at 0.6–14% (Hugues, 2002). These numbers translate to >10 deaths and thousands of hospitalizations annually, worldwide. Numerous approaches have been suggested to prevent OHSS (coasting, albumin infusion, freezing all embryos and more); however, GnRH agonist trigger targets the basic mechanism of OHSS (too many functioning corpora lutea) by causing dramatic luteolysis (Kol, 2004). This mechanism of action explains OHSS prevention even in extreme ovarian response (**Table 1**, subject 5).

The described protocol for ovarian stimulation of the high responder may provide optimal solutions for the clinical dilemmas mentioned above by offering the following advantages: (i) OHSS-free, even in extreme ovarian response (extreme high concentrations of oestradiol); (ii) no need to curb stimulation dose because of OHSS, thereby optimizing oocyte quality; (iii) recombinant-only stimulation (although the choice of recombinant products rather than urinary gonadotrophins has no relation to the risk or the prevention of OHSS); (iv) adequate late follicular LH concentrations ('LH window'); (v) good clinical outcome: even if the fresh cycle yields low pregnancy rate (due to excessive late follicular oestradiol), the large number of frozen embryos ensures excellent 'per retrieval' pregnancy rate.

A fundamental weakness of the proposed protocol is that so far it has never been tested in a formal prospective randomized controlled study against routine human chorionic gonadotrophin (HCG)-triggered ovulation. Randomized prospective trials (Fauser *et al.*, 2002; Beckers *et al.*, 2003) have been reported comparing agonist and HCG trigger; however, hyper-responders were excluded, and therefore the advantage of OHSS prevention was never looked at. These studies have confirmed that the type of trigger (HCG or agonist) does not affect oocyte maturity and quality. A study in the context of OHSS prevention requires allocation of very high-risk patients to the HCG arm. Ironically, the weakness of the proposed approach lies in its tremendous efficacy in terms of OHSS prevention, leading to the inability to establish it as an accepted protocol under current 'golden standard' scientific guidelines. The dissemination of this protocol among practitioners can only be achieved by further clinical research that will take into consideration the above reasoning. Further larger studies are required to establish the proposed protocol as the ultimate solution for OHSS prevention.

References

Acevedo B, Sanchez M, Gomez JS *et al.* 2004 Luteinizing hormone supplementation increases pregnancy rates in gonadotropin-releasing hormone antagonist cycles. *Fertility and Sterility* **82**, 343–347.

Beckers NG, Macklon NS, Eijkemans MJ *et al.* 2003 Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing

hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. *Journal of Clinical Endocrinology and Metabolism* **88**, 4186–4192.

Fauser BC, de Jong D, Olivennes F *et al.* 2002 Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. *Journal of Clinical Endocrinology and Metabolism* **87**, 709–715.

Ganirelix Dose-Finding Study Group 1998 A double-blind, randomized, dose-finding study to assess the efficacy of the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462) to prevent premature luteinizing hormone surges in women undergoing ovarian stimulation with recombinant follicle stimulating hormone (Puregon). *Human Reproduction* **13**, 3023–3031.

Hugues JN 2002 Ovarian stimulation for assisted reproductive technologies. In: Vayena E, Rowe PJ, Griffin PD (eds) *Current Practices and Controversies in Assisted Reproduction*. World Health Organization, Geneva, Switzerland, pp. 102–125.

Kol S 2004 Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome. *Fertility and Sterility* **81**, 1–5.

Shoham Z 2002 The clinical therapeutic window for luteinizing hormone in controlled ovarian stimulation. *Fertility and Sterility* **77**, 1170–1177.

Tesarik J, Mendoza C 2002 Effects of exogenous LH administration during ovarian stimulation of pituitary down-regulated young oocyte donors on oocyte yield and developmental competence. *Human Reproduction* **17**, 3129–3137.

Received 15 November 2004; revised and refereed 20 January 2005; accepted 28 February 2005.