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CASE REPORT

High dose gonadotrophin-releasing hormone antagonist (ganirelix) may prevent ovarian hyperstimulation syndrome caused by ovarian stimulation for in-vitro fertilization

D.de Jong[1], N.S.Macklon[1], B.M.J.L.Mannaerts[2], H.J.T.Coelingh Bennink[2] and B.C.J.M.Fauser[1,3]

[1]Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Dijkzigt Academic Hospital and Erasmus University Medical School, Dr. Molewaterplein 40, 3015 GD, Rotterdam and [2]Scientific Development Group, NV Organon, Oss, The Netherlands

[3]To whom correspondence should be addressed

This case report describes the first attempt to treat imminent ovarian hyperstimulation syndrome (OHSS) by using a gonadotrophin-releasing hormone (GnRH) antagonist. A 33 year old, normo-ovulatory woman undergoing in-vitro fertilization received daily subcutaneous injections of 150 IU of recombinant follicle-stimulating hormone (recFSH) from cycle day 2, together with GnRH antagonist (ganirelix) 0.125 mg from cycle day 7 onwards. On cycle day 10 the patient was found to have a serum oestradiol concentration of 16 500 pmol/l and, on ultrasound examination, four preovulatory (>16 mm) and nine intermediate sized (10–16 mm) follicles. RecFSH injections were discontinued, human chorionic gonadotrophin (HCG) withheld, whereas the ganirelix dose was increased to 2 mg/d. This regimen led to a rapid decrease in serum oestradiol concentrations and the decrease in ovarian size on ultrasound. Since GnRH antagonists will become clinically available for in-vitro fertilization programmes in the near future this suggested regimen might have a role in preventing severe OHSS.

Key words: GnRH antagonists/imminent ovarian hyperstimulation syndrome/in-vitro fertilization/ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of assisted reproduction (Schenker and Weinstein, 1978). OHSS does not occur in the absence of either the endogenous luteinizing hormone (LH) surge, or surrogate human chorionic gonadotrophin (HCG). Conditions which may indicate imminent OHSS include late follicular phase serum oestradiol concentrations ⩾12 675 pmol/l (3500 pg/ml), and the occurrence of >25 small and intermediate sized follicles (Rizk and Aboulghar, 1991). Under these circumstances ovarian stimulation for in-vitro fertilization (IVF) is usually cancelled by cessation of exogenous gonadotrophins, withholding HCG, and continuation of pituitary down regulation by gonadotrophin-releasing hormone (GnRH) agonists in order to prevent unpredictable changes in release of endogenous gonadotrophins. However, it has been reported that the continued administration of GnRH agonists does not affect subsequent ovarian quiescence (Wada *et al.*, 1992). This may be related to prolonged suppression of pituitary function due to slow recovery from down-regulation (Donderwinkel *et al.*, 1993). Some residual gonadotrophin release may remain during GnRH agonist suppression, whereas pituitary release of LH and follicle-stimulating hormone (FSH) may be virtually abolished with the sustained use of a high dose of GnRH antagonist. In this case report we describe an alternative method, using a high dose of a GnRH antagonist which may decrease the risk of a severe OHSS.

Case report

A 33 year old regularly menstruating woman (body mass index 23 kg/m^2) with an infertility duration of 4.5 years due to tubal pathology underwent IVF in our unit. Before initiation of treatment, endocrine screening and sonographic examination appeared to be normal. As part of a multicentre phase II clinical trial (approved by the local ethics review committee), 150 IU recombinant follicle-stimulating hormone (recFSH) (Puregon®; NV Organon, Oss, The Netherlands) daily subcutaneous injections were administered, starting on cycle day 2. From cycle day 7 onwards she was co-treated daily with a GnRH antagonist (ganirelix, Org 37 462; NV Organon) (Nelson *et al.*, 1995) 0.125 mg subcutaneously. Initially normal follicular growth was observed and although oestradiol concentrations rose steadily, they remained within the limits normally associated with controlled ovarian hyperstimulation for IVF. The moderate starting dose of 150 IU recFSH was therefore continued. However, on cycle day 11 the patient presented with a serum oestradiol level of 16 500 pmol/l, a level associated with an increased risk of OHSS (Rizk and Aboulghar, 1991). Transvaginal ultrasound showed four preovulatory (⩾16 mm) follicles, and nine intermediate sized (10–16 mm) follicles. It was decided to cancel the cycle by withholding HCG injection and discontinuing daily recFSH administration. On cycle day 12 ultrasound showed an increase in the number of follicles (six preovulatory and 27 intermediate sized follicles). The patient complained of abdominal discomfort and a pocket of ascites in the pouch of Douglas was demonstrated on ultrasound. The oestradiol concentration was 22 315 pmol/l and the right and left ovaries were enlarged, with respective mean diameters of 72 mm and 54 mm. The ganirelix dose was increased to 2 mg/d to prevent a possible

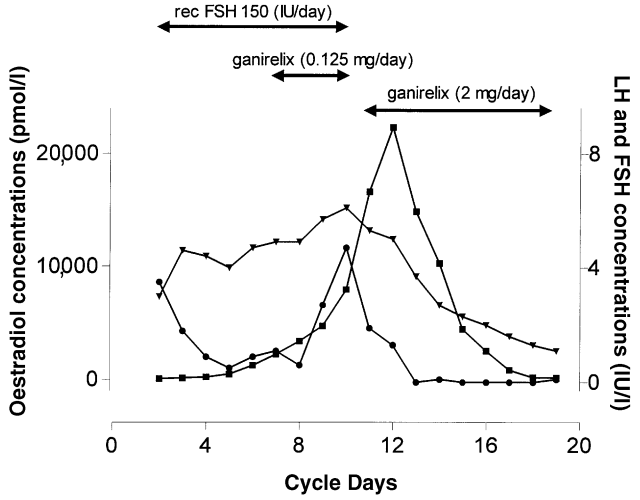

Figure 1. Oestradiol (■–■), follicle-stimulating hormone (FSH) (▼–▼) and luteinizing hormone (●–●) serum levels during treatment with recombinant FSH and ganirelix for in-vitro fertilization in a patient with imminent ovarian hyperstimulation syndrome.

LH surge (Dittkoff *et al.*, 1991) and to further decrease endogenous LH and FSH secretion. Within 3 days oestradiol concentrations returned to levels associated with a normal ovarian response for hyperstimulation in IVF. Moreover, symptoms and ascites disappeared over the following days. In the same period, the mean diameters of the right and left ovary decreased to 65 mm and 47 mm respectively. Daily serum levels of LH, FSH and oestradiol are depicted in Figure 1.

Discussion

Administration of GnRH antagonists in the late follicular phase has recently been applied effectively in IVF programmes to prevent a premature rise in endogenous LH and subsequent luteinization instead of extended administration of GnRH agonists (Diedrich *et al.*, 1994; Olivennes *et al.*, 1994; Felberbaum *et al.*, 1996; Albano *et al.*, 1996, 1997). In contrast to GnRH agonists, GnRH antagonists elicit an immediate effect by competitive blockage of GnRH receptors (Klingmüller *et al.*, 1993). The likelihood of preventing a premature LH rise and subsequent luteinization is clearly dependent on the dose of the GnRH antagonist (Ubaldi *et al.*, 1996). Further evidence for a dose dependent pituitary response is the observation that gonadotrophin secretion could be restored by pulsatile GnRH therapy during GnRH antagonist treatment (Gordon *et al.*, 1990). Since in the late follicular phase growth of follicles and subsequent oestradiol production is dependent on stimulation by both LH and FSH, further development of follicles may be arrested effectively in cases of imminent OHSS through pronounced suppression of pituitary gonadotrophin release by prolonged use of high dose GnRH antagonists. It should, however, be recognized that a spontaneous LH surge may still occur under these circumstances, which could induce OHSS without exogenous HCG. As demonstrated previously (Gordon *et al.*, 1990), GnRH can override the inhibitory actions of antagonist. We therefore elected to increase the ganirelix dose. Simply reducing the dose of recFSH is unlikely to have had a significant effect since follicular sensitivity to FSH increases in the advanced stages of development. There is no clear evidence that reducing the dose of FSH at this late stage has a preventative effect on OHSS.

GnRH receptors have been shown to be present in granulosa–lutein cells (Latouche *et al.*, 1989; Minaretzis *et al.*, 1995) and some studies suggest that steroidogenic activity of cultured granulosa cells may be affected by GnRH (Pellicer and Miro, 1990) suggesting that the human ovary could be a target for direct extrapituitary GnRH action in the human.

For reasons of safety, we considered it mandatory to cancel ovarian stimulation in this IVF patient presenting with clear signs of imminent OHSS. Since spontaneous LH surges may occur after a short period of GnRH antagonist treatment (Ditkoff *et al.*, 1991), sustained administration of a high dose GnRH antagonist could potentially reduce the risk of severe OHSS. Indeed, in-vitro studies demonstrate that chronic administration of GnRH antagonist virtually abolishes GnRH induced LH release from the pituitary (Pinski *et al.*, 1996).

The present case confirms the previously reported efficacy of high dose GnRH antagonist in achieving rapid suppression of endogenous gonadotrophin release even when LH levels have started to rise (Dubourdieu *et al.*, 1994), and in eliciting subsequent ovarian quiescence. It is yet to be determined whether GnRH antagonists act solely through suppression of pituitary function, or whether direct actions at the ovarian level may also be involved. The clinical role played by GnRH antagonist in this case remains uncertain since progression to OHSS may have been prevented by discontinuation of recFSH and withholding HCG. Controlled studies are required to assess the extent to which GnRH antagonist contributes to the early resolution of ovarian hyperstimulation syndrome.

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