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The administration of the GnRH antagonist, cetrorelix, to ooctye donors simplifies oocyte donation

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BACKGROUND: We report our experience on the efficacy of a new regimen of the GnRH antagonist, cetrorelix, and recombinant FSH, Gonal-F, for controlled ovarian stimulation in a donor oocyte programme. METHODS AND RESULTS: Six oocyte donors were commenced on Gonal-F (150 IU) and two on Gonal-F 225 IU daily on day 4 together with cetrorelix 0.25 mg daily on day 8 until the day of administration of hCG. Six premenopausal recipients were down-regulated with intranasal Nafarelin 400 μg twice daily; two women with premature menopause did not require down-regulation for synchronization between donor and recipient cycles. The median (range) of oocytes retrieved and the median (range) fertilization rates were 7 (3–13) and 50% (0–71%) respectively. With the exception of a recipient who had failed fertilization, seven recipients had two embryos transferred. The median (range) number of days of ovarian stimulation, cetrorelix administration and number of Gonal-F ampoules administered for ovarian stimulation were 9 (7–12) days, 5 (3–8) and 18 (14–24) respectively. The clinical pregnancy rate per cycle was 50% (4/8) and one of the latter women miscarried at eight weeks gestation. Three women (37.3%) had full term deliveries. CONCLUSION: This preliminary study has shown that using a combination of cetrorelix and Gonal-F resulted in a high pregnancy rate, reduced the duration of treatment for the donor and simplified oocyte donation.

Key words: cetrorelix/donor/FSH/oocyte/recombinant

Introduction

It is well established that successful outcome from treatment using donor oocytes require synchronization of the donor and recipient. In order to allow synchronization between the donor and recipient, a GnRH agonist is used to down-regulate the pituitary (Marcus *et al*., 1999). While the safety of GnRH agonist for oocyte donation is established (Sauer *et al*., 1996), the latter may result in donors experiencing symptoms due to the GnRH agonist-induced hypo-estrogenic status. In addition, to achieve pituitary down-regulation using a GnRH agonist takes at least 2 weeks using the long protocol and prolongs the treatment period for the donor.

The earlier GnRH antagonists induced histamine release together with allergic side effects (Hahn *et al*., 1985; Reissmann *et al*., 1995). The newer GnRH antagonists have overcome the latter problems (Felberbaum *et al*., 1999). In contrast with GnRH agonists, the GnRH antagonist, cetrorelix, can suppress gonadotrophins within a few hours and has potential advantages over GnRH agonists during ovarian stimulation for assisted conception treatment. The rapid suppression of gonadotrophins allows clinicians to restrict administration of the GnRH antagonist to part of the ovarian stimulation treatment where it is necessary to suppress a premature LH surge. GnRH antagonist suppresses gonadotrophins by dose-dependent effect and through competitive inhibition of the pituitary GnRH receptors.

The efficacy of GnRH antagonist cetrorelix for assisted conception treatment has been reported (Albano *et al*., 1996; 1997; Wikland *et al*., 2001). Albano *et al*. (1996; 1997) reported that a single daily dose of 0.25 mg cetrorelix administered from day 6 of ovarian stimulation with gonadotrophins to the day of administration of hCG was effective in suppressing the premature LH surge. In a randomized study comparing the administration of a single daily dose of 0.25 mg cetrorelix to the day of administration of hCG compared with daily administration of buserelin 600 μg, the incidence of ovarian hyperstimulation syndrome (OHSS) was lower in the cetrorelix group (Felberbaum *et al*., 1999).

We report our experience on the administration of cetrorelix to oocyte donors to evaluate the efficacy of this new method of synchronization of the donor and recipient treatment.

Materials and methods

All eight consecutively-treated oocyte donors were evaluated. The oocyte donors were ≤35 years old, had regular menstrual cycles of 25–35 days, two normal ovaries based on transvaginal scan findings, body mass index (BMI) ≤32 kg/m^2 and agreed to donate their oocytes

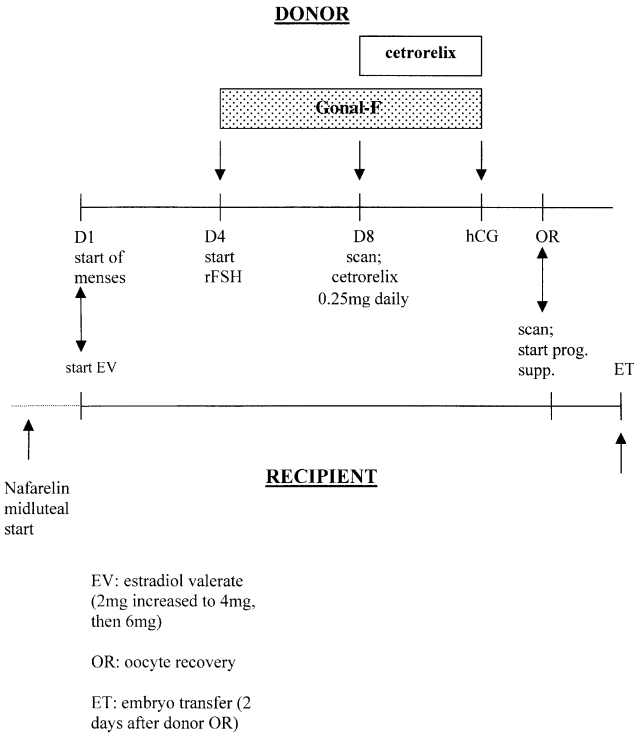

Figure 1. Synchronization of donor–recipient IVF–embryo transfer cycle.

altruistically for treatment. The donors were fit and healthy and had no gynaecological or medical disorders.

All donors were seen at the Assisted Conception Clinic and a detailed medical and social history was taken. Blood was taken for screening to exclude donors who may be carriers of cystic fibrosis genes and to screen for previous viral (Hepatitis B, Hepatitis C, HIV, cytomegalovirus) and treponemal infection. A vaginal swab was taken to exclude *Chlamydia* infection and all donors were assessed by an independent counsellor prior to donation.

All recipients were <50 years old and fit and well. The recipients and their partners underwent blood screening similar to the donors. Recipients >42 years had an electrocardiogram and blood taken for fasting glucose, urea and electrolytes, and cholesterol estimations. Women who were recipients had treatment due to incipient or premature ovarian failure (n = 2) or failed assisted conception treatments due to poor response to ovarian stimulation (n = 6).

The treatment protocol for the donors and recipients is summarized in Figure 1. To allow for synchronization of the donor/recipient, the donor was advised to telephone the Assisted Conception Programme on day 1 of their period (see Figure 1). With the exception of two donors who were started on 225 IU Gonal-F, ovarian stimulation was carried out using recombinant FSH (rFSH) 150 IU (Gonal-F; Serono) on day 4 of the normal menstrual cycle in the remaining six women. The dose of gonadotrophin was fixed during the period of stimulation until the day of administration hCG (Profasi; Serono). Cetrorelix 0.25 mg was administered s.c. daily on day 8 until the day of administration of hCG. Ovarian response was monitored by transvaginal (TV) ultrasound from day 4, with stimulation with additional TV ultrasound scans on day 7 if necessary. When the three largest follicles measured ⩾17 mm, final ovarian maturation was triggered by the administration of a single s.c. injection of 10 000 U hCG (Profasi; Serono). Oocyte recovery was carried out 34–36 h after hCG injection followed by IVF. An hour prior to oocyte retrieval, all donors were given a single i.v. dose of 1.2 g Augmentin (SmithKlineBeecham). Following oocyte retrieval, all donors were given a single dose (1 g) of azithromycin (Zithromax, Pfizer) and were given a follow-up consultation at the clinic.

For all recipients who were still cycling, down-regulation was carried out using the intranasal GnRH agonist (Nafarelin; Searle) 400 μg twice daily for 2 to 4 weeks. A baseline transvaginal scan was carried out prior to down-regulation to ensure that the uterus and adnexa were normal. On the day that the donor telephoned the Unit with the onset of her period, a member of staff in the Unit telephoned the recipient immediately and advised the latter to start oral estradiol valerate (Climaval; Novartis tablets). All recipients took estradiol valerate 2 mg from day 1 to 5, 4 mg from day 6–10 and 6 mg from day 11 to day of donor's oocyte retrieval. Estradiol valerate 4 mg was continued until a pregnancy test 14 days later. The endometrial thickness of the recipient was measured prior to administration of i.m. progesterone. An i.m. injection of 50 mg progesterone (gestone; Ferring) was administered to the recipient on the day of the donor's oocyte retrieval and again the following day. Following this, i.m. gestone 100 mg daily or progesterone vaginal suppositories, Cyclogest (Shire) 200 mg twice daily were administered until pregnancy test. A maximum of two embryos were replaced 48 h after commencing on i.m. progesterone.

If pregnancy was confirmed, women were advised to continue with estradiol valerate 8 mg daily and progesterone vaginal suppositories 200 mg twice daily until 9 weeks gestation. Women who failed to conceive were advised to stop the medications and to go back on hormone replacement therapy, if they had premature ovarian failure.

Assessments

Follicular number and size were measured by transvaginal ultrasonography. Blood samples were taken from the donors for measurement of serum LH carried out on day 4 of stimulation and on subsequent visits. Measurements of serum estradiol were carried out if clinically indicated to assess ovarian response.

The hormonal LH and estradiol assays were carried out using the standard protocols in our laboratory (Vankrieken *et al*., 1999).

Statistical analyses

Values were expressed in median (range) as the data were non-parametric.

Results

In this study of eight patients, the median (range) age of the donors and recipients was 33 years (range 29–35) and 40 years (range 31–49) respectively. Seven out of the eight donors (87.5%) were parous. All of the recipients were nulliparous. All donors had three follicles ⩾17 mm diameter following ovarian stimulation and underwent oocyte retrieval. None of the donors had a premature LH surge or complications post operatively. The mean (range) number of days of cetrorelix and number of Gonal-F ampoules for ovarian stimulation were 5 (3–8) and 18 (14–24) respectively. The median (range) of oocytes retrieved and the median (range) fertilization rate were 7 (3–13) and 50% (0–71%). A solitary parous donor who was 29 years old had four oocytes retrieved and there was no fertilization. With the exception of the recipient who had failed fertilization, all of the remaining seven recipients had two embryos transferred [median 2 (range 0–2)].

The clinical pregnancy rate per cycle commenced based on transvaginal scan findings at seven weeks gestation was 50%

(4/8) and one of the latter women miscarried at 8 weeks gestation. Of the remaining three women who had a clinical pregnancy, all had full term deliveries.

Discussion

This may be the first report on the use of the GnRH antagonist, cetrorelix, to simplify the synchronization of the donor and the recipient. The reported protocol has a clinical pregnancy rate of 50% based on a maximum of two embryos transferred. Sauer *et al*. (1997) reported in a small study of 15 oocyte donors, the use of the GnRH antagonist (Nal-Glu) in their oocyte donation programme and compared this with donors who had down-regulation with leuprolide. No serious side effects were experienced by the women administered Nal-Glu, the clinical pregnancy rate was 46.7%, and there was a reduction in the number of ampoules of hMG administered and the time required for controlled ovarian stimulation.

For donors, the convenience of the reported regimen reduces the duration of treatment to ~2 weeks. If the GnRH agonist long protocol for pituitary down-regulation is used for the treatment of the oocyte donors, the period of treatment (including ovarian stimulation) usually lasts for 4–5 weeks. This long duration of treatment may increase the stress, anxiety, discomfort and inconvenience experienced by some donors. In contrast with GnRH agonist which may result in hypo-estrogenic symptoms due to pituitary suppression, GnRH antagonist(s) are administered over a restricted period and do not result in the latter symptoms.

The safety and efficacy of cetrorelix in controlled ovarian stimulation for assisted reproduction treatment has been reported (Ludwig *et al*., 2001a; Wikland *et al*., 2001). Interestingly, both of the latter investigators reported a low rate of ovarian hyperstimulation syndrome (OHSS). In a review of 1000 cases of oocyte donation, Sauer (2001) reported that the incidence of severe OHSS was 0.7%. The application of the present regimen to oocyte donors may further reduce the risk of OHSS as a low dose of rFSH (Gonal-F) was used, in the majority of women, in our regimen.

This report is confined to the use of cetrorelix for suppression of gonadotrophins to prevent a premature LH surge. Another GnRH antagonist, ganirelix (Orgalutran; Organon) is available commercially and may be used in a similar regimen for management of the oocyte donors. If a higher dose of rFSH (Gonal-F) is employed, it is likely that a significantly higher number of oocytes will be obtained (Wikland *et al*., 2001). However, this may increase the risk of OHSS.

A preliminary report by Olivennes *et al*. (2001) suggested that there was no increased incidence of malformation, using the GnRH antagonist, ganirelix, and rFSH, Puregon (Organon) for assisted conception treatment. In addition, in a follow up study of 227 children born following administration of cetrorelix for ovarian stimulation for IVF/ICSI treatment, the incidence of malformation was 3.1% (Ludwig *et al*., 2001b). The data are reassuring to clinicians who may wish to use a combination of rFSH and GnRH antagonist to simplify their oocyte donation programme. In this report of eight recipients, we had a high pregnancy rate. Further studies on a larger number of patients have to be carried out using this regimen to confirm our findings.

In conclusion, the reported regimen is safe, cost-effective and simplifies the management of the donor in the oocyte donation programme. By restricting the injection of GnRH antagonist to a few days to suppress LH surge, this treatment regimen reduces the exposure of the donors to medication. A starting dose of 150 IU of rFSH for controlled ovarian stimulation should be considered to reduce the cost of treatment and the risk of OHSS.

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