The administration of the GnRH antagonist, cetrorelix, to oocyte 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 mg 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/m² and agreed to donate their oocytes.
All donors were given a single i.v. dose of 1.2 g Augmentin after hCG injection followed by IVF. An hour prior to oocyte retrieval, hCG (Profasi; Serono). Oocyte recovery was carried out 34±36 h triggered by the administration of a single s.c. injection of 10 000 U hCG (Profasi; Serono). Cetrorelix 0.25 mg was administered s.c. daily on day 8 until the day of administration hCG (Profasi; Serono). Cetrorelix administration for oocyte donation

Cetrorelix administration for oocyte donation

alttruistically 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 donorrecipient, 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. Cetrorelix administration for oocyte donation

Cetrorelix administration for oocyte donation

FIGURE 1. Synchronization of donorrecipient IVFembryo transfer cycle.

DONOR

<table>
<thead>
<tr>
<th>D1</th>
<th>D4</th>
<th>D8</th>
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<tr>
<td>start of menses</td>
<td>start rFSH</td>
<td>scan; cetrorelix 0.25 mg daily</td>
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RECIPENT

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<td>oocyte recovery</td>
<td>embryo transfer (2 days after donor OR)</td>
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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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References


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