Levonorgestrel hormone releasing intrauterine system (Mirena[®]) as a contraceptive in egg donors: case report

C. Kailasam,^{1,3} V. Akande,² and U. D. Gordon¹

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We report the safe use of levonorgestrel hormone releasing intra uterine system (Mirena[®]) as a contraceptive in egg donors during a treatment cycle. In the first case report, a 29-year-old egg donor using the Mirena coil for contraception and two egg recipients, aged 41 years and 32 years respectively underwent standard IVF treatment, oocyte retrieval in the egg donor and in vitro fertilization followed by embryo transfer in the recipient. The outcome of IVF cycle using donor eggs was satisfactory with successful pregnancy in the egg recipient. The second case involved a 34-year-old egg donor using the Mirena coil and a 44-year-old recipient. Our findings suggest that egg donors can safely use the (Mirena[®]) as a contraceptive device during treatment, without compromising follicular development and oocyte quality.

KEY WORDS: Contraception; egg donor; IVF; Mirena coil.

INTRODUCTION

Egg donors are potentially at risk of an unplanned pregnancy, due to the fertility enhancing drugs administered as part of their treatment. They are therefore required to use effective contraception during the treatment especially in the days around oocyte retrieval. Contraceptive advice has generally been to abstain from sexual intercourse or to use barrier contraception. Hormonal contraception is not advocated as it may interfere with ovarian stimulation and follicular growth. To our knowledge, this is the first report of a pregnancy in an oocyte recipient where the donor used the levonorgestrel hormone releasing intrauterine system (Mirena[®], Schering AG, Germany) as a contraceptive.

CASE REPORT 1

RD, a 29-year-old gravida 5, para 2 attended the University of Bristol, Centre for Reproductive Medicine, in February 2000 expressing her wish to become an egg donor. She had two children aged 4 and 3 years, interspersed between three first trimester spontaneous miscarriages. All RD's pregnancies were spontaneous conceptions. RD had a Mirena coil fitted for contraception 3 years prior to her attendance and had been amenorrhoeic since then. Apart from mild asthma, she had no other significant medical or surgical history of note. A pelvic ultrasound revealed the Mirena coil to be normally placed within the uterus and both ovaries to be normal. She underwent pre-treatment counselling and relevant investigations, which confirmed her to be a suitable egg donor.

Stimulation Protocol for Egg Donor

Ovarian stimulation was carried out as previously described (1). Essentially pituitary down-regulation was accomplished using a long protocol luteal

¹ University of Bristol, Centre for Reproductive Medicine, 4 Priory Road, Bristol BS8 1TY.

² University of Bristol, Division of Obstetrics and Gynaecology, St Michael's Hospital, Bristol BS2 8EG.

³ To whom correspondence should be addressed at University of Bristol, Centre for Reproductive Medicine, 4 Priory Road, Bristol BS8 1TY, UK; e-mail: chandra.kailasam@repiomed-bristol.co.uk.

phase gonadotrophin releasing hormone agonist, GnRH-a (Buserelin, Shire, Basingstoke, Hants, UK) 600 µg in six divided doses. Following confirmation of ovarian suppression using serum estradiol estimation (<200 pmol/L), ovarian stimulation was undertaken using 225 IU of gonadotrophins (Gonal F, Serono, Feltham, Middlesex, UK). On day 12 of gonadotrophin stimulation, RD had four follicles ≥17 mm, five follicles 15–16 mm and seven follicles <15 mm. Final oocyte maturation was undertaken with human chorionic gonadotrophin 5000 IU (Profasi, Serono, Feltham, Middlesex, UK) and transvaginal ultrasound guided oocyte retrieval undertaken 36 h later. Eleven oocytes were retrieved and the eggs were shared between two recipients, SV and SP.

Stimulation Protocol for Egg Recipient

The first recipient was SV, a 41-year-old lady with primary infertility of 16 years duration. She had previously attempted a treatment cycle of intracytoplasmic sperm injection using her own eggs. Her serum FSH level in the early follicular phase was 10.4 IU/L. This cycle had to be cancelled due to poor ovarian response. Following counselling, she opted for fertility treatment using donor eggs.

Pituitary suppression was achieved using the long protocol GnRH-a regime and the endometrium prepared using 2 mg estradiol valerate tablets, taken orally thrice a day. Administration of estradiol valerate tablets was started on the first day of donor's gonadotrophin injections. On day 9 of estradiol valerate, a transvaginal ultrasound scan measured the endometrial thickness to be 9 mm. GnRH-a Buserelin was stopped on the day of the donors HCG injection. Progesterone pessaries (Cyclogest, Shire, Basingstoke, Hants, UK) were administered vaginally, 400 mg twice a day, starting the day after donor's HCG injection. SV received five oocytes of which four were mature and suitable for ICSI. Following ICSI, all four oocytes fertilised and cleaved normally. At the patient's request, three embryos were transferred in July 2000.

Estrogen and progesterone supplementation was continued for 3 weeks after embryo transfer. The pregnancy test was positive and a pelvic scan was performed at 6 weeks of gestation, which revealed a single viable intrauterine pregnancy. Mrs SV was advised to continue with the hormonal supplementation till 12 weeks of gestation. She went on to deliver a healthy girl at term.

The second recipient SP was a 32-year-old woman who had been diagnosed as a carrier of a Duchenne muscular dystrophy. The treatment protocol was identical to that of the other recipient. She received six donor oocytes, three of which fertilised after conventional IVF. Two embryos were transferred in July 2000.

The one remaining embryo was frozen. Unfortunately, Mrs SP failed to conceive.

CASE REPORT 2

RJ, a 34-year-old gravida 2, para 2 attended our centre in April 2004 expressing her wish to become an egg donor. She had two children aged 5 years and 6 months respectively. All RJ's pregnancies were spontaneous conceptions. She had a Mirena coil fitted for contraception six months prior to her attendance and had been amenorrhoeic since then. She had no other significant medical or surgical history of note. A pelvic ultrasound revealed the Mirena coil to be normally placed within the uterus and both ovaries to be normal. She underwent pre-treatment counselling and relevant investigations, which confirmed her to be a suitable egg donor.

The stimulation protocol for egg donor was as explained in Case Report 1. On day 10 of gonadotrophin stimulation, RJ had seven follicles ≥ 17 mm, one follicle 15–16 mm and seven follicles < 15 mm. Six eggs were retrieved.

The recipient was RB, a 44-year patient with premature ovarian failure. The treatment protocol was as explained in Case Report 1. All six eggs fertilised and two good quality embryos transferred. Unfortunately she failed to conceive.

DISCUSSION

Generally women who are young (less than 35 years of age) and likely to be very fertile are recruited as egg donors (2).

The Mirena contraceptive system was developed by Leiras Oy, Finland and is marketed in most European countries by Schering AG, Germany. It is an effective form of contraception combining the advantages of both hormonal and intrauterine contraception. The Pearl Index is 0 to 0.3 per 100 women years.

The Mirena has a T-shaped body (32 mm × 32 mm) made of polyethylene. An elastomer sleeve is mounted around its vertical part. This sleeve consists of a 1:1 mixture of polydimethylsiloxane

and 52 mg of levonorgestrel. The sleeve is covered with a drug release controlling membrane of medical grade polydimethylsiloxane. This system releases levonorgestrel over an extended time of up to 5 years at a constant rate. The initial release rate of levonorgestrel is 20 µg per 24 h. At the end of 5 years, the release rate is still more than 10 µg per 24 h (3).

The Mirena IUS appears to have a minimal effect on ovarian and pituitary function. The mean plasma concentrations are lower than those seen with contraceptive levonorgestrel implants, combined oral contraceptives, and the minipill (3). Levonorgestrel released into the uterine cavity is absorbed into the systemic circulation and mainly bound to sex hormone binding globulin (4). Plasma concentrations decline over the 5-year period of use (5).

Contraception with the Mirena is primarily achieved by delivering levonorgestrel, a potent progestin, locally within the endometrium (6). As such many women using the Mirena experience a significant reduction in menstrual flow, and 20% become amenorrhoeic (7).

However menstrual bleeding is not a predictor of ovarian function in these patients. The peripheral plasma steroid profiles of levonorgestrel, estradiol and progesterone are similar in menstruating and amenorrhoeic women, with two-thirds of users having ovulatory cycles. The normal estradiol profiles suggest that the device does not cause disturbances in the follicular development of the ovaries (8–10). These suggest that the cyclic function, which is determined by the pituitary, is preserved in women using the Mirena whether they are menstruating or amenorrhoeic. The effect of levonorgestrel on ovarian function however is dose dependent; inhibition of ovulation requires a daily intrauterine release of 50 µg or more (11).

Barbara and Bundren (12) studied the effect of levonorgestrel implants on mouse oocytes. In an in vivo study, they reported that chronic exposure of mouse oocytes to levonorgestrel was found not to have any adverse effect on oocyte quality, oocyte fertilisation or preimplantation development, thereby providing evidence for a lack of toxicity of levonorgestrel.

The present report suggests that normal follicular response to exogenous gonadotrophin stimulation can occur in Mirena users, with no detrimental effect of levonorgestrel on oocyte quality, fertilisation and embryo development.

In contrast, women using subdermal levonorgestrel contraceptive implants may have impaired follicular growth and abnormal endocrine cycles even though ovulation may occur (13,14). In a review of all types of progestin subdermal contraceptive implants (Levonorgestrel, Etonogestrel, Nesterone, Nomegestrol acetate), Horacio *et al.* (15) concluded that follicular growth and the ovulatory process is disrupted with all of them.

The increasing popularity makes it likely that we will see patients who wish to donate eggs while continuing to use the Mirena for contraception. The findings of this report are reassuring and suggest that the Mirena is a suitable contraceptive that can be used safely by egg donors without compromising either follicular growth or oocyte quality. The high efficacy of the device means that egg donors will have a reliable form of contraception during the cycle of oocyte donation, but further studies are needed to confirm this.

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