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Case report

Pregnancy following *in vitro* fertilisation of an anonymously donated oocyte in a patient with premature ovarian failure

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Since the first successful birth in 1978 following *in vitro* fertilisation (IVF), this has become established treatment for infertility and is available at more than thirty centres in the United Kingdom. Oocyte donation has extended the use of IVF technology for conditions where a genetic abnormality exists or where repeated attempts at IVF have failed to achieve fertilisation. In cases where the ovaries are absent or have failed prematurely, the procedure can be combined with steroid replacement therapy to maintain a successful pregnancy. Donated oocytes have been obtained from relatives and friends, but more recently it has been recommended that the donor should remain anonymous. The following case report is of the first such pregnancy achieved in Northern Ireland.

CASE REPORT

A 25-year-old married woman presented to the infertility clinic, Royal Maternity Hospital, Belfast, in 1986, complaining of secondary amenorrhoea. Investigations had been undertaken at the age of 21 and had revealed elevated serum gonadotrophins in keeping with a diagnosis of premature ovarian failure. The chromosome complement was that of a normal female. Hormone replacement therapy with conjugated oestrogens 0·625 mg and norgestrel 0·15 mg (Prempak-C, Ayerst) was commenced. The possibility of pregnancy achieved by IVF using a donated ovum was discussed, and it was advised that an anonymous arrangement would be preferable.

The patient remained on hormone replacement therapy until October 1987 when an IVF programme commenced in Northern Ireland. Hormone therapy was then altered to a maintenance dose of oral oestradiol valerate (Progynova, Schering) 2 mg daily until a potential donor became available. A random serum oestradiol was 2509 pmol/l on this regimen. The dose was increased to 4 mg daily shortly after a potential donor, who was undergoing gamete intrafallopian transfer (GIFT) had commenced superovulation therapy. Eight oocytes were

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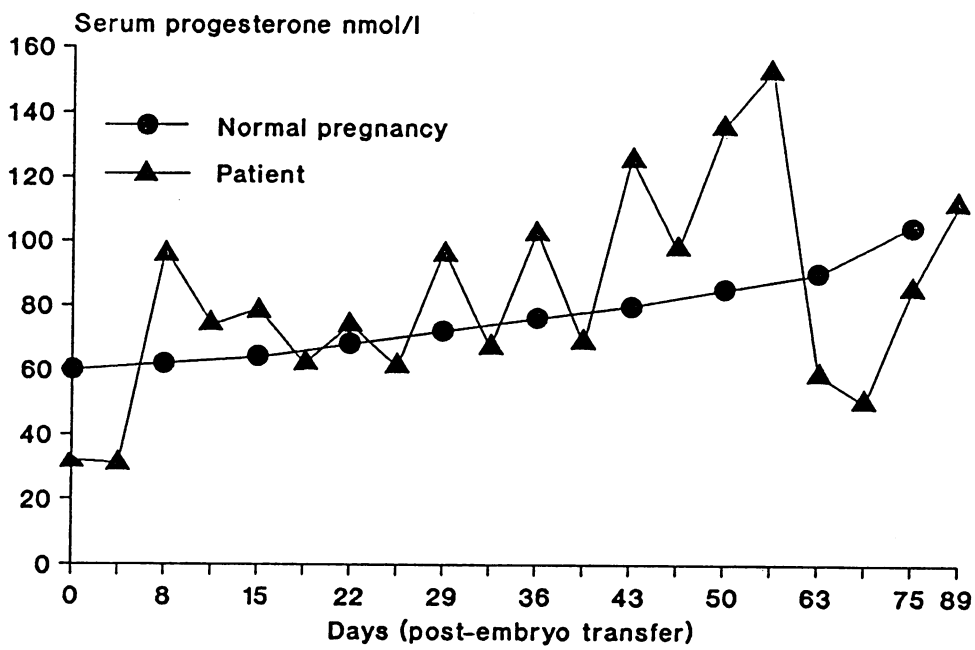
obtained from the donor by laparoscopy, four of which were replaced in her fallopian tubes with capacitated spermatozoa from her husband.

The remaining four oocytes were transferred to prepared culture dishes containing Earle's balanced salt solution with 10% human serum. A sample of the recipient's husband's semen was prepared by a centrifugation and swim-up technique, which enables the motile sperm to be extracted. Four hours later 100,000 sperm were added to each of the dishes containing an individual oocyte, and after 18 hours three oocytes had developed two pronuclei, which confirmed that fertilisation had occurred. At this time the patient was asked to increase her oestradiol valerate to 6 mg daily and was also given progesterone 50 mg (Gestone, Paines & Byrne) by intramuscular injection. This was repeated the following day to coincide with embryo transfer, at which time serum oestradiol was 2591 pmol/l and progesterone was 32·2 nmol/l, both of these levels being within the normal range.

Forty-eight hours after insemination two of the three embryos had divided normally. Embryo transfer was carried out under aseptic conditions, with the patient in the lithotomy position, using a fine plastic catheter which was inserted through the cervical os. The two embryos were placed in the recipient's uterus in 3 µl of medium with the added human serum concentration increased to 75%.

Hormone maintenance therapy was provided by oestradiol valerate 4 mg and progesterone 50 mg daily, and the serum levels of these two hormones checked twice weekly; all values initially followed the normal curve.[1]

Fifteen days after embryo transfer a pregnancy test was positive, and at 40 days a fetal circulation was identified with ultrasound. During the fourth week of pregnancy the progesterone levels fell below the optimal range (Figure), so the dose of progesterone was increased to 100 mg daily. At six and eight weeks the



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serum progesterone again fell below normal and further supplements were given in the form of vaginal pessaries (Cyclogest, Hoechst) with the dose increasing from 400mg daily at six weeks to 1200mg by nine weeks. Oestradiol levels remained well above the suggested range.[2]

At 10 weeks' gestation, both oral oestradiol and the systemic progesterone therapy were withdrawn, and one week later the progesterone pessaries were stopped. At this stage serum oestradiol and progesterone were 11,720 pmol/l and 153·5 nmol/l respectively. The levels dropped sharply after withdrawal of the replacement therapy, then over the next two weeks gradually returned towards the normal range for pregnancy. Serial ultrasonic scans showed a healthy single fetus.

The remainder of the pregnancy progressed satisfactorily until 32 weeks' gestation, when the patient was admitted with a painful antepartum haemorrhage. A diagnosis of placental abruption was made and delivery was carried out by Caesarian section, resulting in a live female infant weighing 1710g. Streak ovaries with no evidence of corpus luteum formation were noted.

The baby required minimal special care and was discharged aged 27 days, weighing 2230g. The mother had no postnatal complications. Measurement of serum oestradiol and progesterone levels was continued, and showed a gradual fall in oestradiol levels and a rise in gonadotrophins. The increase in FSH preceded that of LH, but by four weeks postpartum both had returned to postmenopausal levels.

DISCUSSION

Oocyte donation has been used with a high success rate in animal husbandry for many years.[3] In humans, it was not until the technique of IVF had been perfected that the first pregnancy in a patient with ovarian failure was established.[4] There have, however, been few published accounts of the outcome of pregnancy after donation of oocytes fertilised *in vitro,* and the success rate can vary from zero to 38%.[5]

Where the recipient has normal menstrual function, synchronisation of donor and recipient is necessary to aim for transfer of a four to six cell embryo on day 17–19 of the recipient's cycle. To achieve this it is usual to recruit a designated donor, such as a woman undergoing laparoscopic sterilisation, who has agreed to superovulation with gonadotrophins prior to the procedure. This also allows approximate matching of physical characteristics while preserving anonymity. Synchronisation can be achieved by adjusting the donor's menstrual cycle using oral contraceptive pills or norethisterone.[6]

In patients without ovarian function, a variety of steroid replacement protocols have been used to mimic the normal menstrual cycle.[2, 7, 8] Although it has been established that luteal progesterone is necessary to allow implantation and to maintain pregnancy, the relative importance of oestradiol is unclear.[9] Until further information is obtained from prospective studies, it seems reasonable to simulate the menstrual cycle, thus providing suitable endometrium for implantation, and subsequently to increase steroid therapy to maintain the pregnancy. A positive β-HCG titre may be obtained as early as 10 days after embryo transfer. If still negative three weeks after embryo transfer, it is assumed that the patient is not pregnant, and the oestrogen and progesterone doses are tapered off to allow menstruation to occur.

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A useful and simple method of preparation of a recipient depends on priming the endometrium with an adequate oestrogen dosage, then inducing secretory change in the proliferative endometrium by introduction of progesterone just prior to recovery of the donated oocytes.[10] Thus, the patient can be maintained on oestradiol therapy for several weeks and careful synchronisation with a potential donor is not required, allowing greater flexibility. This regimen is applicable to both normally cycling recipients and to those with ovarian failure. A similar protocol was used in this case, with subsequent requirements in pregnancy determined by twice weekly hormone levels.

Due to the small number of pregnancies achieved in patients with ovarian failure, no definite guidelines exist for when steroid therapy can be safely withdrawn. Csapo et al showed that the shift from ovarian to placental maintenance of pregnancy occurred at around 50–60 days' gestation.[11] Lutjen et al, in their first reported case,[4] withdrew oestradiol therapy at 72 days' gestation. Progesterone withdrawal was attempted from days 63–73, but was reintroduced when serum levels fell, and maintained until day 133. In this case report, serum levels also fell following sequential withdrawal of the progesterone supplements, but there was evidence of an active fetus on ultrasound scanning. Therefore, it was decided to await events and, indeed, progesterone levels returned to normal over the next two weeks. Very early withdrawal of oestradiol at 35 days and of progesterone at 48 days has been reported, with a successful pregnancy.[12]

With the simplified form of steroidal therapy described above, donors assigned in advance are not essential, and use can be made of excess oocytes from consenting patients in a GIFT or IVF programme. This avoids any added risk to a donor from either the gonadotrophin therapy or the oocyte recovery techniques, but the oocytes do however tend to be sub-optimal because those with the best morphology are reserved for the donor. Consenting women undergoing laparoscopic sterilisation should prove to be another acceptable source of donor oocytes, as the potential extra risks are minimal and their fertility has been proven.

Donation of oocytes from friends or relatives of the recipient couple has been used, and has been accepted by the Waller Committee in Australia.[13] However, as the child will be known to the donor, there is the possibility of social and psychological problems arising between donor and recipient, to the detriment of the child. Anonymous donors are therefore preferable, and this is recommended by the Voluntary Licensing Authority in the United Kingdom[14] and the American Fertility Society.[15]

CONCLUSION

Oocyte donation has extended the uses of IVF to enable women previously considered irreversibly infertile, or carrying abnormal genes, to achieve a pregnancy. It can also provide a human model for the assessment of the relative roles of oestrogen and progesterone in the luteal phase and in early pregnancy.

This case report outlines the first successful pregnancy in Northern Ireland following anonymous ovum donation and *in vitro* fertilisation. This was also the first pregnancy achieved in the IVF programme, with the first embryo transfer performed: this must be a unique event.

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