Pregnancy without ovarian function

A case report

K. WISWEDEL, C. NORTH, P. BAILLIE

Summary

A 38-year-old nulliparous woman suffering from premature menopause was stimulated with oestradiol valerate in order to create an artificial endometrial cycle. Three oocytes were donated by a woman on an *in vitro* fertilisation cycle and were inseminated with the patient's husband's sperm. These were then transferred into the patient's uterus after the endometrium had been primed with progesterone to change it to the secretory phase. Pregnancy resulted and proceeded well. Gestation was terminated at the 34th week by caesarean section and 2 healthy boys and 1 girl were delivered.

S Afr Med J 1989; **76:** 70-71.

Andrology Laboratory, Department of Obstetrics and Gynaecology, University of Cape Town and Groote Schuur Hospital, Cape Town
K. WISWEDEL, M.D. (KIEL), F.C.O.G. (S.A.), DIP. MID. C.O.G. (S.A.), M.MED. (O. & G.)
C. NORTH, DIP. MED. TECH., B.SC. (MED.) HONS
P. BAILLIE, F.R.C.O.G.

Accepted 14 Mar 1989.

Oocyte donation is indicated either when a patient has non-functioning ovaries or when ovaries are not present. Other patients requiring donor oocytes are women at high risk of having children with genetic defects and those in whom several *in vitro* fertilisation (IVF) cycles have not been successful in retrieving adequate quality oocytes and in whom ultrasonography shows that the ovaries are inaccessible to oocyte pick-up. Other women who qualify for oocyte donation are those with congenital defects and patients who suffer from premature ovarian failure or who have the resistant ovary syndrome. These women, who constitute approximately 5 - 10% of an IVF population, can now be treated by oocyte donation.

The first report of a successful pregnancy using this procedure was published by Lutjen *et al.*[1] in 1984. They established and maintained a pregnancy in a patient with primary ovarian failure using IVF and embryo donation.

The main problem in these patients has been to prime the endometrium with exogenous oestrogen and progesterone sufficiently to make it receptive to implantation. With the availability of 'spare' oocytes from consenting patients in our IVF programme and the experience we have gained with primate and human oocyte and embryo donation the abovementioned groups of patients can now be treated successfully.

Case report

A 38-year-old nulliparous patient had been diagnosed as having premature menopause at the age of 22 years. She was treated for many years with hormone replacement therapy to prevent early bone loss and changes in the lipoprotein metabolism. On repeat hormonal screening the luteinising hormone level was found to be 44,8 mIU, follicle-stimulating hormone 54 mIU and 17α-hydroxyprogesterone 0,4 mIU; progesterone was non-detectable. A chromosomal analysis was repeated and she was found to be a 46,XX normal female. A laparoscopy was performed and this showed a normal size anteverted uterus with normal fallopian tubes but streak ovaries. Ovarian biopsy was performed bilaterally and histological examination of the specimens showed no primordial follicles. The antinuclear factor was negative.

A prospective donor was recruited from the IVF programme; she was prepared to donate 3 oocytes should we retrieve more than 10 at the time of laparoscopy. This donor was matched to the phenotypic characteristics of the recipient in respect of colour of hair and eyes and approximate body build. The donor and her spouse consented to this procedure. At the beginning of the IVF cycle of the donor we started the recipient on oestradiol valerate orally in slowly increasing doses to mimic a normal proliferative phase (Fig. 1). On day 15 of her cycle the endometrial thickness was 13 mm.

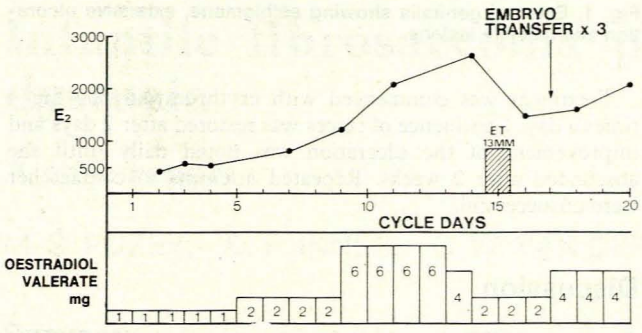

Fig. 1. Scheme of oestrogen medication to induce endometrial proliferation.

On the day the donor received her human chorionic gonadotrophin (HCG) injection, the recipient was started on progesterone supplementation (medroxyprogesterone acetate) to induce the endometrium to change into the secretory phase. At laparoscopy 14 oocytes were retrieved from the donor and 3 of these were inseminated with the recipient's husband's sperm. All 3 oocytes cleaved after 48 hours into the 4-cell stage and were transferred into the uterus of the recipient using a Wallace embryo transfer catheter. The recipient's level of the β-subunit of HCG on day 21 of the cycle was 15,7 mIU/l and rose rapidly to 95,8 mIU/l on day 24 and 920,0 mIU/l on day 29. Ultrasonography on day 38 of the cycle showed 2 sacs but no fetal heart activity. Ultrasonography was repeated on day 45 when a triplet pregnancy was diagnosed with 3 fetal hearts present.

The pregnancy was maintained using rising doses of oestradiol valerate (increased by 2 mg per week of pregnancy to a maximum of 24 mg daily in the 8th week). At the same time medroxyprogesterone acetate was also increased to a maximum of 100 mg per day, then reduced from the 8th week of pregnancy until both medications were finally stopped by the 14th week of pregnancy.

The pregnancy proceeded well without any hormonal support. During the 34th week the patient developed pre-eclamptic toxaemia and was delivered by caesarean section at the end of this week of 3 healthy babies — 2 boys and 1 girl.

Discussion

Oocyte and possible embryo donation opens a completely new door in the treatment of infertility. Although the technique of donation of male gametes has been successfully applied for many years through artificial insemination by donor sperm (AID), only with the regular successful use of IVF are female gametes now also available in sufficient numbers to allow for an oocyte donation programme.[2-4] The records of only a few such pregnancies have been published world-wide and the one described above is the first for the RSA. Although IVF techniques have progressed sufficiently to permit access to a relatively large pool of oocytes, there will always be difficulty in retrieving oocytes, which remain less accessible than male gametes.

The ethical and moral problems of this procedure are of the same magnitude as and comparable with AID, and will therefore probably be acceptable to the majority of patients. The legality of oocyte donation has fortunately been addressed adequately by the latest amendment to the Human Tissue Act, which regulates gamete donation and therefore includes the donation of oocytes. A child born from this procedure will be legally the child of the consenting parents as defined by the Child Care Act.

From an obstetric point of view it was hoped that this pregnancy would proceed without major problems to an advanced stage of gestation. This feeling was supported by the fact that it now seems certain that relaxin is produced by the ovary[4,5] and in a patient with non-functioning ovaries the relaxin level should stay low and not cause softening and dilating of cervix during pregnancy; in a multiple pregnancy particularly this might induce premature labour. Our patient was delivered by caesarean section because of rapidly developing pre-eclamptic toxaemia while the cervix was still closed.

From a pharmacological point of view it is known that oestradiol valerate has no known teratogenic effects on the fetus and that medroxyprogesterone acetate is not converted to its androgenic precursors and therefore should not have any androgenic effects on female offspring. If this procedure was used on a regular basis, a natural progesterone, which unfortunately is not available in this country, would be preferable to medroxyprogesterone. The form of progesterone used by other authors[1,3] is the natural product and is administered in the form of vaginal pessaries in doses of up to 200 mg/d.

It is concluded that oocyte donation closes the last gap in the treatment of female infertility. The minimal precondition is that the woman have a receptive uterus.

REFERENCES

1. Lutjen PJ, Trounson AP, Leeton J. The establishment and maintenance of pregnancy using *in vitro* fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 1984; **307:** 174-175.
2. Lutjen PJ, Trounson AP, Leeton J, Findlay J, Wood C. Pregnancy establishment and maintenance in the absence of ovarian function. *Proceedings of the 7th International Congress of Endocrinology*. Quebec, 1984.
3. Formigli L, Formigli G, Roccio C. Donation of fertilized uterine ova to infertile women. *Fertil Steril* 1987; **47:** 162-165.
4. Weiss G, O'Byrne EM, Steinetz BG. Relaxin: a product of the human corpus luteum of pregnancy. *Science* 1976; **194:** 948-949.
5. Seki K, Uesato T, Tabei T, Kato K. Serum relaxin in patients with hydatidiform mole. *Obstet Gynecol* 1986; **67:** 381-383.