Oocyte donation in women with recurrent pregnancy loss

José Remohí, Ernesto Gallardo, Marcos Levy, Diana Valbuena, María J.de los Santos, Carlos Simón and Antonio Pellicer

Instituto Valenciano de Infertilidad and Department of Paediatrics, Obstetrics and Gynaecology, Valencia University School of Medicine, Valencia, Spain

1To whom correspondence should be addressed

The prognosis of couples with recurrent miscarriage is controversial despite efforts made during this century to learn about the physiopathology and treatment of this troublesome condition. Here we present our experiences of employing oocyte donation in eight couples in whom the woman was a low responder to gonadotrophin stimulation and had a previous history of recurrent abortion with negative routine infertility work-up for repeated pregnancy loss. Patients were desensitized with gonadotrophin-releasing hormone analogues and supplemented with oestradiol valerate for a minimum of 15 days until oocytes were donated from in-vitro fertilization and fertile donors. Then, progesterone was added until day 100 of pregnancy. A total of 12 oocyte donation cycles were performed in these patients. Clinical pregnancy and delivery rates per cycle were 75.0 and 66.6% respectively. The delivery rate per patient was 85.7% in this series, and the miscarriage rate per cycle was 11.1%. The results of oovum donation compared favourably with low responders without a history of recurrent abortion undergoing this treatment during the study period. These results strongly suggest that the oocyte may be the origin of infertility in women with idiopathic recurrent miscarriages. In addition, the results question the role of maternal local and systemic factors in early recurrent pregnancy loss, as well as the paternal contribution to its aetiology.

Key words: oocyte donation/recurrent pregnancy loss

Introduction

Recurrent spontaneous abortion is of great concern to reproductive endocrinologists because, despite numerous studies, the aetiology of repetitive first trimester loss remains obscure (Stirrat, 1990a,b; Tulppala et al., 1993). It is assumed that 50–60% of early pregnancy losses are the consequence of aneuploidic or cytogenetically abnormal concepti (Boué and Boué, 1973; Tulppala et al., 1993). Moreover, gene mutations, toxic embryopathies and other features known to be lethal in animal models may also act early in human life, causing euploidic abortions (McDonough, 1988). From studies performed in unfertilized human oocytes and embryos, Plachot et al. (1988) designed an interesting model to explain the natural selection against chromosome abnormalities. They showed a 38% rate of anomalies at fertilization, with the oocyte being responsible for 26% of them. This percentage was even lower than that reported by Wramsby et al. (1987), who found chromosome anomalies in 50% of oocytes. Thus, it seems that meiotic errors or chromosomal abnormalities within the oocyte may be responsible for at least half of the genetic alterations found in abortuses; in other words, poor oocyte quality may well be the aetiologial factor responsible in at least 25% of human pregnancy losses. The incidence of embryonic aneuploidy is even higher as maternal age increases (Munné et al., 1995). Hence, the chances that the oocyte is responsible in early pregnancy losses may also increase as age advances.

In addition to the genetic causes, several local and systemic factors may also cause euploidic abortions. However, it has been recognized that 50–85% of the abortions will remain idiopathic after complete work-up (Berry et al., 1995). Therefore it seems that the incidence of chromosomal aberrations in spontaneous abortion may be even higher than described because of the fact that the chromosomal analysis of the aborted material or the study of meiotic errors in spermatozoa and oocytes is not performed routinely (Clifford et al., 1994; Kilpatrick and Liston, 1994).

Because women experiencing recurrent miscarriage usually reach the age of 38–40 years without a successful term pregnancy, we have accumulated experience in treating patients with a previous history of at least three pregnancy losses in our oocyte donation programme. The aim of this study was to analyse the outcome of oocyte donation in this type of infertility and to discuss possible pathological features of recurrent abortion based on this in-vivo model in which the genetic origin of an embryo is different from previous miscarriages, while the local and/or systemic factors that may act against implantation may still be present.

Materials and methods

A total of eight patients undergoing oocyte donation because of low response to gonadotrophins and a history of at least three recurrent miscarriages were included in this retrospective study carried out between January 1991 and December 1994. The ages at which they started to have miscarriages and at which they underwent ovum donation, as well as their obstetric histories are listed in Table I. All eight women underwent a standard work-up for repetitive miscarriage consisting of endocrine [serum follicle stimulating hormone (FSH), luteinizing hormone, prolactin, triiodothyronine, thyroxine, thyroid-stimulating hormone, progesterone and glucose], morphological
(hysterosalpingography, hysteroscopy, transvaginal ultrasound of the ovaries), microbiological (cervix and spermatozoa), genetic (karyotyping and human leukocyte antigens) and immunological (lupus anticoagulants and anticardiolipin antibodies) tests.

The subjects underwent a total of 12 ovum donation cycles after informed consent. The treatment was approved by the ethical committee of our institution. The protocol for exogenous steroid replacement has been described previously (Remohi et al., 1995). The definition of pregnancy was the development of a gestational sac on transvaginal ultrasonography.

A control group for the efficacy of oocyte donation in the general population was formed retrospectively of 127 ovum donation cycles in 89 low responders to gonadotrophins who underwent ovum donation during the study period. None of the individuals included in this group had previous miscarriages in their records.

Donors were 12 women undergoing in-vitro fertilization because of male (n = 9) and tubal (n = 3) infertility. They were <35 years old, previously tested for human immunodeficiency virus and hepatitis, and had no personal or family history of congenital malformation or hereditary diseases. All donors voluntarily signed a written agreement according to the Spanish law for assisted conception, in which anonymity is required. The protocol for ovarian stimulation was started by pituitary desensitization with the daily s.c. administration of 1 mg leuprolide acetate (Procrin; Abbott SA, Madrid, Spain) in the mid-luteal phase of the previous menstrual cycle. Serum oestradiol concentrations <60 pg/ml and negative vaginal ultrasonographic scans were used to define ovarian quiescence. On days 1 and 2 of ovarian stimulation, two ampoules/day human menopausal gonadotrophin (HMG, Pergonal, Serono Laboratories, Madrid, Spain) were administered, together with two ampoules pure FSH (Fertinorm; Serono Laboratorios). On days 3, 4 and 5 of ovarian stimulation, two ampoules/day HMG were administered to each patient. Beginning on day 6, HMG was administered on an individual basis according to serum oestradiol concentrations and transvaginal ovarian ultrasound scans. The criteria for human chonic gonadotrophin (HCG) administration (10 000 IU; Profasi; Serono Laboratorios) were the presence of two or more follicles >1.9 cm in diameter and serum oestradiol concentrations >800 pg/ml. Leuprolide acetate and HMG injections were discontinued on the day of HCG administration. Oocyte retrieval was scheduled 38 h after HCG injection.

Data were expressed as means ± SEM. For statistical comparison between the groups, Student's t-test and \( \chi^2 \) test were employed. In addition, a P value <0.05 was considered to be statistically significant. The analysis was carried out using the Statistical Package for Social Sciences (SPSS).

**Results**

Table I shows the clinical characteristics of the eight patients included in the study. They were 39.8 ± 10 years old with a mean abortion rate of 3.6 ± 0.2. The age they started to experience miscarriages was 32.1 ± 1.2 years. The infertility work-up was also assessed in all eight women. The mean serum FSH concentration was 16.7 ± 1.4 mIU/ml, with patient number 4 having 25 mIU/ml. The remaining data are not shown because all explorations fell within the normal ranges.

Table II shows the data from the ovum donation cycle. The clinical pregnancy rate per cycle was 75.0%, while the delivery rate per patient was 87.5%. Table II also shows the outcome of these pregnancies. It is of interest to note that only one patient aborted in this series, although she carried a fetus to term in a subsequent attempt. The take-home baby rate per cycle was 66.6% and per patient was 85.7%. The abortion rate was 11.1%.

Table III shows the outcome of ovum donation in this group of recurrent aborters compared with other low responders with no miscarriage in their obstetric records undergoing the same treatment during the study period. As can be observed, fertilization, pregnancy and implantation rates were similar between the groups, showing that oocyte donation was as effective in recurrent aborters as it was in the remaining population undergoing this type of assisted reproduction technique.

**Discussion**

This study addressed the outcome of ovum donation in women with repetitive pregnancy loss. As observed in Tables II and III, the efficacy of this reproductive modality seems to be at least as good as in other low responders of a similar age. An isolated abortion (11.1% pregnancy loss rate) seems to be lower than expected in the population undergoing ovum donation (Table III), although the numbers are too small to draw final conclusions. Further, a delivery rate of 85.7% compares favourably with that reported for recurrent aborters, in whom a 30–60% term pregnancy can be anticipated when other treatments are applied (Mowbray et al., 1985; Parazzini et al., 1988; Tulppala et al., 1993), although these reports failed to describe the incidence of recurrent miscarriages before a successful term pregnancy occurred (Tulppala et al., 1993).

The second point to be analysed is the mechanism by which oocyte donation may be effective in this subfertile population. One plausible explanation is that the oocytes from these patients were responsible for unbalanced chromosomal rearrangements and/or mutations leading to early abortions. This is not possible to confirm in our study because none of the fetuses aborted in the past was genetically analysed and, even if they had been screened, it would be very difficult to assign responsibility to any of the gametes unless there was a systematically chromosome-linked disease or a meiotic error demonstrated in the oocyte or spermatozoon. The success rate of this limited series, plus the facts that the oocyte seems to be responsible for almost 50% of the chromosomal aberrations found early in human life (Wramsby et al., 1987; Plachot et al., 1988) and these patients were negative in the infertility work-up, suggest that the origin of the abortions in these women may be the quality of their oocytes.
concentrations of progesterone reached by i.m. injections may
(Balasch and Vanrell, 1987). It is possible that the high serum
proliferation and natural killer cell activity (Siiteri et al., 1995); and (iii)
immunosuppressive properties capable of inhibiting macrophage phagocytosis,
lymphocyte proliferation and natural killer cell activity (Siiteri et al., 1977; Hill et al., 1987; Szekeres-Bartho et al., 1990).
Therefore it may be possible that the addition of progesterone
in our patients could block systemic mechanisms against
normal implantation and development in the uterus.

Our study has shown that ovum donation is effective in
women with repeated pregnancy loss. From this analysis,
svum donation could be regarded as a possible alternative to
solve the reproductive challenge represented by recurrent
pregnancy loss. However, this hypothesis has to be rejected
because this is a retrospective study with a small population.
In addition, the ethics of an exchange of oocytes as a solution
for repeated pregnancy loss has to be discussed further before a
medical alternative can be considered to be valid. We have
shown that term pregnancy rates are high, and this fact could
be considered by some physicians as sufficient evidence for
the introduction of recurrent miscarriage as an indication for
ovum donation. However, the potential risks of an exchange
of oocytes, mainly the psychological effects on the recipient
and the newborn, need to be analysed further. In addition, larger
prospective studies need to address this issue in more detail.

Therefore, we would like to conclude by focusing on what
we have learnt about the aetiology of recurrent miscarriage.
We feel that ovum donation has overcome, at least in part, the
cause of pregnancy failure in these patients. An enhancement
of the quality of oocytes may be the most plausible explanation
for this success, although the correction of abnormal endometrial
development or weak immunological disorders cannot be
ruled out because of the use of high-dose progesterone. This
study also suggests that the paternal contribution to the
aetiology of recurrent abortion is low because the success rate
was high despite the use of the same partner's semen in the
ovum donation cycle.

Moreover, an immunological cause of miscarriage cannot
be ruled out in our patients for three reasons: (i) detectable
antibody titres can disappear shortly after abortion; (ii) other
autoantibodies not tested in our patients have also been related
to early pregnancy losses (Berry et al., 1995); and (iii)
progesterone has been shown to have immunosuppressive
properties capable of inhibiting macrophage phagocytosis,
lymphocyte proliferation and natural killer cell activity (Siiteri et al., 1977; Hill et al., 1987; Szekeres-Bartho et al., 1990).

The concept of poor oocyte quality is reinforced further by the
mean age of our population. It is well established that age
increases embryonic aneuploidy, with women aged >40 years
being at highest risk; this is totally dependent on the oocyte
(Munné et al., 1995). As 50% of our patients had reached this age
when they underwent ovum donation, the improved quality
of the donated oocytes has to be regarded as the most plausible
cause of success. Whether oocytes were defective in these
patients even before they reached 40 years remains unknown;
they started to miscarry at age 32.1 ± 1.2 years. Thus it is
tempting to speculate that a substantial group of recurrent
aborters may have abnormal oocytes even before they reach
the age of 40 years.

The second mechanism of recurrent pregnancy loss that
cannot be excluded from this study is luteal deficiency.
Repeated miscarriage may be related to retarded endometrial
development (Serle et al., 1994), which may potentially be overcame
by exogenous steroid administration. The fact that none in our study population had previous abnormal endometrial biopsies and/or low progesterone concentrations in the luteal phase is not surprising because none of these parameters was consistently found to be abnormal in recurrent aborters (Balasch and Vanrell, 1987). It is possible that the high serum concentrations of progesterone reached by i.m. injections may have overcome the defect and thus driven a pregnancy to term.
References


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