

# Oocyte donation to women of advanced reproductive age: pregnancy results and obstetrical outcomes in patients 45 years and older

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We analysed the results of oocyte donation to women of advanced reproductive age ( $\geq 45$  years old) and followed their pregnancies through to delivery in order to assess obstetrical outcomes. Patients ( $n = 162$ ) aged 45–59 years (mean  $\pm$  SD;  $47.3 \pm 3.4$  years) underwent 218 consecutive attempts to achieve pregnancy. Oocytes ( $16.2 \pm 7.2$  per retrieval) were provided by donors  $\leq 35$  years old. Cleaving embryos ( $8.2 \pm 4.8$  zygotes/couple) were transferred transcervically ( $4.5 \pm 1.1$  per embryo transfer) to recipients prescribed oral micronized oestradiol and intramuscular progesterone. Following oocyte aspiration there were six instances of non-fertilization (2.8%) and 212 embryo transfers. A total of 103 pregnancies was established for an overall pregnancy rate (PR) of 48.6%, which included 17 preclinical pregnancies, 12 spontaneous abortions, and 74 delivered pregnancies (clinical PR 40.6%; delivered PR 34.9%). Multiple gestations were frequent ( $n = 29$ ; 39.2% of pregnancies) and included 20 twins, seven triplets, and two quadruplets. Two of the triplet and both of the quadruplet pregnancies underwent selective reduction to twins. Antenatal complications occurred in 28 women (37.8% of deliveries) and included preterm labour ( $n = 9$ ), gestational hypertension ( $n = 8$ ), gestational diabetes ( $n = 6$ ), carpal tunnel syndrome ( $n = 2$ ), pre-eclampsia ( $n = 2$ ), HELLP syndrome ( $n = 2$ ), and fetal growth retardation ( $n = 2$ ). 48 (64.8%) deliveries were by Caesarean section. The gestational age at delivery for singletons was  $38.3 \pm 1.3$  weeks (range 35–41 weeks), with birth weight  $3218 \pm 513$  g (range 1870–4775 g); twins  $35.9 \pm 2.0$  weeks (range 32–39 weeks), birth weight  $2558 \pm 497$  g (range 1700–3450 g); and triplets  $33.5 \pm 0.7$  weeks (range 32–34 weeks), birth weight  $1775 \pm 190$  g (range 1550–2100 g). Neonatal complications (4.6% of babies born) included growth retardation ( $n = 2$ ), trisomy 21 ( $n = 1$ ), ventricular septal defect ( $n = 1$ ), and small bowel obstruction ( $n = 1$ ). There were no maternal or neonatal deaths. We conclude that oocyte donation to women of advanced reproductive age is highly successful in establishing preg-

nancy. However, despite careful antenatal screening, obstetrical complications are common, often secondary to multiple gestation.

*Key words:* donor oocytes/menopausal pregnancy

## Introduction

For over 10 years oocyte and embryo donation has been used to establish pregnancies in women with infertility (Sauer, 1995a). Although applied principally to young women with hypergonadotrophic hypogonadism (Hens *et al.*, 1989; Rotsztein *et al.*, 1990), this method has recently been utilized to treat age-related infertility (Flamigni *et al.*, 1993; Sauer *et al.*, 1994; Lydic *et al.*, 1996). Success rates following oocyte donation to women in their forties and fifties have generally been similar to rates seen in younger women (Serhal and Craft, 1989; Sauer *et al.*, 1992; Sauer, 1994).

Most studies of older recipients are preliminary in nature, and lack meaningful obstetrical follow-up. However, anecdotal case reports imply that outcomes are favourable (Blanchette, 1993). Concerns do exist with respect to extending therapy to older women and are based principally upon beliefs that pregnancy presents a high medical risk for both mother and fetus (Editorial: *Lancet*, 1993). This report details our experience in caring for women nearing or beyond the natural menopause using oocyte donation. Included are both the reproductive and the obstetrical outcomes of this clinical trial.

## Materials and methods

The protocol for oocyte and embryo donation was approved by the Institutional Review Board of the California Medical Center, Los Angeles. Women in good physical and psychological health were considered as potential recipients. Prospective patients underwent medical, reproductive and psychological screening examinations prior to enrolment in the programme. Table I lists the prescreening examinations required of subjects.

In 1990 the protocol was amended to include women up to the age of 59 years. Between January 1990 and July 1994, 199 patients over the age of 45 years were screened. Of these, 37 were not permitted entry into the programme due to the following detected abnormalities, gross distortion of the endometrial cavity by leiomyomata ( $n = 13$ ); abnormal exercise treadmill electrocardiograms ( $n = 11$ ); diabetes mellitus with abnormal glucose tolerance and fasting hyperinsulinaemia ( $n = 7$ ); occult carcinomas ( $n = 4$ ); perceived psychological instability ( $n = 1$ ); and multiple sclerosis ( $n = 1$ ).

A total of 162 women successfully met the screening criteria and were enrolled into the clinical trial. Of these patients, 99 (61.1%) had not previously delivered a child. The mean age of their husbands was  $47.3 \pm 3.4$  years (mean  $\pm$  SD). In the majority of couples, one

**Table I.** Medical and reproductive screening required of recipients >45 years of age prior to attempting oocyte donation

|   |  |
|---|--|
| <b>Medical</b>  |  |
| Treadmill electrocardiogram   |  |
| Mammogram   |  |
| Chest roentgenogram   |  |
| Glucose tolerance test  |  |
| Fasting cholesterol and blood lipoproteins                          |  |
| Blood chemistry panel (SMA 12/60)                                   |  |
| Thyrotrophin (sensitive thyroid-stimulating hormone)                |  |
| Antinuclear antibody, lupus anticoagulant, anticardiolipin antibody |  |
| Complete blood count with platelet count                            |  |
| Papanicolaou test   |  |
| <b>Reproductive</b>   |  |
| Transvaginal ultrasound   |  |
| Endometrial biopsy (day 21)   |  |
| Hysterosalpingogram   |  |
| <b>Infectious disease</b>   |  |
| Human immunodeficiency virus (HIV)                                  |  |
| Venereal Disease Research Laboratory (VDRL)                         |  |
| Hepatitis   |  |

or both members were married for a second time ( $n = 119$ ; 73.5%). The mean duration of the present marriage was  $9.1 \pm 3.1$  years (range 2–34).

Prospective recipients were placed on a regimen of hormone replacement consisting of oral micronized oestradiol and intramuscularly administered progesterone, as previously described (Sauer *et al.*, 1989). In women still experiencing regular menstrual periods pituitary down-regulation with gonadotrophin releasing hormone agonist (GnRHa) was used to render them functionally agonadal prior to the initiation of sex steroids. Recipients completed a 'mock cycle' while using these hormones to assess the response of the endometrium. Endometrial biopsies were obtained on day 21 of the artificial cycle, and in all cases were found to be secretory in nature.

Donors provided gametes after pituitary downregulation with GnRHa followed by ovarian hyperstimulation with human menopausal gonadotrophin. Most commonly gametes were donated anonymously ( $n = 177$ ; 83.5%). In 41 instances oocytes were provided to couples by known designated donors, friends ( $n = 12$ ); daughters from a previous marriage ( $n = 6$ ); sisters ( $n = 2$ ); or the USC programme ( $n = 21$ ). Donors were screened according to the American Fertility Society Guidelines (American Fertility Society, 1993) which included a history and physical examination, pap smear, and testing for hepatitis, human immunodeficiency virus (HIV), and syphilis. The mean age of donors was  $30.3 \pm 4.3$  years, with a range of 21–35 years.

Males were screened using semen analyses, and semen bacterial cultures. In men who had not previously fathered children a hamster egg penetration assay was also performed. If abnormalities were discovered in any of these tests, spermatozoa were incubated in test-yolk buffer before in-vitro insemination in an effort to improve the fertilization rate (Paulson *et al.*, 1992).

Couples were interviewed by psychologists prior to entry into the study. Interviews were open-ended discussions without use of formal psychological tests. Emphasis was placed on issues of parenting and child support especially with respect to advanced age and longevity. All couples were counselled about the known and potential increased obstetric risks associated with pregnancy at an advanced reproductive age (Hollander and Breen, 1990). The possible increased genetic risks associated with conception using spermatozoa of men aged >55 years were also discussed (Stene *et al.*, 1977).

Preclinical pregnancies were defined as women with demonstrable titres ( $>1.5$  mIU/ml; International Reference Preparation) of beta-human chorionic gonadotrophin ( $\beta$ -HCG) in the serum 9 and 12 days

**Table II.** Results of in-vitro fertilization and embryo transfer to 162 women

|                                      |            |
|--------------------------------------|------------|
| No aspirations                       | 218        |
| No cycles without fertilization      | 6          |
| No embryo transfers (ET)             | 212        |
| No pregnancies established (% of ET) | 103 (48.6) |
| preclinical pregnancies              | 17         |
| clinical abortions                   | 12         |
| delivered (% of ET)                  | 74 (34.9)  |
| Implantation rate as % of ET         | 17.4       |

ET = transcervical embryo transfer

**Table III.** Obstetrical outcomes of 74 deliveries

|   | Mean $\pm$ SD        | Range     |
|---|----------------------|-----------|
| <b>Singletons (<math>n = 45</math>)</b> |                      |           |
| Birth weight (g)                        | $3218 \pm 513$       | 1870–4775 |
| Gestational age at delivery (weeks)     | $38.3 \pm 1.3$       | 35–41     |
| <b>Twins (<math>n = 24</math>)</b>      |                      |           |
| Birth weight (g)                        | $2558 \pm 497$       | 1700–3450 |
| Gestational age at delivery (weeks)     | $35.9 \pm 2.0$ weeks | 32–39     |
| <b>Triplets (<math>n = 5</math>)</b>    |                      |           |
| Birth weights (g)                       | $1775 \pm 190$       | 1550–2100 |
| Gestational age at delivery (weeks)     | $33.5 \pm 0.7$ weeks | 32–34     |

Operative deliveries 48 of 74 (64.8%)

following embryo transfer, yet failing to progress to an ultrasonographically detectable gestational sac. Clinical pregnancies were defined as pregnancies with gestational sacs noted on transvaginal ultrasound. Continuing pregnancies progressed beyond the second trimester and were followed until delivery. Obstetrical and neonatal outcomes were gained first-hand from the physician in attendance or by interviewing patients *post partum*. Information on patients was available through to the time of their discharge from the hospital.

## Results

Between January 1990 and July 1995, 218 consecutive attempts at oocyte donation were initiated on behalf of 162 couples. Oocytes ( $16.2 \pm 7.2$  per retrieval) were obtained during each aspiration. Following fertilization, cleaving embryos ( $8.2 \pm 4.8$  zygotes per couple per retrieval) were cultured *in vitro*. At 48–72 h later, embryos were transferred transcervically ( $4.5 \pm 1.1$  embryos per embryo transfer). In six instances fertilization did not occur, thus resulting in 212 embryo transfers. Table II lists the results of in-vitro fertilization and embryo transfer following oocyte donation with respect to the establishment of pregnancy in these women.

Multiple gestations occurred in 29 of 74 delivered pregnancies (39.2%). This included 20 twin, seven triplet, and two quadruplet gestations. Two of the triplet and both of the quadruplet pregnancies underwent selective reduction to twins in the early second trimester. Table III describes the obstetrical outcomes. The age of mothers delivering infants was not statistically significantly different from that of women who failed to conceive ( $47.3 \pm 3.3$  years compared with  $48.1 \pm 3.1$  years). Major or minor antenatal complications occurred

Table IV. Complications

|   |   |
|---|---|
| Antenatal (28 of 74 delivered women, 37.8%) |   |
| Preterm labour                              | 9 |
| Gestational hypertension                    | 8 |
| Gestational diabetes                        | 6 |
| Premature rupture of membranes              | 3 |
| Placenta praevia                            | 3 |
| Placenta accreta (both with praevia)        | 2 |
| Pre-eclampsia                               | 2 |
| HELLP syndrome*                             | 2 |
| Carpal tunnel syndrome                      | 2 |
| Neonatal (5 of 108 infants born; 4.6%)      |   |
| Growth retardation                          | 2 |
| Trisomy 21                                  | 1 |
| Ventricular septal defect                   | 1 |
| Small bowel obstruction                     | 1 |

\*Haemolysis, Elevated Liver enzymes, Low Platelets, as defined by Shaw (1994)

in 28 women (37.8%). Table IV lists the obstetrical and neonatal problems encountered. There were no maternal or neonatal deaths.

### Discussion

Perhaps the most controversial application of oocyte donation has been its use in circumventing age-related infertility in patients nearing or beyond menopause. This practice has become increasingly common, and today a significant percentage of older women in the United States undergo oocyte donation. The trend towards older parenting is consistent with several changes evident in the general population (Baldwin and Windquist Nord, 1984). The number of women between the ages of 35 and 50 is steadily increasing. Also, more women are employed outside the home, and many are electing to delay childbirth for personal, economic or professional reasons. In the last decade, the number of primigravid pregnancies over the age of 30 has doubled and has increased by 80% for mothers nearing 40 years. It is projected that by the year 2000 approximately 10% of all births will occur in women over the age of 35 (Hansen, 1986).

Fertility potential decreases with advancing maternal age, and it is expected that most older women will be unsuccessful in their efforts to reproduce. Extending of oocyte donation to this group of patients allows a critical assessment of factors accounting for the reduced fertility associated with advancing age. Numerous reports document that advanced maternal age does not diminish pregnancy rates in women undergoing oocyte donation (Navot *et al.*, 1991, 1994; Lydic *et al.*, 1996). In fact, as noted by our present study, the implantation and pregnancy rates are the same in perimenopausal women as those rates experienced by younger women undergoing oocyte donation (Sauer *et al.*, 1994). With proper hormone preparation the endometrium retains its receptivity to embryo implantation, suggesting that the decreasing fecundity normally seen in older women is primarily due to ovarian rather than uterine factors (Antinori *et al.*, 1993; Borini, 1995; Sauer, 1995b).

Medical and obstetrical complications occur with increased frequency in pregnant women of advanced reproductive age,

whether the conception is spontaneous or assisted (Cnattingius *et al.*, 1992). It is often difficult to determine if the observed increase is due to age alone or to other confounding variables such as pre-existing disease, obesity, parity and socioeconomic factors. Glucose intolerance clearly increases with age and may present as pregestational or gestational diabetes. This risk is further influenced by obesity. In a review comparing pregnancy in women over the age of 40 years with women under 30, Spellacy described a 4-fold increase in diabetes, complicating up to 7% of the pregnancies in the older age group (Spellacy *et al.*, 1986). Similarly, hypertension also occurs with increased frequency, and advanced maternal age is associated with an increased incidence of pregnancy-induced hypertension (PIH). Various studies have cited up to a 5-fold increase in hypertensive complications in the older gravida (Cunningham *et al.*, 1989; Newcomb *et al.*, 1991). However, a significant proportion of this risk is based upon the presence of pre-existing disease or obesity. In previous reports of older women pregnant following oocyte donation, PIH has been noted in 20–30% of mothers (Serhal and Craft, 1989; Sauer *et al.*, 1995; Shaw and Sauer, 1995).

Advanced maternal age has been reported to impact upon perinatal morbidity and mortality. Complications include low birth weight, intrauterine fetal demise, and neonatal mortality (Naeye, 1983; Flamigni *et al.*, 1993; Flamigni and Borini, 1995). Other studies dismiss the association of age and complications when controlling for pre-existing diseases and prenatal care (Adashek *et al.*, 1993). Information from oocyte recipients has not indicated an increase in neonatal morbidity or mortality. This may be attributable to the excellent health of women prescreened to receive donor oocytes, and the high risk obstetrical care with which they are provided.

Recipients of donor oocytes experience a high rate of operative delivery. Many patients undergo elective induction of labour which is not always successful. The high frequency of multifetal pregnancies further contributes to the high Caesarean rate. While up to 50% of twin gestations can undergo a vaginal delivery, most physicians are reluctant to deliver women over the age of 45 in this manner. This is especially true for primigravid patients who become pregnant following oocyte donation.

Multifetal pregnancies occur in approximately one-third of recipients and carry potentially significant complications, especially if involving higher order gestations (triplets and above). This high incidence of multiple gestations is clearly related to the number of embryos transferred. The number of embryos transferred differs in various studies, but usually ranges from three to six per transfer. In order to make fair and accurate comparisons in implantation rates between older and younger recipients we elected to transfer up to five pre-embryos per patient. We were not expecting that high implantation rates would be maintained in this group of older patients, based upon animal models that show a decline in both implantation and pregnancy rates with ageing (Holinka *et al.*, 1979). Therefore, we were also not anticipating problems with multiple gestations in older recipients. The vast majority of multifetal gestations result from multiple implantations rather than monozygotic events. Although perinatal outcomes for multifetal

gestations have improved dramatically in recent years, these pregnancies remain at risk for first trimester bleeding, anaemia, preterm birth, low birth weight, intrauterine growth retardation, fetal demise and PIH.

In conclusion, the introduction of oocyte donation to establish pregnancy in patients with age-related infertility has allowed many older women a new opportunity to conceive. The reproductive years now extend beyond menopause. Properly screened couples can anticipate a high degree of success in achieving pregnancy. The increased frequency of multifetal gestations deserves attention in the hope of avoiding the higher order multifetal pregnancies that require selective reduction. Consideration should be given to reducing the number of pre-embryos transferred to a maximum of three in order to decrease this risk to a reasonable level. An increased risk for antenatal complications exists, and needs to be carefully assessed during the initial stages of consultation in order to screen out individuals known to have pre-existing diseases that would further complicate a high risk pregnancy. However, when selection is properly carried out, the majority of oocyte donation recipients will experience a good outcome to their pregnancy.

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