

## Efficacy of oocytes donated by older women in an oocyte donation programme

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Population and insemination studies indicate that women experience declining fertility with ageing. The question therefore arises whether older women are suitable oocyte donors. This study addresses this issue by examining the relationship between oocyte donor age and clinical outcome in a large oocyte donation programme. We retrospectively reviewed data from 458 consecutive oocyte donation cycles completed by 164 different designated oocyte donors. Data were divided into two groups: group A, cycles with donors aged 21–30 years at the time of follicular aspiration (193 cycles, 88 donors); and group B, cycles with donors aged 31–40 years at the time of follicular aspiration (265 cycles, 86 donors). Five donors, because of ageing during repetitive donations, contributed data to groups A and B. In a given cycle, all oocytes for a recipient came from only one designated donor. Comparing the two donor groups, there was no difference in the amount of gonadotrophin used to achieve optimal stimulation; however, more oocytes were obtained from group A than group B donors ( $16.8 \pm 6.9$  and  $15.1 \pm 8.1$  respectively,  $P < 0.05$ ). Similar percentages of oocytes were fertilized in each group, resulting in the transfer of comparable numbers of embryos ( $4.5 \pm 1.1$  and  $4.4 \pm 1.3$  respectively). Comparable clinical pregnancy rates were achieved (group A, 36%; group B, 37%). The spontaneous abortion rates were also similar (group A, 20%; group B, 12%), resulting in comparable ongoing and delivered pregnancy rates per cycle (group A, 29%; group B, 32%) and per embryo transferred (group A, 6.4%; group B, 7.3%). In conclusion, women of proven fertility should not be excluded from donating oocytes simply because of their age. There exists a cohort of fertile women who resist the decreasing fecundity and increasing spontaneous abortion rates associated with ageing. With careful screening, many women of proven fertility can donate oocytes until the age of 40 years with an efficacy equal to that of younger women. Given the relative shortage of suitable oocyte donors, and increasing requests from recipients with previous donor oocyte babies to obtain oocytes from the same, now older, donor, the findings of this study are of practical clinical importance.

**Key words:** ageing/embryo quality/fertility/oocyte donors/oocyte quality

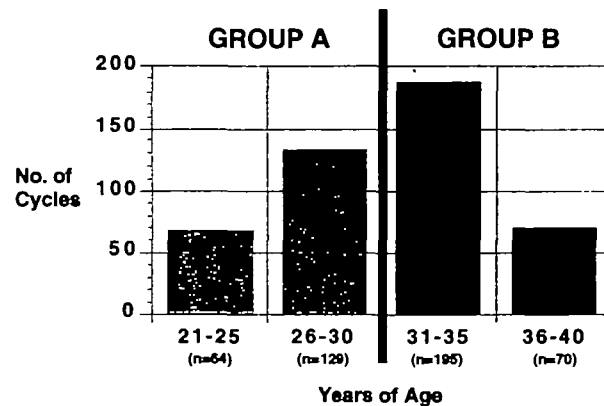
### Introduction

Oocyte donation is a successful and increasingly popular treatment of age-related female infertility. In 1993, 135 programmes in the USA and Canada reported using donor oocytes in 2446 cycles. Both endometrial receptivity and oocyte/embryo quality are enhanced, resulting consistently in the highest pregnancy rates of any assisted reproductive technique [Society for Assisted Reproductive Technology, American Society for Reproductive Medicine (SART), 1995]. Exogenous hormone replacement prepares the endometria of functionally agonadal women in their third, fourth and fifth decades of life for pregnancy (Antinori *et al.*, 1993; Meldrum, 1993; Pantos *et al.*, 1993; Sauer *et al.*, 1993; Balmaceda *et al.*, 1994; Navot *et al.*, 1994; Pados *et al.*, 1994; Borini *et al.*, 1995). Furthermore, detrimental effects of ovarian stimulation and premature luteinization on the endometrium are avoided (Paulson *et al.*, 1990; Hofmann *et al.*, 1993; Legro *et al.*, 1993). Oocyte and subsequent embryo quality are optimized by obtaining donor oocytes from young women, commonly with proven fertility. As data accumulate, it is possible to define factors that influence success. Data gathered from population studies and artificial insemination programmes suggest a decline in female fecundity after the age of 30 years (Tietze, 1957; Schwartz *et al.*, 1982; van Noord-Zaadstra *et al.*, 1991; Shenfield *et al.*, 1993). In-vitro fertilization observations also indicate diminishing oocyte and embryo quality with age (Tan *et al.*, 1992; SART, 1995). This study examines the relationship between oocyte donor age and clinical outcome in assisted reproduction.

### Materials and methods

We retrospectively reviewed data from 458 consecutive oocyte donation cycles completed by 164 different designated oocyte donors between 1988 and February 1995. The protocol for oocyte donation was reviewed and approved by the institutional review board of the California Medical Center, Los Angeles, CA, USA. Data were divided into two groups: group A, cycles with donors aged 21–30 years at the time of follicular aspiration (193 cycles, 88 donors); and group B, cycles with donors aged 31–40 years at the time of follicular aspiration (265 cycles, 86 donors) (Figure 1). Five donors, by ageing during repetitive donation, contributed data to both groups. In a given cycle, all oocytes for a recipient came from only one designated donor. The majority of cycles in both groups involved the anonymous donation of oocytes (group A, 82%; group B, 69%). In no case were

## Distribution of Cycles by Donor Age at Time of Aspiration



**Figure 1.** Data were divided into two groups: group A, cycles with donors aged 21–30 years at the time of follicular aspiration; and group B, cycles with donors aged 31–40 years at the time of follicular aspiration.

oocytes used from infertile women undergoing assisted reproduction. It is our general policy to accept anonymous donors up to the age of 35 years. For recipients providing their own oocyte donor, the age restriction is 40 years. In addition to recommended screening tests (American Fertility Society, 1993), we have been measuring the menstrual cycle day 3 follicle stimulating hormone concentrations of potential donors. To be accepted as a donor, the concentration must be  $<15$  IU/l.

Oocyte donors underwent standardized ovarian stimulation and transvaginal sonographically guided aspiration. Embryo recipients received an established regimen of exogenous oestrogen and progesterone (Sauer, 1995). A total of 334 different recipients received oocytes from the 458 donor cycles: 167 different recipients had embryos transferred from the 193 donor cycles in group A, while 185 different recipients received embryos from the 265 donor cycles in group B. Some 18 recipients received embryos from a donor in groups A and B during different cycles. All embryos were transferred transcervically into the uterine cavity 48–72 h after aspiration. No transfers involving cryopreserved embryos were included in this analysis.

Statistics consisted of a  $\chi^2$  analysis and Student's *t*-test. Numbers are presented as means  $\pm$  SD. Significance was defined as  $P < 0.05$ .

### Results

By definition, donors in groups A and B differed in age ( $26.6 \pm 1.8$  and  $34.2 \pm 1.4$  years respectively;  $P < 0.01$ ). Group A women had significantly less gravidity (group A,  $1.68 \pm 0.89$ ; group B,  $2.86 \pm 0.87$ ;  $P < 0.01$ ) and parity (group A,  $1.22 \pm 0.76$ ; group B,  $2.12 \pm 0.66$ ;  $P < 0.01$ ) when compared with group B women. There were no significant differences in the number of prior spontaneous abortions in the two groups (group A,  $0.17 \pm 0.34$ ; group B,  $0.25 \pm 0.36$ ;  $P = 0.13$ ). Women in group A donated fewer times than those in group B ( $2.8 \pm 1.8$  versus  $3.8 \pm 3.6$ ;  $P < 0.05$ ).

Recipients receiving oocytes from donor group A and recipients receiving oocytes from donor group B were similar in age ( $42.6 \pm 6.5$  and  $41.4 \pm 6.8$  years respectively;  $P = 0.09$ ), gravidity ( $1.45 \pm 1.65$  and  $1.44 \pm 1.47$  respectively;  $P = 0.9$ ), parity ( $0.57 \pm 1.03$  and  $0.50 \pm 0.87$  respectively;  $P = 0.5$ ) and history of spontaneous abortions ( $0.42 \pm 0.75$

**Table I.** Donor response to ovarian stimulation: clinical efficacy of resultant oocytes/embryos

	Group A cycles ( <i>n</i> = 193)	Group B cycles ( <i>n</i> = 265)	<i>P</i> value
No. of vials of gonadotrophins per cycle (75 IU per vial)	$28.6 \pm 5.6$	$29.4 \pm 8.1$	0.24
No. of oocytes per cycle	$16.8 \pm 6.9$	$15.1 \pm 8.1$	0.02*
Percentage of oocytes fertilized per cycle (%)	$52.6 \pm 20.8$	$53.7 \pm 26.0$	0.63
No. of embryos transferred per cycle	$4.53 \pm 1.11$	$4.44 \pm 1.30$	0.44
Clinical pregnancy rate per cycle (%)	36.3 ( <i>n</i> = 70)	37.0 ( <i>n</i> = 98)	0.95
Spontaneous abortion rate per clinical pregnancy (%)	20.0 ( <i>n</i> = 14)	12.2 ( <i>n</i> = 12)	0.25
Ongoing and delivered pregnancy rate per cycle (%)	29.0 ( <i>n</i> = 56)	32.5 ( <i>n</i> = 86)	0.50
Ongoing and delivered pregnancy rate per embryo transferred (%)	6.4	7.3	0.48

\* $P < 0.05$ .

and  $0.49 \pm 0.82$  respectively;  $P = 0.4$ ). Recipients were also similar in the average number of cycles performed (group A,  $1.41 \pm 1.39$ ; group B,  $1.56 \pm 1.49$ ;  $P = 0.3$ ).

A comparison of donor groups A and B in response to ovarian stimulation and the clinical efficacy of the resultant oocytes/embryos are listed in Table I. There was no difference in the amount of gonadotrophin used to achieve optimal stimulation, however more oocytes were obtained from group A than group B donors. Donor semen was utilized in 12% of the cycles in group A and 8% in group B ( $P = 0.2$ ). Semen of comparable average sperm count (group A,  $97 \pm 100 \times 10^6$ /ml; group B,  $102 \pm 76 \times 10^6$ /ml;  $P = 0.5$ ) and percentage motility (group A,  $62 \pm 18\%$ ; group B,  $65 \pm 19\%$ ;  $P = 0.1$ ) were used to fertilize the oocytes. Similar percentage of oocytes were fertilized in each group, resulting in the transfer of comparable numbers of embryos. Comparable clinical pregnancy rates were realized. The spontaneous abortion rates were

also similar, resulting in comparable ongoing and delivered pregnancy rates per cycle and per embryo transferred.

The database was divided into two groups only, with each group containing data from oocytes donated by women within a 10 year age range. Given the sample size of 458 total cycles and designating  $\alpha = 0.05$ , the power of detecting a difference of 10% in the clinical pregnancy rate, the spontaneous abortion rate or the ongoing/delivered rate was 0.71. The power of detecting a difference of 15% was 0.99.

If data were analysed in smaller groupings, e.g. if data in group A were subdivided further into two groups, A1 (cycles in which donors were aged between 21 and 25 years at the time of oocyte donation;  $n = 64$ ) and A2 (cycles in which donors were aged between 26 and 30 years;  $n = 129$ ), and data in group B were subdivided further into two groups, B1 (cycles in which donors were aged between 31 and 35 years at the time of oocyte donation;  $n = 195$ ) and B2 (cycles in which donors were aged between 36 and 40 years;  $n = 70$ ), similar results were also observed. There was no significant difference in the clinical pregnancy rates (groups A1, A2, B1 and B2, 39, 35, 37 and 37% respectively), the spontaneous abortion rates (24, 18, 11 and 15% respectively) and the ongoing and delivered rates (30, 29, 33 and 31% respectively) between the age subgroups. However, the power of detecting a difference was considerably less, reflecting the diminution of power with less data (e.g. the power of determining a difference of 10% would only be  $\sim 0.46$ ).

## Discussion

It has been suggested that oocytes donated by women  $\leq 30$  years of age result in superior pregnancy rates compared with oocytes retrieved from women aged 31–39 years (Rotsztein *et al.*, 1992; Balmaceda *et al.*, 1994). This conclusion is not supported by the findings of this study. Although women aged 21–30 years at the time of oocyte donation (group A) produced significantly more oocytes per stimulated cycle when compared with donors aged 31–40 years (group B) ( $16.8 \pm 6.9$  and  $15.1 \pm 8.1$  respectively;  $P < 0.05$ ), the fertilization rates and numbers of embryos transferred per attempt were similar. More importantly, comparable clinical and ongoing/delivered pregnancy rates resulted. As a measure of the clinical efficacy of the embryos produced, the ratios of the number of ongoing and delivered pregnancies per number of embryos transferred were calculated and found to be similar (group A, 6.4%; group B, 7.3%;  $P = 0.48$ ). Furthermore, although it has been observed that spontaneous abortions occur more frequently with increasing age in a retrospective analysis of reproductive histories (Warburton and Fraser, 1964) and a previous analysis of donor oocyte data (Levran *et al.*, 1991), this was not evident in our comparison (group A, 20.0%; group B, 12.2%;  $P = 0.25$ ). Perhaps, as preliminary studies of preimplantation aneuploidy suggest, an older subgroup of women ( $\geq 40$  years old) must be studied for a higher spontaneous abortion rate to be readily evident (Grifo *et al.*, 1994; Munne *et al.*, 1995).

The issue of whether older women are efficient oocyte donors is of great practical importance. Ideally, the most suitable oocyte donor is of proven fertility, has completed her

own family and is motivated by altruism. Such a woman is often between the ages of 31 and 40 years and represents the majority of women participating in our oocyte donation programme (Sauer *et al.*, 1994). Furthermore, as requests increase from women with previous donor oocyte success to obtain oocytes from the same donor so as to achieve genetic siblings, data are needed to inform recipients of the efficacy of oocytes from proven but ageing donors (Sauer and Paulson, 1993). The results of this study are encouraging. Women of proven fertility should not be excluded from donating oocytes simply because of their age. As previous human and baboon experience with the uterine lavage recovery of pre-embryos suggests, even among a cohort of females of proven fertility, variation exists (Sauer *et al.*, 1987; Pope *et al.*, 1983). Although ageing affects fertility, its effects may be less in this subclass of 'super-fertile' women.

It is our general policy to accept anonymous donors up to the age of 35 years. For recipients providing their own oocyte donor, the age restriction is 40 years. In addition to recommended screening tests (American Fertility Society, 1993), we have been measuring the menstrual cycle day 3 follicle stimulating hormone concentrations of potential donors. To be accepted as a donor, the concentration must be  $< 15$  IU/l. There were two women with regular menses, aged 37 and 40 years, who were rejected as oocyte donors based solely on an elevated day 3 follicle stimulating hormone concentration. Each was a sister of the potential recipient. If poor response is defined as stimulation resulting in less than six recovered oocytes, a poor response was observed with  $< 2\%$  of new donors aged 21–30 years and with  $< 5\%$  new donors aged 31–40 years. Poor responders are not allowed to donate repetitively. With repetitive donation, we have not observed an attenuation in cycle performance. There have been women who have donated periodically for up to 3 years.

One drawback of using oocytes from older donors is the increased risk of fetal chromosomal anomalies. It is estimated that a woman of 21 years of age has a 1 in 526 chance of having a child with a chromosomal abnormality, aged 25 years has a 1 in 476 chance, aged 30 years has a 1 in 385 chance, aged 35 years has a 1 in 178 chance and aged 40 years has a 1 in 63 chance (Hook, 1981). Therefore, theoretically, oocytes from a donor aged 35 years would have three times the risk of the birth of a chromosomally abnormal infant when compared with oocytes from a 21 year old, and oocytes from a donor aged 40 years would have eight times the risk. Accordingly, all recipients are offered prenatal genetic screening, and women utilizing donors  $\geq 35$  years of age are offered prenatal genetic testing. In one instance, a trisomy 21 infant was delivered by a 53 year old recipient who utilized the oocytes of a 35 year old designated donor. Prenatal genetic screening had been negative and prenatal genetic testing had been declined in this case.

Another potential drawback is that the older donors produce less oocytes per cycle (group B,  $15.1 \pm 8.1$  versus group A,  $16.8 \pm 6.9$ ;  $P < 0.05$ ). Although statistically significant, this represents a difference of less than two oocytes. Whether this translates into a clinically relevant difference in the overall

pregnancy rate when frozen–thawed embryo transfers are analysed has to be determined.

In conclusion, there exists a cohort of fertile women who resist the decreasing fecundity and increasing spontaneous abortion rates associated with ageing. With careful screening, many women of proven fertility can donate oocytes until the age of 40 years with an efficacy equal to that of younger women. Given the relative shortage of suitable oocyte donors and increasing requests from recipients with previous donor oocyte babies to obtain oocytes from the same, now older, donor, the findings of this study are of practical clinical importance.

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