Human Reproduction vol.12 no.4 pp.835–839, 1997

Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity

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The purpose of the present study was to determine the cumulative likelihood of pregnancy success after repetitive cycles of oocyte donation and specifically to examine the influence of recipient age and diagnosis upon the cumulative likelihood of pregnancy in an effort to identify any potential subgroup of recipients who might have diminished endometrial receptivity. We retrospectively analysed the outcome of 418 consecutive embryo transfer cycles among 276 recipients of oocyte donation in our institution. We analysed clinical pregnancy and delivery rates in the recipients divided by age groups and diagnostic groups. For the purpose of life-table analysis, only cycles prior to and including the first cycle producing a successful pregnancy were included. Frozen–thawed embryo transfers were not included in the analysis. The overall clinical pregnancy rate was 36.2% (95% CI 31–41%) and the cumulative pregnancy rate after four cycles was 87.9%. The overall delivery rate was 29.3% (95% CI 25–33%) and the cumulative delivery rate after four cycles was 86.1%. There were no statistically significant differences in any of the rates attributable to recipient age or diagnosis. No decline in per cycle success was noted over consecutive cycles. We conclude that neither recipient age nor diagnosis plays a substantial role in the success of oocyte donation, implying that endometrial receptivity is unaltered by age or diagnosis. Furthermore, up to four successive cycles of oocyte donation are associated with the same probability of success.

Key words: assisted reproduction/cumulative pregnancy rates/embryo implantation/endometrial receptivity/oocyte donation

Introduction

Oocyte donation is now a well-established modality in the treatment of infertility among women (Rosenwaks, 1987; Sauer and Paulson, 1990). Initially intended for young women with premature ovarian failure or a heritable genetic defect, the technique has more recently been applied to women in the early peri-menopausal years (Serhal and Craft, 1989; Sauer *et al.*, 1990, 1992; Pantos *et al.*, 1993) as well as after the age of the natural menopause (Antinori *et al.*, 1993; Sauer *et al.*, 1993). Because of the high success rate of the procedure, it has also been applied to women with recurrent failure with standard in-vitro fertilization (IVF) techniques (Pados *et al.*, 1992; Sauer *et al.*, 1994).

Oocyte donation represents a unique physiological configuration, which makes possible the simultaneous optimization of embryo quality and endometrial receptivity (Paulson *et al.*, 1990a, b). This is due to the fact that the oocytes are derived from young fertile women and the resulting embryos are transferred to the uteri of recipients who have been previously prepared with a controlled regimen of exogenous oestrogen and progesterone. It is this unique physiological situation which has consistently produced the highest pregnancy rates of all the assisted reproductive techniques (Medical Research International and the Society for Assisted Reproductive Technology, 1990, 1991, 1992).

Previous retrospective studies have addressed the issue of cumulative success rates after IVF. Guzick *et al.* (1986) demonstrated no decline in per cycle pregnancy rates for up to six cycles. Kovacs *et al.* (1986) performed a similar analysis and found no decline in per cycle pregnancy rates in up to eight cycles. More recently, Hull *et al.* (1992) showed no decline in per cycle success with IVF and gamete intra-Fallopian transfer (GIFT) after four cycles of treatment. By contrast, Tan *et al.* (1992) found a progressive decline in per cycle conception and live birth rates during successive cycles of IVF. However, no such calculation has been performed for repetitive cycles of oocyte donation.

The purpose of the present study was to determine the cumulative likelihood of pregnancy success after repetitive cycles of oocyte donation and specifically to examine the influence of recipient age and diagnosis upon the cumulative likelihood of pregnancy.

Materials and methods

We retrospectively analysed the results of 418 consecutive embryo transfer cycles among 276 recipients of oocyte donation in our institution. The protocol for oocyte donation was reviewed and approved by the Institutional Review Board of the California Medical Center Los Angeles. The recipients were divided into four age groups as detailed in Table I. For the purpose of the analysis, all recipients were assigned to a primary diagnostic group according to the primary reason for their entry into the oocyte donation programme. The

Table I. Age distribution of recipients

Age group	*n*	Cycles
Under 30	10	15
30–39	78	112
40–49	156	248
50–59	32	43

Table II. Diagnostic categories of recipients of oocyte donation

A. Premature ovarian failure (n = 61, cycles = 90). Age under 40, with elevated serum follicle stimulating hormone (FSH) concentrations and amenorrhoea
B. Castrate (n = 9, cycles = 16). All ages, with a history of bilateral oophorectomy
C. Genetic (n = 11, cycles = 12). All ages, with normal ovarian function, who elected to undergo oocyte donation in order to avoid passing on their genes
D. Menopause (n = 50, cycles = 71). Age over 40 with elevated serum FSH levels and amenorrhoea
E. Chemotherapy (n = 9, cycles = 21). All ages in whom the primary reason for compromised ovarian function was a prior history of chemotherapy for malignancy
F. IVF failure (n = 70, cycles = 114). All ages with normal serum FSH concentrations, who had undergone at least one prior IVF attempt with a poor response to exogenous gonadotrophins, or had recurrent failure with IVF in the phase of a normal response to gonadotrophin stimulation
G. Transitional menopause (n = 66, cycles = 94). All ages with persistently elevated day 3 serum FSH concentrations in the phase of normal menstrual cyclicity

diagnostic categories and the number of recipients within each category are detailed in Table II.

The technique of oocyte donation in our institution has previously been described in detail elsewhere (Sauer *et al.*, 1989, 1992). Briefly, donors were young fertile women under 36 years of age, who were previously designated in either an anonymous or non-anonymous fashion. They underwent controlled ovarian stimulation with a combination of leuprolide acetate and human menopausal gonadotrophins. All oocytes obtained by follicle aspiration were donated to the designated recipient. The recipients received a regimen of exogenous oral oestradiol in graduated doses and i.m. progesterone as previously described (Sauer *et al.*, 1989). Recipients with ovarian function were pre-treated with leuprolide acetate prior to initiating oestrogen therapy.

All recipients (with a small number of exceptions made for non-medical reasons) underwent a mock replacement cycle of steroid replacement with a timed endometrial biopsy performed to ascertain appropriate endometrial response. Endometrial thickness was not routinely measured. During the donation cycle, up to five cleaving embryos at one time were transferred by the trans-cervical route. If a recipient failed to become pregnant, another oocyte donation cycle was offered. The steroid replacement dose in subsequent cycles was not altered, since the endometrial biopsy during the prior mock cycle had already demonstrated good endometrial response.

For the purpose of life-table analysis, only cycles prior to and including the first cycle producing either a clinical pregnancy or delivery for each recipient were included. The remaining cycles of the recipient were censored. Frozen–thawed embryo transfers were not included in the analysis. This was done because recipients were not required to transfer all frozen embryos prior to initiating another fresh cycle. Thus, recipients who conceived after a frozen embryo transfer resulting from a cycle which did not produce a pregnancy after fresh embryo transfer were counted as failures. Statistical significance was determined with Fisher's exact test and the log-rank test, as appropriate. All analyses were performed with the SAS statistical package (SAS Institute, Cary, NC, USA) on an IBM-compatible 486-33 personal computer.

Results

In the clinical pregnancy analysis, of the 418 cycles, 40 occurred in women who had previously achieved a clinical pregnancy. Thus, 378 cycles were considered evaluable. A total of 1635 embryos were replaced (4.3 per cycle), resulting in 217 implantations (13.3% per embryo). In total, 137 clinical pregnancies were observed (36.2% per cycle, 95% CI 31–41%). The cumulative clinical pregnancy rate is depicted in Figure 1A. The cumulative clinical pregnancy rate as a function of age and diagnosis is depicted in Figure 1B and C respectively. No statistically significant differences were noted in the cumulative clinical pregnancy rates in any of the age groups or diagnostic categories. The cumulative clinical pregnancy rate after four cycles was 87.9%.

In the analysis of deliveries, 18 cycles of the 418 were censored because they occurred in individuals who had previously had a delivery following a fresh embryo transfer. These 400 transfer cycles resulted in 117 deliveries (29.3% per cycle, 95% CI 25–33%). The cumulative delivery rates are depicted in Figure 2A. The cumulative delivery rates as a function of recipient age and diagnosis are depicted in Figure 2B and C respectively. No statistically significant differences were noted among any of the age groups or diagnostic categories. The cumulative delivery rate after four cycles was 86.1%.

Discussion

Oocyte donation is now a well-established modality in the treatment of infertility. Since the practice of oocyte donation utilizes oocytes which are derived from young fertile women, embryo quality is maximized in these cycles. Since the donor population is relatively homogeneous, with regard to age and ovarian stimulation, the embryo quality component of embryo implantation is relatively constant. Accordingly, pregnancy and delivery rates are primarily dependent on the endometrial receptivity of the recipients. The annual reports from the National Registry have consistently demonstrated pregnancy and delivery rates for oocyte donation which are higher than for any of the other assisted reproductive techniques (Medical Research International and the Society for Assisted Reproductive Technology, 1990, 1991, 1992). However, previously, no report or publication has addressed the issue of cumulative success rates in repetitive cycles of oocyte donation. Therefore, it has previously not been possible to determine if the average endometrial receptivity declines during successive cycles. This would be expected to occur if recipients with the highest endometrial receptivity were to conceive first. In this model, the remaining groups would be expected to have progressively decreasing success rates. However, the data presented here do not indicate decreasing success during successive cycles, suggesting that cycle failure is primarily due to chance. The finding of a lack of decrease in success rates during successive

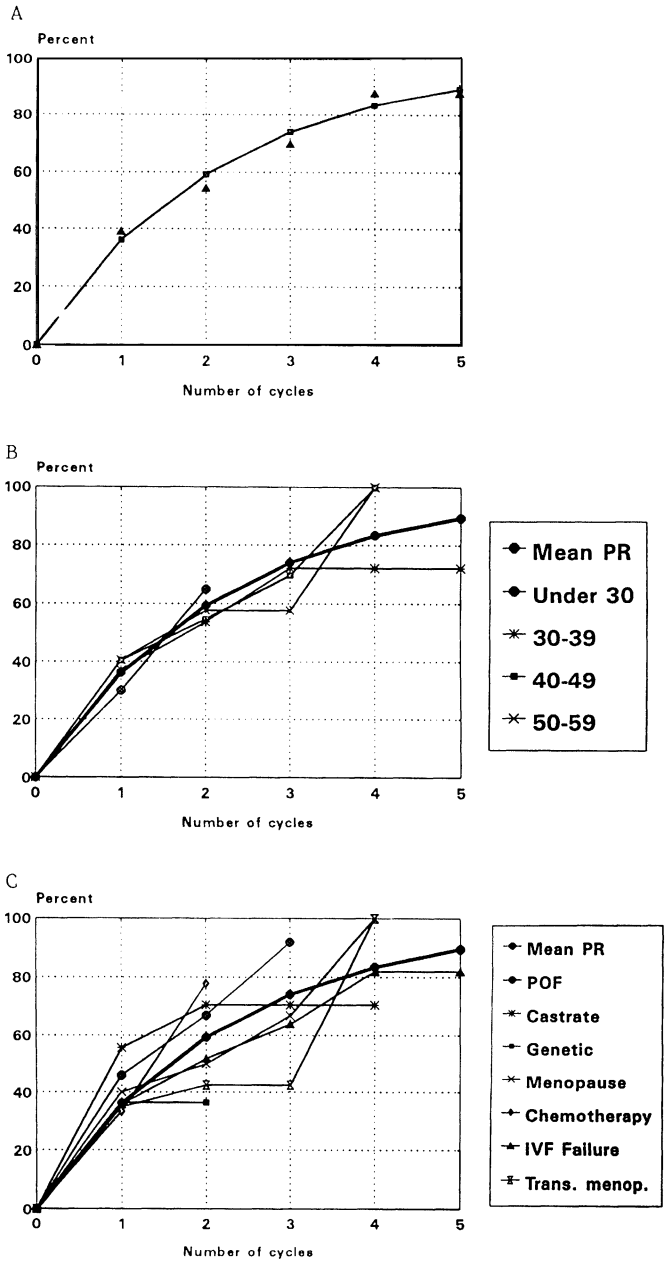

Figure 1. (**A**) Cumulative clinical pregnancy rates after oocyte donation. (▲) Observed rate, (■) mean cumulative clinical pregnancy rate (P) calculated from all mean per cycle pregnancy rate (P) by the formula: $P = 1 - (1 - f)^n$ where n = number of cycles. (**B**) Cumulative clinical pregnancy rate as a function of recipient age. (**C**) Cumulative clinical pregnancy rate as a function of recipient diagnosis.

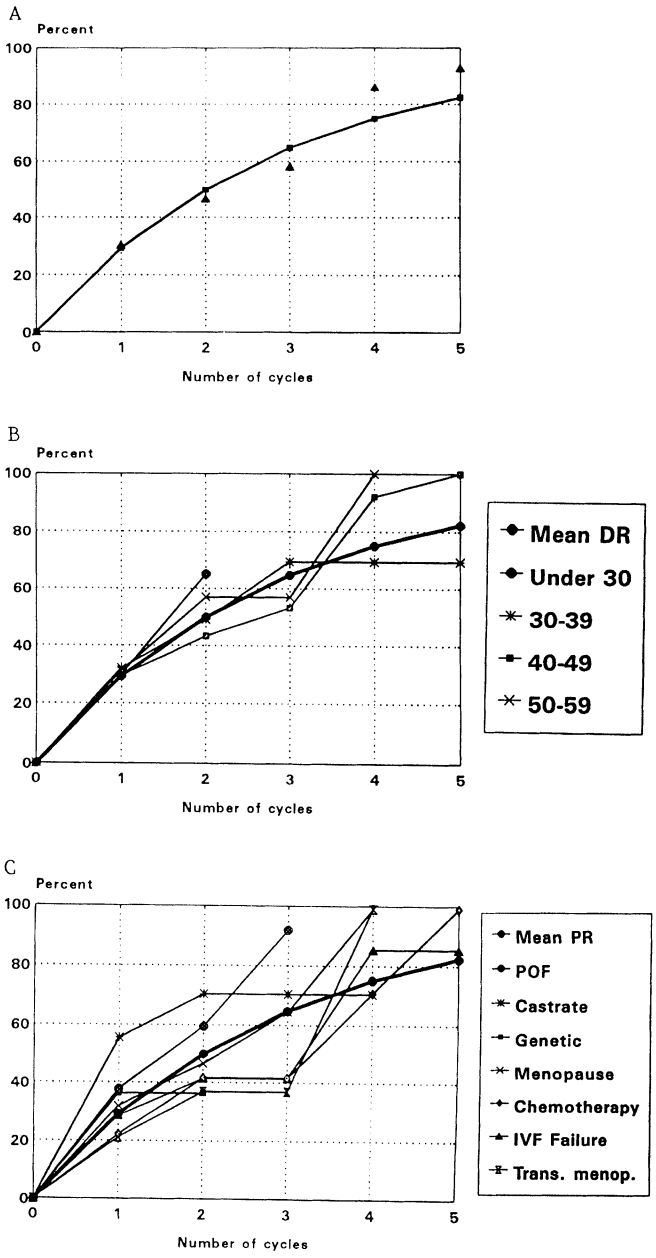

Figure 2. (**A**) Cumulative delivery rates (DR) after oocyte donation. (▲) Observed rate, (■) mean cumulative clinical pregnancy rate (P) calculated from all mean per cycle pregnancy rate (P) by the formula: $P = 1 - (1 - f)^n$ where n = number of cycles. (**B**) Cumulative delivery rate as a function of recipient age. (**C**) Cumulative delivery rate as a function of recipient diagnosis.

cycles parallels the results obtained by most investigators with IVF and GIFT (Guzick *et al.*, 1986; Kovacs *et al.*, 1986; Hull *et al.*, 1992).

In human reproduction, there is a clear age-related decline in fertility, which is manifested as a decline in monthly fecundability. There is little doubt that oocyte quality declines with age (Rotsztejn and Asch, 1991; Schattman *et al.*, 1993), but the issue of whether endometrial receptivity also declines is still somewhat controversial (Abdalla *et al.*, 1990; Meldrum, 1993). The present study found no decrease in per cycle or cumulative pregnancy and delivery rates with increasing age of the recipient. This observation has previously been made by our group (Sauer *et al.*, 1992, 1994) as well as others (Navot *et al.*, 1991), though the cumulative data are presented here for the first time. Thus, this analysis of cumulative success rates does not support the concept of a decline in endometrial receptivity with age and suggests that if such an effect exists, it is very small.

We also found no statistically significant association between cumulative pregnancy rates and recipient diagnosis. Previous reports (Abdalla *et al.*, 1990; Edwards *et al.*, 1991) suggested that amenorrhoeic patients had higher implantation rates than normally cycling women. Our results do not confirm these

findings and suggest that regardless of the cause of ovarian failure, or whether or not the ovarian failure is artificially induced with gonadotrophin-releasing hormone (GnRH) agonists, as long as the uterine response is verified by a biopsy in a prior cycle, receptivity to embryo implantation is maintained. However, as compared with previous studies, the present study has the advantage of a largely homogeneous population of donors. Additionally, in virtually all of the cycles, the protocols for donor stimulation and the recipient endometrial preparation were constant. The advantage of the life-table analysis is demonstrated in Figures 1C and 2C. The curves representing various diagnoses may be noted initially to vary from the mean, only to return to it in subsequent cycles. Notably, we have previously reported a statistically significant decrease in the delivery rate among patients who had previously received chemotherapy (Sauer *et al.*, 1994). This difference was not observed in the current series, although this category did appear initially to have a lower delivery rate than the other categories (Figure 2C). Of note also is the performance of the IVF failure category. It might be intuitive to anticipate that the endometrial receptivity would be lessened in this group, since individuals with a good prognosis would presumably have been eliminated during their prior IVF attempts. However, this group was noted to perform as well as all of the other categories, suggesting that prior IVF failure in this group was due either to poor oocyte production or to an artificial decrease in endometrial receptivity caused by controlled ovarian hyperstimulation (Paulson *et al.*, 1990a) or combination of the two factors (Paulson *et al.*, 1990b). Thus, it is encouraging that individuals with prior IVF failure can be counselled that their likelihood of success with oocyte donation is no less than that of any other group of recipients.

Finally, it is worthwhile to consider the concept of an intrinsic defect in endometrial receptivity. This entity is tacitly postulated in the use of immunotherapy in the treatment of recurrent IVF failure (Coulam *et al.*, 1994) as well as unexplained recurrent abortion (Kwak *et al.*, 1992). Our data suggest that recurrent failure of embryo implantation (i.e. recurrent IVF failure) may successfully be treated with exogenous steroid replacement and oocyte donation. Whereas our data do not specifically address recurrent pregnancy loss, it is nevertheless tempting to speculate that recurrent pregnancy loss may also be treated with this approach.

It should be noted that frozen–thawed embryo transfers were excluded from this analysis. The decision to exclude these cycles was made for the purpose of uniformity and accuracy of the calculations. Since, at the present time, approximately 60% of donor recipient cycles in our programme result in embryo freezing (data not shown) and success rates after frozen embryo transfer are approximately 60% of those of fresh cycles (data not shown), it is intuitive that if frozen–thawed embryo transfers are considered, then the total per aspiration pregnancy rates will rise accordingly. Consequently, the cumulative success rate after repetitive aspiration cycles would also be expected to increase.

In summary, these data confirm prior observations that there does not appear to be any age-related decline in endometrial receptivity. Additionally, recipient diagnosis does not play a significant role in per cycle or cumulative success rates. The lack of decline in success during consecutive cycles does not support the concept of the unmasking of an intrinsic endometrial defect in any of the groups considered here. The observed cumulative delivery rate of 86.1% after four cycles of oocyte donation thus seems applicable to women of all ages and diagnostic categories.

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Received on September 16, 1996; accepted on February 12, 1997