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 estrogen 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
have already demonstrated good endometrial response. It has previously not been possible to determine if the average ovarian stimulation, the embryo quality component of embryo
designated recipient. The recipients received a regimen of exogenous
population is relatively homogeneous, with regard to age and
donors were young fertile women under 36 years of age, who were
utilizes oocytes which are derived from young fertile women,
donor categories are detailed in Table II.
F. IVF failure (n = 70, cycles = 114). All ages with normal serum FSH
concentrations, who had undergone at least one prior IVF attempt with
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 com-
bination 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 cumu-
lative 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 previ-
ously 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 Reproduc-
tive 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

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**Table I. Age distribution of recipients**

<table>
<thead>
<tr>
<th>Age group</th>
<th>n</th>
<th>Cycles</th>
</tr>
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<tbody>
<tr>
<td>Under 30</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>30–39</td>
<td>78</td>
<td>112</td>
</tr>
<tr>
<td>40–49</td>
<td>156</td>
<td>248</td>
</tr>
<tr>
<td>50–59</td>
<td>32</td>
<td>43</td>
</tr>
</tbody>
</table>

**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 amenorrhea
- 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 amenorrhea
- 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
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 amenorrheic 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.

References


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