Age of the uterus does not affect pregnancy or implantation rates; a study of egg donation in women of different ages sharing oocytes from the same donor

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The importance of age of the recipient (uterine age) with regards to pregnancy rate, delivery rate and miscarriage rate following oocyte donation was evaluated using retrospective data analysis of cases where two recipients from different age groups shared oocytes from a single donor and had equal numbers of embryos transferred. A total of 104 women (21–52 years of age) underwent a total of 104 cycles of oocyte donation. They were divided into groups according to age (group A: age 39 years or less and group B: age between 40 and 52 years). The minimum age difference between a pair of recipients was five years.

Hormone replacement therapy (HRT) was given using oestriadiol valerate (6 mg daily) for at least 10 days, followed by a combination of oestradiol with either intramuscular progesterone (100 mg daily), or vaginally administered micronized progesterone (300 µg daily). Women with ovarian function received down-regulation using a luteinizing hormone-releasing hormone (LHRH) analogue before hormone replacement was commenced. A total of 52 transfer cycles was performed in each age group and pregnancy, delivery and miscarriage rates were analysed as outcome measures; 20 pregnancies were achieved in each group (an identical pregnancy rate of 38.5%). In group A seven pregnancies miscarried out of 20 (35%), which was not significantly different from the rate in the older population, group B, where eight out of 20 pregnancies miscarried (40%). The delivery rate in group A was 25% (13 out of 52), again not significantly different from the delivery rate in group B of 23.1% (12 out of 52). In conclusion, using egg donation as a model, the decline in fecundity with age cannot be explained by uterine factors alone.

Key words: hormone replacement therapy/implantation rate/oocyte donation/uterine age

Introduction

There is a significant decline in human fecundity with advancing age. There is also a concomitant decline in success rate following infertility treatment, including in-vitro fertilization (Cano et al., 1995). This reproductive failure could be due to either uterine or ovarian factors. Oocyte donation provides a good model in which to examine these two factors independently. Utilizing this model, Navot et al. (1994) performed a prospective trial in which they showed that the age of the uterus did not affect the outcome of pregnancy when oocytes were taken from the same donor and randomly allocated to recipients below and above the age of 40. There have been two subsequent reports contradicting these findings, showing that an age-related decline in fecundity could also be related to uterine receptivity affecting either implantation rate (Borini et al., 1996) or miscarriage rate (Cano et al., 1995).

In an attempt to clarify this situation we have retrospectively analysed all our egg donation cycles in which oocytes taken from one donor were shared between younger and older recipients. We used strict criteria for inclusion in the study.

Materials and methods

The recipients included in the study all received egg donation at the Lister Hospital between January 1, 1988 and December 31, 1995. The criteria for choosing a pair of recipients were as follows: both must have shared oocytes from the same donor. One recipient was aged 39 or less, the other 40 or above, with at least five years between them. Both recipients received a similar number of eggs (a maximum difference of one egg). Both had a similar fertilization rate and had the same number of embryos transferred (all fresh cycles).

All the donors were between 25 and 35 years and each provided oocytes for two recipients. They all received ovarian stimulation using intranasal Buserelin (Suprefact®; Hoechst, Hounslow, UK) in combination with human menopausal gonadotrophins as described previously (Abdalla et al., 1990).

All recipients awaiting oocyte donation were maintained on a hormone replacement therapy (HRT) regimen which has been described previously (Abdalla et al., 1990). Patients with normal ovarian function had no HRT supplementation in their non-treatment cycles; however, in the cycle in which they had the embryos transferred, their ovarian function was suppressed using the gonadotrophin-releasing hormone (GnRH) analogue Buserelin as a nasal spray (100 µg every 4 h from day 1 of the cycle) together with HRT in the dose described previously (Abdalla et al., 1990). The route of transfer was then determined by the state of the Fallopian tubes. Tubal transfer was performed if both tubes were patent, otherwise intrauterine embryo transfer was performed. In all cases transfer was performed after 3–4 days’ progesterone supplementation.

The results were analysed in terms of the pregnancy rate and the outcome of these pregnancies in the two age groups. Statistical analysis was performed using a χ² test to examine the difference in the pregnancy rate between the two groups. Student’s t test was used to examine the differences in the mean values.

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Results

A total of 899 cycles of fresh oocyte donation was performed at the Lister Hospital between January 1, 1988 and December 31, 1995. Of these 315 (35%) resulted in a pregnancy and 211 (23.5%) resulted in a live birth. We were able to select 52 pairs (104 patient cycles) which met the criteria outlined in Methods. Table I shows the results of this study and, as we expected, the only statistically significant difference between the groups was age of recipient. As shown, the pregnancy rate of 38.5% was identical in the two groups (20 out of 52 in each group); the 95% confidence interval was (–19.1, 19.1). There was no significant difference in the implantation rate in the two groups. The delivery rate was also very similar, 13 out of 52 (25%) in group A and 12 out of 52 (23.1%) in group B. In group A there were 10 singleton deliveries, 2 sets of twins and 1 set of triplets and in group B there were 9 singleton deliveries and 3 sets of twins.

Discussion

Age-related decline in fecundity is a fact. The important question, however, is whether this is due to uterine- or ovarian-associated factors. Oocyte donation provides a unique model in which the contribution of uterine and oocyte factors can be separated. Since oocytes are provided by a different person, the effect of the uterus (age of patient) can be considered independently.

There are conflicting reports in the literature about the age-related decline in fecundity. Only three other reports have analysed this question with a similar study design (namely, oocytes from a single donor randomly allocated to two recipients below and above the age of 40). Two were prospective (Navot et al., 1994; Cano et al., 1995) and one was retrospective (Borini et al., 1996).

Navot et al. (1994) found that there was no significant difference in the pregnancy rate between the older and the younger recipients, nor was there any significant difference in the incidence of pregnancy loss. They therefore concluded that the capacity to conceive and to gestate a conception to term when oocyte quality is controlled appears to be independent of uterine age.

Cano et al. (1995) found that both pregnancy and implantation rates were not significantly different in the two age groups. However, they reported a significantly higher miscarriage rate in women above the age of 40 and attributed this to retardation of steroid synthesis. They suggested that the mechanisms responsible for placental formation and function in the uterus are affected by age.

Borini et al. (1996) found that the pregnancy and implantation rates were higher in women under the age of 40 compared to those above the age of 40 and concluded that this difference is due to uterine factors. There was no significant difference in the miscarriage rate between the two groups.

Although our study is retrospective we have used strict criteria for inclusion in the study to negate any effect that might influence the results in the older population. All the oocytes were randomly allocated between the groups. However, in our opinion, this was not sufficient since the fertilization rate may also differ between the groups for a variety of other reasons. We therefore included only patients who had similar fertilization rates and, more importantly, who had an identical number of embryos transferred. Since age is a continuum we did not include recipients of closer ages. We only considered those pairs with a minimum age difference of five years to accentuate any effect of the age of the uterus.

In our study the pregnancy rate in the two groups was identical. However, the wide confidence interval of 19% due to the small sample size must be noted. The take home rate was also very similar. This suggests that the pregnancy, implantation and miscarriage rates were independent of the age of the uterus. These findings are almost identical to those reported by Navot et al. (1994) in their prospective trial. They are also similar to the other prospective trial by Cano et al. (1995) in terms of pregnancy and implantation rates. Only the results published by Borini et al. (1996) showed a lower pregnancy rate in the older group.

Utilizing a regression model we have previously shown that there was no significant effect of age of the uterus on either pregnancy rate or implantation rate (Abdalla et al., 1993). We have also found that the age of the donor (oocyte) was directly correlated to an increase in miscarriage rate. Leveran et al. (1991) also found that the age of the donor was correlated with the spontaneous abortion rate. Cano et al. (1995) undertook the only study that showed a much higher miscarriage rate in older recipients (48%) which was independent of the age of the donor.

It is important to recognize, however, that the uterus also contributes to implantation; Borini et al. (1995) found a reduction in pregnancy rate if women remained cyclical compared to those who had been down-regulated before HRT supplementation. Michalas et al. (1996) described a flexible approach for preparing the endometrium and showed that

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Table I. Analysis of pregnancy rates following oocyte donation to pairs of patients of different age by the same donor

<table>
<thead>
<tr>
<th></th>
<th>Group A (age ≤39 years)</th>
<th>Group B (age &gt;40 years)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>31.8 (± 3.8) range (21–39)</td>
<td>45.5 (± 3.2) range (40–52)</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Oocytes donated (mean ± SD)</td>
<td>5.9 (± 1.3) range (3–9)</td>
<td>5.6 (± 1.3) range (3–8)</td>
<td>NS</td>
</tr>
<tr>
<td>Oocytes fertilized (mean ± SD)</td>
<td>4.3 (± 1.3) range (2–7)</td>
<td>4.4 (± 1.2) range (2–7)</td>
<td>NS</td>
</tr>
<tr>
<td>Embryos transferred (mean ± SD)</td>
<td>3.0 (± 0.27) range (2–4)</td>
<td>3.0 (± 0.27) range (2–4)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of recipients who became pregnant (95% confidence interval)</td>
<td>20 (38.5%) (–19.1, 19.1)</td>
<td>20 (38.5%) (–19.1, 19.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>17.3 (± 26.0)</td>
<td>16.2 (± 23.0)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of recipients who delivered</td>
<td>13 (25%)</td>
<td>12 (23.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Singleton</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Triplets</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>
administration of oestradiol from 6–11 days is sufficient to prepare the endometrium. Both these studies clearly suggest a uterine role in implantation. Our data, however, suggest that this role does not seem to be affected by age.

We conclude that the decline in fecundity with age cannot be explained by uterine factors alone. The age-related rise in miscarriage rate is due to an egg factor although the contribution of uterine factors cannot be completely excluded.

References


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