# The Effect of the Age of the Recipients on Pregnancy Rates Following Donor-Oocyte Replacement

JEROME H. CHECK,[1,2] H. ALI ASKARI,[1] JUNG CHOE,[1] AMY BAKER,[1] and HARRIET G. ADELSON[1]

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***Purpose:*** *Besides waning ovarian function with advancing age, the question of a uterine senescence factor has been proposed as a cause of decreased fecundity. The replacement of oocytes from younger donors into older recipients allows further investigation into the aging endometrium.*

***Results:*** *The pregnancy rate was considerably lower, 8.5% in recipients in ovarian failure who were ≥40 years old (n = 23) compared to younger recipients, <40 years of age (n = 55), who were also in ovarian failure, which would support the uterine senescence theory.*

***Conclusion:*** *The endometrial factor may be manifested by failure to generate a critical endometrial thickness of 10 mm by sonography in 61% of the older group, compared to only 29% of the younger group. Future studies should address methods of improving the endometrial thickness in the older group, to determine if improved pregnancy rates will occur and to evaluate whether increasing luteal support with extra progesterone may also improve pregnancy rates.*

**KEY WORDS:** aging; endometrial thickness; oocyte recipients; pregnancy rates.

## INTRODUCTION

With the changing life pattern in modern industrialized societies many women delay childbearing. Therefore, the subject of conception and fertility in older women is attaining more importance.

It is generally agreed that the pregnancy rates achieved by in vitro fertilization embryo transfer (IVF-ET) programs decrease as the patients' ages increase (1,2). However, few studies have shown the effect of increasing maternal age of recipients when donor oocytes are used in IVF. The role of uterine aging, in particular, has not yet been clarified in humans. A higher pregnancy rate in oocyte recipients than in general has been reported from several centers (3–5). Although this has been frequently attributed to a superior quality of the donated oocytes, the possibility exists that the uterus of these premature ovarian failure patients provides a more trophic environment than the average patient undergoing IVF-ET. We have previously published a higher implantation rate in recipients versus donors despite equal sharing of the oocytes (6). However, many of these recipients were in premature ovarian failure and not in natural menopause. Thus, it does not necessarily follow that older recipients would necessarily share the same improved prognosis because of a uterine senescense factor, despite the reports of some women over age 50 who had successful pregnancies following oocyte donation (7).

Some IVF programs have reported considerable success in the aged recipients of donor oocytes (8,9). Recently, Sauer *et al.* has reported comparable implantation rates and clinical pregnancy rates in recipients <40 vs ≥40 (10). The possibility exists that high-quality embryos derived from very fertile oocytes might overcome subtle endometrial abnormalities. Since our oocytes are obtained from infertile women who themselves are undergoing IVF-ET but are willing to share half of their oocytes (for financial reasons) with the recipient, this might pose a more critical test for the endometrium of an older

[1] The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey.
[2] To whom correspondence should be addressed at 8002 East Greentree Commons, Marlton, New Jersey 08053.



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patient. Furthermore, our study would evaluate the effect of the aged uterus on endometrial thickness.

## MATERIALS AND METHODS

The subjects of study, 78 consecutive donor-oocyte cycles in our IVF-ET program, were divided into two groups: recipients less than 40 years old and those 40 or older. The former group consisted of 55 patient cycles, with a mean age of 34 ± 3.8 years; the latter group had 23 patient cycles, with a mean age of 44.3 ± 2.7. The mean age of the donors used in the under 40 group was 32.6 ± 3.7, compared to a mean donor age of 32.0 ± 3.5 for the 40 and over group ($P = 0.52$, $t$ test).

Patients qualified as recipients if they either were in complete ovarian failure or had limited ovarian function, though elevated gonadotropins. The source of the oocytes was infertile women undergoing IVF-ET who were willing to share half of their oocytes in exchange for financial assistance. All oocytes retrieved from the donor were randomly allocated between donor and recipient, with the recipient receiving the extra oocyte in cases where the total number of oocytes was odd. Since the availability of recipient cycles is limited due to the waiting lists for donor oocytes, the decision was made to include cycles from recipients who had some ovarian function, as well as those in complete ovarian failure. Patients with some ovarian function were defined as anovulatory provided they still had withdrawal menses after 10 mg of medroxyprogesterone acetate for 10 days but whose serum FSH was >25 mIU/ml on cycle day 3. This group was not on any estrogen replacement therapy prior to starting the leuprolide suppression of the donor, whereas the estrogen deficient group had been treated with cyclic estradiol therapy (2 mg/day) up to the time of starting the replacement protocol.

The method of controlled ovarian hyperstimulation (COH) used in donor cycles was the long-leuprolide acetate (LA) regimen (11,12). On the sixth day of the LA therapy for the donor, the recipient was started on estradiol (ESTRACE TM, Mead and Johnson Laboratories, Evansville, IN), 2 mg/day for 5 days, increased to 4 mg for 4 days, then finally, 6 mg until the day of the donor's hCG injection. Recipients with continued ovarian function were also given LA, 1 mg/day, beginning on day 2 of their cycle and continuing until the day after the donor's hCG injection. On the day after the donor's hCG, the recipient was also given progesterone (P), 50 mg im, and the estradiol was increased to 8 mg. Progesterone and estradiol supplementation continued at this dosage during the luteal phase. All fresh embryo transfers were done 48 hr after retrieval of the donor oocytes using standard techniques (the FET SET catheter). Other parameters relevant to the IVF-ET, including the number of embryos transferred, the embryo quality, and the cell stages of the embryos were kept constant for both groups during the study.

On the day of the donor's hCG injection, careful endometrial sonographic measurements of the recipients were taken by placing electronic calipers on the outer walls of the endometrium in the longitudinal axis of the uterine body as previously described (11).

Endometrial measurements were made using an ATL Ultramark-4 sonography unit (Advanced Technology Lab., Bethel, WA) equipped with a 5-$MH_z$ transvaginal ultrasound transducer. All measurements were done by one sonographer. Chi-square analysis was used to determine whether the pregnancy rates in the two age groups were the same.

## RESULTS

In the younger group (<40 years) 14 pregnancies (requirement for gestational sac seen on sonography) occurred of 55 cycles (25.4%), and in the older-aged subjects there were only two pregnancies (ages 45 and 46) of 23 women (8.5%), a considerably lower percentage than the younger-aged group (chi-square test, $P = 0.095$) (Table I). Power analysis showed that a larger sample size (at least 90 cycles in each group) would have been needed to attain significance for a 15% difference in rates at the 0.05 level with power = 0.8. There were no abortions in the over 40 group (birth rate of 8.5%) and five in the under 40 group (birth rate of 16.3%).

In ultrasonographic studies of the uterus the endometrial thickness measured <10 mm in 29% of the younger patients, compared to 61% in the older

Table I. Pregnancy Rate According to Age

| Group | Mean age | Pregnant | Nonpregnant |
|---|---|---|---|
| <40 | 34 ± 3.8 | 14 (25.4%) | 41 (74.6%) |
| ≥40 | 44.3 ± 2.7 | 2 (8.5%) | 21 (91.5%) |

group (Table II). Power analysis indicated that if the same trend occurred in an expanded group of 90 patient cycles, a statistically significant difference would be attained. In the older group no pregnancies occurred when the endometrial thickness was below 10 mm. In the <40-aged recipients the pregnancy rate was 29.9% among those with an endometrial thickness above 10 mm, while only 10% of the recipients with <10 mm in endometrial thickness achieved pregnancy. As the patients were matched in all other aspects of the medical treatment, the age of the donors, and the number and quality of the transferred oocytes, this difference in endometrial thickness is important and perhaps the best indicator of a poor uterine response to hormonal therapy.

## DISCUSSION

Vital statistics and population studies acknowledge the reduced pregnancy rate in women past their third decade of life (13–15). Many factors are incriminated to explain this age-dependent reduced fertility. Among these are (i) diminished sexual activity, (ii) poor semen quality and factors related to the aging partner, (iii) the decline in the ovulatory function and the poor quality of the oocytes, and finally, (iv) the deteriorating quality of the endometrium. A study of the rate of pregnancy in the older women undergoing donor artificial insemination, by exclusion of the male factors, has already shown the reduced rate of fecundability in older women (16). In this present study exclusion of the two other possible factors provided by donor-oocyte fertilization created conditions needed to study the uterine effect. The low pregnancy rate in the older patients suggests the decreased uterine receptivity in the over forty age group. Shamma *et al.* reported the absence of any difference in uterine receptivity until the age of 39 (17). They did not, however, include older patients in their study.

We have previously reported the relationship between endometrial thickness and the pregnancy rate in IVF patients undergoing luteal-phase LA-hMG COH (11). We have also provided data showing the importance of a minimal 10-mm endometrial thickness in recipients of donor oocytes (18). Ultrasound endometrial studies in this report revealed a higher ratio of the thinner endometrium in older patients, despite the same hormone replacement therapy as younger patients. This may account for the reduced pregnancy rate in the aged recipients and, again, points to the important role of the favorable endometrial conditions in achieving a more successful pregnancy rate in these patients. In a study of uterine responsiveness to estrogens in senescent rats, it was shown that the receptor content per cell clearly decreased with age in the endometrial stroma (19). Considering this decreased endometrial sensitivity, as shown by animal receptor studies and human endometrial thickness studies presented in this report, the trial of a modified therapeutic procedure in preparing the endometria of the older patients for accepting the transferred embryos is a possible step in correcting this problem and obtaining a better pregnancy rate. A significant improvement in pregnancy rate from IVF-ET with donated oocytes is reported in women over 40 whose endometrium was prepared for implantation with an increased amount of progesterone (20). Sauer *et al.* also used twice the dosage of P that we used (50 vs 100 mg/day), and perhaps this increased luteal support or better-quality embryo can overcome the effects of a thinner endometrium (10). Future studies will first address the issue of endometrial thickness by witholding transfer and cryopreserving the embryos and then we will subsequently test the effect of increased P support. Therefore, the problem might be at least partially responsive to endocrine manipulations.

Table II. Pregnancy and Endometrial Thickness

| Age | Endometrial thickness (mm) | % in group | % pregnant |
|---|---|---|---|
| <40 | <10 | 29 | 10 |
| | ≥10 | 71 | 29.9 |
| ≥40 | <10 | 61 | 0.0 |
| | ≥10 | 39 | 20 |

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