

Oocyte donation: does a previous attempt affect a subsequent attempt?

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Objective: To analyze the effect of a previous donor oocyte cycle on the outcome of subsequent attempts.

Design: Retrospective study.

Setting: Oocyte donation program at The New York Hospital/Cornell Medical Center.

Patient(s): Two hundred sixty-seven patients undergoing 354 fresh cycles of oocyte donation.

Intervention(s): None.

Main Outcome Measure(s): Clinical outcomes were divided into groups based on the attempt number of each cycle for each patient. Results were calculated for each recipient cycle.

Result(s): A clinical pregnancy rate of 56.2% and ongoing pregnancy/delivery rate per retrieval of 50.3% were noted. No statistically significant differences in clinical outcomes were found between the first, second, and third attempts. A significant increase was noted in the ongoing pregnancy/delivery rate per recipient cycle for the second attempt in those patients who had a delivery after the first attempt compared with those who did not.

Conclusion(s): We demonstrated an overall clinical pregnancy rate of 56.2% and an ongoing pregnancy/delivery rate of 50.3% per retrieval. Outcome for the second attempt was associated with success or failure during an initial attempt at oocyte donation. (Fertil Steril® 1998;70:222-6. ©1998 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, in vitro fertilization, pregnancy, multiple attempts

The first pregnancy achieved with donor oocytes was reported by Lutjen et al. in 1984 (1). Over the last decade, oocyte donation has been established as a successful method for achieving pregnancy in patients once thought to be permanently sterile. Indications for oocyte donation include ovarian failure (natural, surgical, or caused by antineoplastic therapy), genetic disorders, and poor response to conventional ovarian hyperstimulation. Success rates generally have been high, with improved implantation rates and pregnancy rates (PRs) compared with those seen in younger women undergoing conventional IVF-ET.

A number of groups have reported oocyte donation success rates (2-9). In these reports, PRs range from 20.5% (clinical only) to >50% (all pregnancies, including biochemical). Delivery rates have been reported to range from 20% to almost 40% per retrieval. The 1994 Society of Assisted Reproductive Technology report tabulated >3,000 donor oocyte cycles

with an overall delivery rate of 34.4% per ET (10).

Many patients who previously have undergone oocyte donation will pursue one or more subsequent cycles. These patients often inquire as to whether previous donor oocyte success or failure affects their next attempt. We were able to detect the impact of the outcome of a previous cycle of oocyte donation on subsequent results in only two previous studies (11, 12).

In the first study, of seven patients described, two underwent a second attempt at oocyte donation. Neither achieved a pregnancy on the first attempt and one conceived on the second, but miscarried in the first trimester. In the second study, seven women who previously had been delivered of a child underwent a second attempt. In this report, three women conceived after the first attempt at conceiving a second child. By the third attempt, two additional patients had become pregnant. The other

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two patients attempted only one further cycle of oocyte donation (12).

Remohi et al. (9) recently demonstrated that the live birth rate did not vary by attempt number. In addition, another recent report found a cumulative PR of 87.9% after four attempts with the use of life-table analysis (13). However, in these reports, no attempt was made to analyze the subsequent attempts in light of past failure or success. Currently, the available literature does not permit adequate counseling of a patient who has undergone a previous cycle of oocyte donation and is considering the pursuit of a second or possibly third attempt.

We analyzed the experience at The New York Hospital/Cornell Medical Center of patients attempting multiple donor oocyte cycles and specifically the impact of previous cycle outcome on subsequent cycles.

MATERIALS AND METHODS

A retrospective chart review of all patients who underwent donor oocyte IVF-ET between January 1990 and February 1997 at The New York Hospital/Cornell Medical Center was performed, with analysis of 354 cycles in 267 patients. Clinical outcomes were divided into groups based on the attempt number of each cycle for each patient.

Donors consisted of paid anonymous volunteers, IVF donors, and sisters of the recipients. The selection and screening process for both the donors and the recipients has been reported previously (14, 15). Preparation of the recipient, stimulation of the donor, oocyte retrieval, and donor-recipient synchronization have been described previously (14, 15). In brief, recipients underwent a preparatory cycle before the actual oocyte retrieval and ET. In women without ovarian function, transdermal E₂ (Estraderm; Ciba-Geigy, Summit, NJ) was used to deliver a dose of 0.1 mg on days 1–5, 0.2 mg on days 6–9, and 0.4 mg on days 10–13. Thereafter, the dose was decreased to 0.2 mg/d. The administration of IM progesterone (50 mg) was begun on day 15. The follicular phase was lengthened or shortened to permit synchronization with the donor.

In women with ovarian function, leuprolide acetate (LA) was initiated in the midluteal phase of a previous cycle to create a functionally agonadal state. Transdermal E₂ administration was started as in the patients without ovarian function and progesterone administration was begun on day 15. Donor stimulation generally consisted of luteal phase LA down-regulation followed by a combination of hMG and purified FSH. The gonadotropins were started on cycle day 3 and administered with the use of a step-down approach as previously described (16). Monitoring consisted of obtaining serial serum E₂ levels and performing transvaginal sonography.

Day 14 of the recipient's cycle was commenced when the

donor received hCG. Oocyte retrieval was performed 34–36 hours after hCG administration. Donor oocytes were inseminated with the recipient's husband's sperm in vitro and microsurgical injection was used when indicated. The resultant embryos were transferred on cycle day 18 or 19 of the recipient's cycle.

In general, subsequent attempts did not use oocytes from the same donor. Frozen cycle transfers were not included in this analysis.

The reason for oocyte donation as a therapy for infertility was broken down into the following categories: premature ovarian failure (cessation of menses before the age of 40 years), physiologic menopause (cessation of menses after the age of 40 years), gestational carrier, poor responder (poor response to stimulation for IVF in previous attempts), incipient ovarian failure (elevated biochemical markers of ovarian reserve), and the treatment of cancer with anti-neoplastic agents, including chemotherapy and radiation treatment.

A clinical pregnancy was defined by sonographic documentation of an intrauterine sac. A biochemical pregnancy was indicated by a positive β -hCG level that fell before sonographic documentation. Ongoing pregnancies were those in which the pregnancy was ongoing or delivered at the time of the preparation of this manuscript, all of which were beyond 20 weeks' gestation. Pregnancy rates were calculated on a per-recipient cycle basis. Cycles with fertilization failure were included in the "not pregnant" category.

Statistical analysis was performed with the use of the χ^2 test, analysis of variance, Fisher's exact test, or Student's *t*-test where appropriate. *P* values of <0.05 were considered statistically significant. Institutional review board approval was obtained in accordance with the practices of The New York Hospital/Cornell Medical Center.

RESULTS

Three hundred fifty-four donor cycles with retrievals between January 1990 and February 1997 were reviewed. Sixty-five patients underwent successive cycles ranging from 2–5 attempts. Sixty-five second cycles, 16 third cycles, and 6 cycles after the third cycle were attempted. An overall clinical PR of 56.2% and ongoing pregnancy rate/delivery rate of 50.3% were noted.

Table 1 depicts the demographic data of the patients according to attempt number. No differences were noted between the ages of the patients or the donors between each attempt number.

Figure 1 illustrates the overall PR and the ongoing pregnancy/delivery rate per recipient cycle according to attempt number. When comparing the first attempt with the second and third attempts, no statistically significant differences were noted in achieving a clinical pregnancy or an ongoing

TABLE 1

Demographic breakdown and diagnosis of recipients by attempt number.

Variable	Attempt 1 (n = 267)	Attempt 2 (n = 65)	Attempt 3 (n = 16)	Attempt 4 (n = 6)
Diagnosis				
Poor responder	87	18	5	1
Premature ovarian failure	71	22	8	2
Incipient failure	89	19	2	0
Physiologic menopause	11	4	0	0
Cancer treatment	7	2	1	3
Gestational carrier	2	0	0	0
Mean (\pm SD) patient age (y)	40.2 \pm 5.0	41.0 \pm 5.0	39.7 \pm 4.7	39.8 \pm 5.5
Mean (\pm SD) donor age (y)	28.5 \pm 4.8	28.2 \pm 3.8	28.2 \pm 4.5	27.3 \pm 3.7

pregnancy/delivery. Similarly, there were no statistically significant differences when comparing the different attempts with respect to the overall number of clinical pregnancies.

Figure 2 demonstrates the second attempt at a donor oocyte pregnancy as a function of whether a delivery resulted after the first attempt. A significant increase was noted in the ongoing pregnancy/delivery rate per recipient cycle for the second attempt ($P = 0.03$) in those patients who had a delivery after the first attempt compared with those who did not.

To elucidate why the outcome of a first cycle might affect the outcome of a second attempt, we analyzed the charts of the 65 patients who had undergone at least two attempts. Of these patients, 34 (52.3%) had at least one liveborn infant or ongoing pregnancy beyond the second trimester (group A). This group was compared with the 31 patients who did not have a live birth after two attempts (group B) (Table 2). No differences in the ages of the recipients or the donors and no differences in the presence of male factor infertility were detected when comparing the two groups.

FIGURE 1

Clinical and ongoing PRs based on the attempt at oocyte donation. Clinical PRs are indicated by the *open bar* and ongoing PRs are indicated by the *shaded bar*. There were no statistically significant differences between the first, second, and third attempts at oocyte donation.

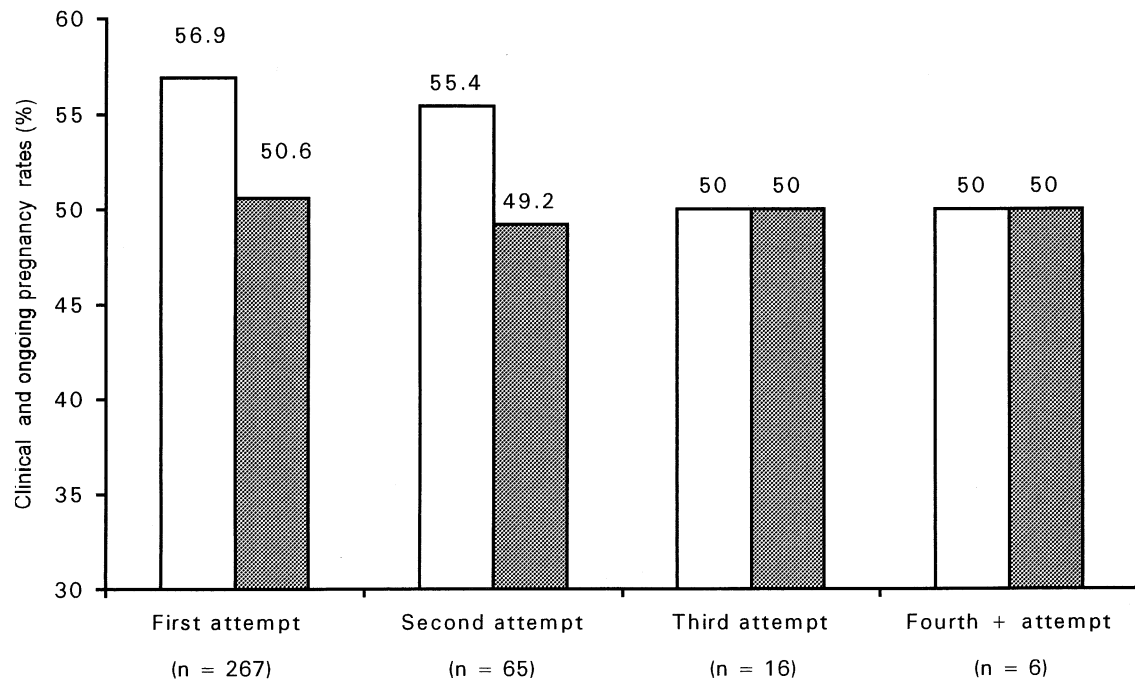
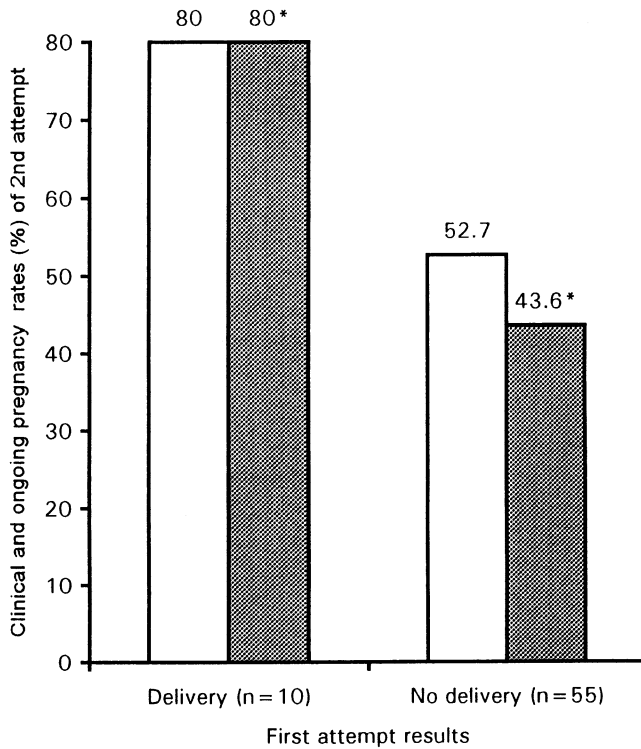


FIGURE 2

Results of the second attempt at oocyte donation based on the outcome of the first attempt. Clinical PRs are indicated by the *open bar* and ongoing PRs are indicated by the *shaded bar*. Patients who had a delivery after the first attempt were more likely to have an ongoing pregnancy after the second attempt ($P = 0.035$, Fisher's exact test).



Group B was more likely to have abnormalities on hysterosalpingography, although the difference was not statistically significant (22.6% versus 5.9%; $P = 0.054$). However, almost half these abnormalities were uncorrectable (diethylstilbestrol exposure, $n = 3$). The other abnormalities found in the group that did not conceive included submucous fibroid (1), subseptate uterus (1), minimal synechiae (1), and a small lower uterine segment filling defect (1). Group B was significantly more likely to admit to current tobacco use (25.8% versus 5.9%; $P < 0.05$).

When analyzing the 14 patients who had a history of no deliveries and who underwent a third attempt at pregnancy with donor oocytes, 6 (43.3%) of these patients had a successful delivery from the third attempt. This is in contrast with the patients who had had at least one delivery from their first two attempts and underwent a third attempt (PR = 100%; 2/2 patients).

DISCUSSION

Many groups have reported success rates after oocyte donation (2–8). None have reported whether success or

failure during a previous attempt was associated with a difference in the PR or delivery rate during a subsequent cycle. This is the first analysis of the possible association between prior success and failure on a subsequent attempt.

Although we found no statistically significant difference in pregnancy success between the first, second, and third oocyte donation attempts, we demonstrated that failure in the first cycle was associated with a compromised outcome in the second attempt compared with success on the first attempt. Patients who had a successful delivery after a single attempt were twice as likely to have a successful delivery after a second attempt (80% versus 43%). This is in agreement with previously published data on multiple attempts with conventional IVF (17, 18). Molloy et al. (17) found a successful delivery after a first IVF attempt to be positively associated with a live birth in a subsequent attempt. This would suggest that a previous delivery is a positive predictor of a successful second attempt at oocyte donation.

Because our donor pool was comprised of young (mean age 28 years) and mostly fertile (fewer than 10% were IVF donors) women, factors other than maternal age must explain the observed differences in pregnancy outcome after an initial success or failure. We demonstrated that a positive history of smoking was more likely to be found in the group of women who had two consecutive failures. Unfortunately, because of the retrospective nature of this study, we had to rely on a patient's self-reported history of smoking and were unable to quantify the level of smoking. However, this finding is consistent with previous findings.

Smoking cigarettes is known to impair natural and assisted fecundity (19, 20). The mechanism of this impairment is unknown. In a study of hamsters, smoking was shown to affect the uterus adversely, impairing the stretchability of the uterine horns as well as the percentage of touching implantation sites (21). Smoking also is known to affect the microcirculation, limiting the ability of vessels to vasodilate (22). Thus, a possible link between unsuccessful oocyte donation and smoking is plausible. Further study of this association is required.

TABLE 2

Factors that may contribute to pregnancy success or failure in patients who undergo at least two attempts at oocyte donation.

Factor	Delivery (n = 34)	No delivery (n = 31)	P value
HSG abnormality (%)	5.9	22.6	0.056
Male factor (%)	36.1	34.5	NS
DES exposure (%)	2.9	6.9	NS
Tobacco use (%)	5.9	25.8	0.04

Note: DES = diethylstilbestrol; HSG = hysterosalpingography; NS = not significant.

There was no difference in correctable uterine abnormalities between the groups that had two consecutive failures compared with the group that had at least one delivery in their first two attempts. However, in this study, we were unable to assess whether other, subtle uterine factors may have been relevant in decreasing implantation rates. Oocyte donation serves as a useful in vivo model to understand further the impaired implantation efficiency seen in older women.

Several investigators have suggested that the successful implementation of oocyte donation in women >40 years of age suggests that the endometrium of older women retains normal receptivity (23, 24). One investigative team failed to show a decrease in the implantation rate per transferred embryo in women >40 years of age who were undergoing donor oocyte transfer compared with younger recipients (11). In a subsequent report, pregnancy outcomes in younger IVF donors were compared with those in respective older recipients who shared oocytes from the same cohort (25). There was no statistically significant difference in the clinical PR and delivery rate between the donors (33% and 23%, respectively) and the recipients (40% and 30%, respectively). These data suggest that oocyte quality, rather than uterine factors, is the primary determinant of human implantation efficiency.

However, other investigators have suggested that uterine factors also may play a role in the age-related decline in fecundity. It has been reported that there may be a slight reduction in the embryo implantation rate in women >40 years of age who are undergoing oocyte donation, which can be offset by doubling the dosage of exogenous progesterone (26). Thus, although oocyte quality appears to be the major factor associated with the reduction in fecundity seen with advancing age, uterine factors and reduced endometrial receptivity also may play a role.

Whether other variables, yet to be identified, are operative should be investigated further.

In conclusion, we demonstrated an overall clinical PR of 56.2% and an ongoing pregnancy/delivery rate of 50.3% per recipient cycle. We also showed that when analyzing each of the attempt numbers separately, no statistically significant differences were present in the PR or delivery rate. However, when analyzing the second attempt on the basis of the success of the first attempt, a significant positive advantage was noted for patients who had a delivery after their first attempt. These data should prove useful in counseling women who are undergoing multiple attempts at oocyte donation.

References

1. Lutjen P, Trounson A, Leeton J, Findlay J, Wood E, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 1984;307:174-5.

2. Pados G, Camus M, Van Waesberghe L, Liebaers I, Van Steirteghem A, Devroey P. Oocyte and embryo donation: evaluation of 412 consecutive trials. *Hum Reprod* 1992;7:1111-7.
3. Sauer M, Paulson RJ, Ary BA, Lobo RA. Three hundred cycles of oocyte donation at the University of Southern California: assessing the effect of age and infertility diagnosis on pregnancy and implantation rates. *J Assist Reprod Genet* 1994;11:92-6.
4. Borini A, Bafaro G, Violini F, Bianchi L, Casadio V, Flamigni C. Pregnancies in postmenopausal women over 50 years old in an oocyte donation program. *Fertil Steril* 1995;63:258-61.
5. Borini A, Bianchi L, Violini F, Maccolini A, Cattoli M, Flamigni C. Oocyte donation program: pregnancy and implantation rates in women of different ages sharing oocytes from a single donor. *Fertil Steril* 1996;65:94-7.
6. Lydic ML, Liu JH, Rebar RW, Thomas MA, Cedars MI. Success of donor oocyte in in vitro fertilization-embryo transfer in recipients with and without premature ovarian failure. *Fertil Steril* 1996;65:98-102.
7. Check JH, Askari HA, Fisher C, Vanaman L. The use of a shared donor oocyte program to evaluate the effect of uterine senescence. *Fertil Steril* 1994;61:252-6.
8. Navot D, Drews MR, Bergh PA, Guzman I, Karstaedt A, Scott RT, et al. Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. *Fertil Steril* 1994;61:97-101.
9. Remohi J, Gartner B, Gallardo E, Yalil S, Simon C, Pellicer A. Pregnancy and birth rates after oocyte donation. *Fertil Steril* 1997;67:717-23.
10. Society for Assisted Reproductive Technology, The American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1994 results from the Society for Assisted Reproductive Technology generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril* 1996;66:697-705.
11. Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Engl J Med* 1990;323:1157-60.
12. Sauer MV, Paulson RJ. Repeat trials of oocyte donation to women with previous donor oocyte success. *Hum Reprod* 1993;8:1851-3.
13. Paulson RJ, Hatch IE, Lobo RA, Sauer MV. Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod* 1997;12:835-9.
14. Moomjy M, Cholst I, Davis OK, Applegarth LD, Rosenwaks Z. Donor oocytes in assisted reproduction—an overview. *Semin Reprod Endocrinol* 1995;13:173-86.
15. Rosenwaks Z, Damario M. Contemporary treatment strategies: egg donation. In: Adashi EY, Rock J, Rosenwaks Z, editors. *Reproductive endocrinology, surgery, and technology*. Philadelphia: Lippincott-Raven, 1996;1430-44.
16. Davis OK, Rosenwaks Z. The ovarian factor in assisted reproduction technology. In: Adashi E, Leung PCK, editors. *The ovary*. New York: Raven, 1993;545-50.
17. Molloy D, Doody ML, Breen T. Second time around: a study of patients seeking second assisted reproduction pregnancies. *Fertil Steril* 1995;64:546-51.
18. Simon A, Ronit C, Lewin A, Mordel N, Zajicek G, Laufer N. Conception rate after in vitro fertilization in patients who conceived in a previous cycle. *Fertil Steril* 1993;59:343-7.
19. Boulumar F, Olsen J, Boldsen J, and the European Study Group on Infertility and Subfecundity. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. *Am J Epidemiol* 1996;143:578-87.
20. Hughes EG, Brennan BG. Does cigarette smoking impair natural or assisted fecundity? *Fertil Steril* 1996;66:679-89.
21. Magers T, Talbot P, Di Carantonio G, Knoll M, Demers D, Tsai I, et al. Cigarette smoke inhalation affects the reproductive system of female hamsters. *Reprod Toxicol* 1995;9:513-25.
22. Zeiher AM, Schachinger V, Minners J. Long-term cigarette smoking impairs endothelium-dependent coronary arterial vasodilator function. *Circulation* 1995;92:1094-1100.
23. Sauer MV, Paulson RJ, Lobo RA. Reversing the natural decline in human fertility. An extended clinical trial of oocyte donation to women of advanced reproductive age. *J Am Med Assoc* 1992;268:1275-9.
24. Antinori S, Versaci C, Gholami GH, Panci C, Caffa B. Oocyte donation in menopausal women. *Hum Reprod* 1993;8:1487-90.
25. Navot D, Bergh PA, Williams MA, Garrisi GJ, Guzman I, Sandler B, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *Lancet* 1991;337:1375-7.
26. Meldrum DR. Female reproductive aging—ovarian and uterine factors. *Fertil Steril* 1993;9:1-5.