# Controlled Ovarian Hyperstimulation Adversely Affects Implantation Following In Vitro Fertilization–Embryo Transfer

JEROME H. CHECK,[1,2] JUNG K. CHOE,[1] DIANE KATSOFF,[1] DONNA SUMMERS-CHASE,[1] and CARRIE WILSON[1]

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***Purpose:*** *Our purpose was to determine if controlled ovarian hyperstimulation adversely affects implantation.*
***Methods:*** *A retrospective comparison of pregnancy rates (PRs) and implantation rates was made between oocyte recipients versus their donors, who shared half of the retrieved oocytes, and regular patients undergoing in vitro fertilization–embryo transfer (IVF-ET) who were not sharing eggs.*
***Results:*** *Higher implantation rates (39.0 vs 22.5%; $P < 0.05$) were found in recipients compared to donors in the stimulated cycle. However, no differences were seen in PRs or implantation rates in frozen ET cycles. The data for standard IVF patients were almost-identical to those for donors.*
***Conclusions:*** *Superior implantation rates and PRs in oocyte recipients versus donors were not related to better oocyte quality for recipients because of egg sharing or to a better uterine environment because of similar results with frozen ET in all three groups. An adverse effect of the hyperstimulation regimen best explains the difference.*

**KEY WORDS:** frozen embryo transfer; implantation; recipient; shared oocytes.

## INTRODUCTION

Most in vitro fertilization (IVF) centers report higher pregnancy rates (PRs) and implantation rates in donor oocyte recipients than in their patients undergoing standard IVF–embryo transfer (ET) (1–5). The higher success rates are generally attributed to the use of oocytes from young fertile donors. We have demonstrated previously that recipients had twice the PR following fresh ET as their respective donors following IVF-ET despite using a common pool of shared oocytes that were equally divided between them (6).

There have been many changes in IVF technology since our previous publication in 1995, resulting in significant improvements in pregnancy and implantation rates of infertile patients undergoing IVF-ET (6). One technique possibly responsible for the higher PRs is salpingectomy for hydrosalpinges prior to ET (7–13).

The present study compared PRs and implantation rates following fresh or frozen ET in donors, recipients, and nondonors undergoing IVF-ET to see if similar improved implantation rates would still be found in recipients vs donors or nondonors having a stimulated cycle now that IVF technology has improved.

## MATERIALS AND METHODS

A retrospective review of all IVF cycles performed between January and October 1997 at the Cooper Institute for IVF was conducted to identify all couples that fell into one of the following three groups: donors in the shared oocyte program, recipients in the shared oocyte program, and women at most 39 years old undergoing IVF-ET with their own gametes.

Oocyte donors are infertile women, at most 39 years old, that donate half of the oocytes retrieved in their IVF cycle in exchange for financial assistance for their own medical treatment. Oocyte recipients in the shared oocyte program receive oocytes from a donor in exchange for financial assistance with the donor's

[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 7447 Old York Road, Melrose Park, Pennsylvania 19027.

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cycle. All oocytes retrieved are divided equally between donor and recipient.

The donor undergoes a luteal-phase leuprolide acetate/gonadotropin controlled ovarian hyperstimulation regimen. Beginning 1 week after ovulation, leuprolide acetate is started at 1 mg for 5 days sq, then reduced to 0.5 mg for 5 days when serum estradiol ($E_2$) and progesterone (P) levels are obtained. If the $E_2$ level is <50 pg/ml and the serum P <2 ng/ml, the leuprolide acetate is reduced further, to 0.25 mg sq daily. If the $E_2$ and/or P level is not sufficiently suppressed, leuprolide is continued for a few more days and the levels are repeated. Once the dosage is down to 0.25 mg, 300 IU of gonadotropins [various combinations of either all follicle stimulating hormone (FSH), half human menopausal gonadotropin (hMG) and half FSH, or all hMG] is initiated im in two divided doses. Human chorionic gonadotropin (hCG; 10,000 U) is given when two lead follicles attain an average diameter of 20mm and the serum $E_2$ is >1000 pg/ml.

Recipients without ovarian function are treated with oral micronized estradiol, 2 mg × 5 days, 4 mg × 4 days, then 6 mg × 5 days, beginning on the sixth day of the donor's leuprolide acetate treatment. Recipients with ovarian function are suppressed with leuprolide acetate before starting the estradiol. Recipients are given progesterone vaginal suppositories, 200 mg twice daily, and frequently 50 mg im P beginning the day after the donor takes hCG, and transfer occurs on the fourth day of P supplementation. Donors and standard IVF patients also take supplemental P after transfer.

Standard IVF patients were treated predominantly with the luteal-phase leuprolide acetate/gonadotropin regimen described for donors but also may have had a short flare protocol (leuprolide was started on day 2 of the menstrual cycle and continued until hCG injection with gonadotropins started on day 5), or a microdose flare protocol (leuprolide dosage was diluted 20-fold), or a modified luteal-phase leuprolide/gonadotropin regimen (only 10 days of 0.5 mg leuprolide is given from the midluteal phase and then gonadotropins are started when leuprolide acetate is stopped).

The embryos were graded as follows: 1, embryos have even round cells; 2, embryos have slightly uneven round cells; and 3, embryos have uneven or irregular cells. Fragmentation was judged as follows: A, no fragmentation; B, ≤25% fragmentation; C, 26–50% fragmentation; and D, >50% fragmentation.

In vitro fertilization outcomes from the shared oocyte program were compared to the outcomes of a similar age group (≤39 years old) undergoing IVF-ET with their own gametes. Supernumerary embryos were cryopreserved and thawed for subsequent transfer in an unstimulated cycle. Also, in cases where the patient was at risk for ovarian hyperstimulation syndrome or the patients had inadequate endometrial development, all embryos were cryopreserved and thawed at a later time for transfer. In general, patients were considered at risk for ovarian hyperstimulation if the serum $E_2$ was >5000 pg/ml on the day of or the day after hCG injection or if there were >30 follicles. The endometrium was considered inadequate if the thickness was <8 mm or there was a homogeneous hyperechogenic pattern on the day of hCG injection (14). Frozen ET could be performed immediately after a deferred fresh ET cycle or pregnancy failure but would be deferred for several cycles following controlled ovarian hyperstimulation to dilute any persisting negative effects of hyperstimulation on the uterine environment.

Main outcome measures were clinical PR/transfer and implantation rates following IVF-ET and frozen ET. The data on frozen ETs includes all cycles performed from January through October 1997 but do not necessarily include only those cycles available from stimulation cycles during this time period. Chi-square analysis was used to compare PRs and implantation rates by group. A $P$ value of 0.05 was considered significant.

**Table I.** Comparison of Age and Average Number of Embryos Transferred by Patient Type

| | Donors | Recipients | Standard IVF |
|---|---|---|---|
| Age | 30.9 ± 4.0 | 41.3 ± 6.6 | 33.8 ± 3.3 |
| Average No. of embryos transferred fresh[a] | 3.0 ± .9 | 3.5 ± .8 | 3.3 ± .9 |
| Age (frozen ET cycles) | 30.5 ± 4.5 | 44.8 ± 5.7 | 33.7 ± 3.6 |
| Average No. of embryos transferred, frozen ET* | 2.9 ± 1.0 | 3.9 ± 1.3 | 3.6 ± 1.1 |

[a] $P$ = NS.
* $P < 0.05$, comparing donors to other groups.

**Table II.** Comparison of Embryo Grades by Patient Type

| Grade | Donors | Recipients | Standard IVF patients |
|---|---|---|---|
| | IVF-ET | | |
| Shape[a] | | | |
| Even round cells | 50 (49.5%) | 38 (36.5%) | 167 (35.7%) |
| Slightly uneven cells | 41 (40.6%) | 56 (53.9%) | 237 (50.6%) |
| Uneven or irregular shape | 10 (9.9%) | 10 (9.6%) | 64 (13.7%) |
| Fragmentation[a] | | | |
| A (0%) | 11 (10.9%) | 12 (11.5%) | 53 (11.3%) |
| B (<25%) | 72 (71.3%) | 77 (74.0%) | 367 (78.4%) |
| C (26–50%) | 14 (13.9%) | 9 (8.7%) | 41 (8.8%) |
| D (>50%) | 4 (4.0%) | 6 (5.8%) | 7 (1.5%) |
| | Frozen ET | | |
| Shape* | | | |
| Even round cells | 8 (25.0%) | 29 (24.2%) | 212 (38.8%) |
| Slightly uneven cells | 22 (68.8%) | 64 (53.3%) | 235 (43.0%) |
| Uneven or irregular shape | 2 (6.3%) | 27 (22.5%) | 100 (18.3%) |
| Fragmentation** | | | |
| A (0%) | 0 (0.0%) | 12 (10.0%) | 55 (10.1%) |
| B (<25%) | 20 (62.5%) | 61 (50.8%) | 404 (73.9%) |
| C (26–50%) | 8 (25.0%) | 34 (28.3%) | 58 (10.6%) |
| D (>50%) | 4 (12.5%) | 13 (10.8%) | 30 (5.5%) |

[a] $P$ = NS.
* $P < 0.05$; donors differ from standard IVF patients.
** $P < 0.05$; donors differ from standard IVF patients and recipients.

## RESULTS

The age and average number of embryos transferred according to group is given in Table I. The morphologic quality of embryos in fresh and frozen ET cycles is given in Table II.

There was no difference in the PRs in fresh cycles between the oocyte recipients and the groups using their own oocytes (Table III). However, recipients had a higher implantation rate ($P = 0.003$). There was no difference in the PRs or implantation rates in frozen ETs among the three groups ($P$ = NS).

Oocyte recipients have a higher PR following fresh ET than frozen ET (66.7 vs 36.1%; $P < 0.05$) and a higher implantation rate following fresh ET compared to frozen ET (39.0 vs 12.1%, $P < 0.05$).

The donors and standard patients have the same clinical PRs in both fresh and frozen transfers (44.1% fresh and 36.4% frozen ET for donors and 53.5% and 42.4% for standard patients). The implantation rates are also comparable (22.5 and 21.9%, respectively, for donors and 23.4 and 20.8%, respectively, for standard patients).

Clinical PRs in patients having a salpingectomy(ies) for hydrosalpinges are given in Table IV.

**Table IV.** Clinical Pregnancy Rate in Patients Having Salpingectomy for Hydrosalpinges

| | Donors | Recipients | Standard IVF patients |
|---|---|---|---|
| No. undergoing salpingectomy | 1 | 2 | 17 |
| IVF-ET cycles | 0% | | 62.5% (5/8) |
| Frozen ET cycles | | 100% (2/2) | 55.5% (5/9) |

## DISCUSSION

There are data suggesting that hydrosalpinges may reduce implantation rates, possibly by passage of toxic material from the hydrosalpinges to the endometrial cavity (15). Thus, one explanation for the improved PRs of the recipients over the donors following fresh ET in the previous study using shared oocytes may have been a more pristine uterine environment in the recipients (6). Though there was a trend for improved PRs following frozen ET in recipients versus donors in the aforementioned study, the differences were not nearly as great as following fresh ET and were not significant (6). Thus, another possible explanation for the superiority of recipients over donors following fresh ET is that the hyperstimulation regimen adversely affects implantation.

Improvements in the IVF program are such that in cycles where ET occurs in the same cycle as controlled

**Table III.** A Comparison of Clinical Pregnancy and Implantation Rates in Donors, Recipients, and Standard IVF Patients

| | IVF-ET (%) | | Frozen ET (%) | |
|---|---|---|---|---|
| | Clinical PR | Implantation rate | Clinical PR | Implantation rate |
| Oocyte recipients | 66.7 (20/30) | 39.0* | 36.1 (13/36) | 12.1 |
| Oocyte donors | 44.1 (15/34) | 22.5 | 36.4 (4/11) | 21.9 |
| Standard IVF patients | 53.5 (77/144) | 23.4 | 42.4 (64/151) | 20.8 |

[a] $P < 0.05$, comparing recipients to other groups.

ovarian hyperstimulation, PRs and implantation rates have doubled since the previous publication. Once again, however, implantation rates were higher for the recipients. However, there was no longer a trend for superior PRs and implantation rates following frozen ET in recipients in the present study.

One of the first studies suggesting that controlled ovarian hyperstimulation may adversely affect implantation was published by Paulson *et al.* (16). They matched IVF patient characteristics to those of oocyte donors with regard to age and previous conception (16). Despite the transfer of similar numbers of embryos and the findings of no difference in embryo morphology between standard IVF parameters and recipients, the clinical and ongoing PRs and implantation rates were significantly higher in recipients (16). However, similar to our previous conclusions using a shared oocyte pool (6), Paulson and co-workers' results could have been influenced by the adverse effect of hydrosalpinges on implantation (17–21), which is now corrected prior to ET at most IVF centers (8–13).

However, even prior to salpingectomy for hydrosalpinges, there was no uniform agreement that the controlled ovarian hyperstimulation regimen adversely affected implantation. A retrospective analysis did not find any differences in PRs or implantation rates in patients who had ETs in stimulated or unstimulated cycles (22). Furthermore, another study using a shared oocyte pool found no adverse effect of controlled ovarian hyperstimulation versus artificial hormone replacement cycles when gamete intrafallopian transfer was used (23).

Thus, the lack of uniform agreement that the controlled ovarian hyperstimulation adversely affects implantation, coupled with the fact that the presence of untreated hydrosalpinges (which would especially more likely be present in donors needing IVF versus recipients with a paucity of oocytes) could have reduced PRs, prompted another study comparing PRs and implantation rates between donors and recipients with these new adjustments.

The present study more clearly supports the concept that the medication used to produce multiple follicles creates a uterine environment that is not as conducive to implantation as in natural or estrogen/progesterone replaced cycles. Another theoretical hypothesis is that the use of graduated estrogen replacement regimen causes a superior environment for implantation.

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