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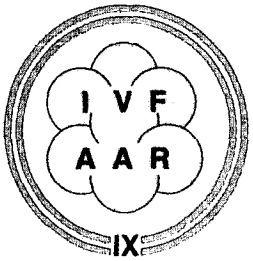

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The effect of endometrial and echo pattern on IVF outcome in donor oocyte-embryo transfer cycles (1)

V. SAPOZNIKOV, J.H. CHECK, A. NAZARI and A. O'SHAUGHNESSY

UMDNJ, Robert Wood Johnson Med. School at Camden (USA)

SUMMARY

We previously found in women undergoing in vitro fertilization-embryo transfer (IVF-ET) following luteal phase leuprolide acetate (LA)-human menopausal gonadotropin (hMG) a significantly higher pregnancy rate (PR) in those patients attaining at least a 10 mm endometrial thickness and a lower rate in those women with an entirely homogeneous hyperechogenic endometrium (pattern C). The present study evaluated the relationship of endometrial thickness and echo pattern to PRs in donor oocyte recipient immediately prior to transfer. There were 16 pregnancies in 58 cycles (27.5%). Conclusions similar to the previous COH study were reached concerning the $\geq$10mm thickness levels correlating with improved PRs (9% vs 38.7%, $p<.01$). In contrast, no correlation with echo pattern was found.

INTRODUCTION

A study by Fleisher et al. in 1986 found no differences in the endometrial thickness in patients who achieved pregnancy versus those who did not when given a similar ovulation induction regimen of hMG-human chorionic gonadotropin (hCG) for IVF-ET (2). However, in 1989 Gonen et al. did find a significant difference in mean endometrial thickness

between the pregnant (thicker) vs non-pregnant (thinner) patients when using a clomiphene citrate (CC)/hMG regimen (3). The same authors also found a correlation with successful pregnancy and endometrial echo pattern with a "triple-line" endometrium as opposed to an intermediate isoechogenic pattern with an absent central echogenic line or an entirely homogeneous hyperechogenic endometrium (4).

A possible explanation for the different conclusions reached by those two studies was that the CC used by Gonen et al. (3) created an adverse endometrial environment in some, but not all, patients. We therefore evaluated the endometrial thickness and texture in patients who conceived vs those who failed to conceive where the method of controlled ovarian hyperstimulation (COH) was the long-LA-hMG regimen (5). We found only 1 pregnancy in 29 cycles (3.4%) when endometrial thickness was $<$10mm compared to 15 of 56 (26.8%) when thickness was $\geq$10mm. The hyperechogenic pattern had a lower PR compared to either "triple-line" or intermediate isoechogenic pattern.

The study presented herein evaluated the relationship of endometrial thickness and echo patterns to PRs in patients who were recipients in a donor oocyte IVF-ET program.

MATERIALS AND METHODS

The 44 patients included in this study underwent a total of 58 IVF-ET cycles as recipients enrolled in a donor oocyte program at one IVF center. Patients qualified as recipients if they were either in complete ovarian failure or had limited ovarian function. The source of the oocytes was infertile women undergoing IVF-ET who were willing to share half of their ooyctes 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 are limited because of the waiting list 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 and to include cycles using frozen embryos. Patients with some ovarian function were defined as anovulatory and who still had withdrawal menses after 10 mg of medroxyprogesterone acetate for ten days but whose serum follicle stimulating hormone (FSH) was >25mIU/mL on cycle day 3. This group was not on any estrogen replacement therapy prior to starting the LA suppression of the donor, whereas the estrogen deficient group had been treated with cyclic estradiol (E_2) therapy (2mg/day) up to the time of starting the replacement protocol. Comparisons were made to ensure these groups were comparable before they were combined for the final analysis.

The method of COH used in donor cycles was the long LA-hMG regimen (5). On the donor's 6th day of LA therapy the recipient was started on oral E_2 2 mg per day for 5 days, then increased to 4 mg for 4 days and then finally 6 mg until the day of the donor's hCG injection. Recipients with continued ovarian function were also given LA 1 mg a 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 50 mg intramuscularly (IM) and the E_2 was increased to 8 mg. Progesterone and E_2 supplementation continued at this dosage during the luteal phase. All fresh ETs were done 48 hours after

retrieval of the donor. For down regulation frozen embryo transfers, the embryos were transferred on the fourth or fifth day of progesterone therapy. Forty-eight hour old embryos were transferred after a thawing period of 12 to 18 hours, 72 hour old embryos were transferred after a thawing period of 3 hours or less. No difficulties in transfer occurred.

On the day of the donor's hCG injection, careful endometrial sonographic measurements of the recipients were made. All measurements were done by one experienced sonographer using one machine to control for inter-observer and machine variation. The endometrial patterns visualized sonographically were graded A, B or C using the following criteria: (6) Pattern A presented as a triple-line pattern or a multi-layered endometrium in which hyperechogenic outer lines and a well defined central echogenic line were visualized with hypoechogenic or black areas seen between these lines; Pattern B was an intermediate pattern in which the endometrium had the same echogenicity as the myometrium with a poorly defined central echogenic line; Pattern C was an entirely homogeneous, echo dense endometrium in comparison with the myometrium in which no central echogenic line could be visualized. Thickness was measured in millimeters (mm) by placing electronic calipers on the outer walls of the endometrium in the longitudinal axis of the uterine body.

Parameters relevant to the IVF cycle including patient's age, number of embryos transferred, embryo quality, cell stages of embryos and conception outcome were also recorded for each cycle.

Cycles using fresh vs frozen embryos were compared in terms of mean total number of embryos transferred, mean number of embryos with at least 4 cells transferred and quality of embryos (graded as good or poor) transferred using t-tests and chi-square tests as appropriate.

The statistical analysis used to compare the PRs for patients with endometrium <10mm versus patients with endometrium ≥ 10mm was the chi-square test with a significance level of $p<.05$ (the cut-off of 10mm was established in our previous study using the same sonographic equipment and techniques (5)). The chi-square test was also used to compare PRs among the different echo pattern groups. Since a larger sample of recipient cycles was not available to conduct a study that would be able to detect a clinically meaningful difference of 15% in the PRs between the groups with power =.8 at the .05 significance level, a power analysis was performed to assess the difference in proportions that would be declared significant at $p\leq.05$ with power of .80 given the available sample size.

RESULTS AND CONCLUSIONS

There were 45 fresh donor embryo cycles evaluated (35 first, 5 second, and 5 third cycles) and 13 donor frozen embryo cycles (all cycle number 2) included in the study. The PR for cycles using fresh embryos was 28.9% (13/45) and 23.1% (3/13) for frozen-embryo transfer (frozen-ET). In cycles using fresh embryos, there was a mean of 4.2 ± 1.1 embryos transferred, a mean of 2.2 ± 1.4 embryos with at least 4 cells transferred and in 66.7% of the cycles the embryos were graded as good. In cycles using frozen embryos, the mean number of embryos transferred was 3.2 ± 1.1 and 1.7 ± 1.2 with at least 4 cells transferred, in 46.2% of the cycles the embryos were graded as good. Since there was no statistical difference in the PRs, or number of embryos transferred between fresh

and frozen cycles, these data were combined for further analysis.

Ten of the 44 recipients in the study had some ovarian function. A comparison of the recipients in ovarian failure to those with continued ovarian function showed no significant difference in the mean age (39.2±6.0 vs 39.3±4.5), estrace dosage (7.6±1.1mg vs 7.6±.9mg), endometrial thickness (10.2±2.0mm vs 10.0±1.3mm) or frequency distribution of echo patterns (6.4% A, 51.0% B, 42.5% C vs 30% A, 40% B, 30% C). However, since there were no differences in the endometrial measurements in the two groups, they were combined for further analysis.

There was a statistically significant difference in PRs between those patients with a thickness of <10mm (9%/cycle) vs those with ≥10mm (38.7%) with $p<0.01$. However, there were no significant differences in PRs according to endometrial echo patterns. In fact, patients with pattern A had the lowest PR/cycle (16.7%).

Power analysis showed that the test, based on available sample size, would only be able to detect a difference in PRs of at least 35% with power =.8 at the .05 level of significance. Therefore, it may be that, as more data becomes available, differences in PRs among the echo patterns will be shown to be statistically significant, since we feel that an increase of at least 15% in PR is clinically significant.

Thus, patients attaining a 10mm endometrial thickness prior to embryo transfer have higher PRs than those with thinner endometria. However, we could not confirm the importance of endometrial echo pattern at least for this type of patient.

Unfortunately, the timing of retrieval is based on the donor's status but if the endometrium of the recipient is at least close to the right level then maybe hCG can be delayed in the donor to allow the recipient's endometrium to attain the proper thickness. Alternatively, the embryos could be frozen and the estrogen replacement supplementation adjusted for the next cycle until the appropriate thickness is attained.

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MONDUZZI EDITORE
VIA FERRARESE, 119/2
40128 BOLOGNA
TEL. (051) 370337 - FAX (051) 370529
TELEX 512654 MONDBO I