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The effect of endometrial thickness and echo pattern on in vitro fertilization outcome in donor oocyte-embryo transfer cycle*

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A study by Fleisher et al. (1) 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 human menopausal gonadotropin (hMG)-human chorionic gonadotropin (hCG) for in vitro fertilization (IVF)-embryo transfer (ET). However, in 1989 Gonen et al. (2) did find a significant difference in mean endometrial thickness between the pregnant (thicker) versus nonpregnant (thinner) patients when using a clomiphene citrate (CC) hMG regimen. 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 (3).

A possible explanation for the different conclusions reached by those two studies was that the CC used by Gonen et al. (2) created an adverse endometrial environment in some, but not all, patients. We therefore evaluated the endometrial thickness and texture in patients who conceived versus those who failed to conceive where the method of controlled ovarian hyperstimulation (COH) was the long leuprolide acetate (LA)-hMG regimen (4). We found only one pregnancy in 29 cycles (3.4%) when endometrial thickness was <10 mm compared with 15 of 56 (26.8%) when thickness was ≥10 mm. The hyperechogenic pattern had a lower pregnancy rate (PR) compared with 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 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 in which the total number of oocytes was odd. Because 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 who still had withdrawal menses after 10 mg of medroxyprogesterone acetate for 10 days but whose serum follicle-stimulating hormone was >25 mIU/mL on cycle day 3 were defined as anovulatory. This group

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was not on any estrogen (E) replacement therapy before starting the LA suppression of the donor, whereas the E-deficient group had been treated with cyclic estradiol (E_2) therapy (2 mg/d) 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 regimen (4). On the donor's 6th day of LA therapy the recipient was started on E_2 (Estrace; Mead and Johnson Laboratories, Evansville, IN) 2 mg/d 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/d 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, 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 using standard techniques (the FET SET catheter; Laboratoire CCB, Paris, France). For down regulation, frozen ETs, the embryos were transferred on the 4th or 5th day of P 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 using an ATL Ultramark 4 Unit (Advanced Technology Laboratories, Bothell, WA) equipped with a 5-MHz endovaginal transducer. All measurements were done by one experienced sonographer using one machine to control for interobserver and machine variation. The endometrial patterns visualized sonographically were graded A, B, or C using the following criteria (5): pattern A presented as a triple-line pattern or a multilayered 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 by placing electronic calipers on the outer walls of the endometrium in the longitudinal axis of the uterine body as illustrated in Figure 1.

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 versus frozen embryos were compared in terms of mean total number of embryos transferred, mean number of embryos with at least four cells transferred and quality of embryos (graded as good or poor) transferred using t-tests and χ^2 tests as appropriate.

The group of recipients with ovarian failure was compared with the group of recipients with the continued ovarian function in terms of mean age of patient, mean endometrial thickness, and relative frequencies of echo patterns observed using t-tests and χ^2 tests as appropriate.

The statistical analysis used to compare the PRs for patients with endometrium < 10 mm versus patients with endometrium ≥ 10 mm was the χ^2 test with a significance level of $P \leq 0.05$ (the cutoff of 10 mm was established in our previous study using the same sonographic equipment and techniques (4)). The χ^2 test was also used to compare PRs among the different echo pattern groups. Because 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 = 0.8 at the 0.05 significance level, a power analysis was performed to assess the difference in proportions that would be declared significant at $P \leq 0.05$ with power of 0.80 given the available sample size.

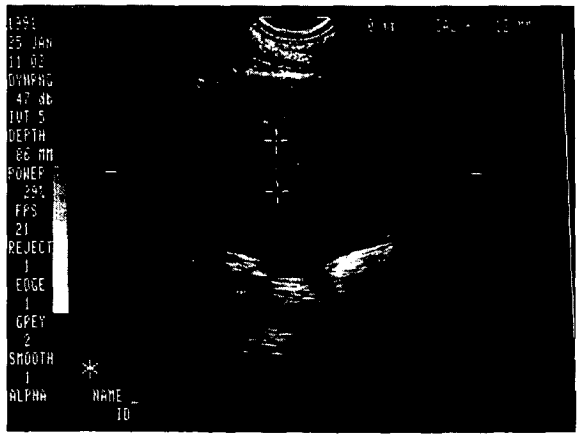

Figure 1 Measurement techniques to demonstrate endometrial thickness.

RESULTS

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 of 45) and 23.1% (3 of 13) for 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 four 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 four cells transferred, in 46.2% of the cycles the embryos were graded as good. Because 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 with those with continued ovarian function showed no significant difference in the mean age (39.2 ± 6.0 versus 39.3 ± 4.5), estrace dosage (7.6 ± 1.1 versus 7.6 ± 0.9 mg), endometrial thickness (10.2 ± 2.0 versus 10.0 ± 1.3 mm) or frequency distribution of echo patterns (6.4% A, 51.0% B, 42.5% C versus 30% A, 40% B, 30% C). However, because there were no differences in the endometrial measurements in the two groups, they were combined for further analysis.

The PRs according to mean endometrial thickness and echo pattern are seen in Table 1. There was a statistically significant difference (using χ^2 test) between those patients with a thickness of <10 mm (9% per cycle) versus those with ≥10 mm (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 = 0.8 at the 0.05 level of significance. Therefore, it may be that as more data become available, difference in PRs among the echo patterns will be shown to be statistically significant because we feel that an increase of at least 15% in PR is clinically significant.

DISCUSSION

Similar to the conclusion reached in evaluated patients undergoing IVF-ET using the luteal phase LA-hMG COH regimen, patients attaining a 10-mm endometrial thickness before ET 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 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 E replacement supplementation adjusted for the next cycle until the appropriate thickness is attained.

These data need corrorboration by other centers and randomized studies comparing fresh ET with <10 mm thickness versus frozen ET on subsequent cycles. Perhaps with a larger series, changes in prognosis related to thickness may be found based on the relationship to endometrial echo pattern.

SUMMARY

There have been some conflicting data concerning the importance of endometrial thickness and echo patterns before transfer in different IVF-ET situations under different COH regimens. We previously found in women undergoing IVF-ET after luteal phase LA-hMG a significantly higher 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

Table 1 Pregnancy Rates in a Shared Donor Oocyte Program According to Endometrial Thickness

	Endometrial thickness at time of donor's hCG		Endometrial echo pattern		
	<10 mm	≥10 mm	A (triple line)	B (endo = myom)	C (hyperechoic)
No. of cycles	22	36	6	29	23
No. of pregnancies	2	14	1	9	6
PR/cycle	9	38.7	16.7	31.0	26.1

(pattern C). The present study evaluated the relationship of endometrial thickness and echo pattern to PRs in donor oocyte recipient immediately before transfer. There were 16 pregnancies in 58 cycles (27.5%). Conclusions similar to the previous COH study were reached concerning the ≥10-mm thickness levels correlating with improved PRs (9% versus 38.7%, $P < 0.01$). In contrast, no correlation with echo pattern was found.

Key Words: Endometrial thickness, echo pattern, donor oocyte, in vitro fertilization-embryo transfer.

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