Effect of triple line vs isoechogenic endometrial texture on pregnancy outcome following embryo transfer according to use of controlled ovarian stimulation (COH) or estrogen/progesterone replacement

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Summary

Purpose: To determine if pregnancy rates following embryo transfer are reduced if the endometrial echo pattern in the late proliferative phase is isoechogenic (IE) vs triple line (TL). *Methods:* Pregnancy and implantation rates were compared according to TL vs IE pattern in the late proliferative phase in women having in vitro fertilization-embryo transfer (IVF-ET), frozen ET, and transfer of embryos derived from donor oocytes. *Results:* There was no difference in pregnancy rates with IE vs TL pattern with fresh or frozen ET or in donor egg recipients. The degree of ovarian reserve did not affect the pregnancy rates according to endometrial echo pattern. *Conclusions:* The presence of an IE pattern in the late proliferative phase should not influence the treating physician to either cancel the cycle and withhold human chorionic gonadotropin (hCG) injection or freeze all embryos and defer transfer.

Key words: Endometrial echo pattern; Late proliferative phase; Embryo transfer; Diminished oocyte reserve.

Introduction

Endometrial echo patterns are determined by the comparison of the echogenicity of the endometrium to that of the myometrium and the distinction of a central echogenic line within the endometrium. Smith *et al*. [1] were the first to describe these patterns during in vitro fertilization-embryo transfer (IVF-ET) cycles: 1) Triple Line (TL) – hypo-echogenic with well-defined outer walls and central echogenic line; 2) Isoechogenic (IE) – isoechogenic with a poorly defined central echogenic line; 3) Homogeneous hyperechogenic (HH) – hyperechogenic with no visualization of a central line.

Gonen *et al*. in 1990 concluded that for IVF-ET using a clomiphene citrate-human menopausal gonadotropin regimen the only echo pattern that correlated with good pregnancy rates when evaluated at the peri-ovulatory time was the TL pattern [2]. However, Check *et al*. in 1991 did not find the TL pattern to be superior to the IE pattern when using a luteal phase leuprolide acetate-gonadotropin regimen [3].

The original study by Check *et al*. evaluated 85 IVF-ET cycles. A subsequent larger retrospective study performed during the "old era" of IVF-ET of 273 IVF-ET cycles using the luteal phase leuprolide acetate-gonadotropin regimen found a clinical pregnancy rate of 24.5% (37/151) with TL, 17.0% (17/100) with IE and 0% (0/22) for HH pattern [4]. This aforementioned study showed a significantly higher pregnancy rate for TL or IE vs HH but did not have enough power to show a significant difference between TL and IE [4].

The adverse effect of an HH pattern in the late proliferative phase was subsequently confirmed by Noyes *et al*. in 1996 in women undergoing IVF-ET who had in utero exposure to diethylstibestrol (DES) [5]. Noyes *et al*. actually found that exposure to DES increased the frequency of the HH pattern from 15.0% to 40.5% [5]. Check *et al*. found the HH pattern to be present in 8% of cycles [4]. Noyes *et al*. did not find any clinical pregnancies in 18 DES exposed women with the HH pattern but interestingly did not see any adverse effect of the HH pattern in non-DES exposed women. However with DES exposed women they had a 60% clinical pregnancy rate (PR) per transfer with TL but only a 22.2% PR with IE [5].

Based on our previous data we have a policy to defer fresh ET and cryopreserve all embryos if an HH pattern is seen on the day of hCG injection [3,4]. However, a TL or IE pattern does not influence the decision of whether to transfer the embryos or cryopreserve. The aim of the present study was based on the non-significant trends for lower PRs with IE pattern in the "old" days of IVF-ET, to re-evaluate this issue with a study with much more power in the modern era of IVF. With improvement in IVF technology, and thus pregnancy rates, if there was a trend for superior pregnancy rates with the TL pattern it might no longer be present.

Furthermore the study would compare the influence of TL vs IE pattern in different clinical circumstances: 1) IVF-ET with normal oocyte reserve vs diminished oocyte reserve; 2) Frozen ET cycles using an artificial graduated estrogen/progesterone replacement regimen; 3) Donor oocyte/recipient cycles using a graduated estrogen/progesterone replacement regimen.

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Materials and Methods

Endometrial echo pattern was evaluated transvaginally (TV) on the day of human chorionic gonadotropin (hCG) injection in women who had IVF-ET and on the day prior to starting progesterone, in the women who had frozen ETs with their own oocytes, and also oocyte recipients who had fresh ETs. Endometrial echo patterns were evaluated by grading the pattern, as previously described, by visualizing the endometrium perpendicular to the sound beam in the longitudinal axis. A woman whose endometrial axis was not perpendicular to the sound beam and could not be accurately optimized and graded TV was scanned transabdominally (TA) to assure accurate grading [6].

IVF-ET cycles, frozen ET and donor oocyte cycles were included from 1/1/1997 to 7/31/09. For IVF-ET cycles all types of controlled ovarian hyperstimulation regimens were included, e.g., luteal phase leuprolide acetate, or gonadotropin releasing hormone antagonist (GnRH-ant) protocols with either cetrorelix or ganirelix. Women with diminished oocyte reserve were treated with mild ovarian stimulation protocols as previously described [7]. The minority of frozen ET cycles that did not use a graduated oral/vaginal estradiol replacement protocol but instead were transferred in a natural cycle were excluded.

To determine if women with diminished oocytes may have the need for a more "perfect" endometrium to achieve better pregnancy rates, women who had controlled ovarian hyperstimulation (COH), oocyte retrieval and ET were evaluated according to whether they had normal oocyte reserve (day 3 serum FSH ≤ 11 mIU/ml) vs diminished oocyte reserve (with serum FSH ≥ 12 mIU/ml). For this study, in contrast to the earlier ones, there was no requirement to attain a 10 mm endometrial thickness. Only the patient's first cycle in each of the treatment categories was used in the analysis.

Analysis of variance (ANOVA) was used to evaluate mean values of potential variables, e.g., age, baseline serum FSH, estradiol (E2), the day of oocyte retrieval, number of oocytes retrieved, and number of embryos transferred. Chi-square analysis was used to compare pregnancy and implantation rates.

Results

The viable (live fetus at 12 weeks) and live delivered pregnancy rates in COH IVF-ET cycles in women with normal oocyte reserve and the live delivered implantation rate per embryo are shown in Table 1. Comparison of mean values was performed by analysis of variance. There were no significant differences or clinically important trends noted when comparing TL vs IE (chi-square analysis) echo patterns in women with normal oocyte reserve undergoing IVF-ET.

The pregnancy and implantation rates in women with diminished oocyte reserve following IVF-ET are shown in Table 2. Although there was a significant difference in the endometrial thickness between the two groups, this did not appear to effect outcome since there was no significant difference in pregnancy or implantation rates according to pattern.

The pregnancy and implantation rates for frozen ET are shown in Table 3. Again there was a significant difference in endometrial thickness (but opposite of finding in IVF-ET with diminished oocyte reserve) but no significant differences in pregnancy rates or live delivered pregnancy rates according to TL or IE pattern.

The pregnancy rates and live delivered implantation rates for recipient cycles (fresh transfers only) are shown in Table 4. As seen with COH, IVF-ET cycles in women with normal and independently in women with diminished oocyte reserve, and in frozen ET (Tables 1-3), no differences in pregnancy or implantation rates were found comparing TL vs IE patterns in the late proliferative phase (chi-square analysis) for donor oocyte recipients.

Table 1. — *Comparison of potential confounding factors and pregnancy rates by endometrial echo pattern in women aged ≤ 40 with normal oocyte reserve following IVF-ET.*

	TL	IE	*p* value
Age	33.8 ± 4	34.1 ± 3.6	0.28
Mean baseline FSH	6.0 ± 2.5	6.4 ± 2.2	0.21
Mean serum E2 day of retrieval	1970.2 ± 1082.4	2058 ± 1032.1	0.25
Endo thickness day of hCG (mm)	10.9 ± 2.4	10.7 ± 2.9	0.25
# oocytes retrieved	11.7 ± 7.2	12.1 ± 7.3	0.43
# embryos transferred	2.6 ± .8	2.7 ± .9	0.08
Viable pregnancy rate	577/1456 (39.6%)	82/232 (35.3%)	0.24
Delivered pregnancy rate	539/1456 (37.0%)	77/232 (33.2%)	0.29
Delivered implantation rate	22.1% (832/3767)	18.9% (117/620)	0.08

Table 2. — *Comparison of potential confounding factors and pregnancy rates by endometrial echo pattern in women aged ≤ 40 with diminished oocyte reserve.*

	TL	IE	*p* value
Age	36.0 ± 3	36.3 ± 3.2	0.55
Mean baseline FSH	20.2 ± 11.7	18.2 ± 8.9	0.30
Mean serum E2 day of retrieval	977.3 ± 834.5	964.6 ± 877.6	0.93
Endo thickness day of hCG (mm)	9.9 ± 2.2	9.1 ± 2.6	0.03
Mean # oocytes retrieved	4.6 ± 4.4	5.6 ± 4.9	0.18
# embryos transferred	2.1 ± 1	2.1 ± 1	1.0
Viable pregnancy rate	109/361 (30.2%)	10/40 (25.0%)	0.62
Delivered pregnancy rate	104/361 (28.8%)	10/40 (25.0%)	0.75
Delivered implantation rate	17.5% (130/742)	14.6% (12/82)	0.62

Table 3. — *Comparison of potential confounding factors and pregnancy rates by endometrial echo pattern in frozen ET cycles.*

	TL	IE	*p* value
Age	34.7 ± 5.8	36.0 ± 6.4	0.33
Mean Endo thickness (mm)	9.9 ± 2.2	10.4 ± 2.2	< 0.0001
# embryos transferred	2.8 ± .8	2.8 ± .8	NS
Viable pregnancy rate	676/1854 (36.5%)	131/390 (33.6%)	0.30
Delivered pregnancy rate	628/1854 (33.9%)	121/390 (31.0%)	0.31
Delivered implantation rate	16.7% (882/5270)	16.8% (186/1108)	0.97

Table 4. — *Comparison of potential confounding factors and pregnancy rates by endometrial echo pattern in fresh recipient cycles.*

	TL	IE	*p* value
Age	41.8 ± 5.2	42.3 ± 5.3	0.37
Mean endo thickness	9.6 ± 2.1	9.5 ± 2.4	0.66
# embryos transferred	2.7 ± .7	2.7 ± .6	1.0
Viable pregnancy rate	289/565 (51.2%)	56/105 (53.3%)	0.76
Delivered pregnancy rate	280/565 (49.6%)	52/105 (49.5%)	0.99
Delivered implantation rate	27.3% (419/1535)	28.5% (81/284)	0.72

Discussion

The starting date for this retrospective study was chosen because this was the initiation of improved pregnancy rates for our IVF center. Also there was clearly no overlap in patients with the previous studies.

This study is by far the largest one of its kind. It clearly shows that the presence of an isoechogenic pattern on the day of hCG injection should not influence the decision as to whether to transfer the embryos fresh or cryopreserve them. This applies even to women with diminished oocyte reserve.

Though the aforementioned study by Noyes *et al*. also found no live pregnancies with an HH pattern in women exposed to DES in utero, they failed to find any adverse effect of the HH pattern in those women not exposed to DES in utero. Since our policy is to freeze all embryos and defer fresh transfer if an HH pattern is present in the late proliferative phase, we unfortunately could not answer the question as to whether this pattern is still a poor prognostic factor for pregnancy in the modern IVF era.

Hopefully this study might influence another IVF center whose policy is not to cryopreserve all embryos with an HH pattern to perform a similar retrospective comparison to see if in the modern IVF era the HH pattern is still associated with a poor prognosis.

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