Original Articles

Reproductive Biology Section

Increasing the dosage of progesterone (P) supplemention from the mid-luteal phase in women not attaining a mid-luteal homogeneous hyperechogenic (HH) pattern with sonography improves pregnancy rates (PRS) following frozen embryo transfer (ET)

J.H. Check, C. Dietterich, R. Cohen, J.K. Choe, J. Amui, D. Brasile

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, NJ (USA)

Summary

Purpose: To determine if a mid-luteal phase non-homogeneous hyperechogenic (HH) endometrial echo pattern may lower pregnancy rates following frozen embryo transfer and to determine if raising the dosage of progesterone improves pregnancy outcome. *Methods:* Women not attaining an HH pattern at the mid-luteal phase following estrogen-progesterone replacement were randomly given (or not) an increase in progesterone dosage. *Results:* Increasing the progesterone dosage in those not attaining an HH pattern significantly improved the pregnancy rate relative to controls not attaining an HH pattern and showed a trend for higher pregnancy rates than those with an HH pattern. *Conclusions:* The mid-luteal phase echo pattern should be evaluated for a non-HH pattern so that an increase in progesterone dosage could be provided possibly resulting in higher pregnancy rates.

Key words: Mid-luteal phase; Echo patterns; Frozen embryo transfer.

Introduction

Sonographically, three echo patterns of the endometrium have been described in the literature; triple line (TL), isoechogenic (IE), and homogeneous hyperechogenic (HH). In the secretory phase, the secretion of progesterone (P) by the corpus luteum causes the sonographic appearance of the endometrium to change from a TL pattern seen at mid-cycle, which results from elevated estrogen levels, to an HH pattern.

Some studies have found lower pregnancy rates (PRs) when an HH echo pattern is not observed by transvaginal sonography in the mid-luteal phase following IVF-ET with controlled ovarian hyperstimulation (COH) and non-IVF cycles using luteal phase P, with or without follicle maturing drugs [1, 2]. The aim of the present study was to determine if failing to attain an HH pattern in frozen ET cycles in women who are on graduated estrogen therapy followed by P in the luteal phase have lower PRs than those attaining an HH pattern. Furthermore, the study would determine if raising the dosage of P could have a positive effect on pregnancy outcome.

Materials and Methods

During a two-year period women who were being prepared for frozen embryo transfer with a graduated estrogen protocol followed by progesterone (while the estrogen was continued) were evaluated on the 7th day of progesterone replacement with transvaginal ultrasound to evaluate endometrial echo patterns.

On a fixed four days of the week if the echo pattern showed either a triple-line pattern or an isoechogenic pattern, the dosage of progesterone was increased. The increase in progesterone did not occur if these patterns were found on the other three days of the week or the woman had a homogeneous hyperechogenic pattern.

All women were initially treated with 200 mg progesterone vaginal suppositories twice daily plus 100 mg IM progesterone once daily. If an increase in progesterone dosage was made at the mid-luteal phase either 200 mg oral micronized progesterone was added or the evening suppository was increased to 400 mg.

Results

A total of 408 women met the inclusion criteria; 66.7% (272/408) had an HH pattern in the mid-luteal phase, 21.3% (87/408) had an IE pattern, and 12% (49/408) had a TL pattern. Triple-line and IE echo patterns were then combined for the remainder of the analyses (non-HH).

None of the 272 women with an HH echo pattern and 77 of 136 women with a non-HH pattern were given an increase in their P dosage in the mid-luteal phase. Although a trend was observed for higher PRs in women with an HH pattern vs non-HH pattern where the P dosage was not increased, the difference was not significant (Table 1).

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None of the 272 women with an HH echo pattern and 77 of 136 women with a non-HH pattern were given an increase in their P dosage in the mid-luteal phase. Although a trend was observed for higher PRs in women with an HH pattern vs non-HH pattern where the P dosage was not increased, the difference was not significant (Table 1).

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Table 1. — *Pregnancy rates in women with no increase in P dosage according to attaining or not attaining a homogeneous hyperechogenic pattern of their endometrium in the mid-luteal phase*.

	HH	Non-HH	*p* value
Clinical PR	37.1% (101/272)	28.6% (22/77)	.2
Ongoing/delivered PR	30.9% (84/272)	23.4% (18/77)	.26
Implantation rate	18.3% (146/798)	14.4% (33/229)	.2

Table 2. — *Comparison of pregnancy rates in women with a non-HH echo pattern by whether progesterone supplementation was increased or not*.

	Increased P Dosage	No Increase	*p* value
Clinical PR	47.5% (28/59)	28.6% (22/77)	.037
Ongoing/delivered	42.4% (25/59)	23.4% (18/77)	.03
Implantation rate	21.1% (36/171)	14.4% (33/229)	.08

Table 3. — *Patient characteristics by increase in progesterone dosage*.

	Increase	No increase	*p* value
Age	34.9 ± 5.0	35.1 ± 5.6	.8a
Number of days of E2 therapy	14.7 ± 1.3	15.0 ± 1.8	.3a
E2 mid-cycle (ng/ml)	1121.6 ± 798.7	1387.2 ± 940	.08a
Mid-cycle endometrial thickness (mm)	9.7 ± 1.4	9.9 ± 1.8	.5a
Mid-cycle echo pattern %			
TL	94.9% (56/59)	96.1% (74/77)	.7[b]
IE	5.1% (3/59)	3.9% (3/77)	.7[b]
Number of embryos transferred	2.9 ± .9	3.0 ± .9	.5a
Mid-luteal serum P (pg/ml)	69.5 ± 29.3	70.8 ± 32.5	.8a
Mid-luteal endo thickness (mm)	10.3 ± 2.6	10.4 ± 2.6	.8a

[a]Independent t-test; [b]Chi-square analysis.

Since the objective of the study was to determine if increasing P dosage in the mid-luteal phase of women with a non-HH echo pattern would be effective, pregnancy rates were then compared in those not attaining an HH pattern by whether the dosage was increased or not. Clinical and ongoing pregnancy rates were significantly higher when P was increased (Table 2).

There were no confounding variables to explain the outcome according to adjusting P dosage (Table 3). Contributing factors were similar between the two groups.

Discussion/Conclusions

With frozen ET, there was a non-significant trend for higher pregnancy rates with a mid-luteal HH echo pattern similar to the findings of fresh ETs and ovulating women without IVF [1, 2]. The data were consistent with another study of pregnancy rates in frozen embryo transfers according to whether the lining converts to an HH pattern in the mid-luteal phase with no adjustment of progesterone dosage [3].

The importance of evaluating the parameters was shown by a significant increase in pregnancy rates after increasing the progesterone dosage from the mid-luteal phase to pregnancy test. However, there was a trend for higher ongoing/delivered PRs (42.4%) in women with a poorer endometrial echo pattern but given a higher P dosage in the mid to late luteal phase than in women with the expected HH echo pattern and constant P dosage (30.9%).

This raises the question as to whether the P dosage should be increased either from the start or in the mid to later portion of the luteal phase in all women. Further study would be needed to answer this question.

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com

times five days. Her peak endometrial thickness in the next cycles only reached 5 mm. Frozen ET was performed; she conceived and delivered a healthy live baby.

Another woman with low-dose gonadotropins conceived with a maximum endometrial thickness of 4 mm. She miscarried and the fetus had aneuploidy (trisomy 18).

Thus conception occurred in 2/28 (7.1%) of fresh transfers (both minimal stimulation however) and in 1/7 (14.2%) of frozen ETs.

Conclusions

These data show that pregnancies are possible following embryo transfer despite a peak endometrial thickness in the late proliferative phase of < 6 mm.

Ten of the 28 fresh transfers were with minimal stimulation. Interestingly, the two clinical pregnancies with fresh transfer both occurred with low-dose stimulation. Thus the clinical pregnancy rate was 20% with low-dose drugs. None of the 18 women with normal stimulation conceived.

There are data supporting that in some cases the controlled ovarian hyperstimulation regimen may adversely effect embryo implantation [8, 9]. Even with low-dose gonadotropins or a graduated estrogen regimen without gonadotropins the clinical pregnancy rate in this group was lower than usual (17.6%, 3/17). The possibility exists that pregnancies would be much more rare with 4-5 mm endometrial thickness in IVF cycles with conventional controlled ovarian hyperstimulation.

Obviously one option for women with thin endometria is to use a gestational carrier. These data could suggest that one option for thin endometria in the late proliferative phase for women needing IVF-ET is either to use low-dose protocols or purposely freeze the embryos for future frozen ET [10, 11].

We did not use low-dose aspirin because we have not found it helpful in improving the endometrial thickness [12].

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