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Effect of Women's Age on Pregnancy Outcome with a Triple Line Pattern in Mid Luteal Phase in Frozen-Thawed Embryo Transfer Cycles

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ABSTRACT

Objectives: *The presence of a triple line (TL) endometrial sonographic echo pattern has been associated with diminished fecundity. The purpose of the present study was to determine if advanced woman's age increases the frequency of mid-luteal TL endometrial echo patterns. Furthermore, to see if the presence of this pattern, despite progesterone (P) supplementation, is associated with diminished live delivered pregnancy rates following frozen embryo transfer (FET).*

Design: *Retrospective Cohort Study.*

Participants/Materials: *Embryos derived from women aged <35 that were frozen and were subsequently transferred were used for this study.*

Setting: *University, IVF Center outside of the hospital-separate building.*

Methods: *All women were treated with the same graduated estrogen/progesterone regimen. Mid luteal phase sonograms were performed, and the type of endometrial echo patterns was determined Live delivered pregnancy rates (LDPRs) were determined according to three age groups at the time of transfer (<36, 36-39, and 40-42) and according to echo pattern.*

Results: *There was 2769 FETs in women <36 years old and 142 showed a midluteal TL pattern (5.4%). There were 907 FETs in women 36-39 and the TL pattern was found in 38 women (4.2%). There were 407 FETs in women aged 40-42 and 11 had the TL echo pattern (2.7%). The LDPR for women <36 was 34.7% (914/2627) for non-TL vs 37.3% (53/142) for TL pattern. In women 36-39, the LDPR for non-TL was 26.5% (230/669) vs 13.2% (5/38) for TL pattern. For women, aged 40-42, the LDPR was 12% (49/408) with non-TL and no live deliveries (0/11) with TL.*

Limitations: *Retrospective studies are not as credible for various reasons as prospective studies including fortuitous bias of the groups being compared. Frequently this disadvantage may be obviated by generally much larger number of subjects in retrospective studies as seen in the present study. The frequency of TL patterns were too low to determine if lower LDPR in women > 36 are real or fortuitous when TL pattern is seen.*

Conclusions: *Though the frequency of persistence of a TL pattern does not increase in frequency with advancing age, persistence of a TL pattern is uncommon. However, the LDPRs may be lower in women with advancing age if the pattern persists. This may be related to a subtle decrease in endometrial receptivity with advancing age only manifested in the extreme situation of persistence of a TL pattern. There is also the possibility that less quality embryos were the ones left for transfer in the women of advancing age. This possible confounding effect could have been negated by a prospective study, but as mentioned, a prospective study would suffer from lack of power.*

Keywords
Advancing age, Frozen embryo transfer, Mid-luteal phase, Endometrial echo pattern.

Introduction

Evaluation of sonographic endometrial echogenic pattern by transvaginal ultrasound in natural cycles has determined that in the mid-luteal phase, the endometrium becomes hyperechogenic with no longer any visualization of a well-defined central echogenic line, and the entirely echo dense endometrium becomes more echogenic than the myometrium [1,2]. This endometrial echo pattern is called a homogeneous hyperechogenic pattern (HH) [1,2].

Failure to obtain an HH pattern by mid-luteal phase has been found to be associated with lower pregnancy rates in natural cycles [3]. Similarly, one study found that fresh embryo transfer (ET) following controlled ovarian hyperstimulation (COH) and in vitro fertilization is also associated with a lower live delivered pregnancy rate (LDPR) despite progesterone supplementation in the luteal phase if there is persistence of a TL pattern by mid-luteal phase [4]. Following the transfer of frozen-thawed day three embryos, another study also found a lower LDPR if there was a triple line echo pattern in mid-luteal phase [5].

The patients used for these studies go back about 18 years ago [3-5]. IVF-ET in the present era has demonstrated much better pregnancy rates following ET (as seen in reviewing yearly statistics from the Society of Assisted Reproductive Technology) and is most likely related to improvements in embryo media . The purpose of this study was to re-evaluate whether the failure to progress from a triple line (TL) pattern in the three days after FET was still associated with lower LDPRs in the modern era. The second objective was to determine if an aging endometrium leads to a greater chance of an endometrial echo pattern remaining a TL even after seven days of P supplementation. The study evaluated only women whose egg retrieval was performed before age 36. Another advantage of only evaluating the LDPRs following FET was that all patients were treated with the same drug regimen prior to FET.

Methods

To avoid using any of the same data as previously published, and to not have the potential of less quality of the embryo related to inferior incubation media, these data only included women whose egg retrieval FET occurred from 2005 to 2022. All egg retrievals were performed in women less than age 36. The LDPRs were compared according to the age of the women at the time of the embryo transfer. Three age groups at the time the FETs occurred were compared: FET performed in women ≤35, 36-39, and 40-42. The frozen embryos used were from IVF cycles were the supernumerary ones following fresh ET, or where all embryos were cryopreserved, usually because of the risk of ovarian hyperstimulation, but sometimes because of either inadequate endometrial thickness at the time of egg retrieval, or a homogeneous hyperechogenic endometrial sonographic echo pattern at the time of peak follicular maturation [6,7]. The mid-luteal phase endometrial echo patterns were deemed either triple line (TL), isoechogenic (IE), or homogeneous hyperechogenic (HH). Sometimes the endometrium could have some mixture of patterns in different segments of the endometrium e.g., IE and HH. Thus, this study centered on whether women still showing TL pattern in mid-luteal phase were less likely to have a live delivery compared to non-TL.

The study not only evaluated whether women still having a TL endometrial lining in mid-luteal phase were less likely to conceive than non-TL, but whether the age of the women at the time of FET had a negative influence. Furthermore, the study would determine whether advancing age increased the frequency of a TL echo pattern in mid-luteal phase. A woman could be used more than once if she had FET two or three different times.

Only cycles were included if the women's protocol to prepare for FET was a graduated estradiol regimen of a 2mg estradiol tablet daily placed intravaginally and an oral regimen of 2mg x 5 days, 4mg x 4 days, and 6mg x 5 days or longer until an endometrial thickness was at least 8mm. If they could not achieve an 8mm endometrial echo pattern, even with extension of the estradiol tablets, they were not included in the study. The estradiol was continued at 6mg total during the luteal phase when progesterone (P) was added. All women received 100mg intramuscular P daily plus vaginal P which varied according to their insurance whether they received commercial vaginal P or compounded P. Statistical analysis was performed using chi-square analysis or Fisher's exact test. All day 3 frozen-thawed embryos were transferred as long as they had a minimum of four blastomeres regardless of the degree of fragmentation or asymmetry.

Results

There was 2769 FETs in women <36 years old and 142 showed a midluteal TL pattern (5.4%). There were 907 FETs in women 36-39 and the TL pattern was found in 38 women (4.2%). There were 407 FETs in women aged 40-42 and 11 had the TL echo pattern (2.7%). Fisher's exact test found no significant difference in the frequency of mid-luteal TL echo patterns across the 3 age groups.

Table 1: Difference in Live delivered pregnancy rates (LDPRs) according to TL pattern and age.

	LDPR in mid-luteal phase non-TL pattern	LDPR in mid-luteal phase TL pattern
<36 years old	34.7% (914/2627)	37.3% (53/142)
36-39	26.5% (230/869)	13.2% (5/38)
40-42	12% (49/408)	0% (0/11)

The LDPR for women <36 was 34.7% (914/2627) for non-TL vs 37.3% (53/142) for TL pattern (Chi-square analysis non-significant) as seen in Table 1. For women 36-39 the LDPRs were 26.5% (230/869) for non-TL vs 13.2% (5/38) for TL (Fishers exact test showed P=NS). For women, aged 40-42, the live delivered pregnancy rate was 12% (49/408) with non-TL and no live deliveries (0/11) with TL (Fisher's exact test, P=NS) (See Table 1). Power analysis found that the number of patients aged

40-42 would have to be twice as high or larger for the difference observed to obtain statistical significance. Chi-square analysis showed that the 34.7% LDPR in women < 36 with a non-TL pattern was significantly higher than the 26.5% in women 36-39 with a non-TL pattern. Similarly, Fisher's exact test showed the 37.3% LDPR in women age <36 with a TL mid-luteal echo pattern was significantly higher than the 13.2% LDPR in women aged 36-39 ($P<0.05$).

Discussion

The frequency of having the adverse infertility factor of TL endometrial echo pattern in midluteal phase in frozen ET cycles does not increase with advancing age of the female partners who were supplemented with 100 mg IM P in oil and vaginal P supplementation 2x/day with either progesterone vaginal suppositories 400 mg/twice daily, Crinone ® vaginal gel 90 mg/twice daily, or Endometrin ® vaginal tablets 100 mg/twice daily.

For younger women age <36, there were similar live delivered pregnancy rates whether the mid-luteal phase echo pattern was TL or non-TL. Though there was insufficient power to show a statistical difference, there was a trend for lower live delivered pregnancy rates in women aged 36-39 with a TL mid-luteal echo pattern with a LDPR that was 50% lower. Advancing age does not decrease pregnancy rates with the transfer of fresh embryos derived from donor eggs [8]. Thus, one question that arises is why was there a trend for lower LDPRs with advancing age despite the fact that the eggs used to form embryos came from younger women <36 years of age. The most likely explanation was because of embryo de-selection. The embryo quality of these day 3 embryos may have been of reduced quality when transferred to women of advancing age since the better-quality embryos were likely used when the woman was younger.

A literature search failed to find any studies in recent times evaluating whether the presence of a TL pattern in midluteal phase is associated with a lower chance of conception stratified by age. One study published in 2009 claimed that there was no difference in mid-luteal phase in endometrial echo patterns in women conceiving vs not conceiving following transfer of embryos derived from donor egg [9]. Interestingly, the statement was made without presenting the actual data. E ven more important, given that the frequency of a TL pattern in mid-luteal phase only occurs in 5% of the cycles, a study would have to have a great deal of power to determine a significant difference in LDPR .

The data suggest that when present, though uncommon, the presence of a TL echo pattern in midluteal phase may be associated with decreased LDPRs in women >36 years old following frozen ET, especially when transferring embryos that may be of lower quality. One could argue that a 5% chance of finding a TL pattern in mid-luteal phase in estrogen/P replaced hormone cycles with subsequent FET may not be worth having the patient come to the facility for another ultrasound. However, finding a TL pattern could allow one to evaluate the possibility of endometritis and/or endometriosis, and consider additional treatments prior to another FET, at least in women over the age of 35, who possibly have only de-selected embryos to transfer. Thus, in the authors' opinion, based on how innocuous is a transvaginal ultrasound, and, considering the expense of embryo transfer, it is probably worth performing this extra procedure. Perhaps one could consider evaluating the endometrial BCL6 inflammation marker in this group of women, and if present, to consider dopaminergic drugs to decrease cellular permeability leading to excessive inflammation, or to empirically use antibiotics to treat a potential infectious endometritis [10-12]. If the patient had a sister or friend willing to be a gestational carrier, or if the couple had the financial means to pay for a gestational carrier, that would be another option. One may at least consider a mock cycle before the next transfer to determine if any intervention corrected the problem of persisting TL pattern before taking more drastic measures e.g., a gestational carrier, to determine if the mid-luteal TL pattern was an isolated event, or a recurrent problem.

Authors Contributions

BN was responsible for writing 60% of the manuscript and JC 40%. 60% of data collection was completed by CW and 40% by BN. CW is our SART liaison, and she was the main person to enter all of the data on the patients and provided the data set that we used for the study. She also added the statistical analysis. All authors independently made editorial changes in the first draft of the manuscript. The final manuscript that is being submitted was approved by all three authors.

Conflict of Interest

All patients on their initial visit are asked to sign a statement that their results may be included in research studies, but their anonymity will be maintained. Generally, 99% sign the statement. Those who do not, their chart is flagged and not used in research studies. Cooper Medical School of Rowan University does not require IRB approval for retrospective studies. Performing a mid-luteal vaginal ultrasound is part of our standard procedure.

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