

Non-homogeneous hyperechogenic pattern 3 days after embryo transfer is associated with lower pregnancy rates

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The purpose of this study was to investigate the relationship between mid-luteal phase echo patterns and IVF-embryo transfer outcome in women who have demonstrated adequate endometrial development by the late proliferative phase. A prospective study was carried out of 86 patients undergoing IVF-embryo transfer and 86 patients undergoing frozen embryo transfer who all underwent sonographic monitoring of the endometrium 3 days after embryo transfer. The cycles were classified into two groups: those with the homogeneous hyperechogenic (HH) pattern and those without it. The women who had an HH pattern had higher clinical pregnancy (32.8 versus 10.7%, $P < 0.05$) and implantation rates in stimulated cycles (14.3 versus 4.1%, $P < 0.05$ respectively) than those that did not. There was no significant difference in the clinical pregnancy or implantation rates by echo pattern (18.2 and 8.1% for non-HH and 18.7 and 8.0% for HH respectively) in frozen embryo transfer cycles. These data demonstrate that in embryo transfer cycles where ovarian stimulation was used, there were decreased pregnancy and implantation rates in cycles where the HH pattern was not observed 3 days after transfer. The failure of the endometrium to display this pattern may indicate some endometrial abnormality resulting in implantation defects.

Key words: echo pattern/IVF/luteal phase/sonography

Introduction

The use of transvaginal ultrasonography has provided clinicians with a non-invasive procedure for monitoring endometrial development throughout the menstrual cycle. Measurements of endometrial thickness and echo pattern in the late proliferative phase have been shown to be correlated with the outcome of IVF-embryo transfer (Gonen and Casper, 1990; Check *et al.*, 1991, 1993; Sher *et al.*, 1991; Khalifa *et al.*, 1992). Endometrial echo patterns seen sonographically have been described as triple line (TL), which appears multilayered with hyper-echogenic outer walls and a well-defined central echogenic line; isoechogenic (IE), where the endometrium has the same echogenicity as the myometrium with a poorly defined central

echogenic line; and homogeneous hyperechogenic (HH), which appears as an entirely echodense endometrium and is more echogenic than the myometrium with no visualization of a central echogenic line (Fleisher *et al.*, 1988; Gonen and Casper, 1990). Studies of the relationship between sonographic measurements of the endometrium in the luteal phase and histological dating of the endometrial biopsy have found no correlation (Grunfeld *et al.*, 1991; Doherty *et al.*, 1993; Ficicioglu *et al.*, 1995; Sterzik *et al.*, 1997). However, some researchers have found that the absence of an HH pattern in the luteal phase is an indication for further evaluation (Grunfeld *et al.*, 1991; Doherty *et al.*, 1993).

The objective of this study was to evaluate the relationship of sonographic assessment of the endometrium in the luteal phase with conception following IVF-embryo transfer. Specifically, the relationship between echo pattern 3 days after embryo transfer with conception outcome of IVF-embryo transfer in women who have demonstrated adequate endometrial development by the late proliferative phase would be assessed. The hypothesis of this study, based on clinical observations, was that the echo pattern 3 days after embryo transfer associated with the highest pregnancy rates was the HH pattern. The study would further explore whether the use of ovarian stimulation had any influence on pregnancy outcome according to echo patterns 3 days after embryo transfer by comparing pregnancy and implantation rates in oocyte retrieval cycles versus the transfer of frozen embryos.

Materials and methods

A prospective observational study was conducted in which all patients undergoing IVF-embryo transfer or embryo transfer using cryopreserved embryos over an 11 month period were required to undergo sonographic monitoring of the endometrium 3 days after embryo transfer. Cycles in which intracytoplasmic sperm injection (ICSI) had been used were excluded. All sonographic measurements were taken using an ATL Ultramark 4 (Advanced Technology Laboratories, Bothell, WA, USA) equipped with a 5 MHz vaginal transducer. Endometrial thickness was measured in mm, by placing calipers on the outer walls of the endometrium as seen in the longitudinal axis of the uterine body. Three types of echo patterns were distinguished: TL, IE and HH. For purposes of the analysis, the cycles were classified into two groups, those with the HH pattern and those without it. One sonographer performed all of the grading to eliminate inter-observer variability. Only cycles in which the woman was aged ≤ 40 years and had at least three embryos transferred were included in the analysis to control for the confounding factors of age and embryo quality. Only the first cycle per patient was included to assure the independence of the observations. A patient used in a retrieval cycle would not be used again in a frozen embryo transfer cycle.

Ovarian stimulation for retrieval cycles included the luteal phase leuprolide acetate/gonadotrophin protocol (Wildt *et al.*, 1986; 54 cycles) or the short flare protocol (Barriere *et al.*, 1987; 32 cycles). Preparation for frozen embryo transfer included down-regulation with leuprolide acetate and oestrogen replacement or oestrogen replacement cycles only. Progesterone was supplemented in the luteal phase of all cycles. The oestrogen replacement consisted of oral micronized oestradiol beginning at 2 mg for 5 days, 4 mg for 4 days, then 6 mg for at least 5 days. Progesterone therapy was added to the oestrogen when the endometrium was at least 8 mm thick and the echo pattern was trilaminar. Progesterone replacement consisted of at least 200 mg progesterone vaginal suppositories twice daily plus 50–100 mg i.m. daily of progesterone (US Pharmacopeia). In stimulation cycles, only vaginal progesterone was used.

Embryo transfer was performed if the patient demonstrated adequate endometrial development on the day of human chorionic gonadotrophin (HCG) administration (endometrial thickness ≥ 8 mm and a TL or IE echo pattern). Otherwise, all embryos were cryopreserved and transfer deferred. Embryo freezing used a simplified protocol and thawing required only a one-step removal of the cryoprotectant 2-propanediol (Baker *et al.*, 1997). Assisted hatching using acidic Tyrode's solution was performed (Check *et al.*, 1996a).

The main outcome measures were clinical pregnancy (sonographic evidence of gestational sacs) and implantation rates (number of gestational sacs/embryos transferred) following embryo transfer. Statistical analysis included χ^2 analysis and *t*-test for independent groups as appropriate. $P < 0.05$ was considered to be statistically significant.

Results

There were 86 women who underwent IVF-embryo transfer cycles. These women ranged in age from 26–40 years with an average (\pm SD) age of 34.2 ± 3.5 years. A total of 21 were treated for tubal factor, seven for endometriosis, 13 for male factor, three for ovulatory dysfunction, eight for unexplained infertility, and 34 for multiple factors. The distribution of echo patterns in the mid-luteal phase was HH = 58 (67.4%), non-HH = 28 (32.6%) (there were four TL and 24 IE patterns). The women who had an HH pattern had higher pregnancy and implantation rates than those who did not. The clinical pregnancy rates were 32.8 versus 10.7% ($P < 0.05$). The delivery rates were 29.3 versus 7.1% ($P < 0.05$) and the implantation rates were 14.3 versus 4.1% ($P < 0.05$) (Figure 1). The miscarriage rates were 10.5% (two out of 19) in the HH group and 33% (one out of three) in the non-HH group.

There was no association between mid-luteal phase endometrial thickness and conception. For those who conceived, the mean thickness was 14.6 ± 3.5 mm as compared to 13.1 ± 3.1 mm for those that did not conceive (not significant) as seen in Table I. There were no significant differences in age, stimulation used, indication for IVF, mid-cycle and luteal phase serum hormone concentrations, number of oocytes retrieved, fertilization rates, or number of embryos transferred between conception and non-conception cycles (Table I). The group with male factor infertility seemed to have the lowest pregnancy rates. This may be related to not performing ICSI in cases of poor quality spermatozoa but where fertilization seemed likely using conventional insemination techniques. Cycles using ICSI were not chosen because

of the fact that some studies have suggested that ICSI lowers subsequent frozen embryo transfer pregnancy rates (Van Steirteghem *et al.*, 1994), although other studies dispute this (Al-Hasani *et al.*, 1996; Hoover *et al.*, 1997). With this debate, we did not want to introduce a possible confounding variable, so no fresh or frozen embryo transfer cycles were evaluated if ICSI had been performed to achieve fertilization.

There were no significant differences in age, stimulation used, or progesterone type with the echo pattern observed (Table II). Serum concentrations of oestradiol and progesterone did not differ with the echo pattern observed.

There were 86 women who underwent frozen embryo transfer and had at least three embryos transferred. These women ranged in age from 26–40 years with a mean age of 33.3 ± 3.4 years. They were treated for tubal factor ($n = 25$), endometriosis ($n = 14$), male factor ($n = 12$), ovulatory dysfunction ($n = 5$), multiple factors ($n = 26$), and unexplained infertility ($n = 4$). The distribution of echo patterns was HH, $n = 75$ (87.2%), non-HH, $n = 11$ (12.8%). There were no significant differences in the pregnancy rates or implantation rates by echo pattern in frozen embryo transfers. The clinical pregnancy rates, delivery rates, and implantation rates were 18.2, 18.2, and 8.1% for non-HH respectively and 18.7, 16.0 and 8.0% for HH (not significant) (Figure 2). The miscarriage rates were 14.3% (two out of four) and 0% (zero out of 11) in the HH and non-HH groups respectively. There was no difference in the mid-luteal phase endometrial thickness by conception outcome (11.3 ± 2.8 mm for non-conceivers and 11.2 ± 2.7 mm for conceivers). There were also no significant differences in the age, cycle preparation, serum hormone concentrations or number of embryos transferred between conceivers and non-conceivers (Table III). There was no relationship between echo pattern and other IVF factors (Table IV) except for the concentration of LH at mid-cycle in frozen embryo transfer cycles.

Discussion

Technology with IVF-embryo transfer has improved over the years and most IVF centres report far higher pregnancy rates than 10 years ago when the first cases recording endometrial thickness and echo pattern at the time of HCG injection were documented. Most studies now conclude that endometrial thickness at time of HCG has only marginal prognostic value when only the extremes of poor growth are seen (Turnbull *et al.*, 1995; Zaidi *et al.*, 1995; Bohrer *et al.*, 1996; Friedler *et al.*, 1996; Oliveira *et al.*, 1997) or when patients take clomiphene citrate (Turnbull *et al.*, 1995). However, the conclusion that the HH pattern at the time of HCG carries a very poor prognosis for pregnancy (Check *et al.*, 1993) was corroborated by more recent studies (Turnbull *et al.*, 1995; Bohrer *et al.*, 1996; Oliveira *et al.*, 1997).

Similarly, the study presented here of endometrial thickness 3 days after embryo transfer did not find that endometrial thickness had much prognostic value. However, similar to previous findings on the day of HCG, the sonographic echo patterns were related to the establishment of clinical pregnancies in fresh embryo transfers. In contrast to the mid-cycle

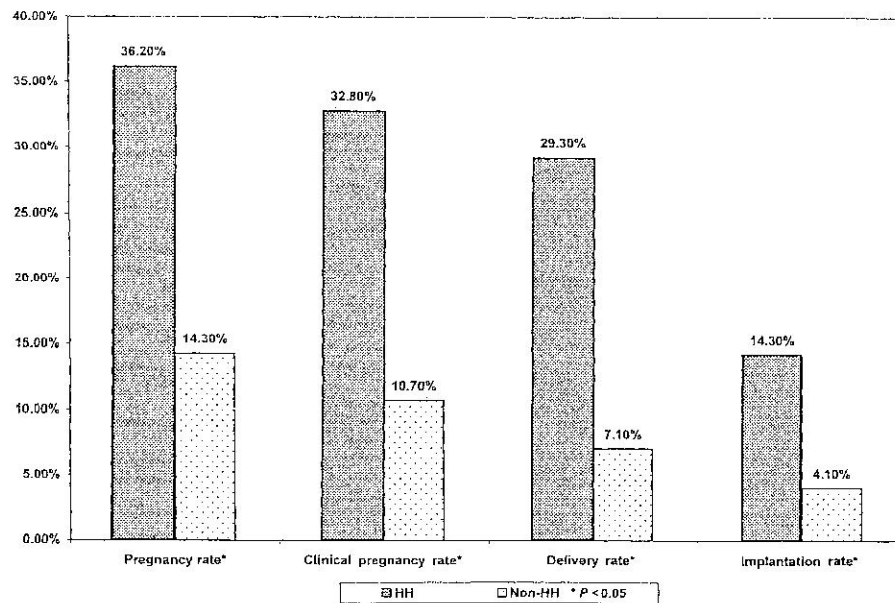


Figure 1. Comparison of pregnancy and implantation rates in 86 women following IVF and embryo transfer by luteal phase echo pattern. HH = homogeneous hyperechogenic pattern.

Table I. Stimulation characteristics in conception and non-conception cycles after fresh embryo transfer. Values are given as means \pm SD, unless otherwise indicated. There was no significant difference between the groups

	Conception cycles ($n = 22$)	Non-conception cycles ($n = 64$)
Mid-cycle		
Oestradiol (pg/ml)	2232.1 \pm 1011.1	1953.3 \pm 922.1
Progesterone (ng/ml)	0.6 \pm 0.3	0.9 \pm 1.0
LH (mIU/ml)	3.1 \pm 1.2	4.2 \pm 1.2
Luteal phase		
Oestradiol (pg/ml)	1165.4 \pm 733.4	1088.1 \pm 824.4
Progesterone (ng/ml)	105.5 \pm 38.8	85.5 \pm 33.9
17-OHP (ng/dl)	753.7 \pm 265.9	648.3 \pm 340.4
Oocytes retrieved (n)	13.8 \pm 6.2	12.1 \pm 6.2
Fertilization rate (%)	62.1 \pm 6.6	56.6 \pm 23.4
Embryos transferred (n)	3.6 \pm 0.5	3.4 \pm 0.5
Age (years)	33.6 \pm 3.3	34.4 \pm 3.6
Infertility factors n (%)		
Tubal	7 (31.8)	14 (21.9)
Endometriosis	1 (4.5)	6 (9.4)
Male	1 (4.5)	12 (18.8)
Ovulatory	3 (13.6)	0
Multiple	9 (40.9)	25 (39.1)
Unexplained	1 (4.5)	7 (10.9)
Endometrial thickness (mm)		
Mid-cycle	13.4 \pm 2.6	12.3 \pm 2.5
Luteal	14.6 \pm 3.5	13.1 \pm 3.1
Stimulation n (%)		
Luteal phase leuprolide-gonadotrophin	12 (54.5)	42 (65.6)
Flare	10 (45.5)	22 (34.4)

17-OHP = 17-hydroxyprogesterone.

data, the echo pattern with the adverse prognosis was the non-homogeneous hyperechogenic pattern 3 days after transfer.

The mechanism for failure to change from triple line to homogeneous hyperechogenic pattern is not known. There was no relationship with the mid-luteal phase serum progesterone values and type of echo pattern. Other studies have not shown

Table II. Stimulation characteristics (embryo transfer same cycle as retrieval) with cycles grouped according to echo pattern. Values are given as means \pm SD, unless otherwise indicated. There was no significant difference between the groups

	HH ($n = 58$)	Non-HH ($n = 28$)
Mid-cycle		
Oestradiol (pg/ml)	2154.9 \pm 963.2	1747.5 \pm 866.7
Progesterone (ng/ml)	0.7 \pm 0.6	1.0 \pm 1.3
LH (mIU/ml)	4.0 \pm 2.6	3.7 \pm 1.5
Luteal phase		
Oestradiol (pg/ml)	1148.3 \pm 802.7	1026.5 \pm 797.5
Progesterone (ng/ml)	92.9 \pm 31.3	86.1 \pm 44.7
17-OHP (ng/dl)	642.3 \pm 338.8	759.8 \pm 273.8
Oocytes retrieved (n)	13.0 \pm 6.8	11.6 \pm 5.3
Fertilization rate (%)	58.1 \pm 22.5	57.7 \pm 21.0
Embryos transferred (n)	3.5 \pm 0.5	3.5 \pm 0.5
Age (years)	34.7 \pm 3.3	34.0 \pm 3.6
Infertility factors (n, %)		
Tubal	18 (31.0)	3 (10.7)
Endometriosis	5 (8.6)	2 (7.1)
Male	8 (13.8)	5 (17.6)
Ovulatory	2 (3.4)	1 (3.5)
Multiple	19 (32.7)	15 (53.6)
Unexplained	6 (10.3)	2 (7.1)
Endometrial thickness (mm)		
Mid-cycle	12.4 \pm 2.6	12.7 \pm 2.6
Luteal	13.7 \pm 3.2	13.2 \pm 3.4
Stimulation n (%)		
Luteal phase leuprolide-gonadotrophin	38 (65.5)	16 (57.1)
Flare	20 (34.5)	12 (42.9)

HH = homogeneous hyperechogenic pattern;
17-OHP = 17-hydroxyprogesterone.

any relationship with the mid-luteal phase triple line echo pattern and the out-of-phase endometrial biopsy (Grinfeld *et al.*, 1991; Doherty *et al.*, 1993; Ficicioglu *et al.*, 1995; Sterzik *et al.*, 1997). Possibly, future studies may find some relationship of the triple line echo pattern and endometrial

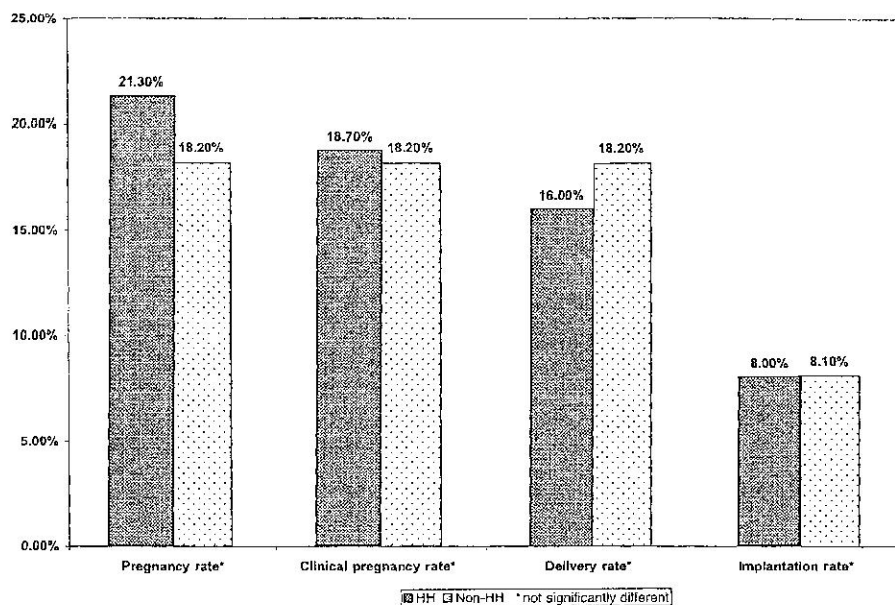


Figure 2. Comparison of pregnancy and implantation rates in 86 women following frozen embryo transfer by luteal phase echo pattern. HH = homogeneous hyperechogenic pattern.

Table III. Stimulation characteristics in conception and non-conception cycles after transfer of frozen embryos. Values are given as means ± SD, unless otherwise indicated. There was no significant difference between the groups

	Conception cycles (n = 16)	Non-conception cycles (n = 70)
Mid-cycle		
Oestradiol (pg/ml)	805.0 ± 485.8	756.9 ± 565.9
Progesterone (ng/ml)	0.3 ± 0.2	0.3 ± 0.3
LH (mIU/ml)	12.3 ± 12.4	20.3 ± 21.8
Luteal phase		
Oestradiol (pg/ml)	803.9 ± 598.2	681.0 ± 698.8
Progesterone (ng/ml)	43.5 ± 33.2	33.2 ± 20.6
17-OHP (ng/dl)	196.5 ± 217.0	134.9 ± 72.1
Embryos transferred (n)	3.9 ± .8	3.5 ± 5.6
Age (years)	34.9 ± 3.3	34.5 ± 3.9
Infertility factors n (%)		
Tubal	4 (25.0)	21 (30.0)
Endometriosis	3 (18.7)	11 (15.7)
Male	1 (6.3)	11 (15.7)
Ovulatory	1 (6.3)	4 (5.7)
Multiple	7 (43.7)	19 (27.1)
Unexplained	0	4 (5.7)
Endometrial thickness (mm)		
Mid-cycle	10.9 ± 1.8	10.9 ± 2.1
Luteal	11.2 ± 2.7	11.3 ± 2.8
Stimulation n (%)		
Natural	5 (31.2)	32 (45.7)
Leuprolide oral oestradiol	5 (31.2)	17 (24.3)
Oral oestradiol	6 (37.6)	21 (30.0)

17-OHP = 17-hydroxyprogesterone.

Table IV. Stimulation characteristics (after transfer of thawed embryos) with cycles grouped according to echo pattern. Values are given as means ± SD, unless otherwise indicated

	HH (n = 75)*	Non-HH (n = 11)*
Mid-cycle		
Oestradiol (pg/ml)	710.3 ± 513.3	1135.7 ± 657.7
Progesterone (ng/ml)	0.3 ± 0.3	0.3 ± 0.2
LH (mIU/ml) ^a	20.6 ± 21.8	9.5 ± 6.9
Luteal phase		
Oestradiol (pg/ml)	638.4 ± 627.5	1207.1 ± 839.2
Progesterone (ng/ml)	35.3 ± 24.5	34.0 ± 16.8
17-OHP (ng/dl)	155.9 ± 124.8	112.5 ± 69.3
Embryos transferred (n)	3.6 ± 0.6	3.4 ± 0.5
Age (years)	33.2 ± 3.5	33.3 ± 3.3
Infertility factors n (%)		
Tubal	21 (28.0)	4 (36.4)
Endometriosis	13 (17.3)	1 (9.1)
Male	11 (14.7)	1 (9.1)
Ovulatory	4 (5.3)	1 (9.1)
Multiple	22 (29.3)	4 (36.4)
Unexplained	4 (5.3)	0
Endometrial thickness (mm)		
Mid-cycle	12.4 ± 2.6	12.7 ± 2.6
Luteal	13.7 ± 3.2	13.2 ± 3.4
Stimulation		
Natural	34 (45.3)	3 (27.3)
Leuprolide/oral oestradiol	19 (25.3)	3 (27.3)
Oral oestradiol	22 (29.3)	5 (45.4)

HH = homogeneous hyperechogenic pattern;

17-OHP = 17-hydroxyprogesterone.

*Significant difference between the groups (P < 0.05).

oestrogen and progesterone receptors or their ratio. A study by Ohno and Fujimoto did not find any relationship with the pre-ovulatory echo appearance and endometrial steroid hormone receptor concentration (Ohno and Fujimoto, 1998). However, the ratio of progesterone:oestrogen receptor concentration was somewhat less when a triple line pattern

was not seen in the pre-ovulatory endometrium (Ohno and Fujimoto, 1998).

The significant difference in serum LH at mid-cycle in frozen embryo transfer cycles between those with HH and non-HH patterns was interesting. Indeed, some studies have suggested poor pregnancy rates with higher follicular phase

serum LH concentrations (Adams *et al.*, 1986; Homburg *et al.*, 1988; Polson *et al.*, 1988; Regan *et al.*, 1990), though other studies did not agree (Check *et al.*, 1996b). In this study the pre-ovulatory LH concentrations were the highest in the group with the HH pattern who have the best pregnancy prognosis. Furthermore, no such relationship with LH and luteal phase echo patterns post-transfer was observed in cycles where oocyte retrieval occurred. No other relationships were noted in stimulated cycles or frozen embryo transfer cycles with any other hormonal concentrations and echo patterns.

There is evidence that ovarian stimulation regimen may have an adverse effect on implantation (Check *et al.*, 1995, 1999). The fact that 28 of 86 (32.5%) patients having oocyte retrievals had a non-HH pattern 3 days post-transfer versus only 11 out of 86 (12.7%) having frozen embryo transfer could suggest that at least some individuals with adverse implantation factors following ovarian stimulation can be identified by observing a non-HH pattern in the luteal phase. At least in subsequent treatment cycles, it may seem reasonable to cryopreserve all embryos for future frozen embryo transfer when a non-HH pattern occurs 3 days after transfer. Unfortunately, since this study required that the same individual could not be used for a fresh and frozen embryo transfer cycle, it cannot be determined from these data if women with non-HH patterns following ovarian stimulation have much less chance of this happening with frozen embryo transfer. Thus, an interesting future study would be to determine the percentage of a non-HH pattern 3 days after transfer following randomization to a fresh or frozen embryo transfer from women who had a non-HH pattern in their first retrieval cycle.

Future studies should probably also include measurement of uterine and subendometrial blood flow in stimulated and non-stimulated cycles and the association with HH and non-HH patterns 3 days after transfer. Though the numbers were too small to make a conclusive statement, not only was a non-HH pattern less common with frozen embryo transfer cycles, but the non-HH pattern was not associated with a decreased pregnancy or implantation rate. Why the adverse effects of ovarian stimulation seem to relate, at least in part, to a non-HH pattern 3 days after transfer, even though this pattern does not seem to impair pregnancies in frozen embryo transfer cycles, is not known. Possibly this information may help to elucidate in the future the mechanism by which the stimulation regimen may impair implantation.

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