Follicular and luteal phase endometrial thickness and echogenic pattern and pregnancy outcome in oocyte donation cycles

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Abstract

Purpose To study the effect of endometrial thickness (ET) and echogenic pattern (EP) in oocyte donation cycles upon pregnancy outcomes.

Methods Seventy-nine cycles resulting in blastocyst embryo transfer were evaluated. Donors underwent ovarian hyperstimulation using rFSH and GnRH-antagonist. Recipients were synchronized to donors using GnRH-agonist down-regulation followed by fixed dose of estrogen (E2) and progesterone (P4) following hCG. Transvaginal ultrasound (US) obtained ET and EP 10–11 days after initiation of E2 and on day of embryo transfer. Primary outcome was ET and EP in pregnant and non-pregnant cycles. Stimulation and embryology data was analyzed in donors to assess differences prior to transfer.

Results Fifty-nine cycles resulted in clinical pregnancy. No differences were observed in pregnant vs. non-pregnant cycles in proliferative or secretory ET and EP. Similar baseline and stimulation characteristics were found in pregnant and non-pregnant cycles. Regression analysis showed end thickness were not predictive of pregnancy outcomes.

Conclusions Endometrial characteristics in recipients prior to and following progesterone were not predictive of pregnancy outcomes.

Keywords Blastocyst · Embryo transfer · Endometrial thickness and pattern · Oocyte donation

Capsule Endometrial thickness and echogenic pattern do not appear to be predictive of outcomes in oocyte donation cycles.

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Introduction

The success of in vitro fertilization and embryo transfer (IVF-ET) cycles depends primarily upon embryo quality and uterine receptivity. With respect to uterine receptivity, endometrial thickness has been used as a surrogate marker to predict pregnancy outcome. Many studies have proposed that a correlation exists between endometrial thickness and uterine receptivity with significantly higher pregnancy rates the greater endometrial thickness and certain type of echogenic pattern in both autologous and donor-oocyte cycles [1–8]. Some studies have suggested a minimal thickness for a successful pregnancy to occur, while others have reported adverse effects of increased endometrial thickness above which pregnancy is unlikely to occur [5, 9, 10]. In contrast, others have failed to demonstrate such a relationship between endometrial thickness, pattern, pregnancy and implantation rates [11–15].

Limitations to these studies include sample size, ultrasound assessment of the endometrium being limited to a

single measurement either at the time of human chorionic gonadotropin (hCG) injection, day before or at the time of oocyte retrieval. Few studies have assessed the endometrium on the day of ET or on both the day of hCG administration and ET. Moreover, many studies have assessed autologous IVF cycles where controlled ovarian hyperstimulation may exert influences, either directly or through its superphysiologic effects, on ovarian hormones or on the endometrium [16–18].

The present study was undertaken to primarily examine the relationship between endometrial thickness in the mid-luteal phase (i.e. day of ET) and pregnancy outcome, and secondarily, the relationship between endometrial thickness and echogenic pattern in the late follicular phase and pregnancy outcome. In order to best assess the relationship of endometrial thickness and pregnancy outcome, we included only oocyte donation cycles and the analysis was limited to those cycles where 2 blastocysts (at least one good quality) were replaced in an attempt to control for confounding variables seen in other clinical studies.

Materials & methods

This study was reviewed and approved by the Institutional Review Board of the University of Wisconsin.

Subjects

From July 2003 to June 2006, 132 fresh oocyte donation cycles were performed and their outcome was retrospectively reviewed. Cycles where two blastocysts (at least one fully expanded blastocyst) were transferred were included in the study for evaluation, while cycles that resulted in a cleavage stage embryo transfer and those in which embryos were biopsied for pre-implantation genetic diagnosis were excluded from the evaluation. Those cycles where a hydrosalpinx or uterine myoma(s) >3 cm were detected were also excluded. This left 79 eligible cycles.

All oocyte donors ($n=52$) [age: 27.0 ± 0.4 years (yrs), mean $\pm$ standard error, range 19–36 years] had a normal day 2–3 serum follicle stimulating hormone level (5.4 ± 0.3 mIU/mL). Sixty-eight recipients (age: 39.9 ± 0.7 years, range 30–56 years) underwent a total of 79 initiated cycles. Fifty-eight recipients (85%) underwent first time cycles, while 10 recipients (15%) were undergoing repeat cycles accounting for 73% ($n=58$) and 27% ($n=21$) of the reviewed cycles, respectively. Oocytes were given as non-split (i.e., non-shared) in 50 cycles ($n=50$, 64%); 2-way split in 8 cycles ($n=16$, 20%); 3-way split in 3 cycles ($n=9$, 11%); and one was a 4-way split ($n=4$, 5%).

Donor protocol

Prior to stimulation, all oocyte donors were placed on one to two months of oral contraceptives. Following a withdrawal bleed, ovarian stimulation was started on cycle day 3 using daily injections of 225 to 300 IU of recombinant follicle stimulating hormone (rFSH) (Follistim™; Organon Inc., West Orange, NJ, USA). All cycles were monitored by transvaginal US and serum estradiol levels starting on cycle day 5, and thereafter, the dose was adjusted according to response. GnRH-antagonist (Ganirelix, 0.25 mg, subcutaneously daily [Organon Inc., West Orange, NJ, USA]) was begun when lead follicles were 13–14 mm, and an additional 75 IU of rFSH/day in a “step-up” fashion was given. When ≥ 3 follicles reached 18–20 mm, urinary hCG 10,000 IU was given and was followed by transvaginal oocyte aspiration 36 h later. Fertilization was performed on the day of retrieval with sperm from a partner or donor using conventional IVF or intracytoplasmic sperm injection (ICSI).

In-vitro insemination and intracytoplasmic sperm injection

All oocytes were fertilized by conventional IVF methods or by ICSI. All normally fertilized embryos were cultured sequentially in Vitrolife's G1.3 and G2.3 media, supplemented with 5% protein. A gas phase of 7% CO₂, 5% O₂ and 88% N₂ was used in a humidified incubator. Embryos were cultured individually in drops under oil (Vitrolife's Ovoil [Vitrolife Inc., Englewood, CO, USA]). Embryo transfers were done at the cleavage or blastocyst stage, depending on the number of normally fertilized embryos available on day-1. Day-3 embryos were evaluated according to cell number, and were graded according to blastomere uniformity and the degree of fragmentation. At least 6 good quality cleavage stage embryos were required to continue culture to the blastocyst stage [≥ 6 cells and grade 2 (slightly to moderately uneven cells and slight to moderate fragmentation)]. Blastocyst quality was evaluated on day-6 according to inner cell mass and outer cell mass morphology and the presence of expansion or hatching

Recipient protocol

All recipients underwent a fluid contrast sonography within 6 months prior to embryo transfer. All cycles were synchronized to the donors using GnRH-agonist down-regulation followed by fixed dose of 2 mg estradiol (Estrace; E2) two times daily (BID) and progesterone (P4) 50 mg intramuscularly BID ($n=34$; 43%), 200 mg suppository three times daily (TID) ($n=37$; 47%), or Crinone 8%

progesterone gel (Columbia Laboratories Inc., Livingston, NJ, USA) intravaginally BID ($n=8$; 10%) supplementation following the day of hCG.

Transvaginal ultrasound was performed to obtain endometrial thickness and echogenic pattern 10 to 11 days after initiation of E2 (late-follicular) in 79 cycles (59 pregnant cycles and 20 non-pregnant cycles) and on the day of embryo transfer (mid-luteal) in 68 cycles (54 pregnant cycles and 14 non-pregnant cycles) using a GE 3600-7 MHz vaginal transducer. Two separate measurements of maximal endometrial diameter in the longitudinal axis were taken by the same sonographer (SL) in the broadest anterior-to-posterior diameter, including a description of the echogenic pattern which was designated as a multilayered or a non-multilayered endometrium.

A multilayered endometrium appeared as a triple-line pattern in which the hyperechogenic outer lines and a well-defined central echogenic line were seen with hypoechogenic, or black, areas between these lines (Pattern 1). A non-multilayered endometrium appeared as a homogeneous endometrial pattern characterized by either an increased reflectivity compared with the myometrium (hyperechogenic endometrium) or the same reflectivity compared with the surrounding myometrium (isoechogenic endometrium) (Pattern 3). An intermediate endometrium appeared as an endometrial pattern that was transitioning into a non-multilayered appearance at the myometrial and endometrial interface, but still had some elements of a well-defined central echogenic line with hypoechogenic, or black, areas between these lines (Pattern 2) [19].

Two embryos were transferred transcervically 6 days post-retrieval and only those cycles with at least one fully expanded blastocyst were included in the study for evaluation. Pregnancy was confirmed by serial serum β -hCG 7 to 10 days following embryo transfer. Clinical pregnancies required ultrasound confirmation of a gestational sac.

Measured outcomes

The primary outcome measured was the endometrial thickness and echogenic pattern in the mid-luteal phase. The

secondary outcome was endometrial thickness and pattern in the late-follicular phase in pregnant and non-pregnant cycles. Endometrial thickness was further evaluated at threshold increments of 1 mm to evaluate its discriminatory ability for clinical pregnancy, multiple pregnancy, and miscarriage rates at both time points.

Furthermore, cycles were also assessed according to the ovum donors' stimulation characteristics including days of stimulation (DOS), total IU of rFSH used, serum estradiol on cycle day 5 and the day of hCG, number of M2 oocytes retrieved and the fertilization rates (FR).

Statistical analysis

Statistical analyses were performed using the SPSS statistical package. Chi-square and Student's t-test were used to assess differences between groups. Multiple logistic regression analysis was used to assess the relationship between variables, and receiver operator characteristics were used to evaluate the discriminatory ability of endometrial thickness. Significance was defined as a p -value < 0.05 .

As such, power calculations were performed using differences in endometrial thickness of 0.5 mm and 1.0 mm, respectively. While it would require 530 subjects and 134 subjects in each arm to achieve a power of 0.80 at an alpha of 0.05, we recognized it was not feasible for us accrue this sample size with the rigid inclusion criteria for our Program to perform. Nonetheless, we performed our review, aiming to provide data on these outcome measures which could be included in future analysis of this issue.

Results

There were 59 clinical pregnancies (59/79; 75% of embryo transfer). Endometrial thickness and pattern were similar in pregnant and non-pregnant cycles in both the follicular phase (9.5 ± 0.3 mm vs. 9.4 ± 0.5 mm; $p = \text{NS}$) and mid-luteal phase (10.5 ± 0.4 mm vs. 11.1 ± 0.9 mm; $p = \text{NS}$) (Table 1). In addition, the change (i.e., delta) from follicular to mid-luteal endometrial thickness was similar in both

Table 1 Endometrial thickness and pattern in pregnant and non-pregnant cycles

	Clinical pregnant cycles	Non-pregnant cycles	p-value
Endometrial Thickness (mm): Follicular Phase ($n=79$)	9.5 ± 0.3	9.4 ± 0.5	NS
Echogenic Pattern: Follicular Phase (A/A-B/B [%]) ($n=79$)	77/17/6	90/10/0	NS
Endometrial Thickness (mm): Luteal Phase ($n=68$)	10.5 ± 0.4	11.1 ± 0.9	NS
Echogenic Pattern: Luteal Phase (A/A-B/B [%]) ($n=68$)	7/22/71	6/13/81	NS
Delta from Follicular Phase to Luteal Phase Endometrial Thickness	+1.3 mm, -0.1 to 2.8 mm	+ 0.7 mm, -0.6 to 4.0 mm	NS

$\pm$ SEM

groups (+1.3 mm, -0.1 to 2.8 mm vs. 0.7 mm, -0.6 to 4.0 mm). There was no significant relationship between endometrial thickness and the age of the recipient ($p=0.2$), type of progesterone ($p=0.59$), and implantation rate ($p=0.42$) (data not shown). Follicular and luteal phase endometrial thickness at 1 mm increments demonstrated no differences in clinical pregnancy, number of sacs and miscarriage rates (Table 2). Moreover, pregnancy outcomes did not appear to be adversely affected by endometrial thickness <7 mm and >13 mm (Table 2).

There were no differences in pregnant and non-pregnant cycles with respect to donor, recipient, and male recipient demographics (Table 3), as well as donor stimulation characteristics (Table 4). Clinical pregnancy outcomes were similar in first time donor cycles (77%, 33/43) versus repeat donor cycles (72%, 26/36, $p=NS$).

To gain further insight into possible uterine and endometrial factors, evaluation of first time versus repeat cycles (i.e., those with previous failed cycles) that perhaps could impact outcomes was also assessed. No differences for first time versus repeat cycles in endometrial thickness in both the mid-follicular (9.5 ± 0.3 mm vs. 9.3 ± 0.4 mm, $p=NS$) and mid-luteal phase (11.0 ± 0.5 mm vs. 10.0 ± 0.4 mm, $p=NS$) and clinical pregnancy outcomes (76% versus 68%, $p=NS$) were noted.

Discussion

In spite of the technical advances that have continued to evolve in the area of assisted reproduction, overall pregnancy and implantation rates have remained relatively low. Significant research has been done to directly assess uterine receptivity, including histologic dating, immuno-histochemical methods for measurement of endometrial sex steroid receptor concentrations, scanning electron microscopy assessing

pinopod expression, and more recently, the role of cytokines, growth factors, and integrin molecules have been studied [20–24]. These methods are obviously not practical in actual ET cycles.

The measurement of endometrial thickness and its echogenic pattern, however, is an easy, non-invasive technique and has been used to assess endometrial receptivity prior to the embryo transfer. It is generally accepted that a thin endometrial stripe on transvaginal ultrasound is associated with a reduced embryo implantation potential [5, 9, 10], while others have reported an adverse effect of an increased endometrial thickness [2]. The echogenic pattern of the endometrium has also been suggested to be a predictor of pregnancy outcome [8, 25]. Conversely, other studies have shown sonographic assessment of the endometrium to be of no benefit in the characterization of uterine receptivity in IVF patients [12–15, 26]. Nonetheless, despite many reports, it is still undetermined whether endometrial thickness and pattern are prognostic factors of implantation.

The aim of this study was to examine possible relationships between endometrial thickness as a surrogate marker of endometrial receptivity on pregnancy rates, implantation rates, and multiple gestation rates in both the late follicular and mid-luteal phase and treatment outcome after oocyte donor IVF-ET cycles. Oocyte donation cycles provide a unique model to eliminate confounding variables that typically occur when comparing groups of patients undergoing autologous IVF where embryo quality and any possible adverse effects of ovarian hyperstimulation on endometrial receptivity cannot be controlled for [5, 7, 12]. Endometrial proliferation strongly correlates with ovarian estradiol production and therefore depends on ovarian function. Since age has an impact on ovarian function, embryo quality, estradiol production, endometrial thickness and pregnancy outcome often change in the same direction. Therefore, in autologous cycles poor endometrial develop-

Table 2 Clinical pregnancy rates, multiple pregnancy rates, and spontaneous abortion rates based on endometrial thickness

Endometrial thickness	# of cycles	Follicular phase clinical pregnancy (%)	Follicular phase multiple pregnancy (%)	Spontaneous abortion (%)	# of cycles	Luteal phase clinical pregnancy (%)	Luteal phase multiple pregnancy (%)	Spontaneous abortion (%)
<7 mm	7	5 (71%)	4 (80%)	0 (0%)	1	1 (100%)	0 (0%)	0 (0%)
7 to 7.9 mm	13	9 (69%)	4 (44%)	0 (0%)	7	5 (71%)	4 (80%)	0 (0%)
8 to 8.9 mm	17	13 (76%)	8 (62%)	3 (23%)	12	10 (83%)	8 (80%)	0 (0%)
9 to 9.9 mm	10	10 (100%)	5 (50%)	2 (20%)	12	10 (83%)	3 (30%)	2 (20%)
10 to 10.9 mm	14	10 (71%)	3 (30%)	0 (0%)	12	10 (83%)	6 (60%)	1 (10%)
11 to 11.9 mm	10	6 (60%)	3 (50%)	0 (0%)	9	7 (78%)	0 (0%)	0 (0%)
12 to 12.9 mm	5	4 (80%)	4 (100%)	0 (0%)	3	2 (66%)	1 (50%)	1 (50%)
>13 mm	3	2 (66%)	0 (0%)	1 (50%)	12	9 (75%)	6 (67%)	0 (0%)

Table 3 Baseline characteristics oocyte donors, recipients, and male recipient partner

	Clinical pregnant cycles (<i>n</i> =59)	Non-pregnant cycles (<i>n</i> =20)	p-value
Donor			
Age (years) of donor	26.6±0.5	26.7±1.1	NS
Day-3 FSH (mIU/mL)	5.3±0.3	5.3±0.7	NS
Recipient			
Age (years) of Recipient	39.8±0.8	40.2±2.3	NS
Age (years) of Male	40.3±0.8	40.1±1.3	NS
Uterine Pathology (%)	37	40	NS
Progesterone Type (IM/Suppository/Crinone [(%)]	48/42/10	30/60/10	NS
Sperm count (M/mL)	103.7±9.8	98.5±11	NS
% Motility	53.5±4.3	42.8±3.2	NS
# Sperm Donors (%)	13 (3)	17 (11)	NS

± SEM

ment could be the sign of poor ovarian function (reduced estradiol production) and therefore is not independently responsible for lower implantation and pregnancy rates. Using an oocyte donation model the endometrium can be built up by administering exogenous sex steroids and the dose can be increased and decreased based on response (measured by serum estradiol level or endometrial thickness); therefore, endometrial proliferation becomes independent of ovarian function. In addition, oocyte donors are typically young women with good ovarian reserve, thus embryos should characteristically be healthy with good implantation potential. Recent studies have shown that blastocyst stage embryo transfer is associated with higher implantation and pregnancy rates [27]. The explanation for this finding is twofold. First, by extending the culturing period, it is ensured that only the highest quality embryos with the lowest incidence of aneuploidy will make it to the blastocysts stage. Second, the transfer on day 5–6 after the egg retrieval is more physiologic for both the embryo and the uterus (window of implantation). Therefore, the oocyte donation model, using only blastocyst stage embryos, should give us the best opportunity to assess the effect of endometrial thickness and pattern on treatment outcome independent of other confounding variables.

Few studies have evaluated the association between endometrial thickness pattern and pregnancy outcome using an oocyte donation model. Noyes et al. retrospectively analyzed 343 oocyte recipient cycles, in which endometrial thickness and pattern was evaluated on cycle day 12. They found that clinical pregnancy rate and live birth rate were significantly lower when endometrial thickness was less than 8 mm than when endometrial thickness was greater than 9 mm [7]. Zenke and Chetkowski reported in 41 recipient pairs with discordant outcomes that endometrial thickness less than 8 mm one week prior to oocyte retrieval was found in failed cycles [5].

However, other studies support our findings. Remohi et al. performed a retrospective review of 465 oocyte donor cycles. They found that there was no correlation between ultrasound appearance of the endometrium the day before embryo transfer and pregnancy rates [28]. Garcia-Velasco performed a matched pair analysis of 365 recipients with discordant outcome and found that endometrial thickness measured on cycle day 15 or 16 was not a significant finding [12].

There are several possible explanations for these inconsistencies. Most studies assessed endometrial thickness and echogenicity on the day of or following hCG administration and on the day of oocyte retrieval, while other studies

Table 4 Stimulation and embryology parameters in oocyte donors and recipients

	Clinical pregnant cycles (<i>n</i> =59)	Non-pregnant cycles (<i>n</i> =20)	p-value
Starting Dose (IU)	257±8	232±25	NS
Total # IU per cycle	2699±158	2702±188	NS
DOS	11.5±0.2	11.5±0.3	NS
Peak E2 (pg/mL)	2528±241	2627±323	NS
# MII oocytes	24.2±1.2	18.3±1.8	NS
ICSI (%)	58	52	NS
TESE (%)	3 (<i>n</i> =2)	5 (<i>n</i> =1)	NS
FR (%)	72±2.5	74±2.8	NS

assessed the endometrium on the day of ET and even less on both the days of hCG administration and ET. Therefore, there remains inconsistency in the optimal timing of endometrial assessment.

To our knowledge, our study is the first one to assess endometrial thickness in oocyte donor cycles and pregnancy outcomes using blastocyst stage embryos only. While our study is limited due to its retrospective design, our results suggest that endometrial thickness in both the late-follicular and mid-luteal phase is not predictive of pregnancy outcomes. The previous reports evaluating the association between endometrial thickness and pregnancy outcome in oocyte donation cycles used either cleavage stage embryo transfer or a mixture of cleavage and blastocyst stage transfer; therefore, they did not maximally control the embryo factor. [5, 7, 12, 28–30]. Clearly our results should be interpreted with caution due to our small sample size.

Concerns of thin and thickened endometrial thickness [31] have also been raised. Our data suggest that thin endometrium (<7 mm) and thickened endometrium (>13 mm) and pattern are not useful indicators of adverse endometrial receptivity (i.e. clinical outcomes). Six of the seven cycles developed luteal phase endometrial thickness <7 mm at the time of ET, of which 67%, 4/6 became pregnant (no miscarriages). Nine cycles went on to develop luteal phase endometrium >13 mm, of which 78%, 7/9 became pregnant (no miscarriages).

What we gleaned most from this study is the need of uniform agreement by investigators to assess endometrial thickness and pattern in a more rigorous and standardized fashion to gain further insight into their relative importance. As a result of these inconsistencies, many of the previous reports in the literature may have had results impacted by these confounding variables. Nonetheless, our results must be taken with caution and larger and well controlled studies should confirm these findings.

Conclusions

In conclusion, our data suggest that endometrial thickness and pattern do not correlate with clinical pregnancy rates in donor egg cycles. This study adds to the growing body of research showing that in donor egg cycles endometrial thickness may not be as helpful in predicting success as previously thought. Based on this data, thin or thickened endometrium should not discourage couples from undergoing an ET in oocyte donor cycles. Further larger studies should confirm the present observations.

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