ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Endometrial pattern, but not endometrial thickness, affects implantation rates in euploid embryo transfers

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Objective: To evaluate the relationship of endometrial thickness (EnT) and endometrial pattern (EnP) to euploid embryo transfer (ET) outcomes.
Design: Retrospective cohort.
Setting: Private academic clinic.
Patient(s): Patients (n = 277; age 36.1 ± 4.0 years) whose embryos (n = 476) underwent aneuploidy screening with fresh (n = 176) or frozen (n = 180) ET from July 2010 to March 2014.
Intervention(s): The EnT and EnP were measured on trigger day and at ET. Patients were stratified by age and cycle type (fresh or frozen). Cycle data were combined at trigger day, but separated at ET day.
Main Outcome Measure(s): Outcome measures were implantation rate, pregnancy rate, and clinical pregnancy rate. Analysis was conducted using χ^2 analysis and Fisher's exact test.
Result(s): A total of 234 gestational sacs, 251 pregnancies, and 202 clinical pregnancies resulted from 356 cycles. The EnT (9.6 ± 1.8 mm; range: 5–15 mm) at trigger day (n = 241 cycles), as a continuous or categorical variable (≤8 vs. >8 mm), was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate. The EnT at day of fresh ET (9.7 ± 2.2 mm; range: 4.4–17.9 mm) (n = 176 cycles) or frozen ET (9.1 ± 2.1 mm; range: 4.2–17.7 mm) (n = 180 cycles) was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate. Type 3 EnP at trigger day was associated with increased serum progesterone at trigger and a decreased implantation rate, compared with type 2 EnP. The EnP at fresh or frozen ET was not associated with implantation rate, pregnancy rate, or clinical pregnancy rate.
Conclusion(s): Within the study population, EnT was not significantly associated with clinical outcomes of euploid ETs. A type 3 EnP at trigger day suggests a prematurely closed window of implantation. (Fertil Steril® 2015;■: ■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Endometrial thickness, endometrial pattern, implantation rate, pregnancy rate, preimplantation genetic screening

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The identification of the optimal conditions for controlled ovarian hyperstimulation (COH) and embryo transfer (ET) is of substantial clinical interest. Improved clinical outcomes have been demonstrated with: particular stimulation protocols (1, 2); embryo handling and culture conditions (3); technical factors, such as use of the transfer catheter and embryo placement during ET (4–9); and embryo selection techniques (10, 11). However, identification of clinical markers of endometrial receptivity for optimization during COH remains a challenge.

During a natural menstrual cycle, and one in the context of COH, the endometrium develops and matures within a complex hormonal environment, proliferating and thickening

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under the influence of estrogens (Es), and decidualizing under the influence of progestins (12–19). Despite recent advances in molecular assays (20–23), ultrasound assessment is the only noninvasive tool in standard clinical use for assessing the endometrium. Endometrial thickness (EnT) directly reflects histologic thickness, whereas endometrial pattern (EnP) changes in lockstep with the menstrual cycle, correlating closely with morphologic assessment of endometrial biopsies (24, 25). Although endometrial histology has long been recognized to inform the optimal window of implantation (26), the influence of EnT and EnP on endometrial receptivity and pregnancy rates has been intensively explored but not conclusively determined (27, 28).

Ultrasound measurements of endometrium at the day of ovulatory trigger (the earliest point of completed follicular development of oocytes) and at ET day (the first interaction between embryo(s) and the uterine environment) may provide a window into the developing egg and the implantation environment. Studies thus far, focusing on the effect of EnT on embryo implantation and receptivity, have yielded conflicting findings. Some have shown that increased EnT on human chorionic gonadotropin (hCG) trigger day are correlated with improved pregnancy outcomes for patients undergoing in vitro fertilization (IVF) (29–34). An EnT of <6–7 mm (35–37), or >10–14 mm (37, 38), on hCG trigger day, has been reported to adversely affect implantation rate. Similar findings were noted in ovum donation cycles in recipients with an EnT of <8 mm on the day of ET (39).

Other studies have documented no association between implantation rates and EnT at trigger or ET day (40–48). Given reports of successful pregnancy with an EnT of <4 mm (49), a thick endometrium is certainly not a prerequisite for pregnancy. One study found a positive correlation between EnT and pregnancy rates in intrauterine insemination but not IVF cycles (50), although this finding has been challenged (51). Recipient EnT at ET day in ovum donation cycles was not predictive of pregnancy outcomes (52).

Several interventions have been developed and employed clinically to increase EnT as a means of improving endometrial receptivity, primarily by promoting E-dependent endometrial proliferation (53, 54). However, given the conflicting studies mentioned, the question remains of whether EnT is a parameter that should be considered for clinical optimization. A recent survey found that 30% of clinicians would defer ET if EnT were ≤6 mm; the percentages were smaller as EnT increased (55).

The EnP reflects the anatomical changes associated with the menstrual cycle after progestin exposure and can be used to track the pre- and peri-implantation uterine environment (19, 56). One possibility is that an optimized EnP will lead to improved reproductive outcomes. However, lack of consensus persists on the predictive power of EnP on reproductive outcomes. A triple-line EnP on ultrasound after ovarian stimulation before or on trigger day has been associated with improved pregnancy rates vs. a homogeneous, hyperechogenic, or intermediate EnP (57–60). Others have failed to observe this association (61), or have confirmed it only in a subset of patients with an EnT of 7–14 mm (36, 62). Some have highlighted the importance of a homogeneous, hyperechogenic endometrium at ET day for achieving implantation (63); others have observed a triple-line pattern more frequently (64).

In all the aforementioned studies, morphology before ET was used for embryo selection. However, morphologic embryo selection alone carries potential limitations (65, 66). The lack of preimplantation genetic assessment of embryos, a major source of variability in implantation across patients (67), limits the generalizability of findings from previous studies on the role of both EnT and EnP.

With the use of preimplantation genetic screening to detect aneuploid embryos (10, 11), a more standardized and systematic analysis of the role of sonographic endometrial measurements on implantation can be performed. This study sought to evaluate the impact of EnT and EnP, as measured on trigger and ET day, in patients undergoing IVF, on cycle implantation rate and pregnancy rate, after controlling for oocyte age and cycle type.

MATERIALS AND METHODS

Patient Population

A single-center retrospective cohort study was performed on patients whose embryos underwent tuberculosis and preimplantation genetic screening, via comprehensive 24-chromosome screening during IVF cycles between July 2010 and March 2014. Aneuploidy screening was offered during routine infertility care. Patient age at the initiation of the assisted reproductive technology (ART) cycle producing the euploid embryo was recorded as a categorical variable (A: age <35 years; B: age 35–38 years; C: age 38–41 years; D: age 41–43 years; and E: age >43 years).

Treatment Protocol

In vitro fertilization stimulation cycles and hormonal adjustments were performed according to standard clinical practice (68). All cycles were autologous. Patients were treated with 1 of 3 protocols, determined by clinician preference. The antagonist protocol used ganirelix acetate (Antagon; Organon) or cetrorelix acetate (Cetrotide, EMD Serono). The down-regulation protocol and the microflare protocol used leuprolide acetate (Lupron, AbbVie Inc) (Supplemental Table 1, available online). In general, antagonist protocols were used in potential hyper-responders, microflare protocols in poor responders, and down-regulation or antagonist protocols in the remaining patients.

Final oocyte maturation (henceforth referred to as "trigger") was induced with 6,500 IU of recombinant hCG alone (Ovidrel, EMD Serono), after confirmation of ≥2 mature follicles of ≥18 mm, using ultrasound. In patients with a strong ovarian response, or at risk for ovarian hyperstimulation syndrome (OHSS), who were undergoing an antagonist protocol, induction was with 40 IU of leuprolide acetate together with 1,000 IU of hCG (Novarel, Ferring Pharmaceuticals). Vaginal oocyte retrieval was performed under transvaginal ultrasound guidance 36 hours later.