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ORIGINAL ARTICLE *Infertility*

Endometrial thickness measurements among Asherman syndrome patients prior to embryo transfer

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STUDY QUESTION: Is there an association between endometrial thickness (EMT) measurement and clinical pregnancy rate among Asherman syndrome (AS) patients utilizing IVF and embryo transfer (ET)?

SUMMARY ANSWER: EMT measurements may not be associated with successful clinical pregnancy among AS patients undergoing IVF.

WHAT IS KNOWN ALREADY: Clinical pregnancy rate after IVF is significantly lower in patients with a thin endometrium, defined as a maximum EMT of <7 mm. However, AS patients often have a thin EMT measurement due to intrauterine scarring, with a paucity of data and no guidance on what EMT cutoff is appropriate when planning an ET among these patients.

STUDY DESIGN, SIZE, DURATION: This is a retrospective cohort study of 45 AS patients treated at a specialized advanced hysteroscopic clinic from 1 January 2015, to 1 March 2019.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Review of EMT measurements prior to a total of 90 ETs, among 45 AS patients. The impact of the maximum EMT measurement prior to ET on clinical pregnancy rate was analyzed.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 25/45 (55.6%) AS patients ultimately went on to have ≥1 clinical pregnancy following a mean ± SD of 2.00 ± 1.26 ET attempts. There was a total of 90 ETs among the 45 AS patients, with 29/90 (32.2%) ETs resulting in a clinical pregnancy. Younger patient age ($P = 0.05$) and oocyte donation ($P = 0.01$) were the only variables identified to be significant predictors for a positive clinical pregnancy outcome on bivariate analysis. The mean EMT measurement prior to all ETs among AS patients was 7.5 ± 1.6 mm. EMT measurement prior to ET did not predict a positive clinical pregnancy on either bivariate ($P = 0.84$) or multivariable analysis (odds ratio 0.91, $P = 0.60$). 31.8% of EMT measurements measured <7.0 mm. In this small cohort, no difference in the clinical pregnancy rate was detected when comparing ETs with EMT measurements of <7.0 mm versus ≥7.0 mm ($P = 0.83$). The mean EMT measurement decreased with increasing AS disease severity; 8.0 ± 1.6 mm for mild disease, 7.0 ± 1.4 mm for moderate disease and 5.4 ± 0.1 mm for severe disease.

LIMITATIONS, REASONS FOR CAUTION: Our small sample size limits our ability to draw any definitive conclusions. In addition, patients utilized various infertility clinics. This limits our ability to evaluate the consistency of EMT measurements and the IVF care that was received.

WIDER IMPLICATIONS OF THE FINDINGS: EMT measurement cutoff values should be used with caution if canceling a scheduled ET in AS patients.

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Introduction

The effort to identify a preferential endometrial state for the timing of embryo transfer (ET) by means of the endometrial thickness (EMT) measurement has been ongoing for nearly four decades (Glissant *et al.*, 1985). Despite this continued research focus, conflicting findings have made it unclear if there is a undisputable association between the EMT measurement and pregnancy rates following IVF (El-Toukhy *et al.*, 2008; Mercé *et al.*, 2008; Liu *et al.*, 2018; Craciunas *et al.*, 2019; Nishihara *et al.*, 2020).

In 2014, Kasius *et al.* (2014) published a systematic review evaluating the impact of ET on the clinical pregnancy rate in IVF. The authors concluded that the clinical pregnancy rate after IVF was significantly lower in patients with a thin endometrium (odds ratio (OR) 0.42; 95% CI 0.27–0.67), when 'thin endometrium' was defined as a maximum EMT of <7.0 mm. However, they cautioned that only 2.4% of all their reported cases had a thin endometrium. In today's practice of IVF, clinicians often cancel ET when it is felt that endometrium is too thin. In one reported series, the rate of ET cancelation was up to 17.4% when an EMT measurement was documented as <8.0 mm (Corroenne *et al.*, 2020). It should be noted, however, that many studies exclude patients with intrauterine pathology, such as intrauterine adhesions (Asherman syndrome, AS). Providers have since been left to extrapolate this data when caring for AS patients pursuing IVF-ET, despite this cohort being left out from the meta-analysis and the knowledge that AS patients often have a thin endometrial lining due to the nature of the disease (Baradwan *et al.*, 2018).

AS is defined as the presence of hysteroscopically confirmed intrauterine adhesions contributing to either pain, dysmenorrhea, menstrual irregularity or subfertility (Khan and Goldberg, 2018). AS can occur following any traumatic insult to the endometrial basalis layer of the uterine lining leading to endometrial fibrosis. In this state, previously normal, hormonally-responsive endometrial tissue is replaced with atrophic, avascular, hormonally unresponsive, fibrotic scar tissue that is often referred to as intrauterine adhesions or synechiae (Deans and Abbott, 2010). Histologic samples of AS patients demonstrate that there is a replacement of normal proliferative endometrium with inactive cubocolumnar epithelium within the connective muscular tissue of the intrauterine adhesions (Deans and Abbott, 2010). Additionally, proliferative or secretory endometrium can be found in the adjacent and surrounding endometrium that is not afflicted by adhesions (Foix *et al.*, 1966). AS patients thus have this heterogeneous endometrial composition with inactive endometrium contained by adhesions that is adjacent to otherwise healthy endometrium. The inactive endometrium does not grow in response to estrogen and thus the endometrial bilayer appears thin on sonographic EMT measurements. Increasing AS disease severity has been associated with thinner EMT measurements (Baradwan *et al.*, 2018). This is in contrast to patients who have thin EMT measurements without intrauterine adhesions, which are instead due to a homogenous endometrial composition afflicted by endometrial atrophy (Ferrazzi *et al.*, 1996; Van den Bosch *et al.*, 2020). The thin EMT measurements among AS patients may lead to ET cancelations and delayed pregnancy given clinician concerns for a lowered implantation success rate with thin EMT measurements.

Nevertheless, serial hysteroscopic lysis of adhesions (LOA) have been associated with conception rates ranging from 48% to 79% (Chen *et al.*, 2017, 2020; Deans *et al.*, 2018). Such outcomes among AS patients supports the notion that only a certain portion of healthy endometrial tissue is required for implantation. As such, should EMT measurement prior to ET be examined in AS patients at all?

Our primary objective was to determine if there is an association between EMT measurements of AS patients undergoing IVF and clinical pregnancy rates. Our secondary objective was to determine the proportion of AS patients undergoing IVF that had a thin terminal EMT measurement (<7.0 mm) prior to fresh or frozen ET.

Materials and methods

Study population

Our study included all patients who underwent a hysteroscopy with adhesiolysis who subsequently attempted conception with the assistance of IVF. Patients were identified through our institution's electronic medical records via the Research Patient Data Registry (RPDR) using the diagnosis code for AS, N85.6: Intrauterine synechiae (2018 International Classification of Diseases (ICD)-10-CM Diagnosis Code), the procedure code for hysteroscopic with lysis of intrauterine adhesions, Current Procedural Terminology (CPT) Code: 58559, followed by a review of their hospital records to identify the patients who attempted conception with the use of IVF. Procedures were performed at the Center for Minimally Invasive Gynecologic Surgery at Newton Wellesley Hospital from 1 January 2015, to 1 March 2019, by one of the three gynecologic surgeons within the practice. This study was approved by the Institutional Review Board at Newton Wellesley Hospital via the Partners Human Research Committee (PHRC), the Institutional Review Board (IRB) of Partners HealthCare: Protocol # 2018P002095, obtained on 19 February 2019.

We identified 45 patients who had undergone hysteroscopic LOA in our clinic and subsequently attempted conception via IVF-ET. All patients were contacted via telephone and invited to complete a scripted survey. Verbal consent for participation was obtained. Patients were surveyed on their attempts at conception since their last hysteroscopic treatment, their IVF treatments, and obstetrical outcomes. From this cohort, 25 patients had all of their care within our institutions hospital system, with IVF and prenatal/obstetrical records easily accessible within our electronic healthcare records. The other 20 patients had their IVF and/or their prenatal/obstetrical care at an outside institution following their hysteroscopic surgeries at our hospital. For these patients, we first obtained a signed release of medical records consent form and subsequently obtained all their IVF treatment notes, pelvic ultrasound reports, prenatal care, and obstetrical care notes from all outside institutions they reported receiving care from following treatment at our hospital. All data were stored within a secure electronic database, *REDCap* (Research Electronic Data Capture).

Medical records were used to document baseline patient demographics that included age, obstetrical history, gynecologic history, medical history, surgical history, hysteroscopic findings, total hysteroscopic procedures completed and total ETs attempted. All IVF notes were utilized to collect information regarding the IVF-ET cycles for each patient. We assessed the utilization of oocyte donation, intracytoplasmic sperm injection, and preimplantation genetic screening and results. We documented embryo type (fresh vs frozen), embryo age

prior to ET (Day 3 or Day 5), and the total number of embryo's transferred. We also documented the maximum serum estradiol level and the maximum EMT measurement taken during the cycle prior to ET. An EMT measurement is ideally obtained with a transvaginal ultrasound probe placed perpendicular to the uterine midline and measuring in the sagittal plane. The EMT measurement should focus on the endometrial area that appears to be the thickest with the calipers placed at opposite points of the anterior and posterior endometrial-myometrial interfaces calculating the total double-layer thickness in millimeters (Leone et al., 2010).

Surgical management

All AS patients presenting to care at our institution underwent both a transvaginal three-dimensional ultrasound and an office hysteroscopy during their initial patient encounter as described in our previous publication on AS management (Santamaria et al., 2020). Intrauterine adhesions were lysed using 5 mm rigid hysteroscope with a 12-degree viewing angle, utilizing the 5-French cold scissors alone until a normal uterine cavity was restored. All intraoperative findings were documented. The severity of patient's AS were documented using the March classification system (March et al., 1978). The categories utilized in this classification system include; mild disease if <25% cavity involved with intrauterine adhesions, moderate disease if 25–75% cavity involved with intrauterine adhesions without ostia involvement, and severe disease if >75% cavity involved with intrauterine adhesions with upper cavity occlusion and ostia involvement.

Postoperatively, patients took oral estradiol 2 mg twice daily for 30 days, and for the last five days, medroxyprogesterone acetate 10 mg daily was added to induce a withdrawal bleed. Patients were seen 2–3 weeks postoperatively and again at 6 weeks postoperatively for repeat office hysteroscopy and further LOA if warranted. If patients demonstrated cervical canal adhesions, they underwent serial cervical canal probing with a Pipelle endometrial biopsy at 2-week intervals for a total of 6 weeks to prevent adhesion reformation within the canal.

Obstetrical outcomes

Obstetrical outcomes were documented for 90 IVF-ET events. 'No implantation' was defined as a negative serum beta human chorionic gonadotropin (beta-hCG) test following ET. 'Biochemical Pregnancy' was defined as a positive beta-hCG following ET without progression to a clinical pregnancy. A 'Clinical Pregnancy' was defined as the presence of a fetal pole with positive fetal cardiac motion documented on pelvic ultrasound. A 'Miscarriage' was defined as any spontaneous loss of a clinical pregnancy <24 weeks of gestation. A 'Termination' was defined as any medical or surgical approach to end a clinical pregnancy. An 'Ectopic Pregnancy' was defined as any pregnancy located outside of the endometrium treated either medically or surgically. A 'Preterm Birth' was defined as any live birth ≥24 weeks of gestation but <37 weeks of gestation. A 'Fullterm Birth' was defined as any live birth ≥37 weeks of gestation. Any patient actively pregnant at the time of our final analysis was documented as 'Currently Pregnant'.

Placenta accreta spectrum (PAS) cases, formerly known as morbidly adherent placentas, were identified based on clinical documentation and histologic reports for all clinical pregnancies that were carried out beyond viability (24-week gestational age). Placenta accreta spectrum is defined as pathologically adherent placenta and includes placenta accreta, increta and percreta. Placenta accreta was defined as any case where the placental chorionic villi attached to the myometrium. Placenta increta was defined as chorionic villi invading into the myometrium. Placenta percreta defined as chorionic villi invading beyond the entirety of the myometrium (Belfort, 2010).

Statistical methods

Descriptive statistics were used to summarize the association between baseline patient characteristics and ET information with the outcome of clinical pregnancy. We utilized Student's *t*-tests for continuous variables and the Pearson χ^2 test for categorical variables. Baseline characteristics were presented as the mean ± SD or as a percentage. *P*-values were two-tailed and considered statistically significant if <0.05.

Multivariable logistic regression analyses were performed to examine if the EMT measurement was an independent indicator of clinical pregnancy after controlling for variables that were identified with significant differences via bivariate analysis. All analysis was performed using STATA IC (Version 15.1.629).

Results

Of the 45 AS patients we identified for our study, 25 (55.6%) ultimately went on to have at least one clinical pregnancy with use of IVF-ET (Table I). Patient age was the only characteristic determined to be significantly different between patients with and without a clinical pregnancy via bivariate analysis, 35.56 ± 4.49 years old versus 37.95 ± 3.35 years old, respectively ($P = 0.05$) There were no significant differences identified between these two groups based on March classification, hysteroscopic findings, obstetrical history or gynecologic history. The mean total number of ET attempts within this cohort was 2.00 ± 1.26, with no significant difference between the two groups.

There was a total of 90 ET's completed for the 45 AS patients. Of these, 29 ET's resulted in a clinical pregnancy (32.2%) (Table II). The mean time from the patients last hysteroscopic LOA's at our hospital to the date of ET was 216.58 ± 216.81 days, roughly 7.2 months, with no significant difference between the ET's that did and did not result in a clinical pregnancy. Oocyte donation was the only characteristic that was identified to be significant predictor for clinical pregnancy, with five out of six (83.3%) ET's utilizing an oocyte donation resulting in a clinical pregnancy ($P = 0.01$). There was no statistical difference between these two groups regarding utilization of intracytoplasmic sperm injection, embryo type (fresh vs frozen), use of preimplantation genetic screening, embryo age prior to ET (Day 3 vs Day 5), total number of embryo's transferred, or maximum serum estradiol level. Preimplantation genetic screening was utilized in 20 (22.2%) of all ET's, with all euploid embryo's identified with the exception of one embryo that was noted to have a mosaicism detected (57% mosaicism for segmental gain on chromosome 1, p36.33-q21.2) that resulted in no implantation or clinical pregnancy following ET. The outcome of one ET was listed as 'Currently Pregnant' as the pregnancy was at 22 weeks 5 days gestational age at time of final data analysis.

A total of 85 of the 90 (94.4%) ET's utilized pelvic ultrasound to document the maximum EMT measurement prior to ET. Of the five ET's that did not measure EMT (5.6%) prior to ET, two resulted in a

Table I Patient demographics—initial encounter.

	All Asherman patients	No clinical pregnancy	Clinical pregnancy	*P*-value
n	45	20 (44.4%)	25 (55.6%)	x
Age	36.6 ± 4.16	37.95 ± 3.35	35.56 ± 4.49	**0.05***
Gravida	1.69 ± 1.14	1.75 ± 1.37	1.64 ± 0.95	0.76
Para	0.47 ± 0.54	0.60 ± 0.60	0.36 ± 0.49	0.16
Asherman syndrome				
March classification—initial encounter				
Mild	25	11 (44.0%)	14 (56.0%)	0.53
Moderate	19	8 (42.1%)	11 (57.9%)	
Severe	1	1 (100.0%)	0 (0.0%)	
% Cavity with adhesions (first visit)	28.22 ± 19.60	31.00 ± 22.33	26.00 ± 17.26	0.42
% Cavity with adhesions (last visit)	11.0 ± 9.69	11.50 ± 10.40	10.60 ± 9.28	0.76
# Hysteroscopic lysis of adhesion procedures	2.47 ± 1.29	2.35 ± 1.27	2.56 ± 1.33	0.59
Presumed etiology of Asherman syndrome				
D&C/D&E—early pregnancy	20	6 (30.0%)	14 (70.0%)	0.67
D&C/D&E—postpartum	7	4 (57.1%)	3 (42.9%)	
Cesarean section	6	3 (50.0%)	3 (50.0%)	
Abdominal myomectomy	5	3 (60.0%)	2 (40.0%)	
Operative hysteroscopy	5	3 (60.0%)	2 (40.0%)	
Unclear	2	1 (50.0%)	1 (50.0%)	
Gynecologic history				
Endometriosis	5	3 (60.0%)	2 (40.0%)	0.46
Adenomyosis	5	3 (60.0%)	2 (40.0%)	0.46
Fibroid uterus	9	4 (44.4%)	5 (55.6%)	1.00
Endometrial polyps	1	1 (100.0%)	0 (0.0%)	0.26
Polycystic ovarian syndrome	5	2 (40.0%)	3 (60.0%)	0.83
Recurrent pregnancy loss	4	2 (50.0%)	2 (50.0%)	0.82
Male factor infertility	5	1 (20.0%)	4 (80.0%)	0.24
Tubal factor infertility	4	3 (75.0%)	1 (25.0%)	0.20
Diminished ovarian reserve	4	2 (50.0%)	2 (50.0%)	0.82
Embryo transfer information				
# of embryo's transfer attempts—mean	2.00 ± 1.26	2.10 ± 1.25	1.92 ± 1.29	0.64

*$P = 0.047$.
Values are mean ± SD or sample size (%).
Bold values denote statistical significance at the $P < 0.05$ level.
D&C/D&E, dilation & curettage/dilation & evacuation.

clinical pregnancy, while three resulted in no clinical pregnancy. There was no difference in the maximum EMT measurement among the ET's that did and did not result into a clinical pregnancy, with a mean EMT measurement of 7.5 ± 1.9 mm versus 7.6 ± 1.4 mm, respectively ($P = 0.84$).

Multivariable analysis was utilized to evaluate the association between EMT measurement and clinical pregnancy outcome after controlling for patient age and utilization of oocyte donation as these were determined to significantly impact the outcome of clinical pregnancy (Table III). ET's that did not have a documented EMT measurement were excluded from this analysis (n = 5). We again identified no association between EMT measurement and clinical pregnancy outcome even after adjusting for these patient characteristics (OR 0.91, $P = 0.60$).

The mean EMT measurement for all ET's was 7.5 ± 1.6 mm (Fig. 1) with 27 of the 85 (31.8%) EMT measurements captured meeting criteria to be labeled as a thin EMT measurement based on the previous mentioned definition of <7.0 mm. There was no difference in the clinical pregnancy rate when comparing ET's that had an EMT measurement of <7.0 mm versus ≥7.0 mm with a 33.3% versus 31.0%, respectively ($P = 0.83$) (Table IV). The mean patient age of those who had an EMT measurement of <7.0 mm versus ≥7.0 mm were also found not to be significantly different at 36.11 ± 4.77 years old versus 36.89 ± 3.66 years old, respectively ($P = 0.42$) (Table IV). The mean

Table II Embryo transfers.

	All Embryo transfers	No clinical pregnancy	Clinical pregnancy	*P*-value
# of embryo transfers	90	61 (67.8%)	29 (32.2%)	x
Last hysteroscopy date to embryo transfer day date (days)	216.58 ± 216.81	212.50 ± 214.48	225.14 ± 225.23	0.80
Oocyte donation				
Utilized	6	1 (16.7%)	5 (83.3%)	**0.01**
Not utilized	84	60 (71.4%)	24 (28.6%)	
Intracytoplasmic sperm injection				
Utilized	32	21 (65.6%)	11 (34.4%)	0.75
Not utilized	58	40 (69.0%)	18 (31.0%)	
Embryo type				
Fresh embryo	28	20 (71.4%)	8 (28.6%)	0.58
Frozen embryo	62	41 (66.1%)	21 (33.9%)	
Preimplantation genetic screening				
Utilized	20	12 (60.0%)	8 (40.0%)	0.40
Not utilized	70	49 (70.0%)	21 (30.0%)	
Embryo quality				
Confirmed euploid embryo utilized	19	11 (57.9%)	8 (42.1%)	0.48
Confirmed aneuploid embryo utilized	1	1 (100.0%)	0 (0.0%)	
Embryo age on transfer day				
Day 3 embryo transfer	16	13 (81.2%)	3 (18.8%)	0.20
Day 5 embryo transfer	74	48 (64.9%)	26 (35.1%)	
Number of embryo's transferred				
1 embryo	58	39 (67.2%)	19 (32.8%)	0.79
2 embryo's	31	21 (67.7%)	10 (32.3%)	
>2 embryo's	1	1 (100.0%)	0 (0.0%)	
Estradiol, serum				
Estradiol, max (pg/ml)	1248.06 ± 1157.50	1033.77 ± 881.42	1719.50 ± 1531.01	0.07
Pelvic ultrasound—endometrial thickness measured				
Measured	85	58 (68.2%)	27 (31.8%)	0.70
Not measured	5	3 (60.0%)	2 (40.0%)	
Endometrial thickness measurement				
Endometrial thickness (mm)	7.5 ± 1.6	7.6 ± 1.4	7.5 ± 1.9	0.84

Values are mean ± SD or sample size (%).
Bold values denote statistical significance at the $P < 0.05$ level.

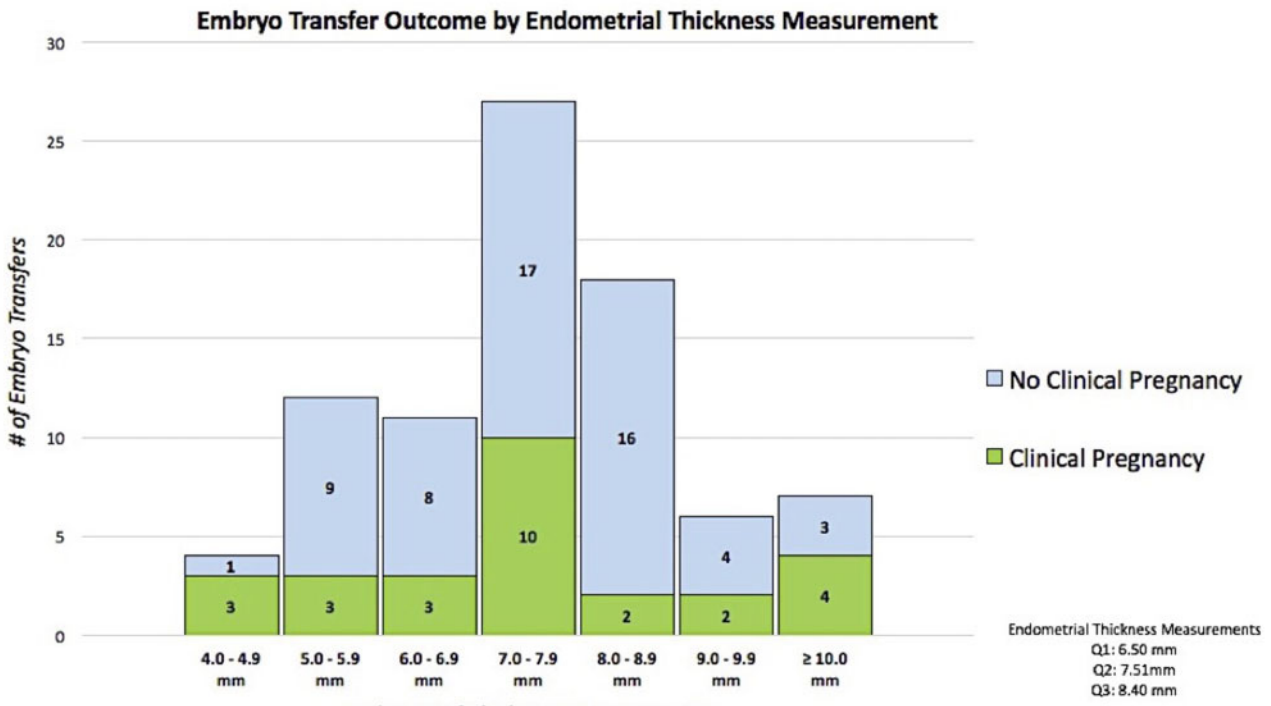
Table III Multivariable logistic regression analysis of endometrial thickness, age, oocyte donation.

Clinical pregnancy	Odds ratio	95% CI	*P*-value
Endometrial thickness	0.91	0.65–1.28	0.60
Age	0.87	0.76–1.00	0.05*
Oocyte donation[a]	x	X	x

Excluded transfers with no endometrial thickness measurement (n = 5).
[a]Oocyte donation predicts clinical pregnancy success perfectly.
*$P = 0.052$.

EMT measurement decreased with increasing AS disease severity. The mean EMT measurement prior to ET was 8.0 ± 1.6 mm for mild AS, 7.0 ± 1.4 mm for moderate AS and 5.4 ± 0.1 for severe AS (Supplementary Table SI).

Given our small sample size and the highly predicative nature of oocyte donation on clinical pregnancy rates, we performed a sub-analysis of our data excluding the use of oocyte donation to see if there were any changes in our original findings. In this sub-analysis, we excluded four patients that utilized oocyte donations, equating to six ETs that utilized oocyte donations. We identified no difference in the patient characteristics associated with clinical pregnancy from our original analysis (Supplementary Table SII), with younger patient age remaining



Endometrial Thickness Measurement	4.0 - 4.9 mm	5.0 - 5.9 mm	6.0 - 6.9 mm	7.0 - 7.9 mm	8.0 - 8.9 mm	9.0 - 9.9 mm	≥ 10.0 mm	EMT Not Measured	All Embryo Transfers
# Embryo Transfers	4	12	11	27	18	6	7	5	90
No Clinical Pregnancy	1 (25.0%)	9 (75.0%)	8 (72.7%)	17 (63.0%)	16 (88.9%)	4 (66.7%)	3 (42.9%)	3 (60%)	61 (67.8%)
Clinical Pregnancy	3 (75.0%)	3 (25.0%)	3 (27.3%)	10 (37.0%)	2 (11.1%)	2 (33.3%)	4 (57.1%)	2 (40.0%)	29 (32.2%)
No Implantation	1 (25.0%)	7 (58.3%)	5 (45.5%)	16 (59.3%)	11 (61.1%)	2 (33.3%)	1 (14.3%)	1 (20.0%)	44 (48.9%)
Biochemical Pregnancy	0 (0.0%)	2 (16.7%)	3 (27.3%)	1 (3.7%)	5 (27.8%)	2 (33.3%)	1 (14.3%)	2 (40.0%)	16 (17.8%)
Ectopic Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (1.1%)
Miscarriage	1 (25.0%)	1 (8.3%)	1 (9.1%)	2 (7.4%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	6 (6.7%)
Preterm Births (< 37 weeks)	1 (25.0%)	2 (16.7%)	1 (9.1%)	3 (11.1%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	9 (10.0%)
Term Birth (≥ 37 week)	1 (25.0%)	0 (0.0%)	1 (9.1%)	5 (18.5%)	2 (11.1%)	1 (16.7%)	1 (14.3%)	2 (40.0%)	13 (14.4%)
Currently Pregnant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (1.1%)

Figure 1. Embryo transfer outcome by endometrial thickness measurement. Histogram distribution of maximum endometrial thickness measurements documented for patients with Asherman syndrome utilizing IVF prior to embryo transfer, stratified by clinical pregnancy outcome. Beneath the histogram are tabulations denoting the total number of embryo transfers completed as well as the clinical pregnancy rate for Asherman syndrome patients when stratified by their maximum endometrial thickness measurement prior to embryo transfer. Detailed tabulation regarding the specific pregnancy outcomes for all embryo transfers based on this stratification system is additionally listed below.

Table IV Embryo transfer outcome for thin versus normal endometrial thickness measurements.

Endometrial thickness measurement	All Embryo transfers	No clinical pregnancy	Clinical pregnancy	*P*-value
<7.0 mm[A]	27	18 (66.7%)	9 (33.3%)	0.83
≥7.0 mm[B]	58	40 (69.0%)	18 (31.0%)	

Excluded transfers with no endometrial thickness measurement (n = 5 embryo transfers).
Values are mean ± SD or sample size (%).
[A]Mean patient age: all embryo transfers 36.11 ± 4.77 years old, no clinical pregnancy 35.44 ± 4.57 years old, clinical pregnancy 37.44 ± 5.17 years old.
[B]Mean patient age: all embryo transfers 36.89 ± 3.66 years old, no clinical pregnancy 37.30 ± 2.90 years old, clinical pregnancy 35.94 ± 4.94 years old.

Table V Endometrial thickness measurements of viable pregnancies (>24-week gestational age) by presence/absence of placenta accreta spectrum.

Placenta accreta spectrum	n	Endometrial thickness measurement (mm)	*P*-value
Present	6	7.5 ± 1.7	0.97
Absent*	14	7.4 ± 1.9	

*Endometrial thickness not measured in two cases of viable pregnancies both were absent of any placenta accreta spectrum.
Values are mean ± SD.

the only predictor of a positive clinical pregnancy ($P = 0.01$). We also confirmed that there was still no difference in the clinical pregnancy rate when comparing ET's that had an EMT measurement of <7.0 mm versus ≥7.0 mm, ($P = 0.21$) (Supplementary Table SIII). The mean patient age of those who had an EMT measurement of <7.0 mm versus ≥7.0 mm were also found not to be significantly different at 35.73 ± 4.43 years old versus 36.44 ± 3.29 years old, respectively ($P = 0.42$) (Supplementary Table SIII).

We investigated the rate of placenta accreta spectrum (PAS) for the AS patients who continued with a clinical pregnancy beyond viability (24-week gestational age). In total, 22 of the 29 clinical pregnancies were carried on beyond viability. There was a total of 6/22 (27.3%) cases of placenta accreta spectrum (four cases of placenta accreta and two cases of placenta percreta) within this group. Cesarean hysterectomy was required in 4/6 (66.7%) of the PAS cases, with two cases of placenta accreta managed without hysterectomy. We identified no association between EMT measurement prior to ET with the presence or absence of PAS among these pregnancies ($P = 0.97$) (Table V).

Discussion

Patients treated in our clinic for AS were identified to have a mean EMT measurement of 7.5 mm when undergoing IVF-ET. An appreciable, 31.8% of EMT measurements obtained for AS patients undergoing IVF-ET cycles were considered to be a thin EMT measurement (<7.0 mm). Despite this, 33.3% of the IVF-ET's with an EMT measurement of <7.0 mm led to a clinical pregnancy. Ultimately, 55.6% of all AS patients went on to have a clinical pregnancy after a mean of 2.0 ET attempts. EMT measurement did not predict clinical pregnancy on either bivariate or multivariable analysis. Younger patient age and oocyte donation were the only characteristics associated with a positive clinical pregnancy outcome on bivariate analysis, emphasizing the importance of oocyte and embryo quality among this patient population.

In our multivariable analysis, we found that patient age was no longer statistically significant for predicting a clinical pregnancy outcome as it was in our bivariate analysis. This is potentially due to the covariate of oocyte donation utilization in the multivariable analysis taking away from the significance of patient age on clinical pregnancy rate. This can occur as donated oocytes are often from donors that are much younger than the recipient utilizing them for ET. We additionally found that oocyte donation correctly predicted clinical pregnancy in all five ETs evaluated. This occurred because the only oocyte donation cycle that did not result in a clinical pregnancy could not be used in the analysis, as it occurred during one of the five ET cycles that did not utilize a pelvic ultrasound and had no documented EMT measurement prior to ET.

We noted no difference in predicting clinical pregnancy in AS patients with a thin (<7.0 mm) versus normal (≥7.0 mm) EMT measurement. These results should be interpreted with caution as our small sample size may limit our ability to detect a statistical difference between these two groups. However, if our results can be validated with a larger cohort of patients, the clinical implication would suggest that an EMT measurement cutoff for deciding on timing of ET should be utilized with caution for AS patients utilizing IVF-ET. The utilization of an EMT cutoff measurement prior to ET would lead to missed clinical pregnancy opportunities and delayed conception. Within our study, we documented a clinical pregnancy that occurred with an EMT measurement of just 4.0 mm. Furthermore, we identified a clinical pregnancy and live birth occurring with an EMT measurement as low as 3.7 mm within literature (Myers and Hurst, 2012).

There is a paucity of data on the impact of EMT measurement during IVF with AS patients. In 2019, Wang *et al.* (2019) evaluated factors associated with pregnancy following treatment of AS and subsequent IVF. They found that EMT measurements were significantly greater among AS patients with clinical pregnancies following IVF than those who did not (Wang et al., 2019). This is contrary to our study's findings, however two factors may explain discordant conclusions. First, our patient cohort was much older with a mean age of 37.95 years old versus their mean patient age of between 31.68 and 33.65 years old (pregnancy vs non-pregnancy group). Additionally, there was an

appreciably higher mean EMT measurement among their patient population at 10.4–11.2 mm (pregnancy vs non-pregnancy group) versus the mean EMT measurement of 7.5 mm in our AS patient population. Their higher mean EMT measurement may be attributed to their younger patient population or less severe AS than our population using different scoring criteria. It has been documented that younger patients have higher endogenous estrogen concentrations in response to IVF stimulation cycles due to the decrease in ovarian reserve that comes with older age (Papageorgiou et al., 2002). Alternatively, their higher mean EMT measurement may be due to a systematic difference in the subjective manner of diagnosing intrauterine adhesions on hysteroscopy or method by which they measure the EMT on sonography. Their mean EMT measurement is closer to that reported by Griesinger *et al.* (2018) for the general population (mean EMT of 11.1 mm over 1401 ET cycles) than what would be expected from a cohort of AS patients (Griesinger et al., 2018). Both of our investigations did note a significant association with younger patient age and clinical pregnancy on bivariate analysis.

Though our investigation was designed only to identify any association with EMT measurement and clinical pregnancy, there has been recent interest in other novel noninvasive methods of determining endometrial receptivity prior to ET that may be of value to evaluate among AS patients. Maged *et al.* (2019) reported that endometrial volume and endometrial perfusion could positive predict pregnancy in patients undergoing IVF, and could be investigated in the future among AS patients to see if similar findings are noted.

A strength of our study is the number of AS patients included given the rarity of the disease. Our study also has strong clinical implications given the widespread use of EMT cutoffs prior to IVT-ET. We hypothesize that patients with AS have normal endometrium adjacent to thin scar tissue and adding the thickness of these two endometrial surfaces often yields a thin lining by ultrasound, as demonstrated in our study. However, we believe that we did not find an association between EMT measurement and clinical pregnancy among AS patients because only the normal portion of endometrium is required for a successful embryo implantation, and is not adequately appreciated by the EMT measurement. Patients with a thin lining without AS have a more homogeneous endometrium not due to scarring and thus the EMT measurements are more likely reflective of an abnormal endometrium. Likewise, adding high doses of estradiol in AS patients with a thin lining does not increase the percentage of normal endometrium.

Limitations of our study include the retrospective study design and possible incomplete data acquisition. As many patients utilized various infertility clinics following care at our hospital, we were unable to evaluate the impact of any specific endometrial preparation protocol on clinical pregnancy as it was inconsistently reported from outside hospital records. In a similar vein, we were not able to evaluate the quality of all EMT measurements obtained as they were acquired from several different institutions. However, given that the distributed care of AS patients at multiple institutions is prototypical of patients of rare diseases, this could perhaps be interpreted as representative of our healthcare system in practice and increase the generalizability of our results.

In conclusion, EMT measurements may not be associated with successful clinical pregnancy among AS patients undergoing IVF. EMT measurement cutoff values should be used with caution for the purpose of canceling a scheduled ET in AS patients.

Supplementary data

Supplementary data are available at *Human Reproduction* on-line.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

P.M. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. J.W. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. T.C. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. B.M. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. J.W. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. A.W. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. H.R. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. J.T. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. M.L. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. S.M. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article. K.I. was responsible for study design and conception, data analysis, first draft of article, review and approval of revisions and the final article.

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Conflict of interest

K.I. reports personal fees from Karl Stroz and personal fees from Medtronics outside the submitted work. The other authors have no conflicts of interest.

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