

Association of Endometrial Thickness with Incidence of Ectopic Pregnancy after Freeze - Thaw Transfer

Dr. Ananthi Babu MS (OG)

DGO, Private practitioner GS Hospital, Madurai
drananthibabu21[at]gmail.com

Abstract: Objective: To investigate whether endometrial thickness (EMT) influences the incidence of ectopic pregnancy (EP) in frozen embryo transfer (FET) cycles. Design: Retrospective cohort study. Setting Single center study. Methods A total of 606 pregnancy cycles after freeze –thaw embryo transfer were included with number of intrauterine and ectopic pregnancies being 182 and 24 respectively. Main Outcome Measure EP was the primary outcome. EMT was the main measured variable. Result: 1. After adjusting for confounders, endometrial thickness could independently predict ectopic pregnancy. The adjusted odd ratios for women with endometrial thickness in the ranges of < 8mm, 8 - 9.9mm, and 10 - 11.9mm were 3.2702, 2.758 and 1.456 respectively, when compared with those having an endometrial thickness of 12 - 13.9mm. 2. Endometrial type and preparation protocol were however not identified as risk factors for ectopic pregnancy. Discussion: 1. After freeze - thaw embryo transfer risks of ectopic pregnancy were significantly higher when the endometrial thickness was < 8 mm. 2. A thin endometrial thickness could be linked with abnormal endometrial peristaltic waves or abnormal endometrial receptivity. 3. Adequate attention should therefore be paid to patients with a thin endometrial thickness to prevent EP or to achieve early diagnosis during the peri - transplantation period. Conclusion: EMT is inversely proportional to EP rate in FET cycles and is therefore a potential quantitative marker of endometrial receptivity and uterine contractibility in an FET cycle. The predictive validity of EMT value must be evaluated in further studies.

Keywords: EMT; blastocyst; ectopic pregnancy, and FET

1. Introduction

Incidence of Ectopic pregnancy is on the rising trend being 2 - 5% which is of 1 - 2% after natural conception. Incidence of ectopic after IVF procedure is 2.8%, Incidence after ICSI is 1.3%. The reason for this rise of ectopic remains unclear. Tubal factor infertility contributes 11% cause of infertility, unexplained factors form 3.5%, Endometriosis form 2% cause of infertility.

Risk factors

Maternal age forms a risk due to age related change in tubal mutuality function. There is three times increased risk among cigarette smokers. There is 15 - 20% recurrence risk in patients with previous tubal pregnancy. Hydro salpinx forms major negative impact on infertility. Previous tubal surgeries like salpingostomy, salpingectomy predisposes to tubal pregnancy.

Theories behind Ectopic

Hydrostatic force generated by transfer media push the Embryo back into tubes. The Gravitational Pull of Embryo itself pushes the embryo back into hanging tubes. Uterine Contraction may cause spontaneous reflex Expulsion of Embryo into the tubes. Faulty Embryo transfer techniques like high placement of embryos in uterine cavity, higher volume of transfer media, rapid transfer and multiple embryo transfers may predispose to Ectopic, Increased E2 level cause reverse rhythmic uterine contractions pushing embryo into tubes.

Embryo factors – E - Cathedrin is a cellular adhesion protein needed for adhesion of blastocyst into endometrium. In IVF embryo is exposed to different cellular adhesion molecule

leading to different localisation of embryo. Stage of Embryo – Cleavage Stage Embryo has tendency of travelling around and is prone to ectopic.

Endometrial Thickness is closely related to uterine receptivity. Endometrial thickness lesser than 8mm has increased risk of EP

Objectives of the study

To investigate whether endometrial thickness influences the incidence of Ectopic pregnancy in FET cycles.

Design

Retrospective cohort study in a single centre.

2. Material and methods

The study was conducted among 606 Pregnancy cycles between Jan 2019 - Dec 2022 comprising 502 Intra uterine pregnancies and 24 Ectopics

- **Mean outcome measure** is Ectopic Pregnancy
- **Mean measured variables** is Endometrial thickness

Assessment of Primary Exposure

Endometrial thickness was measured on the day of endometrial transformation – When last USG exam was performed before progesterone administration. EMT was measured in sagittal view with maximal AP thickness according to Gonen system. Type A is Trilaminar pattern. In Type B, endometrium is homogenous, hyperechoic with Intra Uterine Central Line Echo. In Type C, endometrium is homogenous, hyperechoic without Intra Uterine Central Line Echo.

Demographic data

Variables	Ectopic pregnancy, n = 24	Intrauterine pregnancy, n = 582	P - value
Age (years)	30 (27, 34)	31 (28, 34)	0.059
Body mass index (kg/m ²)	20.93 (19.55, 23.41)	21.48 (19.70, 23.63)	0.175
Infertility duration (years)	4 (2, 7)	4 (2, 6)	0.479
Previous history of ectopic pregnancy			
=0	18 (75%)	426 (84.9%)	0.000*
≥1	6 (25%)	66 (15.1%)	
Tubal factor infertility			
Yes	22 (93.4%)	488 (84.1%)	0.001*
Male factor infertility			
Yes	6 (27.9%)	180 (31.3%)	0.327
Endometriosis			
No	23 (98.9%)	532 (95%)	0.019*
Polycystic ovary syndrome			
No	494 (85.8%)	20 (14.3%)	0.962
Diminished ovarian reserve			
Yes	1 (6.6%)	46 (8.1%)	0.455

Demographic data included variables like age, body mass index, duration of infertility, previous history of ectopic and Etiology of infertility like Tubal factor infertility, male factor infertility, endometriosis, Polycystic ovary syndrome and diminished ovarian reserve. Patients with low BMI has increased risk of ectopic. In previous history of tubal pregnancy, incidence is 75% and p - value is significant (0.001). In endometriosis, due to anatomical distortion of tubes. The incidence is high (98%) and p - value is 0.019. In male factor, PCOD, DOR, there is no association with ectopic pregnancy.

Factors associated with Ectopic

Predictor variables	Odds ratio	95% confidence interval	P value
Previous history of ectopic pregnancy			
=0	1	—	—
≥1	1.573	1.102, 2, 243	0.012*
BMI (kg/m ²)	1.001	1.000, 1.002	0.034*
Tubal factor infertility			
Yes	2.221	1.191, 4.144	0.012*
No	1	—	—
Embryo stage			
Cleavage stage embryo	1	—	—
Blastocyst	0.451	0.297, 0.683	0.000*

On univariate analysis, in previous history of Ectopic odds ratio is 1.573 and p value is significant (0.012). In tubal factor infertility, the odds ratio is 2.221 (p - value<0.05). In Cleavage stage embryo, the odds ratio is 1 compared to blastocyst transfer.

Association of EMT with EP

Predictor variables	Odds ratio	95% confidence interval	P - value
Endometrial thickness (mm)			
12–13.9	1	—	—
<8	3.27	1.113, 9.605	0.031*
8–9.9	2.758	0.987, 7.707	0.053
10–11.9	1.456	0.502, 4.225	0.489
≥14	0	0.000, 0.000	0.996

On multivariate regression analysis, it shows that endometrial thickness of less than 8mm has odds ratio of 3.27 (p - value<0.05). Endometrial thickness between 8 and 9.9 mm has odds ratio of 2.758, EMT of 10 - 11.9 mm has odds ratio of 1.456 and EMT of more than 14 mm has odds ratio is nil.

3. Results

On analysing the results of my study, Tubal factor infertility has increased two - fold risk of EP. Lean BMI has increased risk of ectopic. Cleavage stage embryo has increased two - fold risk of ectopic. EMT of less than 8mm has increased five - fold risk. Blastocyst transfer is protective against ectopic.

4. Discussion

The critical cut off value of endometrial thickness and ectopic pregnancy is controversial. Prior studies suggest that EMT less than 12 mm predisposes to ectopic. It is impractical to weight up to 12mm for a transfer. So, it is logical to consider EMT less than 8mm as a threshold cut off value for risk of ectopic.

There is an association between EMT and Uterine Receptivity. In patients with ectopic have poor uterine receptivity. Why thin endometrium predisposes to ectopic? Thin endometrium brings an embryo in close contact with spiral arteries of basal layer of endometrium which exposes the embryo to higher oxygen concentration which is detrimental to embryo for implantation and pushes the embryo to tubes where there is lower oxygen concentration. Uterine peristalsis in thin EM is closely related to risk of EP.

What can we done to reduce incidence of EP

Mid fundal placement of embryos (5 - 10 mm) from the fundus, Transfer volume of media should be less than 80 µ ml, Tubal occlusion at utero fundal junction in hydro salpinx, to do blastocyst transfer in FET cycles, Early detection of ectopic by serial β HCG, early USG at 5 weeks. Tocolytics, Atosiban should be given if thin endometrium and uterine peristaltic wave is seen.

5. Conclusion

EMT <8mm on the day of endometrial transformation predict EP incidence. EMT is a promising quantitative marker of Endometrial Receptivity. Efforts to increase EM thickness reduces EP risk. Endometrial peristaltic wave exam and endometrial receptivity testing should be done and give corresponding treatment

6. Limitations

The small number of cases in the study may have limited the scope of these findings. This study considered the endometrial thickness of FET cycles in ART. It needs study data from endometrial preparation protocols, stage of embryo transfer, number of embryo transfers

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Author Profile



Dr. Ananthi Babu, M. S. (OG), DGO, is a consultant obstetrician, gynaecologist, and infertility specialist practising in Madurai since 20 years. Interested in infertility presented 5 papers in National conferences. She also participated in many national and international OG conferences. Recently, she was accorded as a Best Doctor Award for rendering an effective service during Covid period.