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Title:

**IS A THIN ENDOMETRIAL LINING ASSOCIATED WITH INCREASED RISK OF
ECTOPIC PREGNANCY IN SINGLE EUPLOID FROZEN EMBRYO TRANSFERS?**

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Objective:

Although the mechanism of action is unknown, ectopic pregnancy rates have been shown to be higher in women who conceive using assisted reproductive technology (ART). Clinicians and researchers continue to investigate risk factors for ectopic pregnancy (EP) in this population, exploring baseline demographics, number of embryos transferred, developmental stage, and ploidy status. It remains unclear whether endometrial factors, particularly endometrial thickness (EnT) and pattern (EnP), play a role in EP risk. A study published by Rombauts et al. reported a 4-fold increased risk of EP in women with an EnT <9mm during fresh IVF transfers compared with >12mm.¹ Studies have shown that single euploid frozen embryo transfers (FET) are associated with the lowest risk of EP,^{1,2} yet no study to date has evaluated the influence of EnT within this cohort. Using a homogenous embryo population of single euploid embryos, we sought to determine whether there is a correlation between EnT/EnP with the incidence of EP.



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Design:

Retrospective, cohort study

Materials and Methods:

The study included patients who underwent a programmed single euploid FET cycle from 2011-2018. Natural cycles were excluded. An EP was identified using natural language processing to identify cycles with the phrase “ectopic pregnancy” or “pregnancy of unknown location” where methotrexate was given or a salpingectomy was performed. Cycles that were manually identified by a clinician as an EP were also included. IVF cycles were separated into two groups based on outcome (EP vs. no EP), and EnT was treated as a continuous variable. A sub-group analysis was performed treating EnT as a dichotomous variable, thin (<7mm) or not thin (≥ 7 mm). Age, body mass index (BMI), gravidity, parity, anti-mullerian hormone (AMH) level, embryo age, EnT and EnP on day of transfer were collected. Data were analyzed using t-tests, Chi-square analysis, and binary logistic regressions with a general estimate equation (GEE) model with an exchangeable working correlation structure to account for repeated measures.

Results:

A total of 3733 single euploid frozen embryo transfer cycles from 2533 patients were included in this study. Baseline characteristics were similar between the two groups, with the exception of parity (Table 1). The overall rate of EP was 3.9% (n=146). There was no statistically significant increase in incidence of EP when looking at EnT as a continuous function (OR 0.97, [95% CI - 0.13-0.06], p=0.47). However, when performing a sub-analysis grouping cycles into 2 groups



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(EnT \geq 7mm and EnT<7mm), there was a statistically significant increase in ectopic pregnancy within the EnT <7mm cohort (OR 1.81 [95% CI 0.5-1.14], $p= 0.03$). EnP at time of transfer was not shown to be a significant risk factor for EP (OR=0.62, [95% CI -1.02-0.07], $p=0.09$).

Conclusions:

In a well-controlled study which minimized heterogeneity of patient and embryo factors by focusing on single euploid frozen embryo transfers, we showed that an EnT of <7mm is an independent risk factor for EP. These findings are consistent with a previous study reporting increased EP with fresh transfers with EnT <9mm as compared to >12mm. The ability to predict endometrial non-receptivity and increased likelihood of EP in a non-invasive fashion will help to minimize the morbidity and mortality from EP. Given that EnT is likely a surrogate for endometrial receptivity, future studies would benefit from correlating EnT with activation of molecular pathways affecting the implantation window.

References:

1. Li Z, Sullivan EA, Chapman M, et al. Risk of ectopic pregnancy lowest with transfer of single frozen blastocyst. *Hum Reprod* 2015; 30(9):2048-54.
2. Sekhon S, Lee JA, Mehta S, et al. Are euploid embryos less likely to result in ectopic implantation? *Fertil Steril* 2016; Volume 106, Issue 3, Supplement, e1-e404.
3. Rombauts L, McMaster R, Motteram C. Risk of ectopic pregnancy is linked to endometrial thickness in a retrospective cohort study of 8120 assisted reproduction technology cycles. *Hum Reprod* 2015; 30(12):2846-2852.



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Table 1:

Patient demographics (*=significant)

	Ectopic pregnancy (N= 146)	Not ectopic pregnancy (N= 3587)	P value
Age (years)	36.13 ± 3.56	36.47 ± 3.97	0.31
Gravidity	1.29 ± 1.26	1.27 ± 1.43	0.84
Parity	0.37 ± 0.65	0.48 ± 0.76	<0.05*
AMH (ng/mL)	4.25 ± 4.67	3.75 ± 4.50	0.28
Embryo Age	Day 5: 90 (61.64%) Day 6: 51 (34.93%) Day 7: 5 (3.42%)	Day 5: 2228 (62.11%) Day 6: 1272 (35.46%) Day 7: 87 (2.43%)	0.75
EnT	9.19 ± 2.17	9.38 ± 2.06	0.27
EnP	2: 14 (9.59%) 3: 132 (90.41%)	2: 534 (14.94%) 3: 3041 (85.06%)	0.10