

Title: ENDOMETRIAL THICKNESS AT THE TIME OF INTRAUTERINE INSEMINATION IN PATIENTS WITHOUT AN IMPAIRED REPRODUCTIVE ABILITY

Authors: Shelley Dolitsky¹, Selena Park¹, Joshua Morris², Elizabeth Clain³, Laura Zalles⁴, Jerry Wang⁵, Samad Jahandideh⁴, Kerry Flannagan⁴, Alan DeCherney¹, Micah Hill^{1,6}, Kate Devine^{1,7}, Phillip Romanski⁵, Matthew Connell⁴

¹ Department of Reproductive Endocrinology and Infertility, National Institutes of Health, Bethesda, MD

² Department of Reproductive Endocrinology and Infertility, Eastern Virginia Medical School, Norfolk, VA

³ Department of Reproductive Endocrinology and Infertility, University of Colorado, Aurora, CO

⁴ Shady Grove Fertility, Rockville, MD

⁵ Shady Grove Fertility, New York, NY

⁶ Department of Reproductive Endocrinology and Infertility, Walter Reed National Military Medical Center, Bethesda, MD

⁷ Shady Grove Fertility, Washington, DC

Background: Research evaluating the association between endometrial thickness (EMT) in intrauterine insemination (IUI) cycles and pregnancy have yielded conflicting results. Studies have been limited by sample size and various arbitrary EMT thresholds (1-4). Most have looked only at patients with unexplained infertility (2-4). With the increasing number of patients who are pursuing IUI as single parents or part of female same-sex couples, there is a need for studies focused on patients without a history of impaired reproductive ability. These patients represent a unique population to study the association of EMT and pregnancy, excluding other contributing factors of pregnancy failure.

Objective: To assess the association between EMT at time of trigger during IUI and pregnancy in patients without a history of impaired reproductive ability who used donor sperm due to single parenthood, same-sex couple, or partner with azoospermia. We tested the hypothesis that in these patients with a trilaminar endometrial lining, a larger EMT at the time of trigger would be associated with increased pregnancy.

Materials and Methods: Retrospective cohort study of patients aged 18-50 years who underwent ovulation induction and IUI between 2010-2023 at US Fertility practices. Primary outcome was pregnancy, defined as having a positive beta hCG measured with a blood test 14 days after IUI. The secondary outcome was ongoing pregnancy, defined as a clinical intrauterine pregnancy and being discharged from US Fertility between 8- and 10-weeks gestation. We included patients with no subfertility diagnosis who underwent ovulation induction with medication and IUI with donor sperm. We excluded patients who did not have a trilaminar endometrial lining and had severe oligospermia (total motile count ≤ 5 million). EMT was examined as a continuous variable. Primary analysis was performed including all patients. Secondary analysis was performed stratifying patients by ovulation induction medication used. We estimated risk ratios (RR) and 95% confidence intervals (CI) using modified Poisson regression models fitted with generalized estimating equations to account for correlation among cycles from the same patient. P values were from Wald tests of the model parameters.

Result(s): A total of 421 patients were included. The average age was 33.7. The most common ovulation induction medication used was Clomiphene Citrate (60.3%), then Letrozole (23.8%),

followed by gonadotropins (15.9%). Patients averaged 1.9 (+/- 1.1) follicles ≥ 14 mm on the day of trigger. For all IUI cycles, both clinical pregnancy (RR 1.05 (95% CI 0.96, 1.15); P=0.26) and ongoing pregnancy (RR 1.06 (95% CI 0.97, 1.16); P=0.21) showed no significant difference based on EMT (Table 1). These results were similar when patients were stratified by ovulation induction medication used in IUI cycles (Table 2).

Conclusion(s): In patients without a history of impaired reproductive ability who underwent IUI treatment with donor sperm and had a trilaminar endometrial lining, EMT was not associated with pregnancy. These results persisted in secondary outcomes and sensitivity analyses. Therefore, in these patients with a trilaminar lining, IUI cycles should not be cancelled based on a thin endometrial lining alone.

Financial Support: None

References:

1. Asante A, Coddington CC, Schenck L, Stewart EA. Thin endometrial stripe does not affect likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles. *Fertil Steril.* 2013 Dec;100(6):1610-4.e1. doi: 10.1016/j.fertnstert.2013.08.035. Epub 2013 Sep 26. PMID: 24074755.
2. Esmailzadeh S, Faramarzi M. Endometrial thickness and pregnancy outcome after intrauterine insemination. *Fertil Steril.* 2007 Aug;88(2):432-7. doi: 10.1016/j.fertnstert.2006.12.010. Epub 2007 Apr 16. PMID: 17434500.
3. Quaas AM, Gavrizi SZ, Peck JD, Diamond MP, Legro RS, Robinson RD, Casson P, Christman GM, Zhang H, Hansen KR; Eunice Kennedy Shriver National Institute of Child Health and Human Development Reproductive Medicine Network. Endometrial thickness after ovarian stimulation with gonadotropin, clomiphene, or letrozole for unexplained infertility, and association with treatment outcomes. *Fertil Steril.* 2021 Jan;115(1):213-220. doi: 10.1016/j.fertnstert.2020.07.030. Epub 2020 Sep 21. PMID: 32972733; PMCID: PMC7796980.
4. Weiss NS, van Vliet MN, Limpens J, Hompes PGA, Lambalk CB, Mochtar MH, van der Veen F, Mol BWJ, van Wely M. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. *Hum Reprod.* 2017 May 1;32(5):1009-1018. doi: 10.1093/humrep/dex035. PMID: 28333207.

Table 1: Comparison of pregnancy outcomes for all IUI cycles based on endometrial thicknesses

Cycle outcome	(n =421)	aRR per 1mm endometrial thickness (95% CI); p-value
Pregnancy		
Clinical pregnancy	100 (23.8%)	1.05 (0.96, 1.15); P=0.26
Ongoing pregnancy	78 (18.5%)	1.07 (0.97, 1.18); P=0.16

Results shown as n (%). IUI = intrauterine insemination; aOR = adjusted odds ratio; CI = confidence interval.

Table 2: Comparison of endometrial thickness and pregnancy outcomes for each ovulation induction medication used

Cycle outcome		aRR per 1mm endometrial thickness (95% CI); p-value
Clomiphene Citrate	n=254	
Clinical pregnancy	56 (22.0%)	1.06 (0.95, 1.19); P=0.31
Ongoing pregnancy	42 (16.5%)	1.12 (1.00, 1.26); P=0.05
Letrozole	n=100	
Clinical pregnancy	28 (28.0%)	0.99 (0.83, 1.18); P=0.93
Ongoing pregnancy	24 (24.0%)	0.94 (0.77, 1.14); P=0.51
Gonadotropins	n=67	
Clinical pregnancy	16 (23.9%)	1.19 (0.88, 1.60); P=0.25
Ongoing pregnancy	12 (17.9%)	1.25 (0.96, 1.62); P=0.09

Results shown as n (%). IUI = intrauterine insemination; aOR = adjusted odds ratio; CI = confidence interval.