Thin endometrial stripe does not affect likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles

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Objective: To determine whether there is a correlation between preovulatory endometrial stripe thickness (EST) and pregnancy rates in clomiphene citrate (CC)/IUI cycles.
Design: Retrospective cohort.
Setting: Infertility clinic of an academic medical center.
Patient(s): A total of 262 patients completed 562 transvaginal ultrasound–monitored CC/IUI cycles from January 2005 through December 2012.
Intervention(s): All patients received oral CC. In 362 of the cycles, a single dose of gonadotropin was administered on cycle day 9 (MinStim). A transvaginal ultrasound was performed on cycle day 10, 11, or 12.
Main Outcome Measure(s): Pregnancy rate per initiated cycle.
Result(s): A total of 91 pregnancies ensued, yielding a pregnancy rate of 16.2% per initiated cycle. Pregnancy rates did not vary with EST <6 mm, 6–9 mm, and >9 mm (14.8%, 16.3%, and 19.0%, respectively). There was no significant difference in mean EST between stimulation types (6.8 mm for CC vs. 6.7 mm for MinStim). When conception and nonconception cycles were compared, no difference in mean EST (6.9 mm vs. 6.8 mm, respectively) was observed. Area under the receiver operating characteristic curve for the probability of pregnancy based on EST was 0.51.
Conclusion(s): Preovulatory EST had no significant correlation with pregnancy rates in CC/IUI cycles. The decision to switch from CC to another treatment strategy should be influenced by factors other than thin endometrial stripe. (Fertil Steril® 2013;100:1610–4. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrial stripe thickness, transvaginal ultrasound, intrauterine insemination

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Since its introduction in 1966, clomiphene citrate (CC) has been used extensively for the purpose of ovulation induction in women with anovulatory infertility or for superovulation in ovulatory women with unexplained infertility. Sonographic endometrial stripe thickness (EST) has been reported to be lower in CC-stimulated cycles compared with natural cycles (1–3); the estrogen antagonist property of CC is hypothesized to be responsible for this effect. However, there is no conclusive evidence of the clinical relevance of this finding with respect to pregnancy outcomes.

Several studies have investigated the effect of EST and endometrial echogenic pattern on pregnancy outcome. Most of the data are from IVF cycles with inconsistent results. Whereas some authors have demonstrated a greater probability of pregnancy once

Received July 9, 2013; revised August 18, 2013; accepted August 20, 2013; published online September 26, 2013.
A.A. has nothing to disclose. C.C.C. has nothing to disclose. L.S. holds stock in Medtronic and Johnson and Johnson. E.A.S. is a Board Member with Bayer Healthcare; has consultancies with Abbott, Gynesonics, and Bayer; has grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and InSightec; receives royalties from UpToDate, Johns Hopkins University Press, and the Massachusetts Medical Society; and has had travel expenses paid by Focused Ultrasound Foundation.
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Fertility and Sterility® Vol. 100, No. 6, December 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.08.035

the endometrium attains a threshold thickness (4–9), others have not reproduced these findings and have not found any relationship between EST and pregnancy outcome in assisted reproduction techniques (10–13).

Very few studies of CC alone or of CC plus gonadotropins have analyzed the effects of EST on pregnancy outcome (14–16), and the findings have been conflicting. It is noteworthy that in all of the previous studies EST was measured on the day of hCG administration. In practice, one would need prognostic indicators that could be used before the day of hCG administration, allowing maximal time for modifications to the stimulation protocol, if necessary. Most practicing gynecologists and fertility specialists typically monitor CC/IUI cycles by performing at least one follicle-tracking transvaginal ultrasound (TVU) scan on cycle day 10, 11, or 12. Findings from studies in which sonographic endometrial assessments were performed on the day of hCG administration may not be relevant to such practitioners.

In the present study we retrospectively analyzed all the CC/IUI cycles from January 2005 through December 2012 at Mayo Clinic in which TVU was performed on cycle day 10, 11, or 12. Our goal was to determine whether there was any correlation between preovulatory EST measured with the TVU and pregnancy outcome in a CC/IUI cycle.

MATERIALS AND METHODS

Patient Population

All patients in the present study were evaluated and treated at the infertility center of Mayo Clinic, Rochester, Minnesota. The study protocol was approved by the institutional review board of Mayo Clinic. All TVU-monitored CC/IUI cycles performed during the study period were considered for the analysis. We included cycles in which one follicle-tracking TVU scan was performed on cycle day 10, 11, or 12, and for which there were at least 5×10^6 total motile sperm after processing for insemination. Exclusion criteria were age $\geq$40 years, body mass index $>$40 kg/m^2, and cycle day 3 FSH $>$10 mIU/mL.

Data were collected for patient characteristics: age, body mass index, menstrual cycle day 3 FSH, indication(s) for fertility treatment, dose of ovulation induction agent(s), number and order of treatment cycle (first vs. subsequent), stimulation characteristics on the day of follicle tracking TVU scan (number of follicles $>$10 mm in size, number of follicles $>$15 mm in size, size of leading follicle, and EST), postprocessing total motile sperm per ejaculate used for insemination, and cycle outcome (pregnant vs. not pregnant). For the purposes of our study, pregnancy was defined as TVU evidence of an intrauterine pregnancy with fetal cardiac activity.

Clinical Protocols

Ovulation induction regimens used were as follows: CC was administered from cycle day 3 through day 7 at a dose of 25 mg (n = 9), 50 mg (n = 168), 75 mg (n = 3), 100 mg (n = 348), or 150 mg (n = 34). In 362 of the treatment cycles, a single dose of gonadotropin injection was administered on cycle day 9 (MinStim cycles). For each cycle, a TVU assessment was performed once, on treatment day 10, 11, or 12. The endometrium was imaged in a longitudinal section, and thickness was measured at the greatest anteroposterior dimension of the endometrium. The endometrial pattern was graded according to the method described by Gonen and Casper (9), as follows: type A, an entirely homogeneous, hyperechogenic pattern without a central echogenic line; type B, an intermediate isoechogenic pattern, with the same reflectivity as the surrounding myometrium and a nonprominent or absent central echogenic line; and type C, a multilayered triple-line endometrium consisting of a prominent outer and central hyperechogenic line and inner hypoechogenic or black regions.

Patients received 10,000 IU of hCG when the diameter of one or more follicles was $\geq$20 mm. A single IUI was performed 36 hours after hCG administration, or 24 hours after detecting an LH surge for patients who did not receive hCG. Patients without menses 14–16 days after IUI did a home urine pregnancy test. Positive home pregnancy tests were confirmed by serum quantitative β-hCG, followed 3 weeks later by TVU verification of fetal cardiac activity.

Outcome Measures

Pregnancy rate (PR) was defined as the number of cycles with at least one viable fetus (as evidenced by TVU of fetal cardiac activity at 7 weeks) per initiated cycles.

Statistical Analysis

Clinical factors were assessed for an association with pregnancies using generalized estimating equations (GEE) to account for correlation between multiple cycles from the same patient. A particular patient may be represented more than once if they completed a course of treatment that culminated in a pregnancy and then re-presented for treatment, or if they returned for treatment after a period of 12 months or more. The cumulative pregnancy rates were estimated using the Kaplan-Meier survival analysis. A receiver operating characteristic (ROC) curve was constructed for EST and pregnancy rate. Statistical analysis was carried out with the χ^2 test and GEE regression where appropriate, using the statistical package SAS 9.3 (SAS Institute). All calculated P values were two-sided, and P values of $<$.05 were considered statistically significant.

RESULTS

A total of 262 patients completed 562 TVU-monitored ovulation induction cycles: 200 CC/IUI and 362 MinStim/IUI cycles. Indications for fertility treatment included unexplained infertility (50%), ovulatory dysfunction (29%), polycystic ovary syndrome (7%), endometriosis (7%), and use of therapeutic donor insemination (8%).

The overall PR per cycle was 16.2% (91 of 562). Stimulation and outcome characteristics of conception vs. nonconception cycles are shown in Table 1; both cycles showed comparable mean EST (6.9 mm vs. 6.8 mm, respectively) and number of follicles $>$15 mm (1.8 vs. 1.6, respectively). Other than maternal age, no other preovulatory parameter reached statistical significance as different between the