Influences on endometrial development during intrauterine insemination: clinical experience of 2,929 patients with unexplained infertility

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Objective: To characterize relationships associated with adverse endometrial development in patients undergoing IUI for unexplained infertility.
Design: A retrospective review of 2,929 patients from 2004–2011.
Setting: Large metropolitan infertility practice.
Patient(s): Patients with unexplained infertility undergoing first IUI cycle at age less than 43 years, with a total motile sperm count ≥ 8 million.
Intervention(s): Clomiphene citrate (CC) with FSH stimulation followed by IUI.
Main Outcome Measure(s): Endometrial thickness, serum E_2 (in picograms per milliliter) levels on the day of hCG trigger administration, body mass index (BMI) (in kilograms per meter squared), total motile sperm, follicle number, and clinical pregnancy.
Result(s): Of the 2,929 patients who met the inclusion criteria, 466 (15.9 %) achieved a clinical pregnancy. Pregnancy rates (PRs) increased significantly with increasing endometrial thickness on the day of hCG administration and with increasing serum E_2 level, but were not significantly related to age, BMI, or follicle numbers according to multiple logistic regression modeling. Peak endometrial thickness declined with age and increasing E_2 levels. The BMI was associated with thicker endometrium, but it was also associated with lower peak E_2 levels.
Conclusion(s): The impact of "endometrial factor" infertility may be underappreciated in IUI therapy. Targeted therapies to optimize the endometrium represent an important new area to improve in current fertility success rates. (Fertil Steril® 2013;100:194–9. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrium, intrauterine insemination, assisted reproductive technologies

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During the past 40 years, there has been a steady increase in fertility treatment success rates due to improvements such as embryo culture techniques and intracytoplasmic sperm injection (ICSI). Historically, when assisted reproductive technology (ART) fails, the assumption has been that the embryo was nonviable. However, there is increasing awareness that implantation failure of otherwise viable embryos may be responsible for a significant portion of IVF failures. New clinical treatments, such as therapeutic endometrial biopsy/injury, have gained recent attention to correct the so-called endometrial factor infertility (1, 2). However, endometrial development during IUI cycles has been less studied.

One of the strongest predictors of implantation is endometrial thickness.

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A number of reports have shown that embryo implantation and clinical pregnancy rates (PRs) are significantly higher in patients with an endometrial thickness >9 mm (3–5). Thin endometria, generally measuring <7 mm, are thought to be less able to support implantation and pregnancy (6).

The thickness of the endometrium is dependent on several influences including reproductive age, phase of menstrual cycle, ovarian hormone (estrogen [E_2] and progesterone [P]) concentration, and endometrial hormone receptor density (7, 8). Infertility diagnoses, such as polycystic ovarian syndrome (PCOS), endometriosis, and recurrent pregnancy loss, have been associated with thin endometria and lower PRs (9). Available treatments for thin, unresponsive endometrium are limited and largely empiric or experimental including high doses of E, hCG, piroxicam, and granulocyte colony stimulating factor (10). Treatments, such as acetylsalicyclic acid, have also been proposed. The results of this intervention are mixed (11–13). Most of these methods are proposed to function in a similar manner, by increasing blood flow to the endometrium and allowing for its thickening and development. Vaginal sildenafil citrate (Viagra; Pfizer) is another treatment that has been suggested for its ability to relax vascular smooth muscle through a cyclic guanosine monophosphate-mediated pathway, and improve uterine artery blood flow (14).

However, the impact of endometrial thickness on PRs has not been studied extensively in an unexplained infertile population of patients undergoing IUI. Here we characterize the endometrial characteristics of a large unexplained infertile population undergoing IUI to explore the link between endometrial thickness and PRs, and to improve the understanding of the influences affecting endometrial development during IUI cycles.

MATERIALS AND METHODS

In this retrospective analysis, we identified 2,929 initial, consecutive, completed IUI cycles from 2004 through 2011 at a large private infertility practice for which we had complete clinical pregnancy outcomes. All consecutive patients less than 43 years of age with a diagnosis of unexplained infertility and undergoing their first cycle of clomiphene citrate (CC)/FSH IUI with more than 8 million total motile sperm were included in this retrospective review under an approved Institutional Review Board protocol. Those with total motile sperm <8 million were excluded to minimize the effect of male factor infertility on clinical PRs, as this threshold has previously been shown to be associated with PRs in our practice (15). Typically, patients received 100 mg of CC on menstrual cycle days 3–7, followed by 150 U of FSH on cycle day 9. Ultrasound and blood monitoring of E_2 were performed on cycle day 13. Once follicles reached 18 mm, trigger was induced with 10,000 U of SC hCG.

A series of univariate and multiple logistic regression analyses were conducted to clarify the complex relationships among patient age, body mass index (BMI, in kilograms per meter squared), trigger day follicle number (≥14 mm), trigger day serum E_2 concentration (in picograms per milliliter), and trigger day endometrial thickness (in millimeters). In these analyses, all other variables were considered to be potentially dependent in relation to patient age. The BMI was treated as an independent variable in relation to trigger day follicle number, serum E_2, and endometrial thickness. Serum E_2 was treated as a dependent variable in relation to follicle numbers, as it is the maturing follicles that are the source of E_2 production. Endometrial thickness was considered to be potentially dependent in relation to E_2 concentration.

The relationships between endometrial thickness on the day of hCG trigger, as well as the potentially confounding variables, and clinical pregnancy (defined as ultrasound identification of a gestational sac) were evaluated by univariate logistic regression analyses. Ectopic pregnancies (EPs) were included as a negative clinical pregnancy. The independent association between endometrial thickness and clinical pregnancy, after adjusting for potential confounding variables, was investigated using multiple logistic regression analysis.

RESULTS

A total of 2,929 eligible treatment cycles were available for analysis. Mean demographic characteristics and treatment cycle outcomes are summarized in Table 1. Sixteen percent of treatment cycles resulted in a clinical pregnancy.

Figure 1 illustrates a flow diagram indicating all of the statistically significant independent associations among patient age, BMI, follicle number, serum E_2 concentration, and endometrial thickness as determined by multiple regression analysis adjusting for other correlated variables. Unadjusted univariate relationships between selected pairs of these variables are illustrated in Figure 2. Age, BMI, and follicle numbers each contributed independently to serum E_2 concentrations (Fig. 1; model $R^2 = 0.24$). Serum E_2 concentrations at trigger increased by approximately 18 pg/mL per year of age ($P<.0001$; Fig. 1; unadjusted univariate relationship illustrated in Fig. 2A), decreased by approximately 16 pg/mL per unit increase in BMI ($P<.0001$; Fig. 1; unadjusted univariate relationship illustrated in Fig. 2B), and increased by approximately 119 pg/mL per additional mature follicle ($P<.0001$; Fig. 1). Age, BMI, and serum E_2 were each independently associated with endometrial thickness (Fig. 1; model $R^2 = 0.03$). Endometrial thickness decreased by approximately 0.032 mm per year of age ($P=.004$; Fig. 1; unadjusted univariate relationship illustrated in Fig. 2C),

TABLE 1

Mean (SD) patient and cycle characteristics.

Subjects (patients)	2,929
Female age (y)	34.8 ± 3.9
Female BMI	24.5 ± 5.0
Endometrial thickness at trigger	8.8 ± 2.2
Serum E_2 at trigger	701.0 ± 393.0
Follicles ≥14 mm at trigger	2.6 ± 1.3
Insemination total motile sperm (millions)	24.1 ± 18.7
Clinical pregnancy	466 (15.9%)
Multiple pregnancy	85 (18.2%)
Twin pregnancies	74 (15.9%)
Triplet pregnancies	11 (2.4%)

Wolff. Endometrial thickness during IUI. Fertil Steril 2013.