Transvaginal Sonographic Assessment of the Follicular Development and Endometrial Thickness in Spontaneous and Clomiphene Citrate-Induced Cycles

Esmat Baroti, M.D.; Elham Nisar Samani, M.D.
Obstetrics and Gynecology Department, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

Received October 2007; Revised and accepted December 2007

Abstract
Objective: To assess follicular development and endometrial growth using transvaginal sonography in spontaneous and clomiphene citrate induced (CC) cycles.
Materials and methods: One hundred consecutive couples with unexplained infertility were recruited for this cross-sectional study from 2003 to 2005. Patients were monitored for the first cycle with no medication while the laboratory routine test results were being prepared. Clomiphene citrate (150 mg) was administered on days 5 to 9 of cycle in 60 women. The pattern of the follicular development and endometrial growth was evaluated between clomiphene citrate-induced cycles and spontaneous cycles. SPSS software and student t test were used for analyzing the results. P value less than 0.05 was considered for statistical significance.
Results: The patterns of follicular development and endometrial growth were similar in both study cycles.
Conclusion: Clomiphene citrate-induced cycles did not show different follicular and endometrial growth patterns compared with spontaneous cycles, so this must be regarded in treatment decision making.
Keywords: Infertility, Clomiphene citrate, Follicular development, Endometrial thickness

Introduction
Traditionally, clomiphene citrate (CC, Clomid, Serophene), has been the first line intervention for medical induction of ovulation. It is a weak synthetic drug that mimics the activity of an estrogen antagonist when given at typical pharmacologic doses for the induction of ovulation (oral dose of 150 mg of CC was administered on days 5 through 9 of the CC-induced cycle). More specifically, CC is thought to bind and block estrogen receptors in the hypothalamus for prolonged periods, thereby decreasing the normal ovarian hypothalamic estrogen feedback loop (1,2,3). In women with unexplained infertility, follicular growth has been found to be enhanced in CC-induced cycles (4-6). Clomiphene citrate has antiestrogenic effects at the level of endometrium or the cervix (1,4,7).

Controversy exists over the existence and significance of the effects of CC on endometrial growth. Endometrial thickness may be either reduced (5, 6, 8, 9), or not reduced but associated with a decrease in glandular density (10). Implantation may be impeded by an antiestrogenic effect on the endometrium, and reduce the pregnancy rate (11). Several studies have correlated endometrial thickness and pregnancy. They have reported that no pregnancy occurred when endo-
metrial thickness was 6–8 mm or less, and that the chance of pregnancy was greater with a thickness of 9–10 mm or more (12,13,14,15). Thus, endometrial thickness may be a factor contributing to the discrepancy between ovulation (80%) and pregnancy rates (40%) with the use of CC. We investigated follicular and endometrial growth characteristics in CC-induced cycles using spontaneous ovulatory cycles as controls.

Materials and methods

One hundred consecutive couples with unexplained infertility were recruited for the study from the infertility clinic of Royan Institute and Mahdieh hospital from 2003 to 2005. The study was approved by the Royan ethical committee and all women signed informed consent after counseling. Inclusion criteria were as the following: age of 21 to 35 years, regular menstrual cycles, normal physical examination and laboratory findings in male and female and laparoscopy demonstrating normal pelvis and tubal patency.

The women were evaluated first in a spontaneous cycle while the laboratory routine test results were being prepared. Clomiphene citrate (clomiphene citrate, Aboureyhan laboratories, Iran) with a dosage of 150 mg/day from day 5–9 of the cycle was prescribed for 60 women. Thus, 40 women did not receive the drug and were evaluated based on their spontaneous cycle. Transvaginal sonography was carried out from day 10 of the cycle until ovulation occurred. It was performed by using a transvaginal probe with a 7.5 MHz transducer (Hitachi EUB 200, Japan). First, the uterus was imaged in the longitudinal axis and endometrial thickness was measured from the echogenic interface at the junction of the endometrium and the myometrium, at the point of maximal thickness. This measurement represented two layers of endometrium. The hypoechogenic halo frequently seen surrounding the more echogenic endometrium was not included because it represents the inner layers of the vascular and compact myometrium. Next, both ovaries were visualized. Follicular measurement was performed in three planes, the probe being rotated 90° for the third plane. Diagnosis of ovulation was made according to the usual ultrasound criteria, namely shrinkage or disappearance of the follicle and accumulation of free fluid in the pouch of Douglas. The day of ovulation was considered as day 0 and the preceding days as day’s −1, −2, −3, −4 and so on. The interobserver and intraobserver variations for follicular diameter were 4.1% and 1.74% and they were 4.76% and 3.03% for endometrial thickness, respectively. The physicians who performed ultrasound evaluation were blinded to the samples, and measurements recorded. SPSS software 11.0 was used to analyze the results. Student t test was applied for the comparison. P value less than 0.05 was considered statistically significant.

Results

The mean age of the women was 27.2±3.6 years. The follicular diameter (range of 8.8–24 mm and 9.8–25 mm in the control and study group, respectively) was not significantly larger in CC-induced than in spontaneous cycles, and it increased progressively from day −4 in both groups to reach a maximum on day −1. There was no significant difference in daily follicular growth rate (2.6 mm/day), average follicular growth (11.42 and 11.55 mm in the control and study group, respectively), and in range of follicular diameter (8.8–24 mm and 9.8–25 mm in the control and study group, respectively). All spontaneous and CC-induced cycles were ovulatory. All spontaneous cycles were monofollicular, with only one dominant follicle that enlarged and released an oocyte. All CC-induced cycles were multifollicular, with an average of three preovulatory follicles (range: 1–5) but only one resulting to ovulation. An L-pattern endometrium was observed in all spontaneous and CC-induced cycles, characterized by three hyperechogenic lines with inner hypoechogenic regions. The endometrial thickness increased progressively from day −4 to day 0 in both groups. Endometrial thickness was not different in CC-induced cycles compared with spontaneous cycles (NS). There were no cases of ovarian hyper stimulation syndrome or multiple pregnancies.

Discussion

Clomiphene citrate-induced cycles did not show different follicular and endometrial growth patterns compared with spontaneous cycles.

In this study, L-pattern endometrium was observed in the preovulatory phase of both spontaneous and CC-induced cycles and there was no aberration in endometrial reflectivity patterns. This study did not demonstrate an adverse effect of CC on endometrial growth during the follicular phase of induced cycles compared with spontaneous cycles. This is in disagreement with other studies carried out in women with unexplained infertility (5,6,8,9). In Sereepapong study (10) endometrial thickness and ultrasonographic appearance of the endometrium were similar in
spontaneous and CC-induced cycles, but CC was given at a lower dosage and earlier in the menstrual cycle than in the present study. This may be an explanation for the differing results.

Endometrial thickness has also been correlated with pregnancy rates in various studies. Studies in non-IVF cycles have shown that the chance of pregnancy is greatest (no matter what program of ovarian stimulation is used) if endometrial thickness is 9–10 mm or more, and no pregnancy occurs when endometrial thickness is 6–8 mm or less (12,13,14,15), so successful implantation is correlated with endometrial thickness (11). This could probably be attributed to the local antiestrogenic effect of CC, which contributes to the poor pregnancy rate in spite of high ovulation rate and supraphysiological serum estradiol levels following CC therapy. Although, in this study none of the women in both groups had endometrial thickness below the critical level of 6 mm, unfortunately, we did not study the pregnancy rate to find out the relation between them.

This study showed that follicular and endometrial growth patterns did not differ in clomiphene citrate-induced cycles compared with spontaneous cycles. However, CC is the treatment of choice for infertile women, side effects and recent concerns of long-term use, including an increased risk of ovarian cancer, should be taken into consideration. Hence, the adverse effects of this drug must be monitored in infertile women with spontaneous ovulation who are given CC.

References