

# Transabdominal Ultrasonographic Evaluation of Endometrial Thickness in Clomiphene Citrate-Stimulated Cycles in Relation to Conception

Igal Wolman, MD, Joseph Sagi, MD, David Pauzner, MD, Israel Yovel, MD,  
Daniel S. Seidman, MD, and Menachem P. David, MD

**Abstract:** The possible antiestrogenic effect of clomiphene citrate on endometrial growth was assessed by serial transabdominal ultrasonographic measurements in 46 women with unexplained infertility. A significantly higher ( $p < 0.05$ ) rate of endometrial growth was observed in the 8 women who conceived compared with the 38 women who failed to conceive. A thicker endometrium ( $4.6 \pm 0.3$  mm) was observed from the third day before ovulation as well as a higher average growth rate in the three days prior to ovulation ( $0.7 \pm 0.1$  mm/day) in the group that achieved pregnancy compared to a lower endometrium ( $2.1 \pm 0.2$  mm) from the third day before ovulation and a slower growth rate in the three days prior to ovulation ( $0.2 \pm 0.0$  mm/day) in the group that did not achieve pregnancy ( $p < 0.05$ ). These data suggest that clomiphene citrate may exert an antiestrogenic effect on the endometrium, and thus interfere with implantation. © 1994 John Wiley & Sons, Inc.

**Indexing Words:** Endometrial thickness · Menstrual cycles, stimulated · Infertility

Clomiphene citrate is well recognized as a useful treatment for the induction of ovulation in normotrophic, gonadotropic, normoprolactinemic, anovulatory infertility. Although about 87% of well-selected patients treated with clomiphene citrate ovulate, only approximately 40% will ultimately conceive.<sup>1</sup>

It has been suggested that the discrepancy between the ovulation and conception rates after clomiphene citrate therapy may in some cases be due to the antiestrogenic effect of clomiphene citrate.<sup>2,3</sup> Clomiphene citrate, acting as an antiestrogen, may severely depress vaginal epithelium, the endocervical crypts, and possibly the endometrium.<sup>2,3</sup> Eden et al<sup>4</sup> showed that clomiphene citrate cycles are characterized by an inhibition of endometrial thickening. Impaired endo-

metrial growth in the early proliferative phase following clomiphene citrate and human menopausal gonadotropin (HMG), compared with growth in normal cycles, was also found by Lenz and Lindenberg.<sup>5</sup> These observations support previous data<sup>6</sup> demonstrating an inhibitory effect of clomiphene citrate on the endometrium during the proliferative phase, despite increased levels of serum estradiol.<sup>4-6</sup> It was suggested that the anti-estrogenic effect of clomiphene citrate on the normal cyclical growth of the endometrium may impede conception in ovulatory cycles,<sup>4</sup> as well as implantation in stimulated cycles associated with in vitro fertilization (IVF).<sup>5</sup>

The aim of the present study was to examine whether the inhibitory effect of clomiphene citrate on endometrial growth was related to the success of implantation.

---

From the Department of Obstetrics and Gynecology "B", Serlin Maternity Hospital, Tel-Aviv Medical Center, Soraski School of Medicine, Tel-Aviv University. For reprints contact Igal Wolman, MD, Department of Obstetrics and Gynecology "B", Serlin Maternity Hospital, Ein Dor St. 15, Tel-Aviv 61070, Israel.

## MATERIAL AND METHODS

The first 46 consecutive patients who presented at our infertility clinic between July 1989 and

January 1992 with unexplained infertility and met our inclusion criteria were prospectively selected for the study. Normotrophic, gonadotropic, normoprolactinemic, anovulatory women were included in this study if they were assigned to receive clomiphene citrate for induction of ovulation. Women with malformed or retroflected uterus, pathologic changes in the uterus, or obesity (defined as body mass index higher than 32 kg/m<sup>2</sup>) were excluded from the study, and thus measurements were not obtained for these women. All cases of male-factor infertility were also excluded from the study.

All patients were treated by clomiphene citrate (Ikaklomin, Ikapharm, Teva, Kfar-Saba) 50 to 150 mg/day. Chorionic gonadotropin (hCG, Chorigon Ikapharm, Teva, Kfar-Saba) 10,000 IU IM, was administered to induce ovulation. Intercourse was recommended 36 hours after hCG administration. Two cycles were followed in four women; thus we obtained a total of 50 clomiphene cycles.

Ovulation was established by the following parameters: The appearance of a dominant follicle, its collapse and the development of a corpus luteum, demonstration of free fluid in the pouch of Douglas, and a serum progesterone >15 ng/mL on the 21st day of the cycle in the subsequent mid-luteal phase.

Daily transabdominal ultrasound measure-

ments were all performed by the same investigator (JS) using an Aloka sector scanner model SSD 248 (Keymed Medical and Industrial Equipment Ltd., Southend-or-Sea, UK) with a 3.5-MHz long focused transducer.

The maximum double layered thickness of the entire endometrium along the longitudinal axis was measured (Figure 1). The mean growth rate per day was calculated for each patient based upon the differences observed between sequential pairs of daily measurements. Women for whom daily measurements could not be obtained for two consecutive days or for a total of three or more days were excluded. The results of the endometrial growth rate measurements were compared between women who conceived and those who did not conceive.

Statistical analysis was performed using the Fisher exact test, Student's *t*-test, and two-way analysis of variance. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

The mean age of the women under study was 26 (range: 24 to 29). All patients were evenly distributed among the three dosage schedules (Table 1).

From the 9th day before ovulation to the 4th day before ovulation no significant differences in endometrial thickness were observed between the

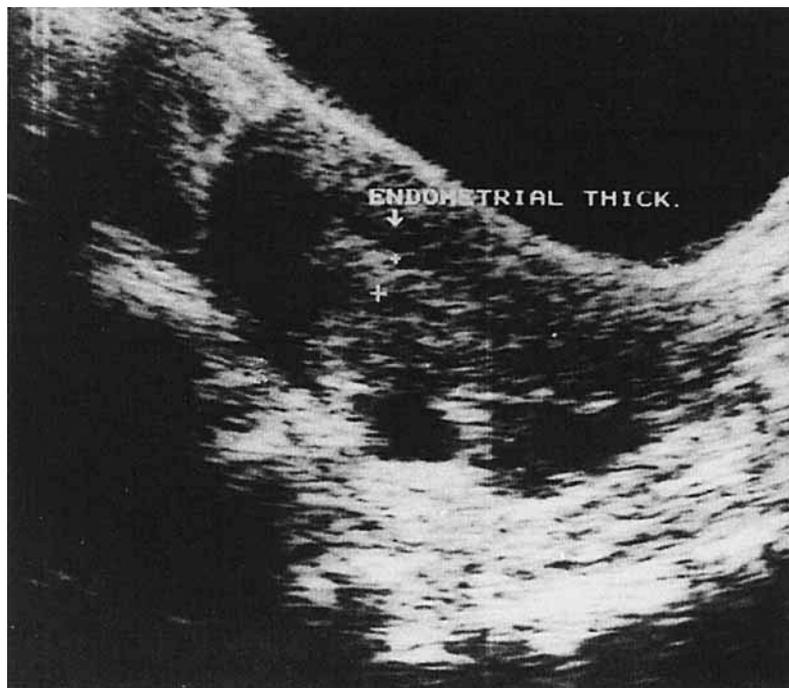


FIGURE 1. Measurement of maximal thickness of the endometrium along the longitudinal axis.

## ENDOMETRIAL THICKNESS IN STIMULATED CYCLES

**TABLE 1**  
The Number of Patients in Each Dosage Schedule of Clomiphene Citrate

	50 mg	100 mg	150 mg
Conceived*	2	2	4
Did not conceive*	14	13	15

\*No statistically significant differences between the three groups, Fisher exact test.

pregnancy group and the group who did not conceive. However, a significantly higher ( $p < 0.05$ ; two-way analysis of variance) increase in endometrial thickness was observed in the period from the third day before ovulation until ovulation in the eight women who conceived (average of 3 daily measurements  $\pm$  SD:  $4.6 \pm 0.27$  mm) compared with the 38 women who failed to conceive (average of 3 daily measurements  $\pm$  SD:  $2.1 \pm 0.22$  mm) (Figure 2).

The mean  $\pm$  SD endometrial growth rate was  $0.7 \pm 0.08$  mm/day in the three days prior to ovulation in the group that achieved pregnancy compared with only  $0.2 \pm 0.01$  mm/day in the non-conception group. The mean  $\pm$  SD endometrial growth rate was calculated by averaging the day-to-day differences observed in the three daily measurements performed prior to ovulation.

### DISCUSSION

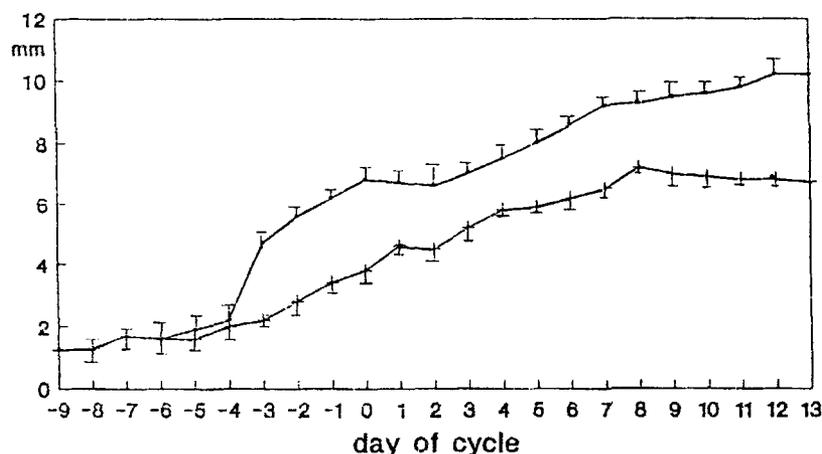
The endometrial thickness and growth has been suggested to be a possible predictor of implantation during stimulated cycles in IVF treatment.<sup>7,8</sup> Because the possible inhibitory effect of clomiphene citrate on endometrial growth has been proposed as a cause for concern regarding the suc-

cess of IVF stimulated cycles,<sup>5</sup> the predictive value of changes in endometrial thickness was suggested. However, although the inhibition of endometrial thickness in clomiphene citrate-stimulated cycles has been shown previously,<sup>4,5,9</sup> the correlation with conception rates was not assessed.

The present study demonstrates a significantly ( $p < 0.05$ ) greater endometrial thickness from the third day prior to ovulation and a higher growth rate in the three days prior to ovulation in women receiving clomiphene citrate who conceived compared with those who did not conceive. Therefore, it may be implied from our data that a possible antiestrogenic effect of clomiphene citrate, as reflected by a poor endometrial growth rate, may exist in the nonconception group.

The addition of estrogens to clomiphene citrate-treatment cycles has been advocated and a beneficial effect on cervical mucous proposed.<sup>2,10</sup> Taubert and Dericks-Tan<sup>11</sup> have demonstrated that high doses of estrogens do not interfere with the ovulation-inducing effect of clomiphene citrate when it is given in a sequential regimen. They therefore concluded that clomiphene citrate followed by ethinyl estradiol or conjugated estrogens might be used in certain cases of otherwise therapy-resistant infertility. In a recent study using vaginal ultrasonography, Yagel et al<sup>12</sup> showed that ethinyl estradiol may reverse the deleterious effect of clomiphene citrate on endometrial growth.

Ultrasonographic measurements of endometrial growth may improve our ability to distinguish between women who will conceive following clomiphene citrate administration and women who may benefit from estrogen supplementation to



**FIGURE 2.** Changes in endometrial thickness (means  $\pm$  SE) during clomiphene citrate stimulated cycles (top: pregnancy group; lower: non-conception group).

clomiphene citrate treatment. The use of transvaginal ultrasonography with high frequency, high resolution probes allows better visualization of small changes in endometrial structure.<sup>13,14</sup> Although transvaginal sonography is currently the recommended method for the evaluation of endometrial changes, we still lack detailed information on the effects of clomiphene citrate on endometrial thickness in regard to conception. Nevertheless, we believe that important clinical references can be made from the present data using transabdominal sonography. Further study regarding the effect of estrogens on endometrial growth in clomiphene citrate-stimulated cycles using serial ultrasonographic measurements is needed to assess its possible influence on conception rate.

#### REFERENCES

1. Adashi EY: Ovulation induction: Clomiphene citrate, In: *Infertility a Comprehensive Text*. Edited by MM Seibel, Norwalk, Appleton & Lange, 1990 p 303.
2. Maxson WS, Pittaway DE, Herbert CM, Garner CH, Colston-Wentz A: Antiestrogenic effect of clomiphene citrate: Correlation with serum estradiol concentrations. *Fertil Steril* 42:356, 1984.
3. Gyslem M, March CM, Mishell D Jr, Bailey ES: A decade's experience with an individualized clomiphene treatment regimen including its effect on the postcoital test. *Fertil Steril* 37:161, 1982.
4. Eden JA, Place J, Carter DG, Jones J, Alaghband-Zadeh J, Pawson EM: The effect of clomiphene citrate on follicular increase in endometrial thickness and uterine volume. *Obstet Gynecol* 73:187, 1989.
5. Lenz S, Lindenberg S: Ultrasonic evaluation of endometrial growth in women with normal cycles during spontaneous and stimulated cycles. *Hum Rep* 5:377, 1990.
6. Fleischer AC, Pittaway DE, Beard LA, et al: Sonographic depiction of endometrial changes oclomiphene citrateurring with ovulation induction. *J Ultrasound Med* 3:341, 1984.
7. Gonen Y, Casper RF: Prediction of implantation by the sonographic appearance of the endometrial during controlled ovarian stimulation for in vitro fertilization (IVF). *J In Vitro Fert Embryo Transfer* 7:146, 1990.
8. Gonen Y, Casper RF, Jacobson W, Blankier J: Endometrial thickness and growth during ovarian stimulation: A possible predictor of implantation in in vitro fertilization. *Fertil Steril* 52:446, 1989.
9. Gonen Y, Casper RF: Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. *Human Reproduction* 5:670, 1990.
10. Van der Merwe JN: The effect of clomiphene and conjugated estrogen on cervical mucus. *S Afr Med J* 60:347, 1981.
11. Taubert HD, Dericks-Tan JE: High doses of estrogens do not interfere with the ovulation-induction effect of clomiphene citrate. *Fertil Steril* 27:375, 1976.
12. Yagel S, Ben-Chetrit A, Anteby A, et al: The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate. *Fertil Steril* 57:33, 1992.
13. Kupfer MC, Schwimer SR, Lebovic J: Transvaginal sonographic appearance of endometriomata: Spectrum of findings. *J Ultrasound Med* 11:129, 1992.
14. Santolaya-Forgas J: Physiology of the menstrual cycle by ultrasonography. *J Ultrasound Med* 11:139, 1992.