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Use of ethinyl estradiol to reverse the antiestrogenic effects of clomiphene citrate in patients undergoing intrauterine insemination: a comparative, randomized study

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Objective: To compare the effectiveness of clomiphene citrate used alone and in combination with ethinyl E_2 for the induction of ovulation in patients undergoing IUI.

Design: Randomized, double-blind study.

Setting: Four infertility treatment centers.

Patient(s): Women aged 25–35 years with infertility of at least 2 years' duration and oligomenorrhea or amenorrhea associated with a positive menstrual response to an IM progesterone challenge.

Intervention(s): A total of 64 patients were randomized to treatment with CC (100 mg daily for 5 days) or CC (100 mg daily for 5 days) plus ethinyl E_2 (0.05 mg daily for 5 days).

Main Outcome Measure(s): The uterine artery pulsatility index, number of preovulatory follicles, endometrial thickness, and pregnancy rate.

Result(s): Both treatment regimens increased FSH, LH, and 17β-E_2 levels, with no statistically significant differences. There was a statistically significant difference in endometrial thickness between the two treatment groups. No statistically significant differences were noted in pulsatility index values or in the number of preovulatory follicles.

Conclusion(s): Ethinyl E_2 can reverse the deleterious effects of CC on endometrial thickness, which may contribute to higher pregnancy rates. (Fertil Steril® 2000;73:85–9. ©1999 by American Society for Reproductive Medicine.)

Key Words: Clomiphene citrate, ethinyl estradiol, IUI

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Clomiphene citrate (CC), a nonsteroidal estrogen agonist/antagonist, was first synthesized in 1956. It was reported to be effective at inducing ovulation by Greenblatt et al. in 1961 (1), and it remains the most commonly used drug in the treatment of infertility (2). Clomiphene citrate is most effective at inducing ovulation in women with anovulation or oligo-ovulation, a wide variety of menstrual disorders, relatively normal (or elevated) gonadotropin levels, and evidence of significant endogenous estrogen production (i.e., World Health Organization group II) (3). The U.S. Food and Drug Administration has approved its use at a dosage of 50 or 100 mg/d for a maximum of 5 days per cycle (4). After spontaneous menses, or the induction of menses by progesterone withdrawal, CC therapy is started on cycle day 3, 4, or 5 at a dosage of 50 mg daily for 5 days.

Obese women tend to require higher doses of CC to achieve ovulation (5, 6). Clomiphene citrate is not stored in adipose tissue, and the need for an increased dose in obese women probably is due to a more intensive anovulatory state with higher androgen levels that produce a more resistant hypothalamic-pituitary-ovarian axis in these patients (7). Increasing the dose of CC eventually produces the same level of success in obese women as is attained in lean women (8, 9).

Over the years, evidence has accumulated indicating that CC is successful at inducing ovulation in 50%–75% of cases (10, 11), but the number of pregnancies achieved after ovulation induction is much lower than expected (12). This discrepancy has been attributed to a negative action of CC in the form of prolonged antiestrogenic effects on endometrial receptivity (13) and cervical mucus (14). Moreover, Hsu et al. (15) demonstrated that CC interferes with uterine blood flow. In an effort to avoid these negative effects, ethinyl E_2 can be given in adequate dosages (8, 16–18).

The aim of this study was to compare pregnancy rates after IUI in two groups of women who were given CC alone or CC in combination with ethinyl E_2. In addition, plasma levels of FSH, LH, and E_2 were determined, follicular recruitment was noted, and endometrial thickness and uterine artery blood flow, both sensitive indicators of uterine receptivity, were measured (19).

MATERIALS AND METHODS

Patients

A total of 64 patients were enrolled in this study. The inclusion criteria were age between 25 and 35 years, infertility of at least 2 years' duration, and oligomenorrhea or amenorrhea associated with a positive menstrual response to an IM progesterone challenge with 100 mg of progesterone-in-oil. All patients had normal serum concentrations of TSH, prolactin, and total testosterone. It was the first cycle of ovulation induction using CC in all cases, and no patient had received fertility medications in the past.

We excluded women whose partners had an abnormal semen analysis according to World Health Organization criteria (20), women who had uterine or tubal abnormalities on hysterosalpingography, and women who had a body mass index of >25 kg/m^2.

Treatment Protocol

The study protocol was approved by the institutional board of research, and all patients gave informed consent before they entered the study. The start of menses was designated as day 1 of the treatment cycle. All patients were randomly enrolled in a double-blind manner in one of two groups.

In group A (n = 32), stimulation began on day 3 with the administration of 100 mg of CC (Prolifen; Chiesi Farmaceutici, Parma, Italy) daily for 5 days. Beginning on day 8, 0.05 mg of ethinyl E_2 (Etinilestradiolo; AMSA, Rome, Italy) was given daily for 5 days.

In group B (n = 32), stimulation began on day 3 with the administration of 100 mg of CC daily for 5 days. Beginning on day 8, placebo was given for 5 days.

Plasma levels of 17β-E_2 were determined, and follicle size and number were assessed by ultrasound examination on days +5, +7, and +12 of stimulated cycles.

All patients were given 10,000 IU of hCG (Gonasi HP; AMSA) IM when the serum 17β-E_2 concentration was >200 pg per mature follicle and there was at least one follicle with a minimum diameter of 18 mm.

Intrauterine Insemination

A single IUI was performed 24–36 hours after the administration of hCG.

Luteal Phase

Starting 3 days after IUI, all patients received an IM injection of 50 mg of progesterone daily (Prontogest; AMSA). Treatment was maintained until β-hCG levels were evaluated.

Laboratory Determinations and Ultrasound Examinations

Plasma concentrations of FSH, LH, and 17β-E_2 were determined by RIA in blood samples obtained on days 1, 5, 9, and 12 of the menstrual cycle. Ultrasound examinations were performed daily beginning on day 1 (to rule out ovarian cysts) and ending when the mean follicle diameter reached 18 mm. The endometrial thickness was estimated on the day of hCG administration. The pulsatility index was recorded in both uterine arteries. A gynecologist experienced in transvaginal sonography performed all examinations with a 5-MHz broad-band probe.

The examiner was blinded to the patient's group assignment. Color Doppler was used to image the uterine arteries on cycle days 2, 8, and 12. The pulsatility index was calculated by subtracting the peak end-diastolic shifted frequency from the systolic shifted frequency and dividing the result by the mean Doppler shift over the cardiac cycle. The intraobserver coefficient of variation for measurement of the pulsatility index was 5.3%. All examinations were performed between 9:00 A.M. and 11:00 A.M. to reduce the effects of circadian variations in the pulsatility index (21).

Determination of Pregnancy States

A biochemical pregnancy was defined as a small, transitory increase in β-hCG levels followed by a decrease within a week. A clinical pregnancy was defined by the visualization of a gestational sac at the first planned ultrasound examination performed at 6–7 weeks of pregnancy or by a serum β-hCG level of $\geq$1,400 mIU in the absence of an ultrasound examination. Ongoing pregnancies were gestations that reached 20 weeks of gestation.

Statistical Analysis

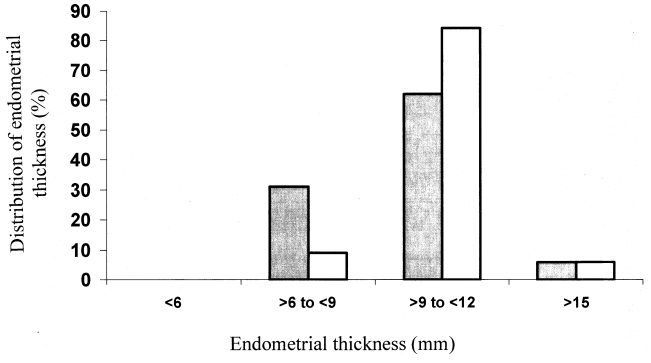
The statistical analysis was performed with the SPSS statistical package (Sigmastat and Sigmaplot; Microsoft Corp., Redmond, WA). The χ^2 test and Fisher's exact test were used. Statistical significance was defined as $P<.05$.

RESULTS

On day +1, before the beginning of treatment, there were no statistically significant differences in the serum levels of

FIGURE 1

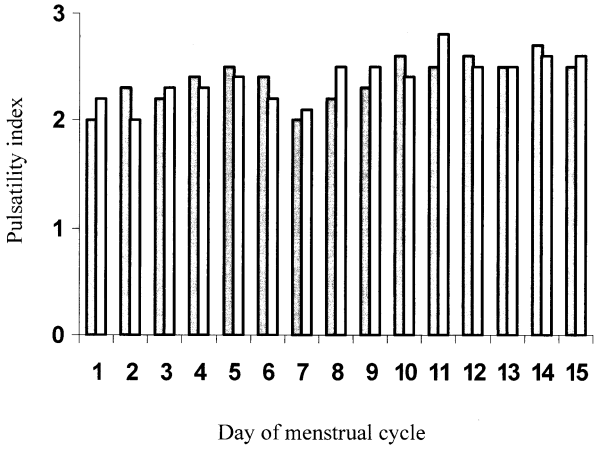
Percentage distribution of endometrial thickness on the day of hCG administration. ■ = CC; □ = CC + ethinyl E_2.



Gerli. Intrauterine insemination. Fertil Steril 2000.

FIGURE 2

Mean (±SE) pulsatility index for patients undergoing ovarian stimulation with CC alone or CC plus ethinyl E_2. ■ = CC; □ = CC + ethinyl E_2.



Gerli. Intrauterine insemination. Fertil Steril 2000.

FSH, LH, and 17β-E_2 between the two treatment groups. Moreover, there were no statistically significant differences in the serum levels of FSH, LH, and 17β-E_2 between the two groups during the entire treatment period (data not shown).

There were no statistically significant differences in follicular development as measured by the number of preovulatory follicles (data not shown).

Endometrial Thickness and Uterine Blood Flow

The endometrial thickness was estimated on the day of hCG administration. In all cases, it was >6 mm. It was 6–9 mm in 10 cases in group B (31.25%) vs. 3 cases in group A (9.37%); 9–12 mm in 20 cases (62.5%) in group B vs. 27 cases (84.37%) in group A; and >15 mm in 2 cases (6.25%) in group B vs. 2 cases (6.25%) in group A (Fig. 1).

No statistically significant differences were noted in pulsatility index values (Fig. 2).

Pregnancy Rate

The miscarriage rate was 6.25% in group A vs. 18.75% in group B. The difference was statistically significant (Table 1).

At the same time, the percentage of ongoing pregnancies was higher in group A (37.5%) than in group B (6.25%). This difference also was statistically significant (Table 1).

DISCUSSION

Clomiphene citrate, which was introduced in 1967, is considered to increase the incidence of spontaneous abortion (22, 23). This increase has been attributed to several factors, including impaired endometrial development (24, 25).

Goldstein et al. (26) reported that E_2 concentrations that were either too low or too high in association with normal progesterone concentrations caused desynchronized endometrial development. An antagonistic effect of CC on the endometrium has long been recognized in histologic studies (23, 24, 27, 28). Further, numerous ultrasound studies have shown that CC may reduce endometrial thickness (29–34).

TABLE 1

Characteristics of patients who received CC plus ethinyl E_2 (group A) or CC alone (group B).

Characteristic	Group A	Group B	*P* value
No. of patients	32	32	—
Mean (±SD) age (y)	28.0 ± 5.6	26.0 ± 4.2	NS
Mean (±SD) duration of infertility (mo)	48.1 ± 18.5	36.7 ± 9.6	NS
No. (%) of pregnancies per cycle			
Biochemical	3 (9.37)	4 (12.5)	NS
Miscarried	2 (6.25)	6 (18.75)	<.05
Ongoing	12 (37.5)	2 (6.25)	<.05

Note: NS = not significant.

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It has been shown that the adverse effects of CC on the endometrium can be prevented by administering estrogen together with or after CC (18). On the other hand, Bateman et al. (33) demonstrated that exogenous estrogens do not improve the quality or quantity of cervical mucus in patients treated with CC. At the same time, the use of CC for IVF does not appear to reduce the implantation rate (35), possibly because the concomitant use of hMG, with its more sustained E_2 production, may have a positive effect on the endometrium.

Our study showed that the addition of estrogens to CC therapy increases endometrial thickness and decreases the risk of spontaneous abortion. The increased pregnancy rate might be explained by an endometrium improved with estrogens (possibly acting to balance the antiestrogenic effects of CC) that facilitates embryo implantation. Results supporting this hypothesis were obtained in a study of IUI cycles (25). In this study, it was estimated that induction of ovulation with the sequential administration of CC and hMG results in a fecundity rate double that achieved with the administration of CC alone, again suggesting a possible positive effect of estrogen on the endometrium. Although Dickey et al. (25) noted an increased pregnancy rate related to an increased number of preovulatory follicles when hMG was administered after CC, they also observed a significant doubling of the implantation rate per follicle. In this study, the level of E_2 per follicle was nearly double in patients who received CC and hMG compared with patients who received CC alone.

The data in the literature and our observations herein may lead to the conclusion that adding estrogens to CC in ovulation induction regimens for IUI is a good strategy for maximizing pregnancy rates while reducing costs associated with serum hormone measurements, ultrasound examinations, and repeated hMG injections.

In conclusion, in agreement with other studies (18, 24), we noted that inadequate endometrial development may have a negative effect on the outcome of implantation. In fact, the preovulatory endometrial thickness is predictive of the risk of miscarriage (36). Adding ethinyl E_2 to treatment protocols that include CC produces a favorable endometrial response. Our data suggest that a combined regimen of CC plus ethinyl E_2 may reverse the deleterious effects of CC on endometrial development.

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