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CLINICAL ARTICLE

A randomized controlled trial evaluating the effect of ethinyl estradiol during clomiphene citrate cycles among women with polycystic ovary syndrome☆

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ABSTRACT

Objective: To investigate the effects of low-dose ethinyl estradiol (EE) on the clinical pregnancy rate among women with polycystic ovary syndrome (PCOS) undergoing ovulation induction with clomiphene citrate (CC). *Methods:* Between March 12, 2011, and February 10, 2013, a randomized, double-blind, placebo-controlled trial was conducted at the Royan Institute Research Center, Tehran, Iran, among women with PCOS who were aged 25–30 years, were undergoing their first intrauterine insemination cycle, and had a history (≥2 years) of infertility, oligomenorrhea, or amenorrhea. Participants were randomly allocated to receive EE (0.05 mg daily for 5 days) or placebo, co-administered with CC cycles (100 mg daily for 5 days). The primary outcome was clinical pregnancy rate. Analyses were per protocol: patients who discontinued the intervention were excluded. *Results:* Analyses included 45 women who received CC and EE, and 50 women who received CC and placebo. The number of women who achieved a clinical pregnancy was higher among participants who received CC and EE (13 [29%]) than among those in the control group (5 [10%]; $P = 0.02$). No adverse effects of EE were reported. *Conclusion:* The combination of CC and EE seems to increase the clinical pregnancy rate among women with PCOS undergoing intrauterine insemination.
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1. Introduction

Polycystic ovary syndrome (PCOS) is a leading cause of female infertility, accounting for approximately 70% of all infertility cases related to anovulation [1]. Clomiphene citrate (CC) is an effective treatment that has long been considered the first-line approach for ovulation induction among women with this condition [2]. Nevertheless, despite reported CC-induced ovulation rates of 60%–85%, the overall conception rate following such treatment remains low (10%–20%) [3]. A widely accepted explanation for this discrepancy is the anti-estrogenic properties of CC on the endometrium [4], cervical mucus [5], and uterine blood flow [6].

Estimates suggest that 15%–50% of women receiving CC exhibit a thin endometrium and non-trilaminar pattern at midcycle [3]. Some studies demonstrated that CC exerts an intrinsic negative influence on the synchronization of glandular development and stromal maturity of the endometrium by promoting a decline in glandular density and a decrease in the number of vacuolated cells [4,7].

Few studies have evaluated blood-flow parameters during CC-stimulated cycles; however, interference of uterine blood flow or endometrial perfusion has been detected in some trials of this drug [6,8]. For example, a study of women who had either polycystic or healthy ovaries found that the uterine artery hemodynamics were markedly different at the baseline ultrasonographic scan and during the CC-induced menstrual cycle [9].

Impaired endometrial development and decreased uterine blood flow might lead to lowered implantation rates [10,11]. Consequently, it seems logical to identify adjuvant therapies that reverse the anti-estrogenic effects of CC. Some investigations have indicated a positive role for estrogens in preventing the adverse effects associated with CC treatment of infertility [4,12,13].

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The aim of the present study was to assess the effect of adding low-dose ethinyl estradiol (EE) to CC on the clinical pregnancy rate among women with PCOS undergoing intrauterine insemination (IUI).

2. Materials and methods

A randomized, double-blind, placebo-controlled trial was performed at the Royan Institute Research Center, Tehran, Iran, between March 12, 2011, and February 10, 2013. The present study was registered and approved by the institutional review board and ethics committee of Royan Institute, Tehran, Iran, in compliance with the Helsinki Declaration. Informed consent was obtained before recruitment.

The target population of the present study was women with PCOS who were undergoing their first treatment cycle of IUI. The diagnosis of PCOS was based on the Rotterdam criteria [14]. Inclusion criteria for the present study were age 25–30 years; body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) less than 30; at least a 2-year history of infertility; oligomenorrhea or amenorrhea; a positive progesterone challenge test result; concentrations of prolactin, free thyroxine, and thyroid-stimulating hormone within the reference range; a normal hysterosalpingography result with normal uterine cavity and unblocked tubes; and a partner with normal semen analysis results according to WHO criteria [15]. Oligomenorrhea was defined as a menstrual cycle longer than 35 days. Amenorrhea was defined as the absence of menstruation for 6 months during the previous year [1].

Eligible patients were randomly assigned to the study (CC and EE) or control (CC and placebo) groups using computer-generated random numbers (SPSS version 18.0; IBM, Armonk, NY, USA) prepared by the statistician (M.R.A.). The allocation was performed by an independent clinician who was not involved in the present study.

All participants received a daily dose of 100 mg CC, which was administered for a total of 5 days from day 3 of the cycle. Participants assigned to the study group were then switched to a daily dose of 0.05 mg of EE, which was administered for a total of 5 days from day 8 of the cycle. The control group received placebo instead of EE during this timeframe. All medications were orally administered. Participants received 10 000 IU of human chorionic gonadotropin (hCG) when at least one dominant follicle (≥18 mm in diameter) was detected; IUI was performed 36–40 hours after the triggering of ovulation. Luteal phase support comprised either a daily dose of 100 mg progesterone in oil administered via the intramuscular route or a twice-daily dose of 400 mg progesterone administered intravaginally. Luteal phase support commenced 2 days after IUI and was maintained until the scheduled pregnancy test was conducted.

Blood samples were taken on day 3 of the cycle to assay the baseline plasma concentrations of follicle-stimulating hormone, luteinizing hormone, and endogenous estradiol (E2). Transvaginal ultrasonography was used to rule out the presence of ovarian cysts on day 3; for serial assessment of the number and size of the developing follicles on days 3, 7, and 12 (and thereafter according to individual patient response); and for measuring endometrial thickness on the day of hCG administration. Transvaginal color Doppler ultrasonography using a 4–8 MHz probe (ProSound Alpha 10; Aloka, Tokyo, Japan) was performed by an experienced radiologist on the day of hCG injection to obtain flow velocity waveforms from the ascending branch of the uterine artery in the para-cervical area at the level of the internal cervical orifice. The pulsatility index (PI) was defined as the variability in flow between the systole and the diastole; this measure was calculated by dividing the difference between the peak systolic and end-diastolic frequencies by the time-average of the maximum frequency shift [16].

Initial determination of the serum β-hCG concentration was performed 17 days after the hCG injection. The primary outcome measure was clinical pregnancy as detected by a positive β-hCG test result and ultrasonographic visualization of an intrauterine sac with fetal heart beat (4–6 weeks after IUI). Spontaneous abortion was defined as pregnancy loss at or before 12 weeks.

Participants, healthcare providers, and researchers assessing the present study outcomes were masked to the treatment allocation. Placebo tablets were identical in appearance to EE and similarly packaged in serially numbered sealed envelopes.

The data were analyzed using SPSS version 18.0. The sample size calculation was obtained from a pilot study based on the primary outcome using PASS version 11 (NCSS, Kaysville, UT, USA). With a power of 80%, at the 95% probability level, the present study aimed to include 49 participants in each group. Patients who discontinued the intervention were excluded from analyses. Mean values are given with standard deviations. Continuous and categorical variables were compared using the *t* test and the Pearson χ^2 or Fisher exact tests, respectively. Pearson correlation coefficients (*r* values) were calculated to evaluate the association between variables. $P < 0.05$ was considered statistically significant.

3. Results

A total of 154 patients underwent randomization, with 77 allocated to each group (Fig. 1). Patients whose cycles of CC were cancelled before hCG administration (n = 59) were excluded from the final analysis. The two groups were similar with respect to cycle cancellation ($P = 0.41$). The most frequent reason for cycle cancellation was failure to achieve adequate follicular development (n = 46).

Table 1 summarizes the patients' demographic and clinical characteristics. No statistically significant between-group differences were detected in any of the characteristics evaluated.

The clinical outcomes are presented in Table 2. Endometrial thickness ranged from 6 mm to 17 mm. The mean endometrial thickness was 9.7 ± 2.1 mm in the study group versus 8.9 ± 1.6 mm in the control group ($P = 0.04$). The addition of EE to CC was associated with lowered PI of both the right ($P = 0.03$) and left ($P = 0.001$) uterine arteries. Furthermore, a marked difference was detected between the study group and the control group with regard to the number of women achieving a chemical pregnancy (14 [31%] vs 5 [10%]; $P = 0.01$) and the number achieving a clinical pregnancy (13 [29%] vs 5 [10%]; $P = 0.02$). No statistically significant between-group difference in ongoing pregnancy rate was observed. No adverse effects of EE were reported.

Among the women who became pregnant, 12 (92%) of 13 in the study group and four (80%) of five in the control group displayed both a PI between 2 and 3, and an endometrial thickness of at least 8 mm. No correlation was found between the mean right or left uterine artery PI and endometrial thickness on the day of hCG administration($r = 0.09$; $P = 0.36$).

4. Discussion

The present study demonstrated that adding low-dose EE as an adjunct to CC in ovulation induction regimens for IUI enhanced endometrial proliferation, uterine perfusion, and clinical pregnancy rate among women with PCOS.

These findings were in line with the data reported in a comparative randomized double-blind study in which the ongoing pregnancy rate was 37.5% among patients with unexpected infertility who received CC in combination with EE versus 6.25% for those who received CC alone [12]. Likewise, a study that enrolled 50 patients confirmed that adding EE to CC created a favorable endometrial response even at low doses [4]. Unlike the present study, however, no statistically significant differences were noted in the mean PI in these two studies [4,12].

The increased rate of pregnancy in the study group in the present study might be associated with increases in endometrial thickness that occur in response to estrogens, which in turn lead to enhanced embryo implantation [12]. Evidence to support a possible positive effect of estrogen on the endometrium was obtained in a study showing that the fecundity and E2 levels among patients receiving sequential administration of CC and human menopausal gonadotropin were double that among patients who received CC alone [17].