

# Effect of Initiation Day of Clomiphene Citrate Treatment on Endometrium and Cervical Mucus

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## ABSTRACT

**Objective:** To compare the antiestrogenic effects of clomiphene citrate (CC) on reproductive end organs in patients where CC was started on different days of the cycle.

**Patients and Methods:** A total of 95 patients who underwent ovulation induction with CC were initially included in this prospective randomized controlled study. Patients were divided into two treatment groups: in day 3 group (n=52), CC was given from day 3 to 7 of the cycle for five days, whereas in day 5 group (n=43), CC was given on days 5 to 9. The antiestrogenic effects of CC in terms of endometrial thickness and cervical mucus quality, cycle characteristics, and treatment outcomes were assessed. To observe possible differences in antiestrogenic effects, only data from ovulatory cycles were analyzed.

**Results:** Forty-four patients in the day 3 group and 34 patients in the day 5 group were analyzed. Endometrial thickness was similar in both groups on the day of human chorionic gonadotropin (hCG). In the day 3 group, the mean cervical mucus score was lower (8.1±2.7 vs. 9.7±2.3, p=0.036). There were no significant differences between the groups in the mean serum estradiol (E2), progesterone levels, and the number of leading follicles on the day of hCG, and ovulation and pregnancy rates per cycle.

**Conclusion:** Endometrial thickness does not differ whether starting CC on day 3 or 5 of the cycle. Nevertheless, poor cervical mucus quality may be more common in the patients where CC was started on day 3 of the cycle compared to day 5.

**Key words:** clomiphene citrate, cervical mucus, endometrial thickness, initiation day

## KLOMİFEN SİTRAT TEDAVİ BAŞLANGIÇ GÜNÜNÜN ENDOMETRİUM VE SERVİKAL MUKUSA ETKİSİ

### ÖZET

**Amaç:** Siklusun farklı günlerinde klomifen sitrat (CC) tedavisi başlanan hastalarda, klomifen sitratın reproduktif organlardaki antiöstrojenik etkisini kıyaslamak.

**Hastalar ve Yöntemler:** Klomifen sitratla ovulasyon indüksiyonu yapılan toplam 95 hasta, bu prospektif randomize kontrollü çalışmaya dahil edildi. Hastalar 2 gruba ayrıldı: 3. gün grubuna (n=52), siklusun 3-7. günlerinde, 5. gün grubuna ise (n=43) siklusun 5-9. günlerinde, toplam 5 gün CC verildi. Antiöstrojenik etkiler; endometrial kalınlık ve servikal mukus kalitesi, siklus karakteristikleri ve tedavi sonuçları değerlendirildi. Antiöstrojenik etkileri incelemek için, sadece ovuluar sikluslara ait veriler analiz edildi.

**Bulgular:** 3. gün grubundaki 44, 5. gün grubundaki 34 hasta antiöstrojenik etkiler için değerlendirildi. İnsan Koronik Gonadotropin (hCG) yapıma günündeki endometrial kalınlık her iki grupta benzerdi. 3. gün grubunda ortalama servikal mukus skoru daha düşük bulundu (8.1±2.7 vs. 9.7±2.3, p=0.036). Gruplar arasında, hCG günündeki serum estradiol (E2), progesteron, önde giden follikül sayısı, siklus başına ovulasyon ve gebelik oranları açısından anlamlı farklılık izlenmedi.

**Sonuç:** Endometrial kalınlık, siklusun 3. veya 5. günü CC başlanan hastalar arasında farklılık göstermemektedir. Bununla birlikte, servikal mukus kalitesi, 3. gün CC başlananlarda, 5. gün başlanarlara göre daha kötü olabilmektedir.

**Anahtar sözcükler:** klomifen sitrat, servikal mukus, endometrial kalınlık, başlangıç günü.

**C**lomiphene citrate (CC) is the most widely used drug in the treatment of infertility. Chemically, CC exhibits both estrogenic agonist and antagonist properties (1). Due to its structural similarities to estrogen, clomiphene competitively attaches to nuclear estrogen receptors. At the hypothalamic level, estrogen receptor depletion prevents the negative feed back of estrogen that activates pulsatile gonadotropin releasing hormone (GnRH) secretion, which in turn results in increased pituitary gonadotropin hormones and ovarian follicular growth (2). In addition to its central actions, CC binds to estrogen receptors at peripheral sites of the reproductive system.

Although CC induces ovulation in 70-80% of patients, it results in pregnancy in only 40% (3). The discrepancy between the rate of ovulation and relatively low pregnancy rate may be partly explained by the peripheral antiestrogenic effects of CC on the endometrium (4, 5) and cervical mucus (6, 7). It has been suggested that the period between the administration of the last dose of CC and preovulatory period is longer when the drug is started earlier and the longer period without CC exposure may decrease the antiestrogenic effects on reproductive end organs (8-10).

The starting day of CC treatment has been determined empirically. It has customarily been started on day 5 of the menstrual cycle. On the other hand, it has been documented that the starting day of CC, whether on day 2 or through day 5 of the cycle, does not influence ovulation and pregnancy rates (11). However, little data are available on the effect of initiation time of CC on the reproductive end organs including endometrium and cervical mucus (8, 9, 12-14). In theory, to start CC earlier in the cycle for diminishing the antiestrogenic effects of the drug on reproductive end organs might improve the pregnancy rates.

In this study we aimed to investigate whether the initiation day of CC affects reproductive end organs. Therefore, we compared the antiestrogenic effects of CC on endometrial thickness and cervical mucus quality in the patients starting on day 3 to day 5.

## Materials and methods

This prospective randomized controlled study was conducted in the infertility outpatient clinic of Zekai Tahir Burak Women's Health Education and Research Hospital. Institutional ethics committee approved the study protocol. All couples were evaluated with medical history,

transvaginal ultrasonography, basal serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol ( $E_2$ ) levels on the third day of a spontaneous or progesterone induced menstruation, hysterosalpingography and semen analysis. Inclusion criteria were age  $\leq 39$  years, basal FSH levels  $\leq 10$  mIU/mL, normal uterine cavity, at least one patent tube and (for the male) 5 million motile spermatozoa. Patients with hypothalamic hypogonadism, hyperprolactinemia, thyroid dysfunction, body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, and endometriosis were excluded. Each patient was evaluated in a single treatment cycle, and informed consent was obtained from all participants after a detailed explanation by the authors of the study.

A couple was considered to have unexplained infertility when the results of hormonal assay, hysterosalpingography and semen analysis were normal. Women with oligomenorrhea-amenorrhea, a normal serum prolactin and thyroid stimulating hormone (TSH) level, and/or polycystic appearance of ovaries by transvaginal ultrasonography were classified as anovulatory infertility.

Patients that fulfilled the inclusion and exclusion criteria were randomized into 2 groups at the beginning of the CC treatment cycle. Randomization by using a computer-generated random number list was done by an investigator, who was not involved in the study. All patients underwent transvaginal ultrasound examination before ovulation induction on the second or third day of spontaneous or progesterone-induced menstruation. After ensuring the absence of follicles greater than 12 mm, ovulation was induced with clomiphene citrate (Klomen<sup>®</sup>, Koçak, Istanbul, Turkey). In the day 3 group (n=52), CC was given from day 3 through 7 of the cycle for 5 days, whereas in the day 5 group (n=43), CC was given on days 5 through 9. The dosage was determined on the basis of body weight and response to previous CC treatments with a maximum dose of 150 mg daily. Transvaginal ultrasound monitoring was started 3 days after the last CC dose and repeated at 2-3 day intervals with measurements of number and size of the follicles and the endometrial thickness. Follicle size was reported as the average of 2 dimensions in the most rounded configuration. Endometrial thickness was measured at the maximum thickness from one basal layer to the other in mid-sagittal plane. All measurements were performed by the same investigator who was blinded to the treatment groups. Human chorionic gonadotropin (hCG, Pregnyl, Organon, Netherlands) 10,000 mIU was administered when at least one follicle was  $\geq 18$  mm.

The number and size of the leading follicles ( $\geq 16$  mm), endometrial thickness measurements, and serum  $E_2$  and progesterone levels were recorded on the day of hCG.

Cervical mucus was evaluated at the hCG administration day. All evaluations were made by the same author (B.S.) who was also blinded to the allocation groups. For the assessment of cervical mucus, the semiquantitative scoring system of Insler et al. was used (15). After the cervix was exposed using a speculum, the amount of mucus on the external os was noted together with the degree of opening and hyperemia. A cervical mucus syringe was then introduced into the cervical canal, and mucus was aspirated. The length of the mucus thread was noted for the Spinnbarkeit score. Mucus samples were spread on slides for assessment of ferning. All assessments were scored, each on a scale from 0 to 3 giving a total out of 12. A score of 9 or more was regarded as satisfactory.

Patients with pure anovulatory infertility were instructed to scheduled vaginal intercourse. In cases of unexplained infertility and male subfertility, a single intrauterine insemination (IUI) was performed 36 hours after hCG injection. All patients were advised to test for mid-luteal phase progesterone levels, 7 days after the estimated time of ovulation based on hCG injection. Ovulation was confirmed when the serum progesterone level was  $\geq 5$  ng/mL. No luteal support was prescribed.

Serum  $\beta$ -hCG test was performed if menses had not occurred 14 days after the IUI procedure or timed intercourse. If the result was positive, the patient was scheduled for a transvaginal ultrasound 2-4 weeks later to confirm clinical pregnancy defined as the presence of gestational sac with fetal heart activity.

To analyze serum concentrations of  $E_2$ , an electro-chemiluminescence immunoassay was used (RSL 17  $\beta$ -Estradiol Kits), progesterone levels were measured by radioimmunoassay (Kodak Amerlex-M Progesterone RIA Kits).

We could not perform a power analysis for this study, because as far as we know, no clear data has been available in the literature regarding the effect of initiation day of CC on cervical mucus. Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, IL). Comparisons were analyzed using Student's *t* test, chi-square test, Mann-Whitney-U test or Fisher's Exact test when appropriate. For all tests, a *p* value of less than 0.05 was considered statistically significant.

## Results

A total of 95 patients were initially recruited into the study; 52 patients in the day 3 group and 43 patients in the day 5 group. The mean age of the patients treated was  $27.6 \pm 4.6$  (range, 20-39 years). The mean duration of infertility was  $5.4 \pm 5.2$  years (range, 1-15 years). The study included small number of patients with prolonged infertility (two patients) who could not afford other more costly methods of infertility treatment; therefore they were treated with CC. There were no differences between the groups regarding the woman's age, infertility period, causes of infertility, and daily dose of clomiphene. Table 1 shows the characteristics of the patients in both groups.

**Table 1.** Demographic and clinical characteristics of the groups.

	<b>Day 3 Group</b>	<b>Day 5 Group</b>	<b><i>p</i></b>
	<b>(CC days 3-7)</b>	<b>(CC days 5-9)</b>	
	<b>(n= 52)</b>	<b>(n=43)</b>	
Age (years)	27.9 $\pm$ 4.5	27.2 $\pm$ 4.8	NS
Duration of infertility (years)	5.2 $\pm$ 4.2	5.6 $\pm$ 6.2	NS
Primary infertility n(%)	35 (67.3%)	30 (69.7%)	NS
<b>Causes of infertility n(%)</b>			
Anovulation	33 (63.5%)	32 (74.4%)	
Unexplained	13 (25%)	8 (18.6%)	NS
Mild to moderate male factor	6 (11.5%)	3 (7%)	
<b>Clomiphene daily dose n(%)</b>			
50 mg/day n(%)	25 (48.1%)	25 (58.1%)	
100 mg/day n(%)	21 (40.4%)	14 (32.6%)	NS
150 mg/day n(%)	6 (11.5%)	4 (9.3%)	

Values are given as mean  $\pm$  standard deviation (SD) or frequencies (percentages within parantheses).

CC: clomiphene citrate, NS: not statistically significant.

**Table 2.** Cycle characteristics of the groups on the day of hCG administration.

	<b>Day 3 Group</b>	<b>Day 5 Group</b>	<b><i>p</i></b>
	<b>(n= 44)</b>	<b>(n=34)</b>	
Serum estradiol (pg/mL)	477.9 $\pm$ 450.1	588.4 $\pm$ 299.3	NS
Serum progesterone (ng/mL)	2.1 $\pm$ 3.5	1.1 $\pm$ 0.7	NS
Endometrial thickness (mm)	9 $\pm$ 1.8	9.3 $\pm$ 1.9	NS
Number of leading follicles ( $\geq 16$ mm)	1.6 $\pm$ 1.1	1.6 $\pm$ 0.8	NS
Size of the leading follicle (mm)	18.3 $\pm$ 3.2	20.4 $\pm$ 4.1	0.048*

Values are given as mean  $\pm$  standard deviation (SD), \**P*<0.05 is considered statistically significant.

NS: not statistically significant.

To observe the possible differences in antiestrogenic effects of the drug, only data from ovulatory cycles were analyzed, because antiestrogenic effects of the drug could be important on reproductive outcomes in ovulatory cycles. Eight patients in the day 3 group and 9 patients in the day 5 group were anovulatory. Therefore, these patients were excluded, leaving 44 patients in the day 3 group and 34 patients in the day 5 group for the assessment of cycle characteristics. Likewise, cervical mucus scoring was performed in confirmed ovulatory cycles.

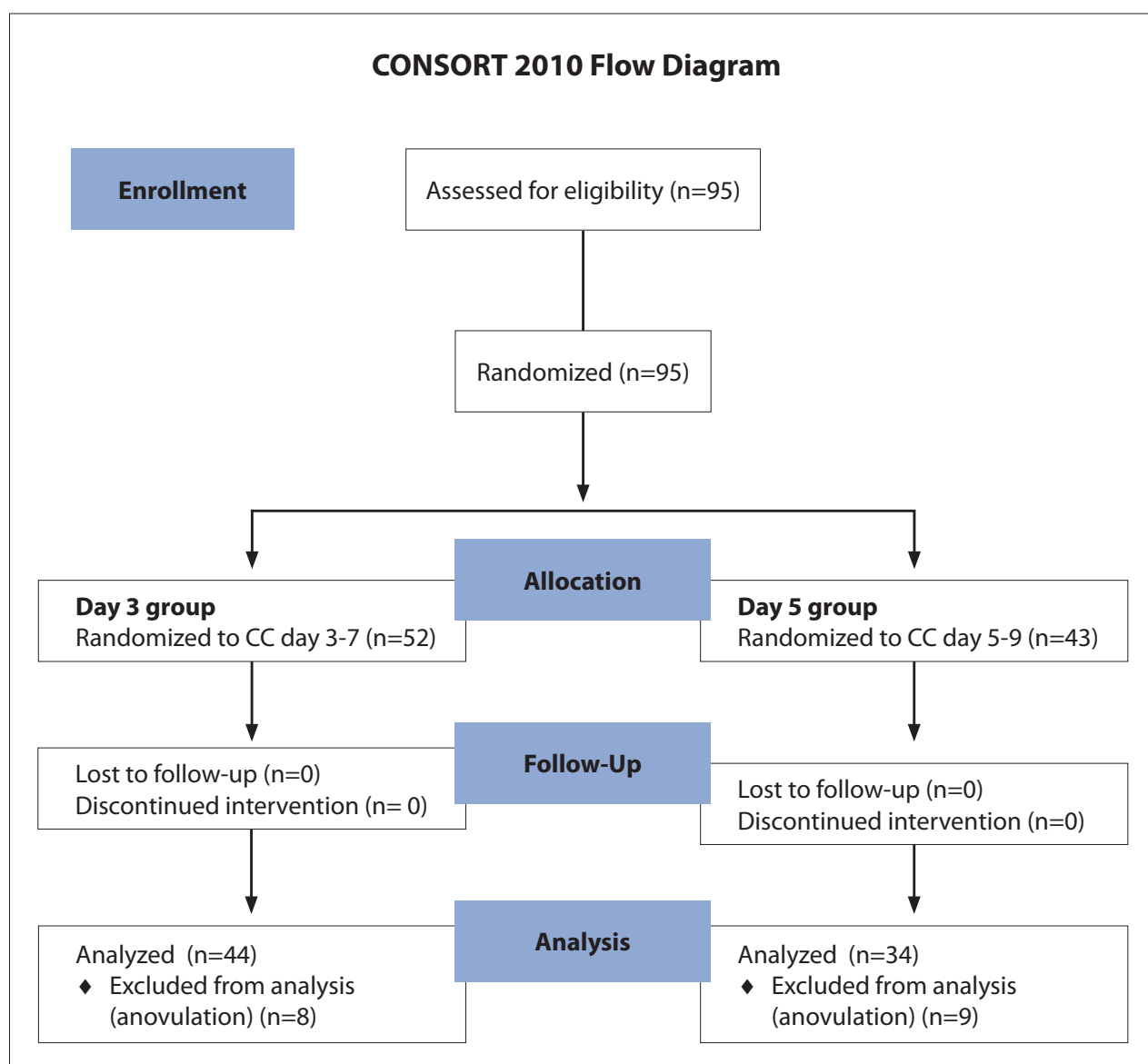
No significant differences in the mean serum  $E_2$ , progesterone levels, endometrial thickness, and the number of leading follicle were noted on the day of hCG. On the other hand, the mean size of the leading follicle was significantly

**Table 3.** Cycle characteristics and the treatment outcomes of the groups.

	<i>Day 3 Group</i>	<i>Day 5 Group</i>	<i>p</i>
No. of patients treated with IUI (n,%)	19/44 (43.2%)	11/34 (32.4%)	NS
Cervical mucus score	8.1±2.7	9.7±2.3	0.036*
Midluteal progesterone level (ng/mL)	20.4±7.9	20.3±7.9	NS
Ovulation rate per cycle (n,%)	44/52 (84.6%)	34/43 (79.1%)	NS
Pregnancy rate per cycle (n,%)	5/52 (9.6%)	5/43 (11.6%)	NS

Values are given as mean± standard deviation (SD) or number (percent), \*P<0.05 is considered statistically significant

IUI: intrauterine insemination, NS: not statistically significant



larger in day 5 group than day 3 group ( $20.4 \pm 4.1$  vs.  $18.3 \pm 3.2$  mm, respectively,  $p=0.048$ ) (Table 2). In the day 3 group, the mean cervical mucus score was lower ( $8.1 \pm 2.7$  vs.  $9.7 \pm 2.3$ ,  $p=0.036$ ) and the frequency of unfavourable cervical mucus (a score of lower than 9) was higher than the day 5 group (57.1% vs. 27.2%, respectively). The number of patients undergoing IUI was comparable among the groups (19/44 and 11/34, for the day 3 and day 5 groups, respectively,  $p>0.05$ ). There were no significant differences in mid-luteal serum progesterone levels, ovulation and pregnancy rates per cycle between the groups (Table 3).

A total of 10 clinical pregnancies were observed (5 in the day 3 group and 5 in the day 5 group). One pregnancy was ended with clinical abortion in the day 3 group.

## Discussion

In this study we showed that poor cervical mucus quality was more common in CC cycles when the drug was started on day 3 of the menstrual cycle compared to day 5. On the other hand, we observed no significant difference between the treatment groups with regard to endometrial thickness.

Pharmacologically, CC has a long plasma half-life; 85% of an administered dose is eliminated after approximately 6 days (16). Therefore, in order to decrease its undesired antiestrogenic effects on reproductive end organs, several investigators have proposed that initiating CC on earlier days of the menstrual cycle might lower its concentration in the sensitive periovulatory and implantation period (8, 9, 12). Abnormal epithelial cell proliferation and delayed glandular maturation are often found in mid-luteal endometrial biopsies of patients treated with CC (17). It has been suggested that a thin endometrium caused by the CC treatment is due to impaired endometrial growth. This impaired development in the early luteal phase might lead to luteal defect and, consequently unfavourable influence on the outcome of implantation (13). In a prospective randomized study, Biljan et al. (9) found higher pregnancy rates in patients where CC commenced earlier days of the cycle. Similarly, Hosie and Murphy (12) demonstrated that the severity of endometrial epithelial abnormalities was related to the timing of its administration within the cycle. They postulated that the longer period without CC may enable the rising  $E_2$  to replace CC from peripheral receptors that is more conducive to pregnancy.

Use of CC is also known to have negative actions on cervical mucus. Previous studies have shown that cervical mucus scores are reduced in ovulatory cycles of CC

treatment compared with spontaneous ovulatory cycles (6, 18). The poor cervical mucus quality in spite of high plasma  $E_2$  levels in CC treated women suggests continued antiestrogenic effects up to the periovulatory phase (19). In some previous trials, adding estrogen therapy during CC treatment did not improve cervical mucus quality (20). Therefore, to decrease these undesired effects, starting CC earlier has been subject of considerable scientific interest.

In our study we focused on the starting time of CC treatment to diminish adverse effects of the drug on the endometrium and cervical mucus. In term of ultrasonographic examination, CC either started on day 3 or day 5 of the cycle has no significant effect on the endometrial thickness according to our data. The most important finding of our study is that the poor cervical mucus quality was more frequently found in the day 3 starting group as compared to the day 5. This is in line with a trend toward higher serum  $E_2$  levels in day 5 compared to day 3 starters in our study group. Similarly, in a study by Triwitayakorn et al. (8), lower serum  $E_2$  levels were found by administering CC on earlier days of the follicular phase. In our study, the size of the leading follicle on the day of hCG was significantly smaller in the day 3 compared to day 5 group. In another study, Marrs et al. (14) proposed that starting CC treatment earlier in the menstrual cycle may not provide enough gonadotropin to support the multiple follicular development. Therefore, it can be postulated that, earlier CC administration may lead to lower estradiol levels, smaller leading follicles, and more frequent poor cervical mucus quality.

Our data concur with a previous report showing similar treatment outcomes in terms of ovulation and pregnancy when CC is started earlier (11). Despite the higher frequency of poor cervical mucus observed in the day 3 group, the therapeutic outcomes were comparable among the groups. This may be due to the presence of more women undergoing IUI in the day 3 starters.

Our study has several limitations. We have been unable to perform the histologic dating of endometrium on the mid-luteal phase. Therefore, it may be inappropriate to conclude that starting CC on either day 3 or day 5 of the cycle does not have any differential effects on the endometrium based on the ultrasonographic endometrial thickness measurement alone. The other limitation of the study is the restricted sample size. To observe unwanted antiestrogenic effects, we analyzed only ovulatory cycles. Pregnancy outcomes could not be evaluated because of this restricted size.

According to our data, endometrial thickness is not different when CC is started on day 3 or 5 of the cycle. Nevertheless, starting CC on day 3 of the cycle is associated with a higher number of patients with unfavourable cervical mucus quality compared to day 5. It seems reasonable that starting CC treatment on different days of the menstrual cycle does not require variable treatment approaches to decrease the adverse effect of the drug on endometrial thickness. On the

other hand, IUI may be performed more commonly to overcome poor cervical mucus quality when the drug is started on day 3 of the cycle. Validation of this suggestion warrants further evaluations in larger prospective studies.

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