CEOG Clinical and Experimental Obstetrics & Gynecology

Delayed administration method of clomiphene citrate during the ovulatory phase in patients with a prolonged menstrual cycle

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Summary

For patients with a prolonged menstrual cycle who do not respond to clomiphene citrate, the drug can be administered again at a higher dose during another cycle. Clomiphene citrate should be administrated two to five days after the start of menstruation; however, enhanced ovulation effects may occur as a potential adverse reaction to high-dose clomiphene citrate therapy, which limits its use. Furthermore, the ovulatory-phase timing of administration differs between normal patients and those with a prolonged menstrual cycle. This indicates clomiphene citrate does not directly act on the ovulatory phase. The authors used a delayed administration of clomiphene citrate without increasing its doses in a patient with a prolonged menstrual cycle who did not respond to conventional clomiphene citrate therapy. They achieved three pregnancies and deliveries in the patient using this method.

Key words: Intracyclic clomiphene citrate therapy; Menstrual cycle; Delayed administration.

Introduction

Clomiphene citrate therapy is the first-line ovulation-inducing method for patients with ovulation disorder who wish to have a child. More than 50 years have passed since Greenblatt *et al.* [1] reported this drug in 1961, however, it is still commonly used in clinical practice. Clomiphene citrate therapy is started in the menstrual phase (days 2 to 5), and administered over five days. For non-responders, the dose of clomiphene citrate is increased in the next cycle [2]. The present authors recently reported modified repeated intracyclic clomiphene citrate therapy as a method of inducing ovulation by establishing a specific interval in patients who do not respond to the conventional administration method. They administered clomiphene citrate for five days, twice in the same cycle [3]. The incidence of excessive ovulation and ovarian hyperstimulation syndrome (OHSS) for this therapy is low. In some patients, the modified therapy is more effective than gonadotropin therapy [4]. Another recently developed therapy, the stair-step method [5], also involves a similar mechanism.

These new administration methods are similar to the conventional method in that ovulation effects are enhanced by increasing the clomiphene citrate dose. For the conventional administration method, the ovulatory phase timing of administration differs in patients with a prolonged menstrual cycle. This indicates that clomiphene citrate does not directly act on the ovulatory phase. The authors adopted a clomiphene citrate administration method with a delayed timing without increasing its dose for patients with a prolonged menstrual cycle who do not respond to conventional clomiphene citrate therapy. Three sessions of infertility treatment with the patient were successful, and pregnancies were achieved, leading to three deliveries.

Case Report

A 29-year-old woman consulted the present hospital with a prolonged menstrual cycle and infertility. In this patient, three sessions of infertility treatment with clomiphene citrate confirmed that the menstrual cycle was prolonged. Ultrasonic tomography did not reveal any pattern of polycystic ovary syndrome (PCOS).

First pregnancy

For the first session of infertility treatment, clomiphene citrate therapy was started five days after withdrawal bleeding according to the conventional method. However, there was no follicular growth. Subsequently, repeated administration was performed without inducing additional withdrawal bleeding. After a five-day drug holiday, clomiphene citrate was administered again in the same menstrual cycle (Figure 1) [3]. During modified repeated intracyclic clomiphene citrate therapy, ultrasonography on the day of the second administration showed a small follicle. Follicular growth and ovulation after the second administration also appeared favorable. After a third administration of clomiphene citrate, similar follicular growth and ovulation were achieved. Therefore, the authors' method was switched with a delay in the start of clomiphene citrate administration. They delayed clomiphene citrate administration to 15 days from the start of menstruation resulting in growth of a mature follicle. Human chorionic gonadotropin (hCG) was administered, and artificial in-

Revised manuscript accepted for publication August 30, 2016

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLV, n. 2, 2018
doi: 10.12891/ceog3853.2018

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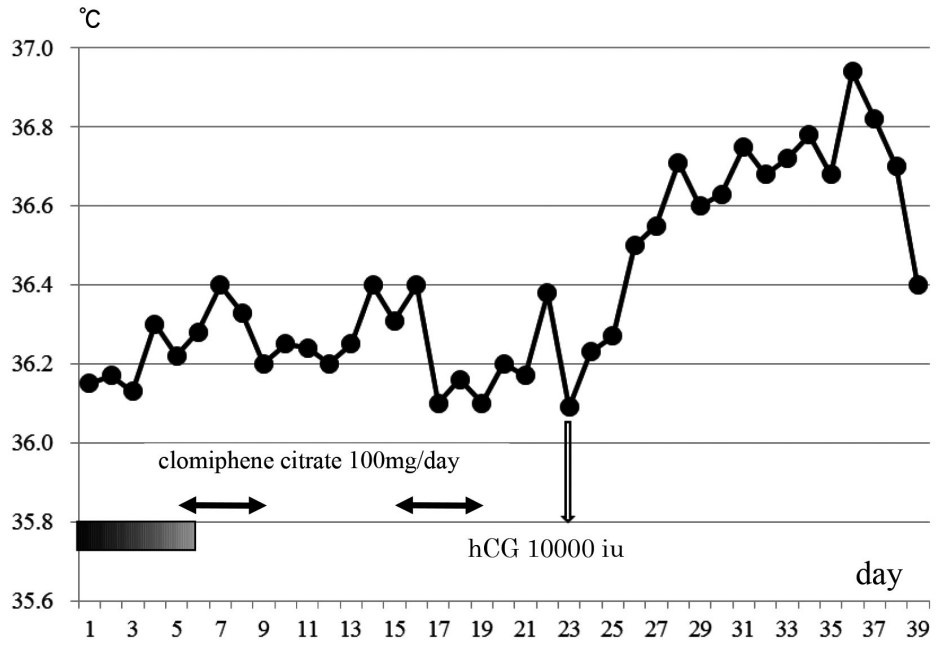

Figure 1. — Modified repeated intracyclic clomiphene citrate therapy basal body temperature (BBT). Clomiphene citrate was administered at a dose of 100 mg/day for five days, beginning on the fifth day after withdrawal bleeding. Clomiphene citrate was readministered at a dose of 100 mg/day for five days after a five-day drug holiday.

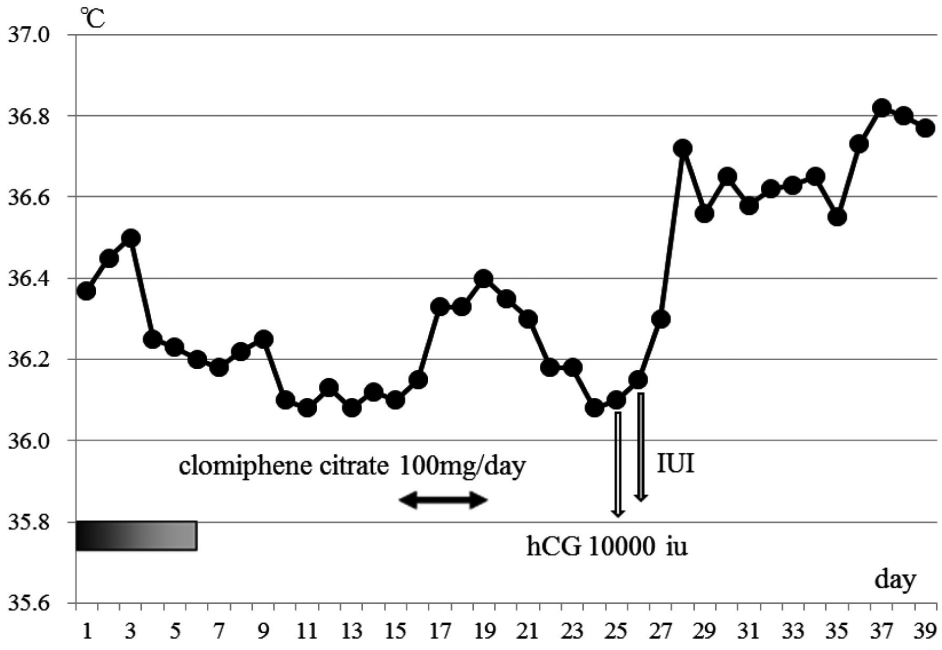

Figure 2. — BBT during elective therapy with clomiphene citrate. Clomiphene citrate was administered at a dose of 100 mg/day for five days, beginning on the fifteenth day after withdrawal bleeding. After follicle maturity was confirmed, hCG was given and intrauterine insemination was performed.

semination was performed, leading to pregnancy (Figure 2, Table 1).

Second pregnancy

For the second session of infertility treatment, clomiphene citrate therapy was also started according to the conventional method; however, the patient did not respond. Therefore, the method was switched to the authors' modified repeated intracyclic clomiphene citrate therapy. Gonadotropin therapy (urine human menopausal gonadotropin [hMG]-hCG: hMG, 150 IU/d, four days; total hMG, 600 IU; hCG, 10,000 IU) was also performed, but pregnancy was not achieved. OHSS developed and the therapy was discontinued. After one menstrual cycle, the authors delayed administration of clomiphene citrate to 15 days after withdrawal bleeding, resulting in ovulation, which led to pregnancy (Table 1).

Table 1. — *Frequency of infertility treatment.*

Infertility treatment	First	Second	Third
Modified repeated intracyclic clomiphene citrate therapy (Day 5)	3	2	0
Gonadotropin therapy	0	1	0
Modified repeated intracyclic clomiphene citrate therapy (Day 10)	2	0	0
Modified repeated intracyclic clomiphene citrate therapy (Day 15)	1	0	1
Elective administration of clomiphene citrate (Day 15)	1	1	6
Frequency of elective administration until pregnancy is achieved	2	1	7
Artificial insemination	1	0	0

( ): Day of administration counted from the start of menstruation

With respect to administration from 15 days after the start of menstruation, patients in whom ovulation was successfully achieved are presented as the elective administration of clomiphene citrate (Day 15). In those without follicular growth (unsuccessful cases), repeated administration led to ovulation; therefore, they are presented as modified repeated intracyclic clomiphene citrate therapy (Day 15).

Table 2. — *Delivery after infertility treatment.*

	First	Second	Third
Gestational age on delivery (weeks)	39	40	37
Birth weight (grams)	3,200	2,840	2,446
Sex	Girl	Boy	Girl

Third pregnancy

For the third infertility treatment session, the authors delayed clomiphene citrate administration to 15 days after the start of menstruation, based on their two courses of treatment. Pregnancy was achieved after the seventh administration (Table 1).

In each infertility treatment session, the authors started administrating clomiphene citrate according to the conventional method. Because there was no response to this method, this treatment was switched to modified repeated intracyclic clomiphene citrate therapy, leading to ovulation. Based on follicular growth and the state of ovulation during this therapy, the authors selected a delay in clomiphene citrate administration of 15 days after the start of menstruation. This was performed ten times through the three infertility treatment sessions to overcome unfavorable responses to clomiphene citrate. On the first and third infertility treatment sessions, ovulation was unsuccessful once each (total: twice, 20%). However, ovulation was successfully achieved eight times (80%, Table 1). There were no problems regarding the pregnancy course or delivery. The three pregnancies led to natural labors and spontaneous transvaginal deliveries (Table 2).

Discussion

Clomiphene citrate therapy is a common treatment for idiopathic infertility or ovulation disorder. To improve the actions of clomiphene citrate, it is combined with other drugs, such as bromocriptine [6], estradiol [7], gonadotropin [8], dexamethasone [9], and metformin [10]. In non-responders to the conventional clomiphene citrate administration method, the drug is administered at a high dose during a subsequent cycle [2]. Another approach for non-responders involves prolonging the clomiphene citrate administration period [11]. Recent studies have reported a method of repeatedly administering clomiphene citrate in the same cycle, establishing a discontinuation period [3-5]. Theses administration methods, like the conventional method, rely on enhancing the effects of clomiphene citrate by increasing its dose. However, patients can have adverse reactions to high-dose clomiphene citrate therapy [12]. With high-dose clomiphene citrate, the risk of multiple pregnancies or OHSS may increase, and a decrease in the volume of cervical canal mucus [13] or endometrial thinning [14] may occur. This may increase the future risk of ovarian or uterine cancer [15]. Another feature of conventional clomiphene citrate therapy is starting administration two to five days after the start of menstruation. Therefore, the conventional administration method, timing may not be synchronized with ovulation in patients with a delayed ovulatory phase, as demonstrated in the present case. Modified repeated intracyclic clomiphene citrate therapy facilitates the effective use of clomiphene citrate for such patients [3, 4]. However, the issue of increasing the dose of clomiphene citrate remains.

Among patients receiving modified repeated intracyclic clomiphene citrate therapy, folliculogenesis (number, size), follicular growth, and ovulation differ. In the "stair-step" method [5], the dose of clomiphene citrate is increased in the second administration. However, in the present authors' previous study [4], the same dose of clomiphene citrate was sufficient in most patients; furthermore, the dose could be decreased in responders. In the present case, the presence of follicles was confirmed at the time of the second administration, and follicular growth or ovulation was favorable after the second administration. Therefore, for modified repeated intracyclic clomiphene citrate, an initial administration may be sufficient in responders in whom low doses of clomiphene citrate may also be possible, however, this applies to the conventional method. Additionally, Farhi *et al.* indicated that the start of clomiphene citrate administration later than commonly done with the conventional method was advantageous [2]. In patients with a delayed ovulatory phase, delaying the start of administration may be a more appropriate timing than that of the conventional method. In the future, appropriate timing for administration clomiphene citrate should be established.

The present authors examined administering clomiphene citrate a second time for a modified repeated intracyclic clomiphene citrate therapy. They considered that the number and growth of follicles with a second administration were not always associated with the efficacy of the first adminis-

tration alone. In patients with irregular menstruation related to a hypothalamic disorder or PCOS, menstruation sometimes occurs through spontaneous ovulation in the absence of treatment. Even in patients with a prolonged menstrual cycle, effective and repeated stimuli from the hypothalamus-pituitary axis to the ovary may induce ovulation. The present authors speculate that this phenomenon of follicular growth might spontaneously appear at the time of the second administration, even when using modified repeated intracyclic clomiphene citrate therapy. During a second clomiphene citrate administration, the number and growth of follicles was not always associated with efficacy of the first administration alone in patients whose clomiphene citrate dose could be decreased. Based on this possibility, the authors attempted a method to induce ovulation through the second administration alone in the latter half of the repeated administration method (delayed administration method). They found that ovulation was successfully achieved eight times (8/10, 80%) during three infertility treatment sessions. Furthermore, each of the sessions resulted in a pregnancy. These findings indicate that, even when the first administration of clomiphene citrate is discontinued, ovulation can be achieved in patients in whom follicular growth is considered to occur at the time of the second administration during modified repeated intracyclic clomiphene citrate therapy. Observation of follicular growth (number, size) related to the first administration of clomiphene citrate and induction of ovulation related to the second administration were useful for evaluating the timing of administration.

If ovulation is induced without increasing the dose of clomiphene citrate, the patients' costs, time-related restrictions, and pain from injection may be reduced. This delayed administration method may be effective in some patients with hypothalamic disorder or PCOS in whom modified repeated intracyclic clomiphene citrate therapy is possible. The authors have encountered patients with PCOS who became pregnant through the delayed administration method (data not published), and there was no anxiety over the risk of multiple pregnancies or OHSS. In the current field of assisted reproductive technology, the entity of mild ovarian stimulation [16] is commonly accepted, and this tendency may be more marked for infertility treatment.

Conclusion

The authors successfully induced ovulation by delaying administration timing of clomiphene citrate without increasing the dosage in patients with a prolonged menstrual cycle. Thus, modified repeated intracyclic clomiphene citrate therapy successfully induced ovulation from the second administration. In some patients with a prolonged menstrual cycle, ovulation spontaneously occurs, but pregnancy is not achieved, as demonstrated in the present case. The authors' delayed administration method is an effective method to achieve pregnancy without increasing the dose of clomiphene citrate in idiopathic infertility patients with a prolonged menstrual cycle.

References

[1] Greenblatt RB., Barfield WE., Jungck EC., Ray AW.: "Induction of ovulation with MRL/41 preliminary report". *JAMA,* 1961, *178*, 101.
[2] Farhi J., Orvieto R., Homburg R.: "Administration of clomiphene citrate in patients with polycystic ovary syndrome, without inducing withdrawal bleeding, achieves comparable treatment characteristics and outcome". *Fertil. Steril.,* 2010, *93*, 2077.
[3] Kawamura M., Aoki Y., Kanda R., Nakagomi H., Tsukahara Y., Hashimura N.: "Repeated intracyclic clomiphene citrate therapy can be more effective than hMG thearpy in inducing ovulation: case report". *Clin. Exp. Obstet. Gynecol.,* 2009, *36*, 82.
[4] Kawamura M., Suzuki A., Kanda R., Kiseki H., Tsukahara Y., Hashimura N.: "Modified repeated intracyclic clomiphene citrate therapy after conventional clomiphene therapy". *Clin. Exp. Obstet. Gynecol.,* 2012, *34*, 317.
[5] Hurst BS., Hickman JM., Matthews ML., Usadi RG., Marshbum PB.: "Novel clomiphene "stair-step" protocol reduces time to ovulation in women with polycystic ovarian syndrome". *Am. J. Obstet. Gynecol.,* 2009, *200*, 510.el.
[6] Kubota T., Kamada S., Aso T.: "Compined rherapy with bromocriptine and clomiphene citrate for patients with normoprolactinemic amenorrhea". *Int. J. Fertil.* 1992, *37*, 277.
[7] Elkind-Hirsch KE., Darensbourg C., Creasy G., Gipe D.: "Conception rate in clomiphene citrate cycles with and without hormone supplementation: a pilot syudy". *Curr. Med. Res. Opin.* 2005, *21*, 1035.
[8] Dom C., van der Ven H.: "Clomiphene citrate versus gonadotropinsfor ovulation stimulation". *Reprod. Biomed. Online,* 2005, *10*, 37.
[9] Elnashar A., Abdelmageed E., Fayed M., Sharaf M.: "Clomiphene citrate and dexamethasone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study". *Hum. Reprod.*, 2006, *21*, 1805.
[10] Dasari P., Pranahita G.: "The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS". *J. Hum. Reprod. Sci.*, 2009, *2*, 18.
[11] Fluker MR., Wang IY., Rowe TC.: "An extended 10-day course of clomiphene citrate (CC) in women with CC-resistant ovulatory disorders". *Fertl. Steril.*, 1996, *66*, 761.
[12] Homburg R.: "Clomiphene citrate end of an era? A mini-review". *Hum. Reprod.*, 2005, *20*, 2043.
[13] Check JH.: "Ovulation disorders: Part II. Anovulation associated with normal estrogen". *Clin. Exp. Obstet. Gynecol.*, 2007, *34*, 69.
[14] Haritha S., Rajagopalan G.: "Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles". *Int. J. Gynaecol. Obstet.,* 2003, *81*, 287.
[15] Trabert B., Lamb EJ., Scoccia B., Morhissi KS., Westhoff CL., Niwa S., *et al.*: "Ovulation-inducing drug and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort". *Fertil. Steril.,* 2013, *100*, 1660.
[16] Matsaseng T., Kruger T., Steyn W.: "Mild ovarian stimulation for in vitro Fertilization: Are we ready to change? A meta-analysis". *Gynecol. Obstet. Invest.,* 2013, *76*, 233.

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