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ORIGINAL ARTICLE

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Usefulness of intermittent clomiphene citrate treatment for women with polycystic ovarian syndrome that is resistant to standard clomiphene citrate treatment

Akihisa Takasaki[1] | Isao Tamura[2] | Maki Okada-Hayashi[1] | Takeshi Orita[1] | Manabu Tanabe[1] | Shoko Maruyama[1] | Katsunori Shimamura[1] | Hitoshi Morioka[1]

[1]Department of Obstetrics and Gynecology, Saiseikai Shimonoseki General Hospital, Shimonoseki, Japan

[2]Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Ube, Japan

Correspondence
Isao Tamura, Department of Obstetrics and Gynecology, Yamaguchi University Graduate School of Medicine, Ube, Japan.
Email: isao@yamaguchi-u.ac.jp

Abstract

Purpose: Clomiphene citrate (CC) has been used as a first-line treatment for anovulatory polycystic ovary syndrome (PCOS). However, some patients with PCOS are resistant to standard CC treatment. In this study, a new CC treatment protocol was developed, named "intermittent CC treatment" (ICT) and its efficacy was investigated on the induction of follicular growth in patients with PCOS who were resistant to standard CC treatment.

Methods: Of the 42 patients with PCOS who were resistant to standard CC treatment (50 mg/day, 5 days), 26 underwent ICT. They were given 100 mg/day of CC for 5 days from the next menstrual cycle day (MCD) 5 (first CC). If follicular growth was not observed on MCD 14, they were given 100 mg/day of CC for 5 days (MCD 14-MCD 18) (second CC). If follicular growth still was not observed on MCD 23, they were treated with CC again in the same way (third CC).

Results: The first CC, second CC, and third CC were effective for 3/26 (11.5%) patients, 12/23 (52.2%) patients, and 6/11 (54.5%) patients, respectively. In total, ICT was effective for 21/26 (80.8%) patients with CC-resistant PCOS.

Conclusion: Thus, ICT is a useful treatment and could be an alternative to gonadotropin therapy for patients with CC-resistant PCOS.

KEYWORDS

clomiphene citrate, clomiphene citrate resistance, follicular growth, infertility, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects at least 7% of infertile women. Most of these women are oligo-or anovulatory.[1,2] Clomiphene citrate (CC) has been used widely as a first-line treatment for anovulatory PCOS because CC treatment is a simple, cheap, and effective method to induce ovulation with minimal side-effects.[3,4] The CC has an antiestrogenic effect by binding to estrogen receptors on the hypothalamus. This stimulates a gonadotropin-releasing hormone pulse that induces gonadotropin secretion from the anterior pituitary gland. However, ~20%-25% of anovulatory women with PCOS do not respond to CC and are considered to be "clomiphene-resistant."[5,6]

A. Takasaki and I. Tamura contributed equally to this manuscript.

Gonadotropin therapy can be used as a second-line therapy in women with PCOS who have CC resistance,[7,8] but it also causes ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. To prevent these side-effects, a low-dose, step-up follicle-stimulating hormone (FSH) regimen is widely used. However, this regimen could result in long-term daily injections of FSH, up to 28-35 days in each cycle, which increases the economic, mental, and physical burden of patients with PCOS. Therefore, a therapy other than gonadotropin therapy is needed for CC-resistant patients and some modified CC treatment protocols have been developed.[9,10]

In patients with PCOS who are receiving low-dose FSH treatment, it is difficult to predict when the follicles will respond to FSH and when follicular growth will start. As a result, the long-term administration of FSH is needed. Another problem is that the response to FSH is different among treatment cycles, even in the same patient. This suggests that there is a window that follicles can respond to gonadotropin and start follicular growth and that the window appears at random times during the treatment cycles. As long-term FSH treatment can keep the serum FSH levels high, this regimen should be able to find this window, even if it appears at random times. Based on this hypothesis, alternative treatments that can maintain high serum FSH levels are also promising for the induction of follicular growth in CC-resistant patients with PCOS. Thus, this study developed a new CC treatment protocol, named "intermittent CC treatment" (ICT). It was hypothesized that maintaining high serum FSH levels by repeating the administration of CC would effectively induce follicular growth in CC-resistant patients. This study was undertaken to investigate whether ICT is a useful treatment method for the induction of follicular growth in CC-resistant patients with PCOS.

2 | MATERIALS AND METHODS

The project was reviewed and approved by the Institutional Review Board of Saiseikai Shimonoseki General Hospital, Shimonoseki, Japan. Informed consent was obtained from all the patients in this study. Recruited to the study were 42 infertile women with the diagnosis of PCOS, which was diagnosed according to the criteria that were proposed by the Japanese Society of Obstetrics and Gynecology.[11] The basal levels of luteinizing hormone (LH), FSH, testosterone, estradiol, fasting insulin, and glucose were examined between day 2 and day 5 of the menstrual cycle.

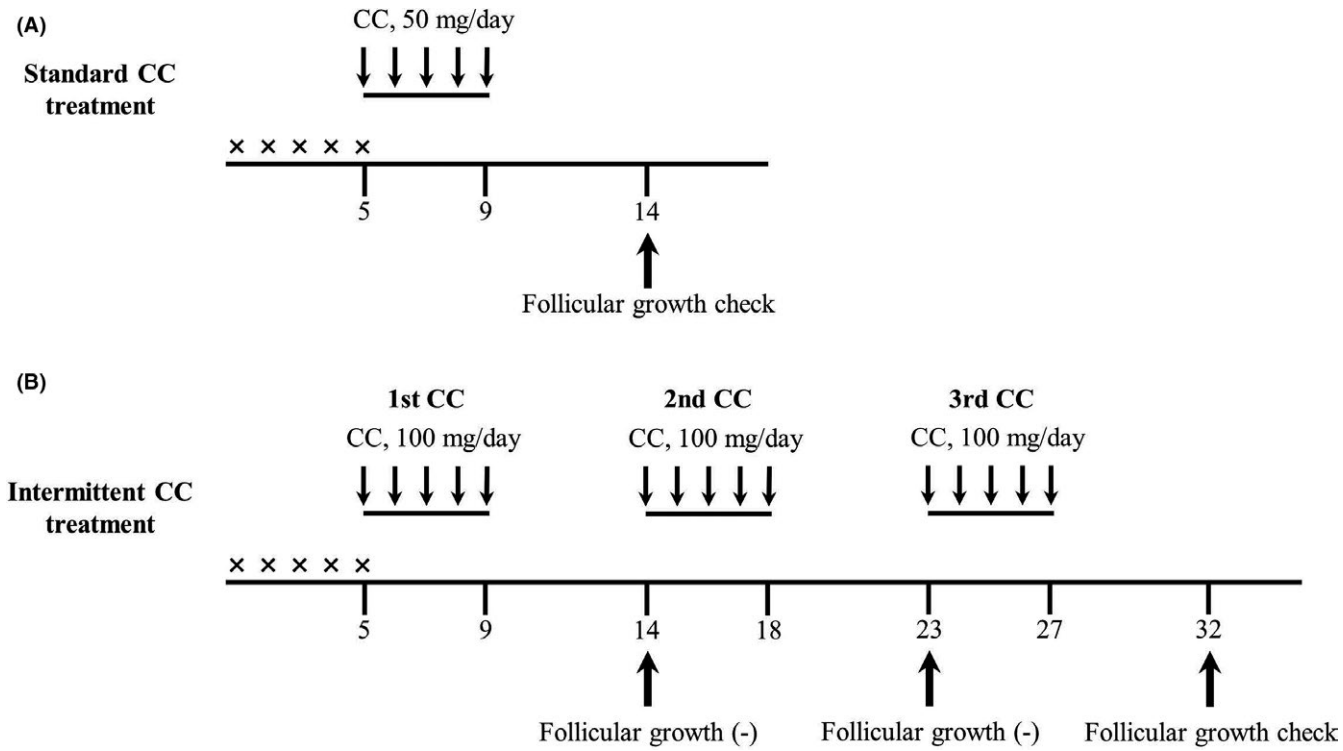

FIGURE 1 Treatment regimens with standard clomiphene citrate (CC) treatment and intermittent CC treatment (ICT). Standard CC treatment: Patients with polycystic ovary syndrome (PCOS) were given 50 mg of CC daily for 5 days, starting on the menstrual cycle day (MCD) 5. Follicular growth was checked on MCD 14. If follicular growth was not observed by the standard CC treatment, they underwent ICT. ICT: The patients who were resistant to the standard CC treatment were given 100 mg of CC daily for 5 days (MCD 5-MCD 9) of the next menstrual cycle (first CC). The follicular growth was checked on MCD 14. If follicular growth was not observed, the patients were regarded as non-responders to the first CC and were given a further 100 mg/day of CC daily for 5 days (MCD 14-MCD 18) (second CC). The follicular growth was checked on MCD 23. If follicular growth still was not observed, the patients were regarded as non-responders to the second CC and were given a further 100 mg/day of CC daily for 5 days (MCD 23-MCD 27) (third CC). If follicular growth still was not observed on MCD 32, they were regarded as non-responders to the third CC

2.1 | Intermittent clomiphene citrate treatment

The 42 patients with PCOS received a standard CC treatment, 50 mg of CC (Clomid; Shionogi Company, Ltd., Tokyo, Japan), daily for 5 days starting on menstrual cycle day (MCD) 5 (Figure. 1A). The follicular growth was checked on MCD 14. If follicular growth was not observed (follicular size: <10 mm), the patients were regarded as non-responders to 50 mg CC and underwent ICT (Figure. 1B). They were given 100 mg of CC daily for 5 days (MCD 5-MCD 9) of the next menstrual cycle (first CC). Follicular growth was checked on MCD 14. If follicular growth was not observed, they were regarded as non-responders to the first CC and were given a further 100 mg/day of CC daily for 5 days (MCD 14-MCD 18) (second CC). The follicular growth was checked on MCD 23. If follicular growth still was not observed, the patients were regarded as non-responders to the second CC and were given a further 100 mg/day of CC daily for 5 days (MCD 23-MCD 27) (third CC). If follicular growth still was not observed on MCD 32, they were regarded as non-responders to the third CC. When the follicles reached ≥18 mm in diameter, 10,000 IU of human chorionic gonadotropin (hCG) (Gonastropin; Asuka Pharmaceutical Company, Ltd., Tokyo, Japan) was administered to induce ovulation. The number of mature follicles (≥18 mm) on the day of the hCG injection was assessed. Ovulation was successfully induced from all mature follicles by the hCG injection. The baseline characteristics were compared between the responders and the non-responders of ICT.

2.2 | Statistical analyses

Statistical significance was determined by a one-way ANOVA. After the ANOVA, the Tukey-Kramer test was applied to analyze differences between groups. All the statistical analyses were performed by using SPSS for Windows v. 13.0 (SPSS, Inc., Chicago, IL, USA). The differences were considered to be significant at $P < 0.05$.

3 | RESULTS

Figure 2 shows the effects of CC on the induction of follicular growth in patients with PCOS. Of the 42 patients, 26 (61.9%) did not show follicular growth by the standard CC treatment. They were diagnosed with CC-resistant PCOS and underwent ICT, in which the first CC was effective for three out of 26 (11.5%) patients. The remaining 23 patients underwent the second CC, and of these, 12 (52.2%) patients responded. The remaining 11 underwent the third CC, and of these, six (54.5%) patients responded. In total, ICT was effective for 21 out of the 26 (80.8%) CC-resistant patients with PCOS. On

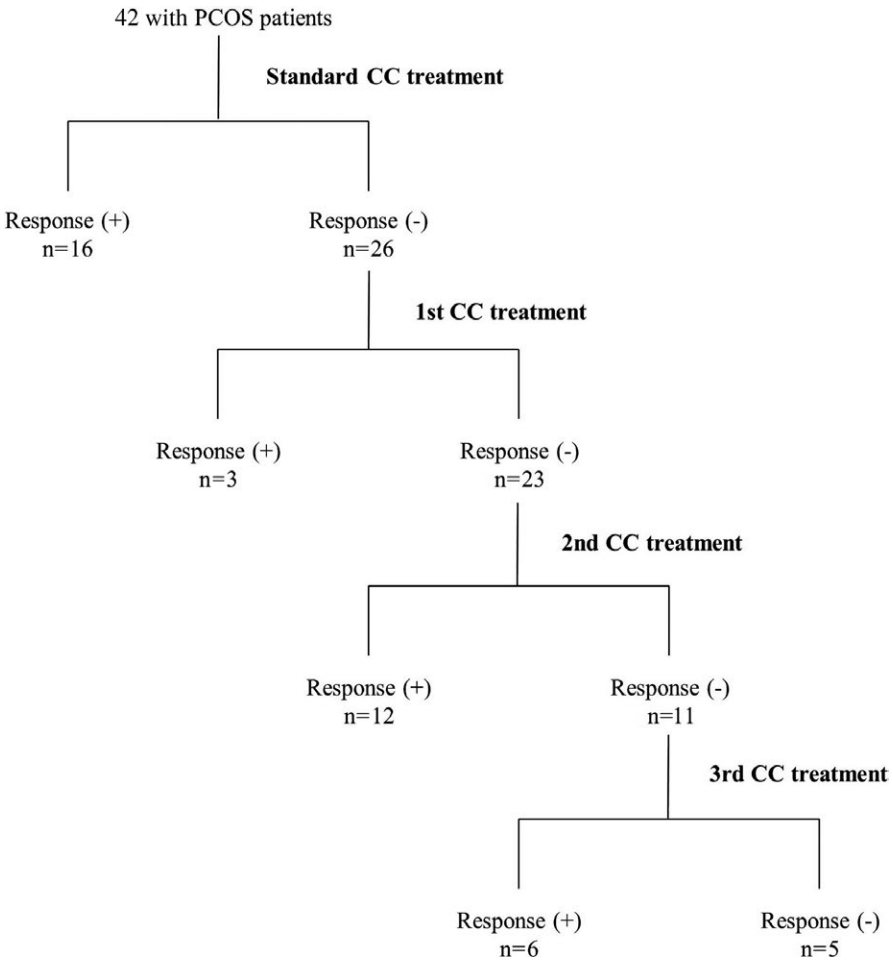

FIGURE 2 Effects of intermittent clomiphene citrate (CC) treatment (ICT) for standard CC-resistant patients with polycystic ovary syndrome (PCOS). The 42 patients with PCOS received a standard CC treatment. A response meant that follicular growth was observed 5 days after the last day of CC administration, but 26 patients were resistant to the standard CC treatment and underwent ICT (first CC, second CC, and third CC)

TABLE 1 Comparison of the baseline characteristics between the responders and the non-responders

Characteristic	Responders			Non-responders
	First CC (n = 3)	Second CC (n = 12)	Third CC (n = 6)	(n = 5)
Age	29.7 ± 5.7	28.8 ± 4.1	28.0 ± 2.6	31.0 ± 4.5
Body Mass Index	24.8 ± 7.5	22.2 ± 5.4	22.5 ± 3.8	27.2 ± 7.2
LH (mIU/mL)	6.7 ± 2.0	10.5 ± 4.0	10.5 ± 4.2	8.5 ± 3.0
FSH (mIU/mL)	5.4 ± 1.8	4.9 ± 1.0	5.0 ± 1.2	4.8 ± 1.4
LH/FSH	1.3 ± 0.2	2.1 ± 0.6	2.1 ± 0.5	1.8 ± 0.4
Testosterone (ng/mL)	0.5 ± 0.5	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.4
Estradiol (pg/mL)	36.7 ± 17.2	46.6 ± 16.7	38.3 ± 10.9	46.4 ± 24.8
Fasting insulin (mU/mL)	5.5 ± 4.0	9.3 ± 13.7 (n = 7)	8.2 ± 5.1 (n = 5)	9.2 ± 8.4
Fasting glucose (mg/dL)	88.3 ± 4.9	89.0 ± 8.3 (n = 7)	87.4 ± 7.9 (n = 5)	89.8 ± 6.5
HOMA-IR	1.2 ± 0.8	2.2 ± 3.5 (n = 7)	1.8 ± 1.2 (n = 5)	2.1 ± 2.0

Data are shown as the mean ± standard deviation. CC, Clomiphene citrate; FSH, follicle-stimulating hormone; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LH, luteinizing hormone.

the day of the hCG injection, a single mature follicle was observed in 18 patients, whereas double mature follicles were observed in three patients, who underwent the second CC. Three of the 21 patients became pregnant by ICT during the study cycle. No case of OHSS or multiple pregnancies was observed. The baseline characteristics between the responders and the non-responders were not significantly different (Table 1).

4 | DISCUSSION

Clomiphene citrate has been used widely as a first-line treatment for anovulatory PCOS. However, ~15%-40% of women with PCOS are resistant to the standard CC treatment.[12] The present study showed that ICT is a useful treatment method for the induction of follicular growth in patients with PCOS who are resistant to the standard CC treatment.

In general, a low-dose, step-up FSH treatment is considered as a second-line therapy for CC-resistant patients with PCOS. About 70% of women receiving low-dose FSH step-up regimens ovulate.[13] However, these women need long-term daily injections of FSH. Gonadotropin therapy still has the potential risk of multiple pregnancies or OHSS, even if a low-dose, step-up method is applied.[14] This study's results showed that 80.8% of the patients with PCOS who were resistant to the standard CC treatment obtained follicular growth by ICT. Furthermore, ICT induced a single follicular growth in most cases and did not cause OHSS. Compared to gonadotropin therapy, CC is more convenient (oral administration) and cheaper. Therefore, ICT seems to be preferable for the prevention of multiple pregnancies and OHSS but with a high efficiency in achieving follicular growth in CC-resistant patients with PCOS. Thus, ICT can be a treatment to be tried before moving to gonadotropin therapy in these patients. Increasing the dose of CC up to 150 mg/day is an effective method for CC-resistant patients,[1] while 22.4% of the 100 mg CC-resistant patients obtained follicular growth by the 150 mg CC treatment.[5] In contrast, in this study, 78.2% (18 out of 23) of the non-responders to the first CC, who were resistant to 100 mg of CC, obtained follicular growth by the following second and third ICT. These results show that ICT is a much more effective method for the 100 mg CC-resistant patients than increasing the dosage of the CC. Therefore, ICT could be tried for the 100 mg CC-resistant patients before 150 mg CC is tried.

However, ICT was not effective in 19.2% (five out of 26) of CC-resistant patients. The baseline characteristics were compared between the responders and the non-responders in order to identify the clinical predictors of the response to ICT. Although high levels of a Body Mass Index, LH, LH/FSH ratio, testosterone, and the Homeostatic Model Assessment of Insulin Resistance were reported to be associated with CC resistance,[5,15,16] this study found no difference in these factors between groups. Further studies are needed to identify the predictors of the response to ICT.

Although ICT was found to be useful for CC-resistant patients, the mechanism remains unclear. It is speculated that there is a window in which follicles can respond to gonadotropins and start follicular growth and that this window appears at random times in anovulatory patients with PCOS. The intermittent administration of CC induces continuous ovarian stimulation and can be a useful method to find the window in anovulatory patients with PCOS.

Taken together, these results show that ICT can be an alternative before proceeding to gonadotropin therapy for CC-resistant patients with PCOS. However, the ultimate goal of CC treatment for infertile patients is a successful pregnancy and live birth. A large-scale,

randomized controlled trial will be necessary in order to evaluate the efficacy of ICT on a successful pregnancy outcome for patients with PCOS.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human rights statement and informed consent:* The project was reviewed and approved by the institutional review board of Saiseikai Shimonoseki General Hospital, Shimonoseki, Japan. Informed consent was obtained from all the patients in this study. *Animal studies:* This article does not contain any study with animal participants that were performed by any of the authors.

ORCID

Isao Tamura http://orcid.org/0000-0002-0737-5556

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