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Usefulness of Newly Devised Clomiphene Citrate Administration Method Compared with the Conventional Method in Ovulation and Pregnancy

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Abstract

Objective: Since not all women wish to conceive a child through aggressive treatment, we investigated the usefulness of modified repeated intracyclic clomiphene citrate (CC) therapy (repeated CC therapy) as a newly devised administration method. Methods: We evaluated the effects of CC administration on menstrual cycle length and retrospectively compared ovulation and pregnancy in 220 women who received CC at our hospital. Patients in the conventional method group received 50 mg per day for five days, starting on the fifth day of menstruation (withdrawal bleeding). Groups with and without menstrual cycle shortening after conventional CC administration were compared. The repeated CC therapy group was also compared with the non-shortened group. Repeated CC therapy was administered for the first five days as in the conventional method, and a second five-day repeat treatment was administered after an interval of five to seven days. Pregnancy rates, including indirect pregnancies, were evaluated by three different methods. Results: Ovulation and pregnancy rates were significantly better in the shortened group than in the non-shortened group ($P < 0.001$ and $P = 0.010$, respectively). Even in the non-shortened group, ovulation and pregnancy rates including indirect pregnancies were significantly improved when ovulation was observed with repeated CC therapy ($P < 0.001$ and $P = 0.022$, respectively). Conclusions: For patients whose menstrual cycle was not improved or shortened, repeated CC therapy as the newly devised CC administration method is useful as the next step after the conventional CC administration method.

Keywords

Clomiphene Citrate, Infertility, Menstrual Cycle, Ovulation Induction

1. Introduction

Indications for ovulation induction include ovulatory disorders such as ovarian dysfunction and infertility. Clomiphene citrate (CC) has long been the first-line treatment for ovulation induction [1] [2] [3]. Although unexplained infertility still accounts for a significant proportion of cases [4], some studies suggest that CC is not effective in unexplained infertility [5] [6]. Anovulation and ovulation disorders requiring ovarian stimulation account for 25% to 50% of all infertility cases [7] [8] [9]. Nevertheless, CC has been used empirically for ovarian stimulation in unexplained infertility and has been widely used to increase ovulatory capacity [10].

The discrepancy between ovulation and pregnancy rates has been attributed to the anti-estrogenic effect of CC on the cervix and endometrium by interfering with implantation, sperm transport, and early embryonic development [11] [12]. Gonadotropin therapy is usually evaluated as a next step in cases of poor response to CC or in those that do not result in pregnancy [2] [13] [14] [15]. However, the next step after unsuccessful CC treatment is not necessarily gonadotropin therapy, and continuation of CC therapy may be considered [16]. The ovulation rate of 65% to 68% and pregnancy rate of 12.5% to 32% for clomiphene therapy for infertility are not as expected for clomiphene therapy, while a relatively high multiple pregnancy rate of 11.1% to 12.5% has been reported [9] [17]. The cumulative effect of repeated administration of CC has been reported as a cause of multiple pregnancies [18], and long-term use of CC may also lead to the formation of ovarian cysts associated with luteinized unruptured follicle syndrome [19]. To address the possibility of continuing CC therapy in cases of repeated failure of the conventional CC administration method and to avoid CC-induced hyperstimulation while effectively continuing CC treatment, a newly devised method of CC administration was developed that improves the conventional CC administration method. Homburg *et al.* stated: "For CC, this may not be the end of an era, but it may be the beginning of the end." [10]. In other words, CC therapy has its limitations, but it has a role in ovulation disorders and infertility treatment.

Modified repeated intracycle CC therapy (repeated CC therapy) has also been reported. This involves administering CC at intervals during the same cycle without withdrawal bleeding if the patient does not respond to conventional CC administration [20]. Delayed CC administration may be as effective as increasing the dose [21]. In our hospital, gonadotropin therapy is avoided as much as possible as the next step after conventional CC administration. Instead, a newly devised method of CC administration, repeated CC therapy, has been adopted.

We hypothesized that CC may boost the menstrual cycle, including short and normal cycles, and may have different effects on long menstrual cycles. Repeated CC therapy is applicable to patients with long menstrual cycles, and CC has been shown to be effective [20]. Not all women wish to conceive a child through aggressive treatment. Ovulation induction is necessary in cases of poor response to

clomiphene citrate to avoid OHSS and multiple pregnancy. In this study, we evaluated the usefulness of a newly devised method (repeated CC therapy) by focusing on the length of the menstrual cycle.

2. Methods

This study was approved by the Kohseichuo General Hospital Institutional Review Board (No.2022-05), and informed consent was conducted in accordance with the tenets of the Declaration of Helsinki.

The purpose, effects, and side effects of the CC administration methods (i.e., conventional and repeated CC therapy as a newly devised method) were explained to the patients at the time of initial prescription, and the patient's consent was obtained before administration. We also explained that repeated CC therapy required at least 3 days of hospitalization per month and obtained their consent.

2.1. Study Design and Population

This retrospective cohort study included patients who received CC for more than six months for the purpose of achieving pregnancy at our hospital between May 2009 and July 2021. The following patients were excluded from the study: patients without cycles for follow-up after CC administration, patients without cycles for ovulation confirmation, patients with early menopause, and patients with abnormal semen analysis, hysterosalpingogram, or BMI. Patients requiring hysteroscopy and laparoscopy were given priority for surgery before CC administration. Patients in the conventional method group (group A) received 50 mg (25 mg) per day for five days, starting on the fifth day of menstruation (withdrawal bleeding) [22] [23] [24]. Patients in the repeat CC therapy group (group B) received the conventional method for the first five days as in the conventional method, followed by 5 - 7 days of follicular development monitoring, during which a second five-day repeat treatment was administered [20]. The second dose of repeated CC therapy is not simply an additional dose to the conventional CC administration. For patients with long menstrual cycles, at the time of the first dose of conventional CC administration, a second dose was also considered in case of poor response. Therefore, this treatment was designated as a separate group, group B. Repeated CC therapy was based on an initial dose of 50 mg/day for five days, and additional doses were administered at the same dose. Based on the response to the first cycle, we considered decreasing the dose by 25 mg/day or increasing it by 100 mg/day in the next cycle. The treatment period was 5 cycles if the response was favorable, followed by a 1- or 2-month rest period, and then another 5 cycles were attempted. The cost-effectiveness of repeated CC therapy is high. In a study comparing repeated CC therapy with gonadotropin therapy, the total cost of repeated CC therapy was approximately 1/6 that of gonadotropin therapy for successful ovulation [25]. In delayed CC administration, the first dose was omitted and only the second dose was administered based on

follicular development in repeated CC therapy [21].

2.2. Subgroups and Definitions

Repeated CC therapy was used in cases where ovulation occurred later than usual and women had a menstrual cycle of ≥35 days. In addition, this treatment required observation of follicular development for at least three days per month. On the first day, we checked for residual follicles and luteinized unruptured follicles at the start of CC administration. On the other two days, we checked the number of follicles and their development at the beginning and end of the second CC administration to predict the effective response to CC and to avoid multiple pregnancies and OHSS. Depending on the situation, the second dose of CC was reduced or stopped after the first dose. In group A, those with cycles < 35 days were designated as group NL, and those with cycles ≥ 35 days were designated as group L. Cases in the NL group with menstrual cycles that remained shortened after conventional CC treatment were designated as group NL-NL; conversely, cases with longer cycles were designated as group NL-L. Cases in the L group with sufficient improvement in ovulatory function and menstrual cycle shortening were designated as the L-NL group. In this group, sufficient follicular development was confirmed seven days after conventional CC administration. On the other hand, in cases where follicular development could not be confirmed, patients who could only attend the clinic one or two days per month were followed up. These patients were referred to as the L-L group. Finally, for the group receiving repeated CC therapy, if the second dose was canceled because of a good response to the first dose of CC, they were referred to as the L-NL group (**Figure 1**).

Cases that included even one cycle in which ovulation did not occur were considered possible cases of ovulatory dysfunction. The ovulation group was defined as the cases in which ovulation was observed in all cycles, and the ovulation group rate was defined as the percentage of the total number of cases in this group. The pregnancy rate was defined as the percentage of all cases in which pregnancy was achieved. A cycle length of more than ≥35 days [17] [26] and monophasic basal body temperature [26] have been reported to define ovulatory dysfunction. Factors contributing to the development of ovulatory dysfunction include luteinized unruptured follicle (LUF) syndrome and/or luteal phase defects [26], obesity [27], and age [8]. There is also a report describing the relevance of inhibin B levels in PCOS [28]. Ovulation is defined as a mid-luteal phase serum P level ≥ 10 ng/mL or clinical pregnancy confirmed by detailed follicular changes on ultrasound [17]. In this study, ovulation was also confirmed by follicular loss on ultrasound and clinical pregnancy, and the appearance of fluid in the pouch of Douglas can also be used for evaluation [9]. Confirmation of LH surge [17] and a home urinary luteinizing hormone kit [29] have also been reported. Pregnancy was confirmed using urine pregnancy tests and transvaginal ultrasound [9], and we used a similar method. In this study, pregnancies in cycles

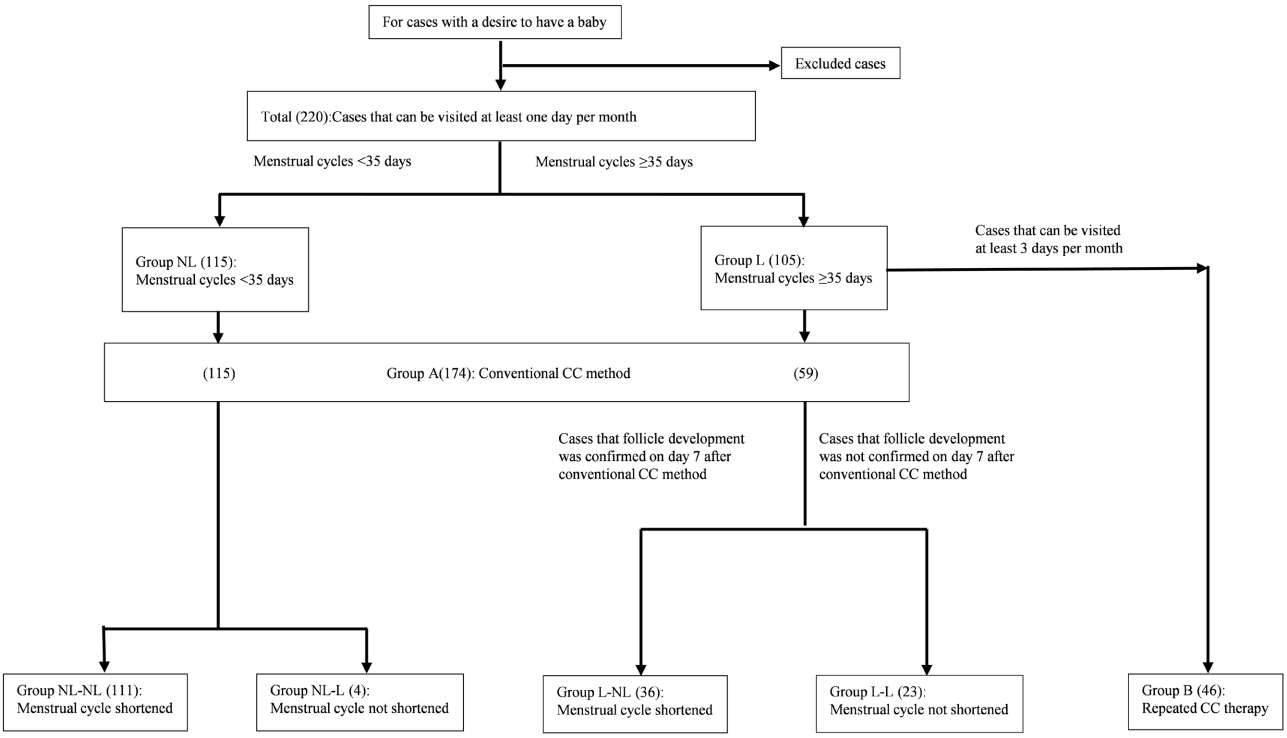

Figure 1. Flow chart of the study participant's enrollment.

in which CC was not administered in the next cycle following conventional CC administration were considered indirect pregnancies. In the case of repeated CC therapy, pregnancies resulting from conventional CC administration and delayed CC administration [21] that resulted in a reduction in CC dose were also considered indirect pregnancies, in addition to pregnancies in which CC was not administered at all.

2.3. Statistical Analysis

The ovulation group and pregnancy rates were examined for the following comparison. In one study focusing on the length of the menstrual cycle, the NL and L groups were compared (Comparison 1), and the (NL-NL) + (L-NL) and (NL-L) + (L-L) groups were also compared (Comparison 2). In another study, which focused on the effects of shortened menstrual cycles, the L-NL and L-L groups were compared (Comparison 3). When the menstrual cycle is not shortened by conventional CC administration, a newly developed method is required. The L-L group was considered a case of adaptation to repeated CC therapy, because the cycles of this group remained long even after conventional CC administration. In a study focusing on the effects of repeated CC therapy, L-L and B were compared (Comparison 4).

In this study, there were several cases in which the presence or absence of ovulation could not be confirmed. Therefore, we used the ovulation group rate to evaluate ovulation because this method does not take into account these missing data. Since this method assumes the same ovulation group even though

the number of cycles is different, it is not impossible to evaluate the different effects on ovulation in each case. Cases with a high number of cycles will result in strict criteria, whereas lenient criteria will result in less confidence in the test results. The number of cases in which repeated CC therapy was performed during data collection from medical records was 46. Based on our experience, we estimated that the number of cases in which these treatments were not performed was approximately the same as the number of cases in which these treatments were performed. We also noted the impression that the number of cases in which these treatments were not performed was approximately the same as the number of cases in which these treatments were performed. Thus, the following numbers of cases were estimated from the daily medical records: 50, repeated CC therapy (group B); 100, with a menstrual cycle ≥ 35 days (group L); and 100, with a menstrual cycle < 35 days (group NL). The total estimated number of patients (group A) was 200.

Fisher's exact probability test was used to analyze ovulation and pregnancy rates, and statistical analyses were performed using StatView version 5.0. Statistical significance was set at <0.05.

3. Results

Of the 220 patients in the study, 174 were finally assigned to group A and 46 to group B. At the time of conventional CC administration, there were 115 patients in the NL group and 59 in the L group. The number of patients in the NL-NL and NL-L groups was 111 and 4 in the NL group, respectively. The number of patients in the L-NL and L-L groups was 36 and 23 in the L group, respectively (**Figure 1**).

The ovulation group rate was significantly higher in the NL group than in the L group ($P < 0.001$); however, we found no significant differences in pregnancy rates between the two groups, including indirect pregnancies ($P = 0.848$ and $P = 1.000$, respectively) (**Table 1**). The ovulation group rate was significantly higher in (NL-NL and L-NL) than in (NL-L, L-L) ($P < 0.001$), the pregnancy rate and the pregnancy rate including indirect pregnancies tended to be higher ($P = 0.073$ and $P = 0.091$, respectively) (**Table 2**). In addition, ovulation group rates, pregnancy rates, and pregnancy rates including indirect pregnancies were significantly higher in the L-NL group than in the L-L group ($P < 0.001$, $P = 0.005$, and $P = 0.030$, respectively) (**Table 3**). Comparing groups B and L-L, the ovulation rate? Was significantly higher in group B than in group L-L ($P < 0.001$); there was no significant difference in the pregnancy rate ($P = 0.253$). However, when pregnancy rates, including indirect pregnancies, were evaluated, the pregnancy rate was significantly higher in group B than in group L-L ($P = 0.022$) (**Table 4**). It has been reported that there were no multiple pregnancies or OHSS with repeated CC therapy [25], and both were not found in this study.

4. Discussion

We focused on the differences in menstrual cycle changes after CC administration

Table 1. Comparison of group NL and L.

	Variables	Group NL	Group L	*P* Value
Ovulation	Total	115	59	<0.001
	Ovulation group	110	38	
	Non-ovulation group	5	21	
	Percentage (%)	95.7	64.4	
Pregnancy	Total	115	59	0.848
	Pregnancy group	25	14	
	Non-pregnancy group	90	45	
	Percentage (%)	21.7	23.7	
Including indirect pregnancy	Total	115	59	1.000
	Pregnancy group	29	15	
	Non-pregnancy group	86	44	
	Percentage (%)	25.2	25.4	

Table 2. Comparison of groups (NL-NL, L-NL) and (NL-L, L-L).

	Variables	Group (NL-NL, L-NL)	Group (NL-L, L-L)	*P* Value
Ovulation	Total	147	27	<0.001
	Ovulation group	138	10	
	Non-ovulation group	9	17	
	Percentage (%)	93.9	37.0	
Pregnancy	Total	147	27	0.073
	Pregnancy group	36	2	
	Non-pregnancy group	111	25	
	Percentage (%)	24.5	7.4	
Including indirect pregnancy	Total	147	27	0.091
	Pregnancy group	40	3	
	Non-pregnancy group	107	24	
	Percentage (%)	27.2	11.1	

Table 3. Comparison of groups L-NL and L-L.

	Variables	Group L-NL	Group L-L	*P* Value
Ovulation	Total	36	23	<0.001
	Ovulation group	31	7	
	Non-ovulation group	5	16	
	Percentage (%)	86.1	30.4	
Pregnancy	Total	36	23	0.005
	Pregnancy group	13	1	

Continued

	Non-pregnancy group	23	22	
	Percentage (%)	36.1	4.3	
Including indirect pregnancy	Total	36	23	0.030
	Pregnancy group	13	2	
	Non-pregnancy group	23	21	
	Percentage (%)	36.1	8.7	

Table 4. Comparison of groups B and L-L.

	Variables	Group B	Group L-L	*P* Value
Ovulation	Total	46	23	<0.001
	Ovulation group	43	7	
	Non-ovulation group	3	16	
	Percentage (%)	93.5	30.4	
Pregnancy	Total	46	23	0.253
	Pregnancy group	7	1	
	Non-pregnancy group	39	22	
	Percentage (%)	15.2	4.3	
Including indirect pregnancy	Total	46	23	0.022
	Pregnancy group	16	2	
	Non-pregnancy group	30	21	
	Percentage (%)	34.8	8.7	

in women with long menstrual cycles. In the group with short menstrual cycles after conventional CC administration, keeping the cycle short from the beginning was advantageous for ovulation. In the long menstrual cycle group, shortening the menstrual cycle is beneficial, and a newly devised method is needed to shorten the menstrual cycle in patients whose cycles remain long with conventional CC administration.

Comparison 1 (menstrual cycle length) showed that the ovulation rate was significantly lower in group L (with long menstrual cycles) than in group NL (with short menstrual cycles). Comparison 2 (length of menstrual cycle after CC administration) showed that group (NL-NL, L-NL) had a significantly higher ovulation rate than group (NL-L, L-L) and tended to have higher pregnancy rates and pregnancy rates including indirect pregnancy. Even in groups NL or (NL-NL, L-NL), which had a high ovulation rate, there was no pregnancy rate corresponding to the ovulation rate. This may be due to the negative effects of antiestrogens during the ovulatory phase [5] [30] [31]. Finally, if a stronger effect is expected with CC, the dosage should be increased. There are two ways to increase the dosage. One is the conventional method of increasing the daily dose while increasing the total dose in the next cycle. However, there are methods to

increase the total dose by extending the dosing period. A study with a 10-day dosing period reported that the extension of the treatment duration was more important than the total CC dose [32]. The method of extending the dosing period is not simply to increase the total dose, but to move the last day of CC dosing closer to the ovulatory phase. It can be concluded that prolonging the dosing period is similar to repeated CC therapy [20] [33], as both involve leaving the beginning and end of the dosing period and eliminating the middle. Therefore, repeated CC therapy may be an effective method of administering CC to patients with long menstrual cycles.

In comparison 3 (effect on shortened menstrual cycles with CC administration), ovulation and pregnancy in the L-NL group (with shortened menstrual cycles) and the L-L group (without shortened menstrual cycles) were examined with regard to changes after conventional CC administration. Ovulation and pregnancy rates were significantly higher in the L-NL group than in the L-L group. The shortening of the menstrual cycle meant that the last day of CC administration was closer to the ovulatory phase, which was a result of improved ovulatory function. Thus, it can be inferred that this improvement was related to improved ovulation and pregnancy. In addition, pregnancies have been reported following CC treatment even in cycles without CC administration, suggesting that CC is effective [18] [33]. Pregnancy rates, including indirect pregnancies, were significantly higher in the L-NL group than in the L-L group. For the L-L groups, it is necessary to shorten the interval between the last day of administration and the ovulatory phase.

In comparison 4 (strategies for cases in which menstrual cycles are not shortened), if no additional doses were administered in the repeated CC therapy, the patients would be in the L-L group. Therefore, we compared groups B and L-L. The ovulation rate was significantly higher in group B than in group L-L, which probably included some failed cases of conventional CC with very long menstrual cycles. Although it can be inferred that there were similar cases in group B, the large difference in ovulation rates between the two groups suggests that repeated CC therapy may be effective even in cases of conventional CC failure. Repeated CC therapy is a method that can compete with gonadotropin therapy at an average hMG dose of 1500 IU [25], proving that repeated CC therapy is a powerful ovulation induction method. There were no significant differences in pregnancy rates; however, a comparison of pregnancy rates, including indirect pregnancies, showed that the pregnancy rate was significantly higher in group B than in group L-L. The pregnancy rate, including indirect pregnancy, in group B improved to the same level as that in group L-NL. To improve ovulation function in the group that did not have a shortened menstrual cycle, repeated CC therapy with stronger ovulation induction was required. This method can be used without easily increasing the CC dosage, and the effect of CC is enhanced despite such safety considerations. The method has been reported to be as effective as gonadotropin therapy [20] [25]. However, considering the characteristics

of CC, even with increasing CC dose, the dose contributes to the ovulation rate and may not favorably affect the pregnancy rate. Buinetz *et al.* [34] found that women who ovulated in the "stair-step" protocol (SSP) [35] will ovulate again in subsequent cycles with the CC dose of their previous ovulation. Therefore, even in cases of ovulatory failure requiring SSP or repeated CC therapy, once ovulation occurs, the ovulatory environment improves, resulting in a lower CC dose. In this study, pregnancy rates, including these indirect pregnancies, were also significant in cases that improved with repeated CC therapy. Therefore, repeated CC therapy is useful as a next step for women whose cycles are not shortened after conventional CC administration.

5. Study Limitations

This study had several limitations. First, ovulation was evaluated on a case-by-case basis using ovulation group rates. Because the number of cycles in the ovulation group differed from case to case, the effects of ovulation also differed; however, these differences could not be accounted for. In addition, the percentage of ovulation failure in each case could not be evaluated; therefore, the ovulation rate per cycle could not be examined in the non-ovulation group. During pregnancy, the number of treatment cycles, once established, was not taken into account. Therefore, the effect of treatment cycle on pregnancy could not be evaluated. Second, the study focused on the short-term effects of modified repeated CC therapy on ovulation and pregnancy rates. It would be valuable to investigate the long-term outcomes, such as live birth rates and safety of the treatment, to provide a more comprehensive assessment of its usefulness. Finally, in cases eligible for repeat CC therapy, the first dose can be administered on the third day of menstruation, with a 5-day interval between the first and second doses. However, we were not able to include cases that met these criteria in our study.

6. Conclusions

In women with long menstrual cycles, ovulation and pregnancy rates were significantly improved when long menstrual cycles were shortened by CC administration. Even in cases where the menstrual cycle was not shortened, shortening the interval between the last day of administration and the ovulatory phase would improve both ovulation and pregnancy rates. Our results suggest that the newly devised CC administration method may be useful as a next step after conventional CC administration in patients whose menstrual cycles do not improve and shorten. However, repeated CC therapy is still associated with low pregnancy rates and the timing of administration may not be ideal. The future challenge is to determine the optimal timing to maximize the efficacy of these methods.

Authors' Contributions

MK designed this study and drafted the manuscript. MK, ES, YO, and RK conducted this study. MA and RN collected and collated the data. MK and RK par-

ticipated in the analysis and interpretation of the data. All authors read and approved the final version of the manuscript.

Conflicts of Interest

The authors report no competing interests for this article.

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