Modified repeated intracyclic clomiphene citrate therapy after conventional clomiphene therapy

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Summary

Purpose of investigation: We compared modified repeated intracyclic clomiphene citrate therapy (RICCT) to gonadotropin therapy to determine whether this modified regimen was an effective alternative after conventional clomiphene therapy. *Methods:* Patients with ovulation disorder received treatment with modified RICCT and gonadotropin, and ovulation, pregnancy, total drug cost, and adverse effects were compared. *Results:* Among a total of 16 patients, 14 successfully ovulated after modified RICCT and 11 ovulated after gonadotropin therapy; two did not respond to either therapy. The total drug cost was US $36.3 ± 17.9 for modified RICCT, which was significantly lower than the cost of gonadotropin therapy, US $213.9 ± 100.4 (p = 0.0001). *Conclusions:* Because modified RICCT does not require the discomfort of daily injection and has excellent ovulation-inducing effects, it is a useful treatment after conventional clomiphene therapy.

Key words: Clomiphene citrate; Gonadotropin; Infertility; Ovulation disorder; Multiple pregnancy; Polycystic ovary syndrome.

Introduction

Ovulation induction agents are used in treating patients with ovulation disorders due to abnormalities of the pituitary or hypothalamus, polycystic ovary syndrome (PCOS), or infertility. Clomiphene citrate is usually selected as first-line treatment [1, 2], and gonadotropin therapy is typically evaluated as the next step [3]. However, nonresponders to clomiphene citrate might require a high dose of human menopausal gonadotropin (hMG) until ovulation while undergoing gonadotropin therapy, which can lead to adverse effects such as multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). There has been no intermediate alternative between these two therapies.

During clomiphene citrate therapy, the drug is usually initially administered at a dose of 50 mg/day for five days. The dose is increased to 100 mg/day in patients who have a poor response in the cycle after withdrawal bleeding. If there is still no response, the daily dose is increased to 150 mg [3, 4]. The effectiveness of this regimen soon reaches a limit, however, and its ovulation-inducing effect is lower than that of gonadotropin therapy. In a previous study, we developed a new method of administering clomiphene cirate and obtained an ovulation-inducing effect comparable to that of hMG therapy [5]. In the present study, we compared modified repeated intracyclic clomiphene citrate therapy (RICCT), a new clomiphene citrate regimen, with gonadotropin therapy with regard to ovulation rate as well as drug cost, psychological burden, time required, and adverse effects.

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Materials and Methods

The subjects were chosen from infertility patients who visited our hospital and a hospital which cooperates with our hospital from 2000 through 2010. Modified RICCT and conventional gonadotropin therapy were explained to the patients, and the treatments were given to those from whom we obtained consent. Modified RICCT was given first, and gonadotropic therapy was performed after observing one or two episodes of withdrawal bleeding. In the modified RICCT regimen, clomiphene citrate was given for five days, starting five days after withdrawal bleeding, and the second course was started after an interval of five to ten days. The dose of the second course was basically identical to that of the first course [5]. In gonadotropin therapy, the daily dose was 150 or 300 IU, in principle, and urinary hMG was used in all patients. No patient performed self-injection. Variables such as total dose, total drug cost, number of days of administration, number of ovarian follicles, presence or absence of adverse effects, and pregnancy status were compared between the two therapies.

Statistical analysis was performed using the paired t-test. A p value less than 0.05 was considered to indicate statistical significance. Drug prices were calculated using an exchange rate of US $1 = ¥82 resulting that the cost of the drugs in Japan was ¥113 ($1.38) per tablet of clomiphene citrate and ¥1,896 ($23.12) for 75 IU, ¥2,236 ($27.27) for 150 IU, and ¥2,916 ($3.56) for 300 IU of hMG.

Results

Eleven of a total of 16 patients responded to both therapies, and the total dose of clomiphene citrate and hMG was 1,295.5 ± 638.0 mg and 1,509.1 ± 911.9 IU, respectively. Total drug cost was $36.3 ± 17.9 and $213.9 ± 100.4, respectively; modified RICCT was significantly cheaper (p = 0.0001). Three patients responded to modified RICCT but not to gonadotropin therapy, and two did not respond to either therapy (Table 1).

The number of ovarian follicles, number of hospital visits, occurrence of OHSS, and pregnancy status were compared between patients receiving the two therapies

Table 1. — *Comparison of dosing conditions between modified RICCT and gonadotropin therapy*.

Patients		RICCT					Gonadotropin (hMG) therapy			
		Dose (mg/day)	Duration of dosing period	Number of dosing periods	Total dose (mg)	Cost (US$)	Dose (IU/day)	Duration of dosing period	Total dose (IU)	Cost (US$)
1	Y.S.	100	5	2	1,000	28	300	4	1,200	143.2
2	R.A.	100	5	2	1,000	28	150	4	600	110
3	M.S.	150	5	2	1,500	42	300	8	2,400	286.4
4	A.T.	50	5	2	500	14	200, 150	2,1	550	82.5
5	A.T.	150	5	3	2,250	63	150	10	1,500	275
6	K.T.	100	5	2	1,000	28	225	5	1,125	158.5
7	M.T.	100	5	2	1,000	28	225, 150, 75	4, 1, 1	1,125	177.6
8	K.W.	150	5	3	2,250	63	300	13	3,900	465.4
9	A.T.	150	5	3	2,250	63	300, 150	6, 1	1,950	242.3
10	M.M.	100	5	2	1,000	28	150	7	1,050	192.5
11	S.Y.	50	5	2	500	14	150	8	1,200	220
				Mean	1295.5	36.3*		Mean	1509.1	213.9*
				SD	638.0	17.9		SD	911.9	100.4
1	M.I.	100	5	2	1,000	ovulation	150	11	(1,650)	anovulation
2	Y.K.	150	5	2	1,500	ovulation	150	11	(1,650)	anovulation
3	K.W.	150	5	3	2,250	ovulation	150	8	(1,200)	anovulation
4	M.I.	150	5	3	(2,250)	anovulation	300	5	(1,500)	anovulation
5	Y.I.	150	5	2	(2,250)	anovulation	150	8	(1,200)	anovulation

The 11 patients shown above achieved ovulation with both therapies, and the five shown below showed no ovulation with either or both therapies.
*Significant at $p = 0.005$.

Table 2. — *Comparison of the results of modified RICCT and gonadotropin therapy*.

Patients		Follicles				No. of hospital visits***		OHSS		Pregnancy	
		Mature*		Immature**							
		CC	hMG	CC	hMG	CC	hMG	CC	hMG	CC	hMG
1	Y.S.	2	2	0	0	3	5			Abort	On-going
2	R.A.	1	6	1	12	3	6		Mild		
3	M.S.	1	2	1	10	3	9		Mild		
4	A.T.	1	4	1	9	3	4				
5	A.T.	1	1	0	0	3	11				
6	K.T.	2	4	0	20	2	8				
7	M.T.	1	2	0	10	3	7		Moderate		On-going
8	K.W.	2	3	0	12	3	14		Mild		Abort
9	A.T.	1	3	0	5	3	8				
10	M.M.	2	3	0	30	3	8		Mild		
11	S.Y.	1	1	1	6	3	8				
Mean		1.36	2.82	0.36	10.36	2.91	8.00				
SD		0.48	1.40	0.48	8.25	0.29	2.63				

*Significant at $p = 0.01$; **Significant at $p = 0.005$; ***Significant at $p = 0.0005$.

(Table 2). The numbers of mature and immature follicles and hospital visits were significantly lower with modified RICCT ($p = 0.01$, $p = 0.005$, $p = 0.0005$, respectively). No OHSS was observed during administration of modified RICCT, but moderate and mild OHSS were observed in one and three patients, respectively, during gonadotropin therapy. The only patient who became pregnant through modified RICCT had a miscarriage. Three patients became pregnant while receiving gonadotropin therapy; pregnancy is ongoing in two and was aborted in one.

Patients in whom follicular development could not be expected even with continued treatment, those in whom only immature follicles increased, and those who were not given human chorionic gonadotropin (so as to avoid the risk of OHSS) and consequently did not ovulate were classified as poor responders.

Discussion

Clomiphene citrate therapy is selected as the first-line treatment in many patients with ovulation disorders or infertility, and gonadotropin therapy is available as second-line therapy. While 10-day [6, 7] and 8-day [8] regimens have been reported for clomiphene citrate therapy, conventional clomiphene citrate therapy is usually limited to five days [3, 4]. The effect of the drug is increased simply by raising the daily dose, but a limit is soon reached. It has also been reported that gonadotropin therapy is not usually effective in poor responders to clomiphene citrate because of interference between endogenous and exogenous gonadotropins [1]. In gonadotropin therapy, both the ovulation-inducing effect and frequencies of adverse effects such as multiple preg-

nancies (number of ovulated ova) and OHSS are greater than in clomiphene citrate therapy, and these therapies differ greatly.

Modified RICCT is a new treatment that might prove more effective than gonadotropin therapy [5]. In the present study, as compared with patients receiving gonadotropin therapy, the pregnancy rate was lower, but the number of patients who ovulated was higher and the incidence of OHSS was lower among those receiving RICCT. The small number of mature follicles is likely to have affected the pregnancy rate, but the therapy appears to suppress the occurrence of multiple pregnancies and OHSS. Thus, we believe that modified RICCT should be considered before gonadotropin therapy is selected. Two methods resembling RICCT have been reported, one for disorders of the hypothalamus [1] and the other for PCOS [9]. In both reports, clomiphene was first administered for five days, followed by another 5-day administration if there was no without withdrawal bleeding. This regimen was reported to sensitize the pituitary-hypothalamus-ovary system, which resulted in recovery of menstruation, as we suggested previously [5]. These therapies conform to our modified RICCT, in that 5-day administration was repeated during the same menstrual cycle, although the dose was increased for the second course.

Our modified RICCT showed more favorable results as compared with gonadotropin therapy with regard to the analyzed variables other than pregnancy and miscarriage. Because the numbers of mature and immature follicles were lower, and the ovulation rate was higher, the therapy had a sufficient ovulation-inducing effect even when the dose of the second course was identical to that of the first course. Therefore, a dose increase in the second course might lead to over-responsiveness. Our experience with modified RICC suggests that the dose could even be reduced for the second or third course.

In comparison with gonadotropin therapy, drug cost was clearly lower for modified RICCT, giving it an overwhelming economic advantage. The smaller number of injections results in less physical, psychological, and temporal burdens and makes the therapy more acceptable, particularly among patients with a limited desire for children. Recently, recombinant follicle-stimulating hormone (FSH) has become widely available, but it is more expensive than conventional urinary hMG despite the superior effectiveness and side-effect profile of hMG. Currently, the efficacy of FSH does not differ markedly from that of urinary hMG [10, 11]; therefore, the relative benefits of modified RICCT would remain, even if the present study were done using recombinant FSH.

Although modified RICCT may be superior to gonadotropin therapy in many respects, it was inferior with regard to pregnancy rate and miscarriage. Poor penetration of sperm due to the inferior characteristics of cervical mucus is a side effect of clomiphene citrate therapy [12, 13]. Indeed, when we examined patients who became pregnant during modified RICCT, artificial insemination was needed when clomiphene citrate was given at a daily dose other than 50 mg/day (unpublished observation). The necessity for artificial insemination is likely to increase further if the dose of clomiphene citrate is increased or the treatment period is prolonged. Combinations of clomiphene therapy with hMG have been reported to enhance the advantages of both agents [14, 15], and combinations of modified RICCT with hMG will be indispensable in the development of clomiphene citrate therapy.

It has been reported that patients with PCOS are likely to develop diabetes or dyslipidemia and that long or irregular menstrual cycles increase the risk of diabetes [16]. The use of combined estrogen/progesterone preparation to induce withdrawal bleeding is insufficient for treating women with disorders of the hypothalamus, and functional improvements from clomiphene citrate administration are necessary [2]. From this perspective, methods of ovulation induction that are advantageous in preventing conditions such as OHSS should be recommended, even if the pregnancy rate is lower.

Conclusion

Clomiphene citrate therapy has been used as first-line treatment because of its favorable side-effect profile, but gonadotropin therapy poses many problems as a second-line therapy. Modified RICCT might prove superior to gonadotropin therapy and is a second-line treatment that can be given to a wide range of patients after clomiphene citrate therapy.

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