Repeated intracyclic clomiphene citrate therapy can be more effective than hMG therapy in inducing ovulation: case report

M. Kawamura[1], *M.D.*; Y. Aoki[2], *M.D.*; R. Kanda[1], *M.D.*; H. Nakagomi[3], *M.D.*; Y. Tsukahara[1], *M.D.*; N. Hashimura[1], *M.D.*

[1]Department of Obstetrics and Gynecology, Kohseichuo General Hospital
[2]Department of Obstetrics and Gynecology, Nihon University School of Medicine; [3]Nakagomi Clinic, Tokyo (Japan)

Summary

Purpose of investigation: When clomiphene citrate is ineffective in the treatment of anovulation, hMG administration is typically selected. However, high-dose hMG therapy is associated with a variety of adverse events. We describe the use of a modified clomiphene citrate regimen that was successful in increasing the effectiveness of ovulation induction. *Case report:* A patient who did not initially respond to clomiphene citrate therapy required a total dose of 2400 IU hMG to prodeuce mature follicles. However, because of the physical and emotional burdens on the patient, and the possibility of multiple pregnancy and ovarian hyperstimulation syndrome, re-treatment with clomiphene citrate was then selected. Two courses of clomiphene citrate administered at a fixed interval during the same cycle safely induced ovulation. After initial induction of ovulation, her ovulatory failure improved and natural ovulation occurred. *Conclusions:* Repeated intracycle clomiphene cirate therapy may be more effective than hMG therapy in inducing ovulation in some patients.

Key words: Clomiphene citrate; hMG; Multiple pregnancy; Amenorrhea; Anorexia nervosa.

Introduction

Clomiphene citrate is the first-line treatment for anovulation. If a favorable response to clomiphene citrate is not obtained even after the dosage is increased, human menopausal gonadotropin (hMG) therapy is typically selected. In such cases, high-dose hMG therapy may be necessary to induce ovulation. However, a high-dose hMG regimen is associated with higher incidences of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). In recent years, improved hMG preparations have been developed to minimize such adverse reactions [1]. Nevertheless, hMG therapy places considerable physical and emotional burdens on patients and requires a substantial time commitment due to the need for frequent hospital attendance.

Although clomiphene citrate therapy is free from these problems, the standard regimen [2-5] may not be effective for inducing ovulation. In patients who require high-dose hMG citrate for the induction of ovulation, favorable results may not be possible if standard clomiphene citrate therapy is re-administered.

Because our patient had not responded to standard clomiphene citrate therapy, hMG therapy was administered. High-dose hMG therapy did result in the formation of mature follicles, but the patient had great anxiety about the treatment (especially concerning the daily injections). Due to the patient's concerns and risk of adverse events, administration of hMG was not continued. Instead, treatment with a modified clomiphene citrate regimen was chosen, with the hope of improving the results of the standard treatment. This report was written with the informed consent of the patient.

Case Report

Past history

The patient was a 29-year-old married woman who presented to the clinic of one of the authors with a 2-year history of infertility associated with anovulation and amenorrhea; she had become amenorrheic due to anorexia nervosa while working as a model. However, at the time of her clinic visit, she had stopped modelling and her eating habits had returned to normal. At the first hormonal examination, low gonadotropin and E2 levels were detected (Table 1-a). As she showed no response to clomiphene citrate therapy at a dose of 50 mg/day for five days, the dose was increased to 100 mg/day for five days. However, her ovarian function still did not respond, and an additional 100 mg/day for five days (a total of 1000 mg) was administered during the same cycle. After she did not respond to this regimen, hMG was prescribed for four days at 150 IU/day. However, her ovaries still did not react. Then, hMG was administered at a dose of 300 IU/day for eight days (total dose: 2400 IU). Two mature follicles were observed on the ninth day of treatment; approximately ten small follicles were also detected. The hCG injection was subsequently stopped due to the development of these small follicles. Luteinzing hormone (LH)-kid analysis on the ninth day showed that her urine was negative for presence of the LH surge, indicating that she had not ovulated. Natural withdrawal bleeding occurred seven days later. After her ovaries did not respond to two subsequent cycles of clomiphene citrate therapy at a dose of 100 mg/day for five days, she was referred to our Department of Gynecology.

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Table 1. — *Hormone levels at each treatment phase.*

Stage of treatment	LH (mIU/ml)	FSH (mIU/ml)	E2 (ng/ml)	P (pg/ml)
a Initial medical examination at previous clinic	0.3	1.3	10	-
b After first WB in our hospital	0.53	2.8	23.6	0.11
c Final day (Day 27) of the second course of CC therapy	6.9	5.3	203	0.36
d Mid-luteal phase (Day 34) after first ovulation	0.89	0.75	86.5	15
e Day 48 (December)	3.2	6.9	21.3	0.18
f About two months after WB (next year)	2.9	6.8	28.1	0.3

WB: withdrawal bleeding; CC: clomiphene citrate.

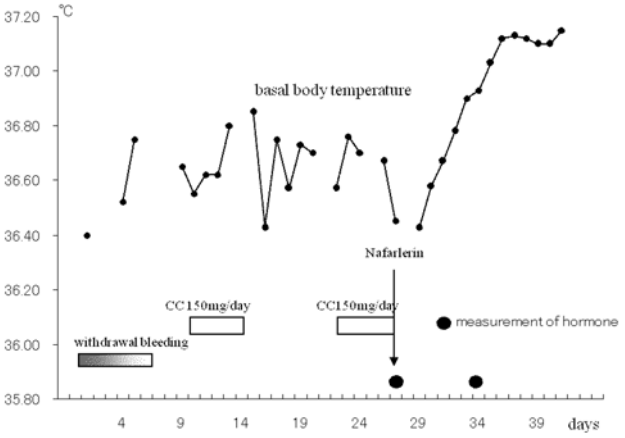
Table 2. — *Patient response during hMG therapy and repeated CC therapy.*

	hMG therapy	Repeated CC therapy
Before the treatment		
Daily life	good	good
Hormonal level	LH: 0.3, FSH: 1.3, E2: 10	LH: 0.53, FSH: 2.8, E2: 23.6
Cycle of ovulation	anovulation	anovulation
CC 100 mg x 5 days	no response	no response
During the treatment to induce ovulation		
Mature ovarian follicles	2	1
Small follicle	10 or more	1
LH surge	(–)	(+) (Gn-Rha)
OHSS		(–)
After the treatment		
CC 100 mg x 5 days	no response	ovulation

CC: clomiphene citrate.

Clinical course

At the time of the patient's first visit to our hospital, there were few follicles in either ovary and amenorrhea was still present. Hormone levels (Table 1-b) measured after a withdrawal bleed did not appreciably differ from the baseline values obtained at the previous clinic. Although she remained hopeful of successful conception, it was felt that physically and emotionally taxing treatments should be avoided because of the patient's considerable anxiety about her ovulatory failure and the treatment (especially the daily injections). Treatment with clomiphene citrate was therefore selected. At this time, approximately seven months had passed since the hMG treatment. The growth of follicles was not noted when clomiphene citrate was administered at a dose of 150 mg/day for five days, beginning on the tenth day after withdrawal bleeding. Clomiphene citrate was re-administered at a dose of 150 mg/day for five days after an 8-day drug holiday. On the final day of the second course of clomiphene citrate therapy, one mature follicle was noted in the left ovary and one small follicle was seen in the right ovary. Hormone levels at this time were appropriate for ovulation (Table 1-c), so Gn-RHa (Nafarelin: 1200 mg) was administered in the evening. One week after administration, ovulation was confirmed by ultrasonography and hormone levels (Table 1-d) (Figure 1). After ovulation, the patient's response to clomiphene citrate improved. The improved function of the pituitary and ovaries was confirmed by the hormone levels measured 48 days after menstruation (6 months after admission) (Table 1-e) and two months after withdrawal bleeding (10 months after admission) (Table 1-f). One year later, it was possible to induce ovulation by a single course of clomiphene citrate therapy at a dose of 50 mg/day for five days. Two years later, natural ovulation and emmenia were confirmed although they were slightly irregular.



CC: clomiphene citrate.

Figure 1. — Repeated intracyclic clomiphene citrate therapy protocol.

Discussion

As our case illustrates, patients with amenorrhea may have considerable anxiety [6] due to the great physical and emotional burdens associated with daily injection of hMG. For this reason, hMG therapy is not immediately indicated after patients show no response to clomiphene citrate. In addition, hMG therapy may result in multiple pregnancy and/or OHSS, leading to additional hardship. In recent years, improved hMG preparations have been developed to minimize such adverse reactions [1]. However, it has not been possible to markedly decrease the frequency of administration or the dosage of hMG [7]. Moreover, hMG therapy imposes a heavy economic burden on patients [8].

Clomiphene citrate continues to be administered in almost the same manner as that detailed in the first report of its clinical use by Greenblatt *et al.* in 1961 [9]. The usual dose of clomiphene citrate is 50 to 100 mg/day. If a response is not obtained, the daily dose is increased to 150 to 250 mg [3]. Using the standard protocol, the response to clomiphene citrate therapy is not much better than the response to hMG therapy. The duration of clomiphene citrate administration is usually five days, although durations of three days [4, 5] and ten days [10, 11] have been reported. Apart from reports describing combination therapy with other drugs [12-14], few reports have shown that the effect of clomiphene citrate was enhanced by methods other than an increase in dosage.

In the present case, daily injections of hMG were required to obtain a mature follicle. However, this regimen could not be sustained due to the physical and emotional strain it placed on the patient. Re-treatment using a modified clomiphene citrate regimen was therefore chosen, as it was less stressful for the patient. Because her ovulation disorder had not substantially improved since the time of her hMG therapy, clomiphene

citrate therapy was necessary to obtain effects similar to those of high-dose hMG treatment. Repeated intracyclic clomiphene citrate therapy was initiated at the dose of 150 mg/day for five days. This had no effect, so a second round of clomiphene citrate treatment was performed during the same cycle. Fortunately, ovulation was stimulated without any adverse effects.

A modified clomiphene citrate protocol was reported by Hamada *et al.* in 1976 [15]. In this regimen, clomiphene citrate is administered a second time without any withdrawal bleeding if the induction of ovulation by standard clomiphene citrate therapy cannot be confirmed after approximately one month. The authors believed that gonadotropin secretion might be activated and follicles might partially grow during the first course of clomiphene citrate therapy, and that follicles might grow further and ovulation might be induced during the second course. This regimen could enhance the sensitivity of the ovaries to gonadotropin and therefore result in ovulation. On the basis of this hypothesis, we developed a reported clomiphene citrate regimen with a recovery period. In this regimen, the duration of the first and second courses of treatment is five to seven days [16]. In standard clomiphene citrate therapy, clomiphene citrate is re-administered after withdrawal bleeding if the ovary activity is poor. In repeated clomiphene citrate therapy, the second and third courses of treatment are added according to the response of the patient, so that an additive effect is obtained. With this method, the day clomiphene citrate therapy is initiated (50-200 mg/day for 5 days), and the interval between the first and second course of treatment (range: 5-10 days) can be scheduled at the patient's convenience.

In this study, hMG and clomiphene citrate were administered to the same patient and the conditions just before both administrations were almost identical. We evaluated changes during and after the administration of hMG and clomiphene citrate (Table 2). Our results in the present case illustrate the advantages of repeated intracyclic clomiphene citrate therapy as compared to hMG therapy, which can lead to considerable stress due to the need for daily treatment and to possible multiple pregnancy and OHSS. Our findings show that when ovulation is induced in repeated intracyclic clomiphene citrate therapy, the hormonal environment may improve resulting in a better response to treatment during the next cycle. If a patient does not respond to repeated intracyclic clomiphene citrate therapy, the possibility of successful subsequent hMG treatment would not be adversely affected. Although the cervical mucus and/or endometrium may be affected by clomiphene citrate, it is important to initially select the treatment method that is least burdensome for patients with chronic amenorrhea.

Conclusion

In the treatment of anovulation, it is obviously important to induce ovulation that results in pregnancy. However, it also essential to avoid multiple pregnancy and/or OHSS. Our results indicate that repeated intracyclic clomiphene citrate therapy may be more effective in inducing ovulation than hMG therapy for some patients.

References

[1] Aboulghar M.A., Mansour R.T., Serour G.I., Amin Y.M., Sattar M.A., El Attar E. *et al.*: "Recombinant follicle-stimulating hormone in the treatment of patients with history of severe ovarian hyperstimulation syndrome". *Fertil. Steril.*, 1996, *66,* 757.

[2] Marrs R.P., Vargyas J.M., Shangold G.M., Yee B.: "The effect of time of initiation of clomiphene citrate on multiple follicle development for human invitro fertilization and embryo replacement procedures". *Fertil. Steril.*, 1984, *41,* 682.

[3] Wolf LJ.: "Ovulation induction". *Clin. Obstet. Gynecol.,* 2000, *43,* 902.

[4] Gol K., Gursoy R., Karabacak O., Yildirim M.: "The effects of 3-day clomiphene citrate treatment on endocrine and ovulatory responses". *Gynecol. Endocrinol.*, 1996, *10,* 171.

[5] Kelekci S., Saygili-Yilmaz E., Inan I, Eminsoy G.: "A trial of a new regimen with clomiphene citrate administration to reduce the antiestrogenic effects on reproductive end organs". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2004, *116,* 54.

[6] Mehler P.S.: "Diagnosis and care of patients with anorexia nervosa in primary care ettings". *Ann. Intern. Med*., 2001, *5,* 134, 1048.

[7] Yarali H., Bukulmez O., Gurgan T.: "Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomipnene citrate-resistant, normogonadotropic, chronic anovulation: a prospective randomized study". *Fertil. Steril.,* 1999, *72,* 276.

[8] Zwart-van Rijikom J.E., Broekmans F.J., Leufkens H.G.: "From HMG through purified urinary FSH preparations to recombinant FSH: a substitution study". *Hum. Reprod*., 2002, *17,* 857.

[9] Gleenblatt R.B., Barfield W.E., Jungck E.C., Ray A.W.: "Induction of ovulation with MRL/41". *JAMA,* 1961, *178*, 127.

[10] Hughes E., Collins J.: "Vandekerckhove P. Clomiphene citrate for unexplained subfertility in women". Cochrane Database Syst Rev. 2000, 2, CD000057.

[11] Djurovic M., Pekic S., Petakov M., Damjanovic S., Doknic M., Diegez C. *et al.*: "Gonadotropin response to clomiphene and plasma leptin levels in weight recovered but amenorrhoeic patients with anorexia nervosa". *J. Endocrinol. Invest.*, 2004, *27,* 523.

[12] Cristello F., Cela V., Artini P.G., Genazzani A.R.: "Therapeutic strategies for ovulation in infertile women with polycystic ovary syndrome". *Gynecol. Endorinol.*, 2005, *21,* 340.

[13] Suginami H., Hamada K., Yano K., Kuroda G., Matsuura S.: "Ovulation induction with bromocriptine in normoprolactinemic anovulatory women". *J. Clin. Endocrinol. Metab.,* 1986, *62*, 899.

[14] Diamant Y.Z., Evron S.: "Induction of ovulation by combined clomiphene citrate and dexamethasome treatment in clomiphene citrate nonresponders". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1981, *11,* 335.

[15] Hamada K., Tanaka B., Honda Y., Yamazaki Y., Shiode S., Onda H. *et al.*: "Induction of ovulation with clomiphene two step method". *Acta Obstet. Gynecol. Japonica*, 1976, *28,* 1483 (Japanese).

[16] Kawamura M., Iwagaki F., Chiyokura Y., Mishima M., Nakagomi H., Yokoyama M. *et al*.: "Induction of ovulation with repeated clomiphene administration". *Tokyo J. Obstet. Gynecol.*, 1990, *39*, 34 (Japanese).

Address reprint requests to:
M. KAWAMURA, M.D.
1-11-7 Mita Meguro-ku Tokyo
153-8581 (Japan)
e-mail: mkawamura@kohseichuo.jp