

The stair-step approach in treatment of anovulatory PCOS patients

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Ther Adv Reprod Health

2020, Vol. 14: 1–6

DOI: 10.1177/
2633494120908818

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Abstract

Clomiphene citrate (CC) is a widely accepted first-line treatment for anovulatory patients with polycystic ovarian syndrome (PCOS). The current practice is to prescribe CC with gradual dose increments until ovulation is achieved. Typically, progesterone withdrawal bleeding is induced between each dose increment and before the commencement of gonadotropin therapy in CC-resistant patients. It has been recently suggested that dose increments of CC can be administered once failure to induce ovulation at a certain dose has been documented, without induction of progesterone withdrawal bleeding, and this approach has been nicknamed the clomiphene-citrate stair-step (CC-SS) protocol. The same principle has been found feasible before introducing gonadotropin therapy in CC-resistant PCOS patients. Our objective was to review the world literature on the CC-SS protocol and to summarize our own experience with extending the CC-SS approach to initiation of gonadotropin therapy. Studies on CC-SS protocol ($n=4$) have found that this approach leads to a significant reduction of the time to ovulation and to an increased ovulation rate. In our own retrospective case series, 18 CC-resistant PCOS patients initiated gonadotropin stimulation without induction of progesterone withdrawal bleeding, using the chronic low-dose regimen. The time to ovulation in the study group was 54.2 ± 6.2 days, while the estimated time to ovulation calculated according to the traditional approach was approximately 110 days. The clinical pregnancy rate was 44% (8/18), and all pregnancies were singletons. One patient miscarried; hence, the live birth rate was 38.9% (7/18). In summary, the CC-SS approach and its extension to the initiation of gonadotropin therapy results in considerable reduction of the time to ovulation, and favorable ovulation rates and reproductive outcome. Large-scale confirmation of these findings by properly designed randomized controlled trials may lead to a change of practice in the treatment of anovulatory infertility in PCOS patients, allowing simplification of treatment and a shorter time to ovulation and pregnancy.

Keywords: Polycystic Ovarian Syndrome, Clomiphene Citrate, Gonadotropins, Ovulation Induction, Stair-step

Received: 11 June 2019; revised manuscript accepted: 22 January 2020.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women, and accounts for 75% of cases with anovulatory infertility.^{1–3} The prevalence of PCOS ranges from 9–13% in reproductive-aged women depending on the definitions used and the populations studied.¹ International evidence-based

guidelines for assessment and management of infertile women with PCOS have been recently published by a multidisciplinary international expert panel.⁴ The panel concluded that the aromatase inhibitor Letrozole should now be considered as first-line medical intervention for ovulation induction in anovulatory PCOS patients. The panel, however, also reported that

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subgroup analysis comparing studies that included women with PCOS who were therapy naïve there was no difference between letrozole and clomiphene citrate (CC) for any of the reproductive outcome measures that were studied.

Thus, CC is commonly prescribed for the treatment of PCOS-associated anovulatory infertility, and is still regarded by many as first-line treatment worldwide, because it is an inexpensive, simple, and effective therapy with insignificant side-effects.^{2,3} A recent web-based survey on the management of infertility in PCOS patients revealed that CC was regarded as first-line treatment by 68% of respondents.⁵ CC acts by reducing the negative feedback of estrogen on the hypophysis and the hypothalamus, therefore increasing the secretion of follicle-stimulating hormone (FSH) from the hypophysis and encouraging follicular growth followed by ovulation.

CC is taken orally, with a starting dose of one tablet of 50 mg daily for 5 days. Traditionally, it is started between the second and the fifth day of menses which occurs spontaneously or after a progestin-induced bleeding. Ovulation generally occurs after 5–12 days after the last tablet. If there is no response for the original dose, progestin withdrawal bleeding is induced and the dose is augmented by 50 mg.² About 52% of PCOS patients ovulate in response to treatment with 50 mg, 22% and 12% ovulate with higher doses of 100 and 150 mg, respectively.^{2,3} Because a minority of the patients who fail to respond to 150 mg will ovulate with a dose of 200 and 250 mg, these doses are rarely used.

Approximately 85% of PCOS patients will ovulate in response to CC at the maximal common dose used of 150 mg,^{2,3} and failure to ovulate in response to CC is regarded as clomiphene resistance. For many years, the recommended second-line therapy for clomiphene-resistant women has been gonadotropin ovulation induction (OI). Some researchers, however, have advocated that injectable FSH may be an appropriate first-line treatment for women with PCOS and anovulatory infertility, particularly older patients.⁶ Once clomiphene resistance has been established, progestin withdrawal bleeding is often induced before beginning gonadotropin therapy. This practice causes a treatment delay of 10–14 additional days. Altogether, induction of progestin withdrawal bleeding before CC treatment, between each CC dose increment,

and after the diagnosis of CC resistance is established, it would take a protracted course of about 3 months before gonadotropin OI can be initiated.

It has been recently suggested that dose increments of CC can be administered once failure to induce ovulation at a certain dose has been documented, without induction of progesterone withdrawal bleeding, and this approach has been nicknamed the clomiphene-citrate stair-step (CC-SS) protocol. To the best of our knowledge, our team was the first and only so far to apply the same principle before introducing gonadotropin therapy in CC-resistant PCOS patients. Our objective was to review the world literature on the CC-SS protocol and to summarize our own experience with extending the CC-SS approach to initiation of gonadotropin therapy.

The CC-SS protocol

Hurst and colleagues⁷ suggested an original CC OI regimen including a ‘stair-step’ (CC-SS) protocol, with the aim of shortening the interval to ovulation in nonresponders. When there was no response to CC, the dose was immediately increased without inducing a progestin withdrawal bleeding; if there was no response again, the dose was increased once more without delay until either ovulation was accomplished or the diagnosis of clomiphene resistance was established. With the ‘stair-step’ protocol, the time to ovulation was reduced by 32–53 days compared with historical controls with traditional use of CC regimen, and the dose-dependent ovulation rate was 64% at 100 mg compared with 22%, respectively. The conclusion was that it is not required to induce menses before increasing CC doses in nonresponsive PCOS patients.

The benefit of the CC-SS protocol is a shorter time to ovulation when dose increments of CC are required. In addition, inducing a menstrual bleeding with progestin before CC therapy in anovulatory women has been shown to be unnecessary⁸ and has been associated with a lower conception and live birth rates compared with women in whom CC was started in the follicular phase remote from spontaneous or induced menses.⁹

Recently, Jones and colleagues¹⁰ completed a retrospective study of women who remained anovulatory with the initial starting CC dose of 50 mg.

A total of 109 patients were included in the analysis with 66 (60.6%) receiving a traditional CC regimen and 43 (39.4%) receiving the CC-SS protocol as described by Hurst and colleagues.⁷ The time to ovulation was reduced in the CC-SS protocol group compared with the traditional protocol group (23.1 ± 0.9 days *versus* 47.5 ± 6.3 days). Ovulation rates were greater in the CC-SS group compared with the traditional group at 150 mg [16 (37%) *versus* 8 (12%), $p=0.004$] and at 200 mg [9 (21%) *versus* 3 (5%), $p=0.01$]. Pregnancy rates were comparable between groups once ovulation was achieved [12 (18.1%) *versus* 7 (16.3%), $p=0.08$]. An important concern of the CC-SS protocol was that it was linked with an increased incidence of mild side-effects compared with the conventional protocol [vasomotor flushes, headaches, gastrointestinal disturbance, mastalgia, changes in mood; 18 (41%) *versus* 8 (12%)]; however, there was no difference in the incidence of severe side-effects (headaches, visual disturbances). It was concluded that for women with anovulatory PCOS, the CC-SS protocol is associated with decreased time to ovulation and increased ovulation rates at higher doses when compared with the conventional protocol.

A randomized controlled trial (RCT) by Deveci and colleagues¹¹ once again demonstrated that the CC-SS protocol offers a significantly shorter treatment period without any detrimental effect on the ovulation and pregnancy rates. A total of 60 PCOS patients who failed to respond to 50 mg/day of CC for 5 days, were randomly allocated to the control (traditional protocol) and study (CC-SS protocol) groups. Ovulation and pregnancy rates were similar between the CC-SS and the control groups (43.3% *versus* 33.3%, respectively) (16.7% *versus* 10%, respectively). The duration of treatment was significantly shorter in CC-SS compared with traditional protocol (20.5 ± 2.0 *versus* 48.6 ± 2.4 days, respectively). Once again there were no significant differences in the systemic side-effects between the groups. The uterine anti-estrogenic effect of CC was evaluated by endometrial thickness and uterine artery Doppler ultrasound testing; no significant differences were observed in CC-SS compared with the traditional protocol. Similar findings were recently reported in an RCT by Agrawal and colleagues.¹² A summary of the studies that evaluated the CC-SS protocol is presented at Table 1.

Table 1. Summary of the Main Characteristics and Outcomes of Previous Studies Using the Clomiphene Citrate Stair-step (CC-SS) Protocol.

Authors	Study design	Time to ovulation with CC-SS	Time to ovulation with 'traditional protocol'	Ovulation rate CC-SS protocol	Ovulation rate with 'traditional protocol'
Hurst and colleagues ⁷	Retrospective 31 patients, compared with historic controls	23–35 days	55–88 days	64% on 100 mg CC* 74% on ≤ 150 mg CC*	22% on 100 mg CC* 35.5% on ≤ 150 mg CC*
Deveci and colleagues ¹¹	Randomized controlled trial 30 patients CC-SS 30 traditional CC protocol	20.5 ± 2 days*	48.6 ± 4 days*	43%	33.3%
Agrawal and colleagues ¹²	Randomized controlled trial 30 patients CC-SS 30 traditional CC protocol	13.65 ± 6.7 days* (ovulatory patients)	32.8 ± 20.4 days* (ovulatory patients)	66.7%	50%
Jones and colleagues ¹⁰	Retrospective 43 CC-SS 66 traditional CC protocol	23 ± 0.9 days*	47.5 ± 6.3 days*	88%*	39%*

CC, clomiphene citrate; CC-SS, clomiphene-citrate stair-step.
* $p < 0.05$.

The enhanced ovulation rates achieved using the CC-SS protocol^{7,10–12} are considered to be the result of an additive effect of multiple doses. The half-life of clomiphene is 5–7 days, but may be longer resulting from variability in metabolism.^{13,14} When patients take their additional SS dose, active isomers are still present in the circulation, making the total circulating concentration higher than in traditional protocols, where CC has ample time to wash out.

Direct initiation of gonadotropin therapy in CC-resistant PCOS patients

Taking these novel findings^{7–12} into account, we sought to further simplify OI treatment in CC resistant PCOS patients and apply the same therapeutic approach during the transition phase between CC treatment and gonadotropin therapy. Instead of inducing progestin withdrawal bleeding before initiation of gonadotropin therapy, we began the administration of gonadotropins using the chronic low-dose protocol once it was clear that the highest CC dose that was used failed to induce ovulation. Our retrospective report included 18 consecutive CC-resistant PCOS patients for whom the CC-SS protocol was extended further to include gonadotropin therapy.¹⁵ The primary outcome measure was the time to ovulation from the beginning of CC treatment until the day of the ovulatory trigger. This was matched with the time to ovulation according to the traditional approach, which includes inducing progesterone withdrawal bleeding between each CC dose increment and before initiating gonadotropin therapy.⁷ The time to ovulation in the study group was 67.0 ± 6.8 days. The estimated time to ovulation according to the traditional approach was approximately 110 days. The clinical pregnancy rate was 44% (8/18), and all pregnancies were singletons. One patient miscarried; hence, the live birth rate was 38.9% (7/18). The suggested CC-SS gonadotropin sequence decreases the time to ovulation and pregnancy compared with conventional CC and gonadotropin regimens, which include induction of menses between dosage increments and drug changes. In addition, considerable reduction of the time to ovulation has been found to be both safe and efficacious. It is beneficial for patients who generally desire active management and are very distressed by delays caused by having to await spontaneous or

induced menses. Long intervals and recurrent treatment failures have been shown to rise patient frustration and anxiety¹⁶ and may be a cause for dropout from treatment. To the best of our knowledge, our study was the first to describe the direct CC-SS-gonadotropin sequence, and our findings await confirmation by large-scale RCTs.

The biological plausibility of the CC-SS approach

How can the benefits of the stair-step approach be explained? Diamond and colleagues⁹ studied 2809 OI cycles of with CC alone, metformin alone, or CC plus metformin in 626 women with PCOS. Surprisingly, conception and live birth rates were inferior in women with menses, either medically induced or spontaneous before OI as compared with women who started OI treatment without bleeding. There may be negative effects on reproductive outcome for spontaneous or induced bleeding before initiating OI in PCOS patients. Potential deleterious effects may include an indirect effect of progestin on the hypothalamic–pituitary–ovarian axis, as well as direct or indirect effects of alterations in the androgenic and metabolic milieu.⁹ In addition, CC may act as an estrogen receptor (ER) antagonist in peripheral target tissues such as the endometrium, as well as in the brain.¹⁷ As it has been shown that CC use for OI is linked with a thin endometrium in some patients,¹⁸ if endometrial shedding occurs before the administration of CC, the patient is starting with a thin endometrium that may not respond well if ER depletion secondary to CC use occurs. Thus, it may be reasonable to believe that if there is no endometrial shedding and the endometrium is already near the suitable thickness needed for implantation at the time CC is started, ER reduction may have much less effect and the endometrial lining may be satisfactory once ovulation occurs. In line with the above hypothesis, lack of withdrawal bleeding in the CC-SS gonadotropin sequence may explain the relatively high pregnancy and live birth rates observed in our series.

Conclusion

In conclusion, the CC-SS protocol and the CC-SS gonadotropin sequence represent significant advances in the treatment of anovulatory infertility in PCOS patients. Progesterone withdrawal bleeding is unnecessary and should

be avoided before dose increments during CC therapy and at the transition phase between CC and gonadotropin therapy in clomiphene-resistant patients. The CC-SS protocol and the CC-SS gonadotropin sequence both shorten the time to ovulation, without an adverse effect or pregnancy and live birth rates and without increasing the risk for multiple pregnancy. Once the above findings are confirmed by properly designed RCTs, they may lead to a change of practice in the treatment of anovulatory infertility in PCOS patients, allowing simplification of treatment and a shorter time to ovulation and pregnancy.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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