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A Novel Alternative to Sequential Protocol in Clomiphene Citrate-Resistant PCOS Patients with a Combined Regimen of Clomiphene Citrate and Recombinant Gonadotropin

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ABSTRACT

Purpose: The aim of this study was to compare treatment outcomes of different ovulation induction (OI) protocols with combination of clomiphene citrate (CC) and recombinant gonadotropin in infertile women with polycystic ovary syndrome (PCOS) undergoing an intrauterine insemination (IUI) cycle.

Methods: In this retrospective cohort study, 75 patients with PCOS undergoing OI and IUI cycles with a combination of CC and recombinant gonadotropins were evaluated. Participants were divided into two groups according to their (OI) protocol: group 1 [sequential protocol (SP): OI with CC plus gonadotropin started on the fourth or fifth day of CC treatment; n=37], group 2 [modified sequential protocol (MSP): OI with CC was started on days 2-5 of the cycle, and gonadotropin was added once the dominant follicle size reached over 10 mm; n=38].The two groups were compared for cycle cancellation, absence of follicular development, multifollicular development, ovulation rate (OR), implantation, clinical pregnancy, ongoing pregnancy and abortion rates.

Results: Demographic features were distributed homogenously between the groups. The number of days of gonadotropin use was also significantly higher in group 1 (6.37±2.58 days) than in group 2 (3.15±1.74 days) ($p<0.0001$). Similarly, the total gonadotropin dose was significantly higher in group 1 (477.36±316.19 IU) compared to group 2 (188.15±168.83 IU) ($p<0.0001$). Multifollicular development in group 1 was significantly higher than in group 2 ($p=0.01$). The OR was 84.8% in group 1 and 89.5% in group 2. The ongoing pregnancy rate was 14.3% for group 1 and 11.8% for group 2.

Conclusion: MSP may help reduce multifollicular development, potentially lowering costs and improving patient compliance by decreasing the duration and doses of gonadotropin treatment compared to SP in PCOS patients resistant to CC. Furthermore, when compared to SP, MSP can provide similar ongoing pregnancy rates.

Keywords: Ovulation induction, clomiphene citrate, sequential protocol, modified sequential protocol, polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS), with a prevalence of 5-10%, is a common endocrinological disorder in reproductive-aged women.[1] Women with PCOS who fail to ovulate or conceive with clomiphene citrate (CC) are recommended to undergo ovulation induction with gonadotropin.[2] Recently, a combination of CC plus gonadotropin treatment has been tested as a method for ovulation induction in women resistant to CC.[3-6] This protocol, termed a "sequential protocol (SP)," was first described by Kistner[7] and performed with a combination of CC and human menopausal gonadotropin (hMG). In SP, a low-dose gonadotropin treatment is initiated on the day following the fourth or fifth day of CC administration.

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Acceptable fecundity rates have been reported in CC-resistant patients with SP when compared to ovulation induction with gonadotropin.[8] SP has been demonstrated to decrease the gonadotropin dose required for optimum induction when compared to gonadotropin-only induction in women who fail to respond to CC.[9] Previous studies have shown that CC + gonadotropin combinations reduce costs and provide effective ovulation induction in infertile cases resistant to CC [10].

We have developed a "modified sequential protocol (MSP)" to initiate gonadotropin therapy in CC-resistant patients with PCOS. In this protocol, gonadotropin treatment is initiated in conjunction with CC when a leading follicle reaches >10 mm, as determined by ultrasonography (USG).

The main aim of this study was to achieve successful inductions with less multifollicular development and lower gonadotropin doses as a potential alternative to SP. We compared ovulation induction cycles conducted with SP and MSP protocols. The treatment outcomes were evaluated by comparing pregnancy results, cycle cancellation rates, and the doses of medications used.

METHODS

This retrospective cohort study was performed in the infertility unit of tertiary health center between 2012 and 2016. The study was approved by the Marmara University Ethics Committee (approval number: 09.2024.169, date: 09/02/2024). In our clinic, informed consent for the use of personal data is obtained from all patients at the start of treatment. The data is anonymized when used.

Inclusion criteria were a diagnosis of infertility due to PCOS, having at least one patent fallopian tube on hysterosalpingography and having normozoospermic male partners, as per WHO guidelines.[11] PCOS diagnosis was based on the revised Rotterdam criteria.[12] Women who failed to ovulate or conceive with CC despite doses of 150 mg/day or six cycles and were considered CC-resistant cases and were included in this study.

Women with bilateral tubal occlusion confirmed with hysterosalpingography or with hypo/hypethyroidism, hyperprolactinemia, or other endocrinopathies (such as adrenal hyperplasia, insulin resistance, or diabetes) that might affect ovulatory response were excluded from the study.

Demographic features, maternal habits (smoking, alcohol consumption), cycle characteristics, and presence of hirsutism (evaluated at a minimum of eight points by the Ferriman-Gallwey scores) were recorded.[13] Body mass index was calculated by the standard formula: wseight (kg) divided by the height squared (m^2). Measurements included tubal patency, day 2 basal hormone levels and levels of thyroid stimulation hormone and prolactin on a random day, as well as the progressive motile sperm count of the male partner.

The participants were randomly selected in a 1:1 ratio. This selection was made based on patient file numbers, using arithmetically increasing numbers as a reference.

Group 1 (Sequential Protocol)

Group 1 received CC (50-150 mg daily) (Klomen® Koçak Farma, İstanbul, Turkey) from day 2-5 of the menstrual cycle for 5 days. On the day following the fourth or fifth day of CC administration, gonadotropin (GONAL-f®; Merck KGaA, Darmstadt, Germany) therapy was initiated at a low dose (37.5-75 IU) until human chorionic gonadotropin (hCG; Ovitrelle® Merck Serono, Geneva, Switzerland) administration. The gonadotropin dose was adjusted according to the follicular response.

Group 2 (Modified Sequential Protocol)

Group 2 received CC (50-150 mg daily) from day 2-5 of the menstrual cycle for 5 days. Following CC induction, low-dose (37.5-75 IU) gonadotropin treatment was started when a dominant follicle (≥10 mm) was observed on the transvaginal (TV)-USG examination. Daily gonadotropin injections were continued until the day of hCG administration. The subsequent gonadotropin dose was adjusted according to the follicular response.

The protocol used for ovulation induction continued until one or two follicles reached a size of 17 mm or more. The adjusted gonadotropin dose was adjusted by the clinician based on follicle diameter and estradiol levels.

Cycle Monitoring

Follicular development was monitored by TV-USG. The first ultrasound examinations were repeated every 2 days until the hCG day.

The hCG injection was administered as a single dose (10.000 IU) to trigger ovulation when one or two leading follicles had reached at least 17 mm in diameter. IUI was performed 36 h after the administration of hCG following a standard swim-up procedure under transabdominal guidance, as previously described.[14] A daily intravaginal progesterone administration (400 mg) was also initiated for luteal support. Vaginal progesterone used for luteal phase support was continued until the 8th week of pregnancy. Serum β-hCG concentrations were determined at 14 days following IUI.

Cycles with an absence of follicular development or with multifollicular development were cancelled. An absence of follicular development was defined as no follicular development observed or failure of a follicle to achieve a diameter large enough for ovulation after selection of a dominant follicle. Multifollicular development was defined as the development of three or more than three follicles.

Outcome Measures

Ovulation was accepted as observation of shrinkage of follicle(s) >17 mm in diameter on TV-USG following hCG administration. Implantation was defined as a positive β-hCG reading 14 days after IUI. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heart beat detected by TV-USG at 7 weeks of gestation. Ongoing pregnancy was defined as a positive heartbeat at or beyond 12 weeks of gestation. Abortion was defined as the termination of a gestation before 20 weeks.

The primary outcome measures were cycle cancellation, absence of follicular development, multifollicular development, ovulation rate (OR), implantation rate, clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR) and abortion rate (AR).

Statistical Analysis

A post hoc power analysis was conducted to evaluate the statistical power of the study after data collection. Data were expressed as mean ± standard deviation for continuous data or frequencies (n) with percentages (%) for categorical data. Kolmogorov-Smirnov test was used to test normality of data. For variables with normal distribution, Student's t-test was used, whereas for non-normally distributed variables, the Mann-Whitney U test was applied. Chi-square test and Fisher's exact test were used for comparisons of categorical data. A p value less than 0.05 was considered as statistically significant in all analyses.

RESULTS

In this study 75 women who were infertile due to PCOS and needed IUI cycle treatment were retrospectively reviewed. They were divided into the, SP (group 1, n=37) and MSP groups (group 2, n=38) according to the OI protocol used.

Evaluation of Basal Characteristic Features

Comparison of the demographic and basal characteristic features of the participants revealed no significant differences between the two groups (Table 1).

Evaluation of Ovulation Induction Cycle Characteristics

There was no significant difference between the groups in terms of the start of CC treatment and the total dose of CC (p=0.5 and; p=0.9 respectively). The number of days of gonadotropin used was also significantly higher in group 1 than group 2 (p<0.0001). The total dose of gonadotropin used was also significantly higher in group 1 than in group 2 (p<0.0001). Groups 1 and 2 did not differ significantly in terms of the number of follicles obtained (p=0.2) (Table 2). In terms of CC treatment, 12 participants received 50 mg/day, 42 participants received 100 mg/day, 18 participants received 150 mg/day, and 3 participants received 200 mg/day of CC treatment.

Evaluation of Treatment Results

The cycle cancellation rate did not differ significantly between groups 1 and 2 (p=0.1). Follicular development failed in 13.5% of the cases in group 1 and in 10.5% of the cases in group 2. The absence of follicular development did not differ significantly in groups 1 and 2 (p=0.7). Multifollicular development was observed in 10.8% of the cases in group 1 but was not noted in any patient in group 2. Multifollicular development was therefore significantly higher in group 1 than in group 2 (p=0.01) (Table 3).

The OR was 84.8% in group 1 and 89.5% in group 2. The OR did not differ between groups 1 and 2 (p=0.7).

In group 1, β-hCG positivity and clinical pregnancy were achieved in 5 (17.9%) of 28 cases who had ovulation, but abortion was observed in 1 case (1/5, 20%) in the later period

Table 1. Demographic features and baseline characteristics of two groups

	Group 1 (n=37)	Group 2 (n=38)	p
Age (years)	26 (21-36)	27 (21-39)	0.2
BMI (kg/m²)	29.01±4.45	28.65±4.51	0.732
Duration of infertility (years)	4 (2-17)	4 (1-17)	0.57
Infertility type (n, %) **Primary** **Secondary**	 31/37 (83.8%) 6/37 (16.2%)	 31/38 (81.6%) 7/38 (18.4%)	 0.801
Habits **Smoking (n, %)** **Alcohol (n, %)**	 1/37 (2.7%) 0	 0 0	 0.5 0.999
Hirsutism (n, %)	34/37 (91.9%)	36/38 (94.7%)	0.621
Cycle length (days)	49.76±27.6	58.61±30.37	0.3
Tubal patency **One tubal occlusion (n, %)**	 1/37 (2.7%)	 2/38 (5.3%)	 0.4
Day 2 basal hormone levels **FSH (mIU/mL)** **LH (mIU/mL)** **FSH/LH** **E2 (pg/mL)**	 6±1.26 7.6 (2.5-12.6) 0.78 (0.46-2.36) 38 (13-94)	 6.23±1.38 6.1 (1.2-33.0) 1.03 (0.26-3.08) 36.5 (13-117)	 0.447 0.084 0.049 0.736
TSH (μU/mL)	2.00 (1-5.3)	2.00 (1-5.2)	0.183
PRL (ng/mL)	12 (4-23)	12 (4-25)	0.531
PMSC (x10⁶)	35.18±19.3	45.89±40.72	0.2

BMI: Body mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TSH: Thyroid stimulating hormone, PMSC: Progressive motile sperm count, PRL: Prolactin

Table 2. Ovulation induction treatment characteristics of two groups			
	Group 1 (n=37)	**Group 2 (n=38)**	***p***
Start day of CC **Day 2 (n, %)** **Day 3 (n, %)** **Day 4 (n, %)** **Day 5 (n, %)**	3 (2-5) 9/37 (24.3%) 20/37 (54.1%) 5/37 (13.5%) 3/37 (8.1%)	3 (2-5) 9/38 (23.7%) 24/38 (63.2%) 4/38 (10.5%) 1/38 (2.6%)	0.507
CC total dose (mg)	500 (250-1000)	500 (250-1000)	0.943
Start day of gonadotropin	7 (5-8)	10 (6-14)	**<0.0001**
Total day of gonadotropin use	7 (2-11)	2.5 (2-11)	**<0.0001**
Gonadotropin total dose (IU)	375 (100-1200)	150 (50-1050)	**<0.0001**
Dominant follicle count (n)	11 (0-18)	12 (0-20)	0.203
Dominant follicle diameter (cm)	15.5 (0-19)	16.75 (0-21)	0.413
hCG day	11 (0-18)	12 (0-20)	0.548
IUI day	13 (0-20)	14 (0-22)	0.710
CC: Clomiphene citrate, hCG: Human chorionic gonadotrophine, IUI: Intrauterine insemination			

Table 3. The comparison of the outcome of ovulation induction and intrauterin insemination cycle between two groups			
	Group 1	**Group 2**	***p***
Cycle cancellation (n, %)	9/37 (24.3%)	4/38 (10.5%)	0.1
Absence of follicular development	5/37 (13.5%)	4/38 (10.5%)	0.7
Multifollicular (≥3) development	4/37 (10.8%)	0	**0.01**
Ovulation rate (n, %)	28/33 (84.8%)	34/38 (89.5%)	0.7
Implantation rate (n, %)	5/28 (17.9%)	7/34 (20.6%)	0.7
Clinical pregnancy rate (n, %)	5/28 (17.9%)	6/34 (17.6%)	0.8
Ongoing pregnancy rate (n, %)	4/28 (14.3%)	4/34 (11.8%)	0.9
Abortion (n, %)	1/5 (20%)	3/7 (42.9%)	0.2

of pregnancy, giving an OPR of 14.3% (4/28). In group 2, β-hCG positivity was observed in 7 (20.6%) of 34 patients who underwent IUI, while 6 (17.6%) clinical pregnancies were detected, 4 (11.8%) had ongoing pregnancy, and 3/7 cases of pregnancy had abortion (42.9%).

The power analysis based on multifollicular development data revealed that, with alpha set at 0.05 and beta at 80%, 66 participants were required in each group. Conversely, to detect at least a 50% reduction in gonadotropin dose with alpha set at 0.05 and beta at 80%, 20 participants per group were found to be sufficient.

DISCUSSION

The present study showed that MSP may reduce the risk of multifollicular development and there was lower gonadotropin doses and a shorter duration of gonadotropin administration compared to SP in CC resistance PCOS patient. Furthermore, when compared to SP, MSP can provide similar ORs, and comparable clinical and ongoing pregnancy rates but there was twice the rate of abortion in the MSP group. Once again, because of the small group sizes, it would be necessary to confirm this finding in larger groups.

The development of this protocol is based on two factors. Firstly, the role of decreased FSH secretion in monoovulatory cycles is well-known.[14] In the SP protocol, the endogenous FSH effect provided by CC is continuously augmented with exogenous FSH stimulation. As a result, multiple follicle development emerges as a complication. Therefore, it is anticipated that initiating exogenous FSH administration after the selection of the dominant follicle will help restrict the formation of multiple follicles. It is generally considered that follicle selection is completed when the follicle diameter is above 8-9 mm.[15,16] Therefore, we preferred to continue with exogenous FSH support after observing a 10 mm follicle. Secondly, it has been reported that continuing to support the cycle with exogenous FSH during the gonadotropin-dependent phase of follicular development is important.[17] In patients with PCOS, follicular development may be halted due to the local androgenic environment, leading to ovulation disorders.[15] After the selection of a dominant follicle through MSP, exogenous FSH support can ensure the continuation of follicular development, potentially increasing success rates in IUI cycles. Considering that this study was conducted on CC-resistant patients, success rates may be higher in PCOS patients who are not resistant to CC. However, further evidence from studies conducted on different patient populations is needed to clarify the efficacy of these combinations.

Nowadays, studies on combinations of agents used for ovulation induction are increasingly being conducted.

The goal is to achieve an effective treatment option while minimizing side effects and complication rates. Recent studies have shown that in CC-resistant PCOS cases, CC is being combined with other ovulation-enhancing agents such as letrozole and coenzyme Q10 have had a beneficial effect.[16,17] Moreover, successful cycles have been reported using combinations of gonadotropins with other ovulation induction agents.[18] Recent studies on the combination of letrozole and gonadotropins can be found in the literature[19] The current study demonstrated that the combination of CC and gonadotropins can be used more effectively in ovulation induction by reducing side effects and costs. However, we would like to emphasize that while achieving this, the cycle cancellation rates increased due to the absence of follicular development. Nevertheless, in both groups, whether due to multifollicular development or the absence of follicular growth, the similarity in overall cycle cancellation rates makes MSP a safer option in terms of side effects.

The total gonadotropin dose required was lower and the total days of gonadotropin administration were shorter with MSP than with SP in the present study. Researchers have previously compared ovulation induction cycles with gonadotropin and SP, and they found SP to be more cost-effective than gonadotropin induction cycles but gave similar pregnancy rates.[20,21] This study demonstrated that the combination of CC with gonadotropins offers a new alternative in the application protocol, achieving OI success rates similar to the SP protocol while providing lower multifollicular development and reduced costs. Although cost-effectiveness was not directly assessed in this study, MSP may offer practical advantages. Considering the shorter duration and lower total dose of gonadotropin use, MSP achieves similar ovulation, clinical pregnancy, and OPRs compared to SP, suggesting it could be a viable alternative for selected patients

Ovulation induction cycles can be cancelled due to the absence of follicular development and ovulation or due to multifollicular development. Ovulation can fail in 20-25% of patients with PCOS, despite recurrent CC induction.[22,23] Some publications have reported ORs of 51% with CC and 95.7% with SP.[24,25] However, no similar data are available related to MSP. In the present study, the cycle cancellation rates (24.3% in SP and 10.5% in MSP) were lower in the MSP than in the SP group. However, no statistically significant difference was detected, probably due to the low number of participants in the study groups. In addition, MSP exhibited an apparent lower rate of multifollicular development compared to SP in our study. However, our study was underpowered to draw firm conclusions about the rate of multifollicular development and so larger, powered studies are required to confirm the trend we noted. MSP decreased cycle cancellation rates due to a decrease in multifollicular development when compared to SP. MSP may be an ovulation induction protocol that results in less multifollicular development and also similar absense of follicle development compared to SP.

None of our cases developed ovarian hyperstimulation syndrome (OHSS) or multiple pregnancy, although multifollicular development increases the risk of both of these conditions and both are accepted as complications of ovulation induction.[23,26] Therefore, MSP can be viewed as better than SP in light of the lower rate of multifollicular development and the subsequently decreased risk of multiple pregnancy and OHSS. Previous research has confirmed lower rates of multiple pregnancy and OHSS with SP than with ovulation induction with hMG[7]; for example, the OHSS risk was 0.2% in SP that used a CC and hMG combination[8] and 16% in a gonadotropin induction in patients with PCOS.[27] Our study group did not include patients induced with only gonadotropin; however, a higher dose of gonadotropin is required in SP than in MSP due to the earlier addition of gonadotropin to CC. The lower gonadotropin dose used in MSP than in SP decreases the risk of multifollicular development; therefore, MSP seems to be more a rational approach than gonadotropin protocols for reducing OHSS.

Pregnancy rates are higher with SP than with CC induction in patients with PCOS and the fecundity rates are acceptable with SP compared to OI with gonadotropin in CC-resistant patients.[8] Also, we found similar implantation, clinical pregnancy, ongoing pregnancy and ARs were found in our study between the SP and MSP groups and the participants in our SP and MSP groups consisted of CC-resistant cases. Of note, the abortion rate in the MSP group was more than twice that of the SP group (43% vs. 20%), but this may have been due to small numbers of pregnancies and abortions (3 vs. 1). It has been shown that pregnancy rates are similar in PCOS patients regardless of the ovulation induction protocol used. In additionally, the number of previous unsuccessful cycles does not significantly reduce pregnancy rates following IUI.[28] This rate can vary between 13% and 24%.[29,30] A pregnancy rate of 18% was reported by Hock et al.[31] with SP (day 2-7, 50-100 mg CC; day 9, hMG injection), consistent with our results. In the present study, the clinical pregnancy rates were 17.9% and 17.6%, respectively, falling within acceptable limits.

If follicular development is stimulated with a combination of CC plus gonadotropin in all PCOS cases, not only the CC-resistant cases, higher pregnancy rates would be probably achieved, in agreement with previous studies. For example, one previous study reported a CPR of 14.2% and a live birth rate of 12.5% in 416 cycles with SP using a CC and hMG combination.[8] In this study, OPRs were determined as 14.3% and 11.8%, respectively. However, it should be noted that these rates may have been lower due to the study population consisting exclusively of CC-resistant patients.

Among the limitations of the study is the emergence of letrozole therapy as a prominent ovulation induction protocol for PCOS patients in recent years. CC used to be the first-line treatment for ovulation induction, but in recent years, letrozole has replaced it.[32] Additionally, combination therapies with ovulation-inducing agents have gained importance A recent study has reported successful ovulation induction cycles using a combination of letrozole and gonadotropins.[19] However, gonadotropins and CC remain widely used ovulation induction agents and continue to maintain their significance. Although the post hoc analysis demonstrated that the sample size used for evaluating the agents in the IUI protocol was sufficient, the sample size for demonstrating multifollicular development fell below the expected level. This is because multifollicular development was a relatively rare complication.

CONCLUSION

In CC-resistant infertile PCOS patients, MSP may help reduce multifollicular development, potentially lowering costs and improving patient compliance by decreasing the duration and doses of gonadotropin treatment compared to SP. Further studies with larger sample sizes are needed to more thoroughly evaluate the potential benefits of MSP in this patient group.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Ethics Committee (approval number: 09.2024.169, date: 09/02/2024).

Informed Consent: In our clinic, informed consent for the use of personal data is obtained from all patients at the start of treatment.

Authorship Contributions

Surgical and Medical Practices: Ü.K.T., E.N.T., T.P., Concept: Ü.K.T., T.P., Design: Ü.K.T., T.P., Data Collection or Processing: Ü.K.T., T.P., Analysis or Interpretation: E.N.T., Ü.K.T., Literature Search: Ü.K.T., E.N.T., Writing: Ü.K.T., E.N.T.

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