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Research Article

Efficacy of extended clomifene citrate regimen in comparison with gonadotropins in clomifene citrate-resistant women with polycystic ovary syndrome

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ABSTRACT

Background: Gonadotropins are successful treatment for women with clomifene citrate (CC)-resistant polycystic ovary syndrome (PCOS). The aim of this study was to test the hypothesis that extended CC treatment may be an alternative to gonadotropins in the management of CC-resistant women with PCOS.

Methods: A randomized controlled trial comprised 200 women with CC-resistant PCOS were allocated to two equal treatment groups. Patients in the CC group were given 100 mg of CC daily starting from the third day of menses for 10 days. Patients in the gonadotropins group were given follitropin-alfa according to step-up regimen starting on the 3rd day of menses. The primary outcome measure was the biochemical pregnancy rate [diagnosed by measuring serum β -human chorionic gonadotropin (β -HCG) 16-days after HCG injection] and clinical pregnancy rate (confirmed by vaginal ultrasound at six-weeks of amenorrhea). Secondary outcomes were: ovulation rate, endometrial thickness at HCG injection, and adverse drug events.

Results: There were no statistically significant differences between the CC group and the gonadotropins group regarding biochemical pregnancy rates [21%, 24%; respectively, $P=0.735$; relative risk (RR)=0.88, 95% confidence interval (CI), 0.52-1.47], and clinical pregnancy rate [19%, 21%; respectively, $P=0.86$; RR=0.9, (95% CI, 0.52-1.58)]. No significant difference was displayed regarding ovulation rate, endometrial thickness at HCG, and adverse drug events.

Conclusions: The extended CC regimen appears to constitute a good alternative to gonadotropins therapy in patients with CC-resistant PCOS. Further multi-center studies are needed to confirm our results and to provide more powerful evidence.

Keywords: Clomifene resistance, Gonadotropins, Follitropin-alfa, Polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproduction age. The prevalence of PCOS, using different diagnostic criteria, has been reported to be 6.8-18%.¹ Clomifene citrate (CC) has been widely used as the standard first line treatment for ovulation induction in women with PCOS for more than four decades.² Although CC treatment will frequently restore ovulation in approximately 80% of women, those 20% of women that do not ovulate on the

maximal daily dose of 150 mg are referred to as CC resistant.³ Obesity, insulin resistance, and hyperandrogenemia denote the major factors involved in CC resistance; prevent the ovaries from responding to raised endogenous follicle-stimulating hormone (FSH) levels following CC therapy.⁴ In addition, a genetic predisposition was suggested for the CC resistance.⁵ Alternatives to CC therapy in CC resistant PCOS patients include aromatase inhibitors, tamoxifen, insulin-sensitizing agents, ovarian drilling, gonadotropins, and *in vitro* fertilization.⁶

The action of CC is based on raised endogenous FSH that falls again after the typical five days course of therapy is completed.⁷ Meanwhile, ovulation induction using gonadotropins therapy is based on the physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles.⁸ There is no evidence of a difference between recombinant FSH, urinary FSH, and highly purified FSH for ovulation induction in CC resistant PCOS women.⁹ However, gonadotropins administration is characterized by the need of intensive ovulation monitoring, increased risk of multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), and high direct and indirect costs.¹⁰

In the present study, we hypothesized that a prolonged use of CC for 10 days in ovulation induction might overcome the CC resistance, and provide comparable treatment outcomes when compared with gonadotropins therapy in CC resistant PCOS patients in the form of biochemical and clinical pregnancy rates as well as the ovulation rate.

METHODS

We conducted this randomized trial in the Infertility Clinic of a large Governmental Hospital, Dhahran, Saudi Arabia from June 2011 to June 2013. The present study included 200 infertile women with PCOS and with clomifene resistance. All participants were divided equally and allocated either to a prolonged CC (Group 1), or to follitropin-alfa (Group 2) for induction of ovulation. The protocol was approved by the Local Institutional Ethics and Research Committee and a written informed consent was taken from all participants before conducting the study. All the procedures, in this trial were conducted in compliance with the ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki).

Diagnosis of PCOS was made according to the Rotterdam's criteria when two of three features are present including: oligo-ovulation or anovulation, hyperandrogenism (either clinical and/or biochemical), and the presence of polycystic ovaries.¹¹ The clomifene resistance in women with PCOS was defined as failure to ovulate after receiving 150 mg of CC daily for five days per cycle, for at least three cycles.³

A thorough evaluation of all participants was carried out via history taking, physical examination; and routine infertility work up for PCOS patients. The routine infertility work-up performed for all participants included baseline trans-vaginal ultrasound, early follicular serum FSH, luteinizing hormone (LH), and testosterone, homeostatic model assessment of insulin resistance (HOMA-IR),¹² hysterosalpingogram and husband semen analysis. Husband's semen analysis was considered normal according to WHO 2010 criteria.¹³

Inclusion criteria for participation were: the presence of a written consent, clomifene resistance, age >16 years and ≤35 years, normal hysterosalpingogram, and normal semen analysis parameters. Exclusion criteria were baseline ovarian cysts or uterine pathology, infertility due to causes other than PCOS or due to combined factors, and a known allergy to clomifene or follitropin-alfa.

Women, who were meeting the study criteria and consented for participation, were randomly allocated to one arm of the study trial. Group 1 included a woman who received clomifene 100 mg (Clomid[®], Sanofi-Aventis, Paris, France) for 10 days starting on day three of induced or spontaneous cycle. Meanwhile, group 2 included a woman who received follitropin-alfa (Gonal-f[®], Merck Serono, Geneva, Switzerland) according to the low dose step up protocol, starting on day three of a spontaneous or induced cycle by means of subcutaneous injections of 75 IU/day. If no ovarian response was detected after one week, the daily dose was increased to 112.5 IU for one week, and then to 150 IU.⁹

The randomization list was generated by the study statistician (using the online research randomizer software

<http://www.graphpad.com/quickcalcs/index.cfm>) using permuted block randomization with block sizes varying from 4 to 8. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, sealed, and opaque envelopes. Envelopes were opened after the enrolled participants completed all baseline assessments and it was time to assign the intervention. The study was open labeled; thus, women and clinicians were aware of the treatment allocation scheme.

Ovulation induction was monitored by vaginal ultrasound every second to third day starting on day nine of the cycle. Triggering ovulation was made by intramuscular injection of 10,000 IU human chorionic gonadotropin (HCG; Profasi HP[®], Serono S. A., Geneva, Switzerland) when the leading follicle reached ≥18 mm diameter. Free sexual intercourse was encouraged from the day of HCG administration only in cases when no more than three follicles bigger than 17 mm were observed; then, HCG injection was not administered and protected sexual intercourse was recommended in order to avoid high-order multiple conception. Biochemical pregnancy was assessed by serum β-HCG assay 16 days after HCG injection and clinical pregnancy was confirmed by vaginal ultrasound at six weeks of amenorrhea.

The primary outcome measures were the biochemical and clinical pregnancy rates, while the secondary outcomes included the percentage of women succeeded to have mature follicles ≥16 mm in average dimension, endometrial thickness at the time of HCG injection, mid-luteal serum progesterone and the rate of adverse drug events including OHSS.

The required sample size was calculated using the PS - Power and Sample Size Calculation, version 3.0.43 (Department of Biostatistics, Vanderbilt University, Nashville, TN, USA). The primary outcome measures in this trial were the biochemical and clinical pregnancy rates. On the basis of previous studies,¹⁴ 94 participants were required in each group to detect this difference with a 5% level of significance (α error=0.05) and 80% power ($1-\beta=0.8$).

Statistical analysis was performed using the Statistical Package for Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, version 6 (GraphPad Software Inc., La Jolla, CA, USA). Analysis was performed on an intention-to-treat basis. The Shapiro Wilk test was performed to test the Gaussian distribution of continuous variables. Normally distributed numerical data were presented as mean and standard error of mean. Non-normally distributed data were presented as median and range. Qualitative data were presented as the number and percentage. Normally distributed numerical data were compared with unpaired Student's *t*-test. Non-

normally numerical data were compared with the Wilcoxon rank-sum test. Qualitative data were compared using the Fisher exact test. Relative risk (RR) with 95% confidence interval (CI) was evaluated for the outcome measures of both groups. For all tests, the statistical significance was assumed when $P<0.05$ with two tails.

RESULTS

A total of 272 women initially recruited to participate in this clinical trial; however only 200 participants were included in the study and randomized into two equal groups (Figure 1). Table 1 demonstrates that the two study groups were comparable as regards factors that may affect the ovulation induction or the pregnancy rate.

There was no statistically significant difference between the two studied groups regarding age, BMI, oligomenorrhea, hirsutism, Waist to hip ratio, prior pelvic surgery, HOMA-IR, basal FSH and LH, testosterone, sperm count and motility, and other baseline characteristics.

Table 1: Baseline characteristics of the study groups.

Variable	CC group (n=100) (%)	Follitropin-alfa group (n=100) (%)	P value
Age (years)	28.5 ± 0.37	28.7 ± 0.41	0.718
BMI (kg/m ²)	28.9 ± 0.63	28.1 ± 0.82	0.44
Duration of infertility (years)	3 (2-6)	3 (2-5)	0.342
Type of infertility			
Primary	63 (63)	66 (66)	0.768
Secondary	37 (37)	34 (34)	
Prior pelvic surgery	22 (22)	19 (19)	0.726
Oligomenorrhea	65 (65)	63 (63)	0.883
Acne	22 (22)	24 (24)	0.867
Hirsutism	45 (45)	42 (42)	0.776
Waist to hip ratio	0.83 ± 0.09	0.84 ± 0.08	0.935
HOMA-IR	2.8 ± 0.47	2.5 ± 0.52	0.669
Basal FSH (mIU/ml)	4.8 ± 0.19	5.2 ± 0.17	0.119
Basal LH (mIU/ml)	6.9 ± 0.36	7.3 ± 0.28	0.382
Testosterone (nmol/l)	0.042 ± 0.002	0.045 ± 0.001	0.19
Sperm count (million/ml)	51.2 ± 1.99	53.4 ± 2.14	0.451
Total sperm motility (%)	64.7 ± 0.94	64.2 ± 1.07	0.726
Progressive sperm motility (%)	44.3 ± 0.82	43.7±0.93	0.624
CC: Clomifene citrate, BMI: Body mass index, HOMA-IR: Homeostatic model assessment of insulin resistance, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone. Data are expressed as mean ± standard error of mean, median (range), or number (%). $P<0.05$ is significant			

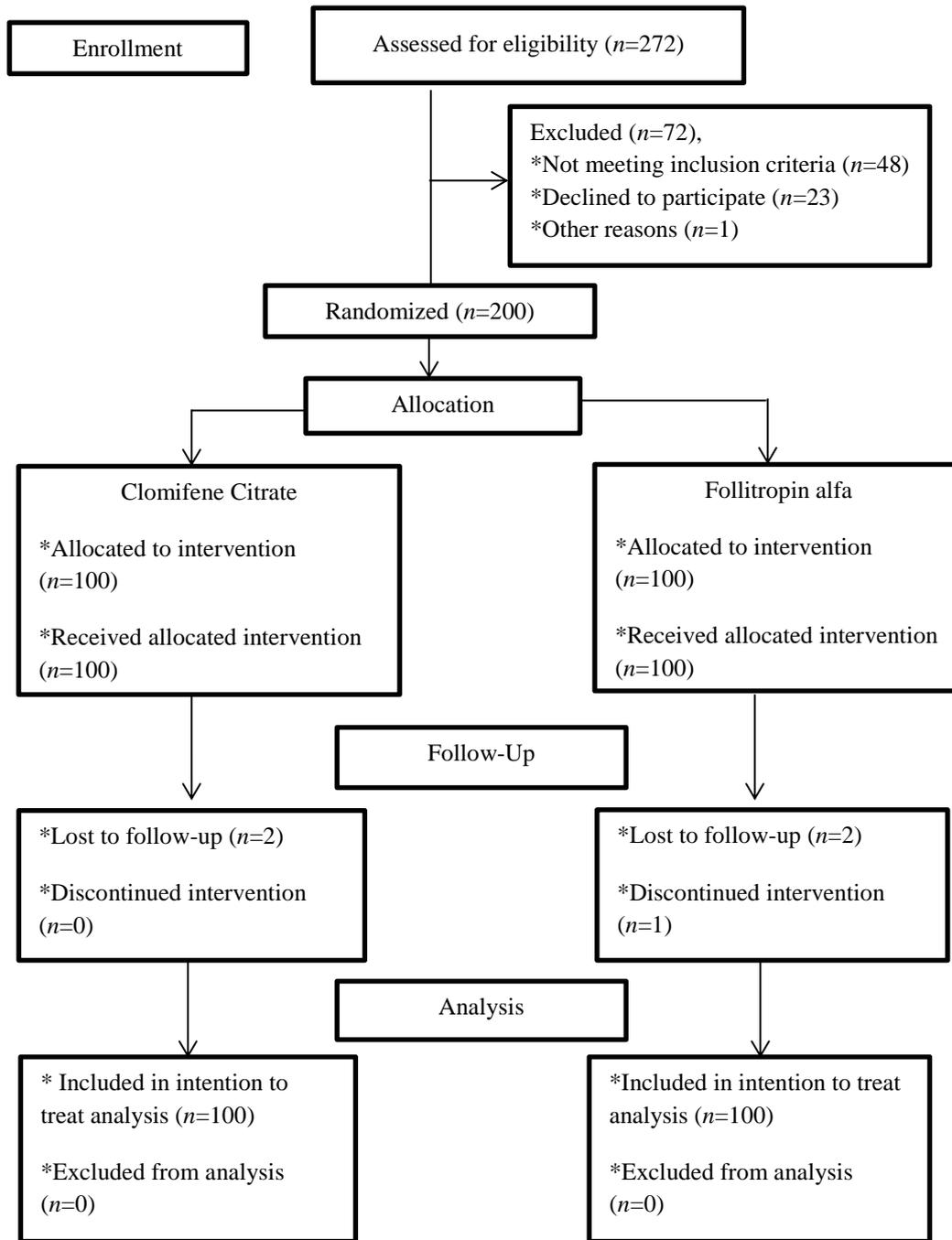


Figure 1: Patients flow chart, CONSORT.

Table 2 shows that there was no statistically significant difference between the two study groups regarding ovulation rate, endometrial thickness, serum estradiol on the day of HCG injection, and mid-luteal serum progesterone level. The conception rates in both groups were similar. The biochemical pregnancy rate was 21% in the clomifene group compared with 24% in the follitropin-alfa group [$P=0.735$; $RR=0.88$, (95% CI, 0.52-1.47)]. As well, the clinical pregnancy rate was 19% in the clomifene group compared with 21% in the follitropin-

alfa group [$P=0.86$; $RR=0.9$, (95% CI, 0.52-1.58)]. As regards the adverse drug events there was no statistically significant difference between the two groups concerning OHSS, gastrointestinal upset, or flushing (Table 2). Cases with OHSS in both groups (one in the CC group and three in the gonadotropins group) were of the mild form. All cases of OHSS were managed conservatively as an outpatient in the Infertility Clinic and none of them got pregnant.

Table 2: Outcomes measures.

Variable	CC group (n=100) (%)	Follitropin-alfa group (n=100) (%)	P value	RR (95% CI)
Patients with mature follicles (≥ 16 mm)	51 (51)	56 (56)	0.571	0.91 (0.7-1.18)
Endometrial thickness	9.1 \pm 0.29	9.4 \pm 0.31	0.766	
Estradiol level on day of HCG injection (pmol/l)	4274.1 \pm 240.5	4459.2 \pm 228	0.577	
Patients with progesterone ≥ 30 nmol/l	46 (46)	49 (49)	0.777	0.94 (0.7-1.26)
Biochemical pregnancy	21 (21)	24 (24)	0.735	0.88 (0.52-1.47)
Clinical pregnancy	19 (19)	21 (21)	0.86	0.9 (0.52-1.58)
Adverse drug events				
OHSS	1 (1)	3 (3)	0.621	0.33 (0.04-3.15)
GIT discomfort	5 (5)	1 (1)	0.212	5 (0.6-42)
Flushing	2 (2)	0	0.498	
CC: Clomifene citrate, RR: Relative risk, CI: Confidence interval, HCG: Human chorionic gonadotropin, OHSS: Ovarian hyperstimulation syndrome, GIT: Gastro-intestinal tract. Data are expressed as mean \pm standard error of mean, median (range), or number (%). $P < 0.05$ is significant				

DISCUSSION

Ovulation induction in women with PCOS who present with CC resistant anovulatory infertility remains a major challenge in gynecologic endocrinology.¹⁵ Classical alternatives for CC-resistant patients include gonadotropins therapy and laparoscopic ovarian diathermy. However, due to the cost and risk inherent in these therapies, alternative treatments are attractive.¹⁶ In this randomized trial, we have evaluated the effectiveness of prolonged use of CC for 10 days as a first line method of ovulation induction in PCOS women with CC resistant in comparison with follitropin-alfa. Both treatment strategies provide comparable outcomes. The biochemical pregnancy rate was 21% in the CC group, and 24% in the follitropin-alfa group [$P=0.735$; RR=0.88, (95% CI, 0.52-1.47)]. Similarly, the clinical pregnancy rate was 19% in the CC group, and 21% in the follitropin-alfa group [$P=0.86$; RR=0.9, (95% CI, 0.52-1.58)]. Furthermore, no differences have been detected between both groups in the ovulation rate or the adverse drug events.

Though numerous studies and reviews have evaluated CC resistance in patients with PCOS, yet the data focusing on the etiology behind the occurrence of CC resistance are still lacking. Indeed, the major manifestations of PCOS include menstrual cycle irregularities due to anovulation and signs of androgen excess.¹⁷ A proposed mechanism for anovulation in PCOS patients is that, under the increased stimulatory effect of LH secreted by the anterior pituitary, encouragement of the ovarian theca cells activity is increased. In turn, theca cells increase the production of androgens. As there is a decreased level of FSH relatively to LH, the ovarian granulosa cells would not aromatize the androgens to estrogens, which result in decreased estrogen levels and subsequent anovulation.¹⁸ On the other hand, the effectiveness of CC in induction of

ovulation is mainly attributed to actions at the level of the hypothalamus. Diminution of hypothalamic estrogen receptors precludes correct interpretation of circulating estrogen levels. The reduced levels of estrogen feedback generate normal compensatory mechanisms that alter pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion to motivate increased pituitary gonadotropin release that consequently stimulate ovarian follicular activity.⁶ In ovulatory women, CC treatment elevates GnRH pulse frequency.¹⁹ Women with PCOS have an anovulation with abnormally high GnRH pulse frequency. CC treatment, in anovulatory women with PCOS, increases pulse amplitude but not frequency.²⁰ During CC treatment, the levels of both LH and FSH rise, then they are falling again after the typical 5-day course of therapy is completed.²¹ If this FSH rise fulfilled the requirements of the leading follicle/s they will be pushed through the final part of their growth progression till ovulation.²² It has been suggested that the duration of FSH rise is more important than magnitude for follicular development.²³ In successful CC treatment cycles; follicular growth occurs in parallel with increasing serum estrogen, eventually prompting LH surge and ovulation. It has been advocated that FSH levels are maintained high with the 10 day protocol denoting that the hypothalamus remains responsive to CC for up to that duration.²⁴

Previous studies that assessed follitropin-alfa for ovulation induction in women with CC resistant PCOS, have reported that the pregnancy rate per stimulated cycle was approximately 18-20%.^{8,25-27} However, the current trial revealed comparable biochemical and clinical pregnancy rates (21% and 19% respectively) upon using CC for 10 days in ovulation induction for CC resistant Patients. Furthermore, our data emphasized that the pregnancy rates of CC 10 day protocol were similar to follitropin-alfa therapy. Our data were consistent with

Fluker et al.²⁸ that conducted a retrospective study to evaluate the CC 10 day protocol in CC resistant patients and reported 47% ovulation rate and 17% pregnancy rate. Furthermore, a more recent randomized controlled trial by Badawy et al. established that the extended CC regimen resulted in modest ovulation and pregnancy rates (28.1%, 11.4%; respectively), and it deserved the trial before other expensive and more sophisticated alternatives.²⁹

In conclusion, prolonging the duration of CC for 10 days is as efficient as follitropin-alfa in inducing ovulation, and achieving pregnancy in PCOS patients with CC resistance. However, CC is cheap, easy to administer, and has rare side-effects. It can be used as a first line management for CC resistance before other alternatives. Further larger multi-centric studies are required to confirm our data and to provide a more powerful conclusion.

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Conflict of interest: None declare

Ethical approval: The study was approved by the local institutional ethics committee

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