Adding Prednisolone During Ovulation Induction with Clomiphene Citrate in Lean Women with Clomiphene Citrate Resistant Polycystic Ovarian Syndrome

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Abstract

Background: polycystic ovarian syndrome (PCOS) is a common cause of chronic anovulation; insulin resistance is considered an accepted mechanism for anovulation in PCOS especially in obese patients. Excess adrenal androgens are observed in patients with PCOS. An inverse relationship exists betweenDehydroepiandrosterone sulfate (DHEAS) the body mass index (BMI). The use of corticosteroids could improve ovulation in PCOS by decreasing serum androgen level.

Objective: Evaluation of the efficacy of concomitant administrationof prednisolone and clomiphene citrate (CC) for the ovulation inductionin infertile lean women having CC-resistant polycystic ovarian syndrome(PCOS).

Methods: Three hundred infertile lean women with clomiphene citrate (CC) resistant PCOS were randomly divided into two groups. Group 1:150 patient received clomiphene citrate (5 consecutive days of 150mg daily starting from the second day of the cycle) and prednisolone tablet (10 consecutive days of 10mg daily starting from the second day of the cycle). Group 2:150 patientreceived the same protocol of CC plus placebo (10 consecutive days of 0.5mg folic acid daily starting from the second day of the cycle). All patientsshowed clinical manifestations of Hyperandrogenism (variable degree of hirsutism and/or acne) where 18 patients were dropped out, and data on all relevant outcomes were available for 282 women and data were analyzed from 143 women in the CC-Prednisolone group and 139 in the CC-placebo group. The main outcome was the ovulation rate. Secondary measures included a number of follicles 18 mm or more, endometrial thickness on day of HCG administration and clinical pregnancy rate. Ovarian follicular response was monitored by transvaginal ultrasound and mid-luteal phase serum progesterone. HCG 10000 IU was given when at least one follicle measured 18 mm, and timed intercoursewas advised.

Results: There were no statistically significant differences between groups as regards age, duration of infertility, BMI,the serum level of FSH, LH, TSH,and prolactin. The mediannumber offollicles ≥18 mm) at the time of HCG administration and the mean endometrial thickness wassignificantly higher in the prednisolone group than in the placebo group ($P < 0.001$).Similarly, there were significantly higher rates of ovulation (58.7% versus 23%) ($P < 0.001$) in the prednisolone group. The clinical pregnancy rate was significantly higher in the prednisolone group ($p = 0.006$).

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Conclusion: The addition of prednisolone to CC in CC-resistant PCOS infertilelean patients was significantlyassociated with a higher ovulation rate, number of ovarian follicles ≥18 mm and endometrial thicknesson day of HCG administration, and number of patients becameclinical pregnant.

Keywords: PCOS, CC-resistant, prednisolone, ovulation rate,and clinical pregnancy rate

Introduction

Chronic anovulation due to PCOS can be treated with CC as a first line of the treatment (1). However, resistance to CC, defined as ovulation failure after receiving of CC daily for 5 days in a dose of 150mg daily per cycle for at least 3 cycles, which may be occurred in 15 - 40% in women with PCOS. (2).Overweight and hyperandrogenism are the major factors involved in CC resistance (3).Hyperandrogenism adversely affects female fertility asthe increase in androgen concentrations will interfere with the development of ovarian folliclesthrough FSHaction down-regulationon the granulosa cells (3). It was reported that the ovarieswere considered to be the main source of patients with PCOS androgen excess,but also the increase in adrenal androgen levels have been observed in those patients (4). The adrenal glands have been reported to be the main source of dehydroepiandrosterone sulfate (DHEAS)(5), which was found to be high in 22–25% of PCOS patients (6). Kumar et al. (7) and Moran et al. (8) have been postulated that a negative co-relation between DHEAS and BMI or fasting insulin among PCOS patients, so the proportion of adrenal androgen excess may be higher in nonobese PCOS patients.Jones et al, 1953, is considered the first study refers to the using of corticosteroid in ovulation dysfunction treatment(9). The improvement in ovulation with corticosteroid treatment through its decreasing effect of androgens of the adrenal source on folliculardevelopment (10,11).

Patients and Methods

Thiswasa prospective placebo-controlled study that was conducted in Mansoura University Hospital(infertility care unit) andoutpatient's clinic fromFebruary 2015 to December2018. The study was approved by the local Institutional Research Ethical Committee "institutional research board". 384 infertile patients enrolled in our study,with PCOS as defined by the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) (12), all of them were diagnosed as CC resistance (defined as failure of ovulation after receiving 150 mg/day of CC for 5 consecutive days per cycle, for at least 3 cycles),and showed clinicalhyperandrogenism (variable degree of hirsutism and/or acne), 84 patients were excluded (70 did not meet inclusion criteria, 8 were declined to participate, and 6 due to other reasons)(Figure 1). Our inclusion criteria were: 1) agebetween 20 and 35 years. 2) body mass index between 18.5 and 25. 3) normal serum Prolactin and TSH.Exclusion criteria included patients aged < 20 or > 35 years, body mass index (BMI) < 18.5 kg/m2 or > 25 kg/m2, presence of any infertility factor other than anovulatory PCOS, previous history of ovarian surgery or surgical removal of one ovary, previous exposure to cytotoxic drugs or pelvic irradiation, oral hypoglycemic drugs or hormonal therapy either currently or in the preceding 3 months, and metabolic or hormonal abnormalities. All patients underwent history taking, examination, basic laboratory investigations, and hormonal profile (Follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and (TSH) thyroid stimulating hormone. The remaining 300patients were selected randomly to receive CC and either prednisolone or placebo using closed dark envelopes, so patients classifiedinto two groups; 150 patients in each one. Women in the CC-Prednisolone group **(group 1)** received CC (5 consecutive days of 150mg daily starting from the second day of the cycle) and prednisolone tablet (10 consecutive days of 10mg daily starting from the second day of the cycle), women in the CC-placebo group **(group 2)** received the same protocol of CC plus placebo (10 consecutive days of 0.5mg folic acid daily starting from the second day of the cycle).Transvaginal sonographic (TVS) folliculometrywas performed regularly starting from day 10 of the stimulation and repeated every 2-3 days. When there was at least one follicle ≥18 mm in diameter, final oocyte maturation was induced by intramuscular administration of 10000 IU of human chorionic gonadotropin (HCG) and timed intercourse was advised. If there was no follicle ≥ 12 mm by day 16 of the cycle, monitoring of follicular growth was discontinued and the

cycle was presumed to be anovulatory. Ovulation was documented by TVS scan one week after triggering of oocyte maturation and was confirmed by assessing the mid-luteal serum progesterone level. Each woman was subjected to ovarian stimulation for a maximum of 3 consecutive cycles except if she became pregnant in the first or second cycle. The data collected to evaluate the effect of concomitant prednisolone administration with CCfor ovulation induction through registration of ovulation rate, number of ovarian follicles 18 mm or more and endometrial thickness on HCG administration day, and clinical pregnancy rate throughout 3 months follow up period.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for nonparametric data and mean, the standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. The significance of the obtained results was judged at the 0.05 level and all tests were 2 tailed. Chi-square test and Fischer exact test were used for categorical variables, to compare between different groups as appropriate. Student-t-test was used for parametric quantitative variables, to compare between two studied and Mann Whitney test was used for nonparametric quantitative variables, to compare between two studied groups.

RESULTS:

The study was carried out on 300 patients diagnosed as clomiphenecitrate-resistantPCOS, classified into two groups;CC-Prednisolone group and CC-placebo group (150 in each group), 7 women in the CC-Prednisolone group were lost to follow-updue to various reasons and 11 women in the CC-placebo groupwere dropped out, 8 of them due to difficult to follow up and 3 did not receive the allocated intervention. Data on all relevant outcomes were available for 282 women and data were analyzed from 143 women in the CC-Prednisolone group and 139 in the CC-placebo group (Figure 1). The study revealed that patient's mean age was 26.47±3.7 in CC-Prednisolone group and 26.97±4.1 for CC-placebo group. The mean BMI was 22.49±1.76 in CC-Prednisolone group and 22.53±1.77 in CC-placebo group with no statistically significant difference asregards demographic data between two groups as shown in table1. The data from table1 showed that there was no statistically significant difference in infertility duration and hormonal profile between the studied groups, whereas, the median follicle number >18 mm or morewas 2.0(0.0-5.0) in CC-Prednisolone group and 0(0.0-2.0) in CC-placebo group, in addition, the endometrial thickness median was 9.69±2.22 in CC-Prednisolone group and 8.01±1.7 in CC-placebo group with a highly statistically significant difference between CC-Prednisolone group and CC-placebo group as shown in table2.Regards the ovulation incidence was 84(58.7%) in CC-Prednisolone group, and 32(23.0%) in CC-placebo group, while the clinical pregnancy was 26(18.2%) in CC-Prednisolone group, and 10(7.2%) in CC-placebo group with a highly statistically significant difference between CC-Prednisolone group and CC-placebo group. There was no statistically significant difference between two groups in the occurrence of ovarian hyperstimulation syndrome as shown in table 2.

Discussion:

Resistance to clomiphene citrate (CC) during ovulation induction for PCOS patients is attributed to overweight and Hyperandrogenism (3).Although the ovaries are the main source of androgen excess in PCOS, excess adrenal androgen levels have also been observed in PCOS patients(4). Circulating adrenal androgens are converted into testosterone in the ovarian follicles. It was reported that circulating DHEA-Which is exclusively secreted by the adrenal glandacts as 48% of the testosterone precursor found in follicular fluid(13).High intraovarian androgens concentration interferes with ovulation as it impairs the selection of the dominant follicle (14). An inverse relationship between DHEAS and BMI or fasting insulin among PCOS patients has been reported by Kumar et al.(7) and Moran et al.(8), so the proportion of adrenal androgen excess may be higher in nonobese PCOS patients.In our study,the prednisolone groupwas associated with a significantly higher ovulation rate. In addition, the prednisolone groupwas associated with a significantly higher number of

follicles 18 mm or more at the time of HCG administration than in the placebo group. These results are agreed with Isaacs et al(11) and Reyes et al(15) studies. There are suggested mechanisms by which prednisolone could improve the ovarian function. Glucocorticoids decrease circulating adrenal androgens by nearly 40 % (16). The ovulation improvement can be achieved bydecreasing the effect of androgens of the adrenal source on follicular development (10,11). The endometrial thickness mean was significantly higher in the prednisolone group than in the placebo group. The adverse effect of CC on the endometrium is attributed to its relatively long half-life (5 days), which is not seen with prednisolone. The endometrial thicknessmean for prednisolone group was 9.65mm versus 7.9 mm for the placebo group. Casterlin et al. (17) demonstratedthat 7–11 mm endometrial thickness is the suitable thickness for the occurrence of pregnancy. The clinical pregnancy rate was significantly higher in the prednisolone group when compared to the placebo group. This may be attributed to higher ovulation rate and better endometrial thickness in the prednisolone group. This finding agreed with studies performed by Isaacs et al (11)and Reyes et al(15).The findings of our study are similar to those reported by other studies as Elnashar A et al. 2006(18), Parsanezhad ME et al. 2002(19), and Daly DC et al. 1984(20)through using dexamethasone in addition to clomiphene citrate. Prednisolones was recommended by Isaacs et al (11) because when compared with dexamethasone it has the advantage of shorter pharmacologic duration and less potency so can suppress adrenal androgens and not complete adrenal suppression

Conclusion

Prednisolone combined with CC for management of CC-resistant PCOS is economic and effective. It provides safety advantages when compared to other alternatives as gonadotropin therapy and laparoscopy and thus should be tried first.

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Table (1): Demographic characteristics and hormonal profile between studied groups

	Group A N=150	Group B N=150	Test of sig
Age /years Mean±SD	26.47±3.7	26.97±4.1	t=1.05 p=0.29
BMI Mean±SD	22.49±1.76	22.53±1.77	t=0.13 p=0.89
Infertility duration/ years Mean±SD	3.34±1.07	3.29±1.13	t=0.31 p=0.76
FSH Mean±SD	5.71±1.21	5.68±1.19	t=0.18 p=0.86
LH Mean±SD	7.16±1.64	7.09±1.66	t=0.33 p=0.74
TSH Mean±SD	2.28±0.52	2.36±0.60	t=1.9 p=0.28
Prolactin Mean±SD	14.77±4.45	14.59±4.38	t=0.35 p=0.73

t: Student t test SD: Standard deviation

Table (2): ET, Follicles number>18 mm, ovulation incidence, pregnancy,and OHSS between studied groups.

	Group A N=150(%)	Group B N=150(%)	Test of sig
Follicles number >18 mm median(min-max)	2.0(0.0-5.0)	0(0.0-2.0)	z=8.37 p<0.001*
ET/mm Mean±SD	9.69±2.22	8.01±1.7	t=7.17 p<0.001*
Ovulation			
-ve	59(41.3)	107(77.0)	χ^2=37.14
+ve	84(58.7)	32(23.0)	p<0.001*
Clinical pregnancy			
-ve	117(81.8)	129(92.8)	χ^2=7.64
+ve	26(18.2)	10(7.2)	p=0.006*
OHSS			
-ve	139(97.2)	138(99.3)	FET
+ve	4(2.8)	1(0.7)	P=0.37

χ^2: Chi-Square test FET: Fischer exact test *statistically significant (if p<0.05) t: Student t test SD: Standard deviation.

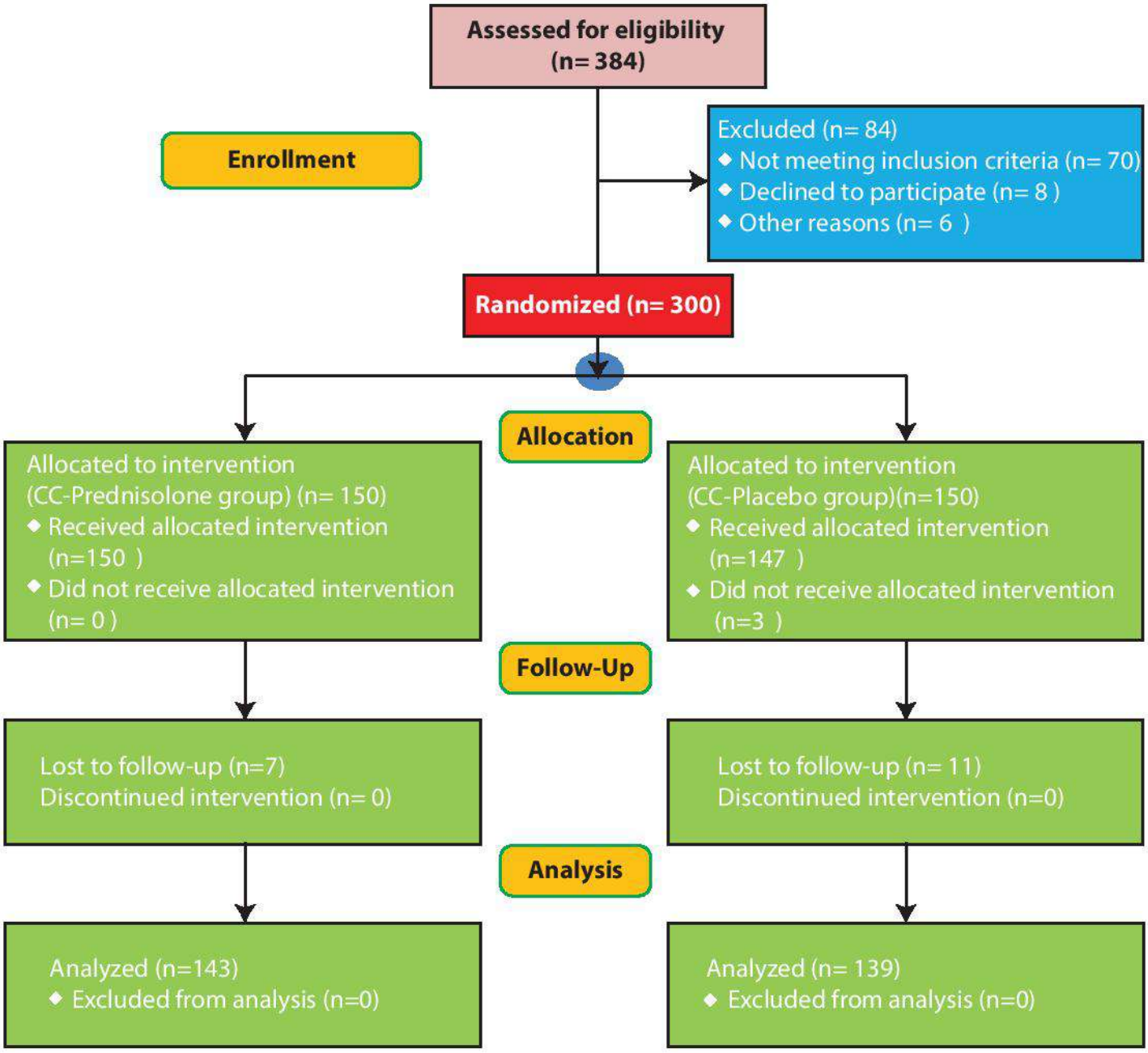

Figure 1: Study flow diagram.Abbreviation: CC, clomiphene citrate