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Clomiphene Citrate plus Modified GnRH Antagonist Protocol for Women with Poor Ovarian Response Undergoing ICSI Treatment Cycles: Randomized Controlled Trial

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Abstract

Objective: To compare Clomiphene Citrate (CC) and lower dose of Human chorionic Gonadotropins (HMG) plus Gonadotropins Releasing Hormone (GnRH) antagonist with conventional mid-luteal long agonist GnRH with higher dose of HMG in women with poor ovarian response, undergoing Intracytoplasmic Sperm Injection (ICSI). Poor ovarian response was defined as the development of less than 3 follicles ≥ 17 mm on HCG day in a previous midluteal GnRH agonist-IVF/ICSI cycle or women with age >35 years old.

Method: Pilot non blind two arms parallel randomised controlled. Seventy women with a history of previous poor ovarian response undergoing controlled ovarian hyperstimulation (COH) for ICSI. Interventions: The control group (n=35) received a conventional mid-luteal long GnRH agonist treatment with daily injections of HP HMG, starting on day 2 of the cycle at a dose of 300 IU /day. In the study group (n=35), pre-treatment with luteal E2 supplementation was administrated followed by clomiphene citrate for 5 days, starting on day 2 of the cycle followed by daily injections of 225 IU HP HMG and GnRH antagonist from cycle day 6 onward.

Results: There was no evidence of statistically significant difference between both groups regarding the clinical pregnancy rate per women randomized (5/35 (14%) versus 3/35 (9%); 95% CI: 0.39-8.09, p=0.43). The cost of ovarian stimulation per cycle worked out to be USD 208, 8 and 557.3 for CC ovarian stimulation group and conventional ovarian stimulation group respectively.

Conclusion: CC and a lower dose of HMG plus GnRH antagonist preceded by mid-luteal E2 supplementation is as effective as the conventional ovarian stimulation in producing similar ICSI outcomes at lower cost in women with poor ovarian response.

Keywords: Clomiphene citrate; Poor ovarian response; IVF/ICSI

Introduction

One of the most frustrating problems in IVF today is the low pregnancy rate in women with poor ovarian response. Poor responders are estimated to comprise approximately 9-24% of IVF/ICSI patients [1]. Various stimulation protocols have been tried to improve pregnancy outcomes in poor responder women [2]. Since most studies included small numbers of patients and used different definitions of poor response, the best stimulation protocol is still unknown.

Most treatment comparisons include high doses of gonadotropins and only vary in their means of pituitary suppression [3]. However, high doses of gonadotropins are an expensive and do not compensate for the age-related decline in retrievable oocytes and lower pregnancy rates [4] and may result in embryos of higher aneuploidy rate [5]. Moreover, such a demanding protocol is more burdensome to the patient particularly in developing countries as most medication and treatment cost are not covered by insurance [6].

Alternatively, mild ovarian stimulation in the form of the administration of GnRH antagonist co-treated cycles plus fewer days or mild doses of exogenous gonadotropin, and oral compounds such as clomiphene citrate or aromatase inhibitors for ovarian stimulation for IVF/ICSI has been proposed to be a more patient friendly [7]. But the efficacy of mild stimulation approaches in women with poor ovarian response may be counterproductive as most couples could only afford one, at most two cycles. Hence a conventional ovarian stimulation with massive ovarian stimulation could better serve them by maximizing success. Clomiphene citrate in a dose of 100 mg from days 2 to 5 of the cycle, together with a GnRH antagonist and daily adjusted gonadotropin injection have been evaluated in 25 womens, defined as difficult responders by their ovarian response to a previous treatment with a GnRH analog protocol. A lower cancellation rate, better oocyte retrieval, and higher pregnancy and implantation rates, compared with these patients' previous ovarian outcomes, was obtained, however, the difference was not statistically significant [8].

Therefore, the purpose of this RCT was to we evaluate whether modified GnRH antagonist protocol in the form of combined administration of oral Clomiphene Citrate (CC), lower dose of HP HMG, and GnRH antagonist administration (fixed protocol) preceded by luteal estradiol administration compared may be as effective as conventional midluteal long agonist GnRH protocol with higher dose of HP HMG for poor responders women undergoing ICSI treatment.

Materials and Methods

Study design

The study presented here is a pilot prospective randomized controlled

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trial and was conducted in 70 women aged 35-42 years with a history of primary or secondary infertility enrolled in an Intracytoplasmic Sperm Injection (ICSI) program at the Egyptian International Fertility IVF center between April 2009 and January 2010. The trial had been set up to compare two protocols for ovarian stimulation. In the control group, a conventional midluteal long GnRH agonist protocol with higher dose of HMG was applied, whereas patients allocated to the study group underwent a modified treatment protocol with GnRH antagonist plus Clomiphene citrate and mild dose of HMG.

Randomization was performed at the outpatient clinic. A computer-generated random numbers concealed in opaque sealed envelopes was used. The study received Institutional Review Board approval by the local institute's Ethics Committee and a written consent was obtained from participating women. The patients included in the study were women who had a history or an evidence of poor ovarian response with normal menstrual cycles, BMI <27 kg/m^2, both ovaries are present. Basal FSH on day 3 is ≤ 12 IU/L. Exclusion criteria were clinically or medically significant systemic disease. Poor ovarian response was defined as the development of less than 3 follicles ≥ 17 mm on HCG day in a previous midluteal GnRH agonist-IVF/ICSI cycle or women with age >35 years old.

Multifollicular ovarian stimulation

Thirty-five women (study group, Group=I) received Luteal oral estradiol valerate (E2) (Progynova) two tablets daily was initiated on luteal day 21 of the preceding cycle and stopped at day 1 in the next menstrual cycle. Transvaginal ultrasound and serum estradiol, LH and FSH were arranged on day 2 of the period. After confirmation of quiescent ovaries, 100 mg clomiphene citrate (Clomid 50 mg) was given from day 2 to 6 of the menstruation. Fixed 225 IU daily dose of HP HMG (Menopure-Ferring-Denmark) was initiated from cycle day 7, (225 IU). GnRH antagonist, cetrorelix 0.25 mg S.C (Cetrotide, Serono Laboratories, Aubonne, Switzerland) has been given on day 6 of stimulation (fixed protocol) to prevent premature lutenization, until the day of HCG administration.

Thirty-five women (control group, Group=II) underwent COH with a midluteal long GnRH agonist protocol: triptorelin acetate SC (Decapeptyl 0.1 mg, Ferring, Denmark) was administrated in the midluteal phase at a daily dose of 0.1 mg of the preceding cycle. Two weeks later, once desensitization was achieved (E2 ≤ 50 pg/ml, no evidence of ovarian cysts on ultrasound and endometrial thickness <5 mm); ovarian stimulation was commenced with daily fixed dose of HP HMG 300 IU. I.M (Menopure-Ferring-Denmark). Decapeptyl was continued until the day of HCG administration. Ovulation was triggered with 10000 IU of i.m. HCG (Chorimon 5000 IU, IBSA, Italy) when at least three mature follicles ≥ 16 mm were detected on ultrasound scan. This was followed by transvaginal ultrasound-guided oocyte retrieval 36 hours later. Cycles in which ≤ 2 mature follicles developed, were either cancelled or converted to intra-uterine insemination in patients with patent tube(s).

ICSI was performed depending on the number of embryos available, up to three embryos were transferred on day 3 after oocyte retrieval. All patients received luteal phase support with vaginal suppositories (Cyclogest 400 mg, Alpharma ,England)once daily starting on the day of oocyte retrieval. A clinical pregnancy was established when there was a gestational sac seen on ultrasonography.

Outcome measures

In this pilot study, the primary endpoint was the clinical pregnancy rate (defined as presence of fetal heart pulsation 2 weeks after a positive β-HCG test. Secondary endpoints included number of COCs retrieved, number of metaphase II oocytes, fertilization rate, number of embryos transferred, and implantation rate, duration of ovarian stimulation, amount of gonadotropin used and cancellation rate (defined as discontinuation of the controlled ovarian stimulation or cancellation of oocyte retrieval). The criteria for cycle cancellation were; no ovarian response after 7 days of ovarian stimulation or ≤ 2 follicles on the day of HCG. Demographic and clinical characteristics such as age, BMI and basal hormonal profile were also collected

Statistical analysis

Differences between treatment arms are presented as mean ± SD and absolute number, percentages with corresponding 95% CI and *P*-values for each comparison made for continuous and categorical variables respectively. Differences between groups were assessed by using the student's *t*-test for independent samples and Fisher's exact tests or by Pearson Chi-square test for continuous and categorical variables. All tests were two-sided and a *P*-value of <0.05 was considered statistically significant. Data were analyzed using SPSS17.

Results

A total of 70 patients were randomly assigned to either the control group (n=35) or the study group (n=35). Baseline characteristics of the study grous are presented in Table 1. The groups did not significantly differ with regards to demographic characteristics such as age, BMI, basal FSH,LH,E2 levels on cycle day 3 and duration of infertility. A flow diagram with the phases of the trial is shown in Figure 1.

	Mild stimulation group (n= 35) Mean ± SD	Standard stimulation group (n= 35) Mean ± SD
Age (yr)	38.2 ± 1.4	38.8 ± 1.3
BMI (Kg/m^2)	23.6 ± 3.6	22.8 ± 2.8
Duration of infertility (yr)	8.7 ± 3.0	8.5 ± 3.3
Basal FSH D3 (IU/l)	11.1 ± 3.3	11.8 ± 3.4
Basal LH (IU/l)	10.1 ± 3.3	9.9 ± 3.3
Basal E2 (pg/ml)	34.1 ± 3.3	33.9 ± 2.1

BMI: Body Mass Index; **FSH:** Follicle Stimulating Hormone; **LH:** Luteinizing Hormone

Table 1: Baseline characteristics of the patients in the two groups.

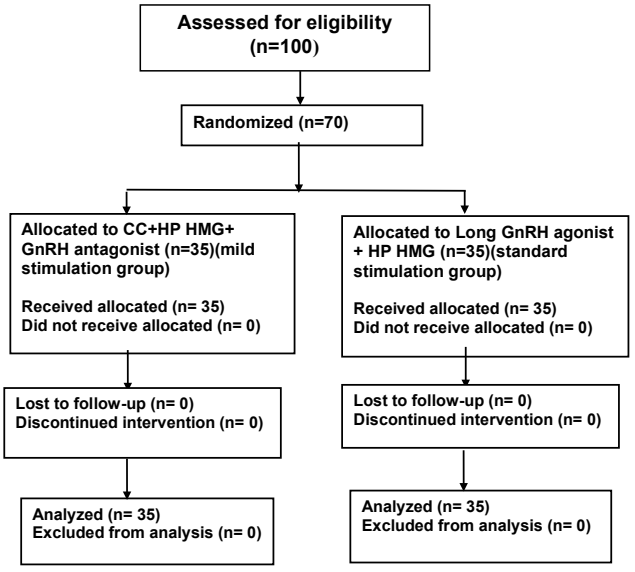

Figure 1: Flowchart showing patient randomisation, allocation and analysis.

	Mild stimulation group (n=35) Mean ± SD	Standard stimulation group (n=35) Mean ± SD	*MD*[a]	*95% CI*	*P*
Total stimulation duration (Days)	8.5 ± 2.7	12.5 ± 2.4	4.00	2.80- 5.20	<.0001
No of ampoules	25.4 ± 8.1	50 ± 4.5	24.60	27.67-21.53	< .0001
No of mature follicles ≥ 16 mm	3.9 ± 2.2	3.39 ± 2.63	0.51	0.63-1.65	0.38
Endometrial thickness on day of HCG (mm)	10.6 ± 2.3	11.5 ± 2.8	0.90	2.10-0.30	0.14
			OR[b]		
Cancellation rate (%)	14/35 (36%)	12/35 (34%)	0.48	0.48-3.38	0.62

Note: [a]MD: mean difference, [b]OR: odds ratio

Table 2: Comparison of the ovarian response and outcome of the IVF treatment.

	Mild stimulation group (n=35) Mean ± SD	Standard stimulation group (n=35) Mean ± SD	*MD*[a]	*95%* CI	*P*
No. of oocytes/retrieval	4.89 ± 3.02	4.62 ± 4.17	0.27	1.44-1.98	0.76
No. of fertilized oocytes (fertilization rate %)	3.89 ± 2.00 (71.2%)	3.00 ± 2.92 (53.6%)	0.89	0.28-2.06	0.14
No. of embryos transferred	2.32 ± 0.58	1.50 ± 0.83	0.80	0.48-1.16	<.0001
			OR[b]		
Implantation rate (%)	6/44 (13.6%)	4/30 (13.3%)	1.03	0.26-4.00	0.97
Clinical pregnancy per Women randomized (%)	5/ 35 (14%)	3/35 (9%)	1.86	0.40-8.55	0.43

Note: [a]MD: mean difference, [b]OR: odds ratio

Table 3: Laboratory and pregnancy outcomes.

Table 2 summarizes the outcome parameters of both treatment protocols. There was no evidence of statistically significant difference between the groups in the number of COCs retrieved (4.89 ± 3.02 vs. 4.62 ± 4.17, *P*=0.76), mature oocytes MII (3.9 ± 2.2 vs. 3.39 ± 2.63, *P*=0.38), fertilization rates (71% versus 54%) and endometrial thickness on day of HCG(10.6 ± 2.3 versus 11.5 ± 2.8, *P*=0.14). High cancellation rates were found in both groups (study group vs. control: 14/35 (36%) vs. 12/35 (34%). Most of these cycles were cancelled for poor ovarian response, but two of the clomiphene citrate stimulated cycles was cancelled due to premature LH surges and failure to retrieve follicles. Overall, the amount of gonadotropin used was 50% lower (25.4 ± 8.1 vs. 50 ± 4.5, *P*=<0.00) and the period of administration was significantly shorter in study group(8.5 + 2.7 vs. 12.5 ± 2.4 day, *P*=<0.00).

The clinical pregnancy rates per women randomized was higher in the study group (5/35 (14%) versus 3/35 (9%); 95% CI: 0.39-8.09), but, no statistically significant differences was reached for the comparison with the current study sample (*P*=0.43). Although the number of embryos transferred was significantly higher in the study group, because of the availability of higher proportion of usable embryos (2.32 ± 0.58 versus 1.50 ± 0.83, *P*=<0.00), the implantation rates were similar between the two groups 14% (6 gestational sacs per 44 embryos) and 13% (4 sacs per 30 embryos) respectively for study and control group (*P*=0.97) (Table 3).

Based on total ovarian stimulation expense,the cost of ovarian stimulation per cycle worked out to be USD (208.8 ± 66 and 557.3 ± 43, p=<0.000) for clomiphene citrate ovarian stimulation group and conventional ovarian stimulation group respectively.

Discussion

This study shows that modified mild stimulation approach in the form of Clomiphene citrate plus lower dose of HP HMG in GnRH antagonist protocol preceded by luteal E2 supplementation yields a comparable clinical pregnancy rate compared with a conventional midluteal long GnRH agonist protocol with high dose of HMG in poor responder's patients treated by ICSI. Significantly lower doses of used gonadotropins and shorter duration of stimulation and cost of medications used for COH were also observed in the study group. Moreover, the use of ICSI procedures in all cycles possibly allowed a better comparison between the ovarian stimulation protocols by overcoming minor sperm anomalies that could have impeded fertilization.

Using a similar protocol, a pseudo randomized clinical trial compared clomiphene citrate, high-dose recombinant human FSH, and a delayed, multidose GnRH antagonist with a standard midluteal long GnRH agonist protocol [9]. D'Amato et al. demonstrated improved number of retrieved oocytes, pregnancy rate and implantation rate. Although the study included 120 womens, the study enrolled a heterogeneous group of poor responders either <35 years old or >35 years old.

It has been postulated that elevated endogenous FSH underline the synchronization of early antral follicles [10]. Follicular size heterogeneity has been shown to be negatively affecting the reproductive outcomes, GnRH agonists and OCP pills are used to abolish this discrepancy [11]. However, the use of OCP is associated with a significant lower ongoing pregnancy rate with no statistically significant gain in the number of COCs [12]. Fanchin et al. suggested that adjuvant luteal E2 pretreatment supplementation can reduce the size and improve the homogeneity of early antral follicles count [13]. It has been shown that E2 pretreatment for anticipated poor responder patients may improve delivery rates [14,15]. Our results showed that the luteal E2 combined with Clomiphene citrate and GnRH antagonist gave a better ovarian response as compared with conventional midluteal long GnRH protocol. Gonadotropin dose and duration were decreased with a trend of higher number of COCs and clinical pregnancy rate, although not significantly in the study group, this may reflect more coordinated stimulation process resulting from improved follicular size synchronization.

Several investigators assume that the use of high doses of gonadotropins could lead to a better ovarian response and pregnancy and reduce cancellation of a great number of cycles [8]. Gonadotropin starting dose for responders usually vary from 300 IU/day [16,17] 600 IU/day [18,19]. However, still the oocyte yield and the total number

of obtained embryos remain low. In our study, the administration of oral compounds such as Clomiphene citrate followed by mid follicular initiation of exogenous lower doses of gonadotropins prevents the closure of FSH window [20,21], resulted in similar COCs being retrieved with comparable MII oocytes and fertilization rates. Although, cycle cancellation rate was high in both treatment groups, the study showed that the modified mild approach of ovarian stimulation produced more number of embryos available for transfer than the conventional approach. Coincidently, it has been shown that mild approach is associated with a lower embryo aneuploidy rate with similar number of chromosomally normal embryos [5]. Moreover, shorter duration and reduced stimulation minimize patient discomfort, drop out and multiple pregnancies, the cost of treatment [22] and adverse effects on endometrial receptivity [23]. Sustaining the later hypothesis, we observed a similar endometrial thickness on day of HCG, implantation and clinical pregnancy rate in both treatment groups even though the number of embryos available for transfer was significantly higher in the study group. This may have biased the pregnancy rate toward the study group.

In this study, the cost of Controlled Ovarian Hyperstimulation (COH) per cycle was twofold higher in the conventional ovarian stimulation group compared to the modified mild approach study group. Therefore, the modified mild approach could be an alternative for poor ovarian response patients with financial constraints and low to middle income countries. Moreover, the reduced duration of exogenous gonadotropins will markedly reduce monitoring and patients 'discomfort. Furthermore, Treatment can be performed in consecutive cycles. Thus, the cumulative pregnancy rates would be higher in the long term [24]. However, this small inconclusive study was not set up as an equivalence trial or cost effective study. However, it is an interesting aspect of stimulation protocols that would require a larger and more complex cost effective analysis.

There were a few limitations in our study design which may have affected the outcome. First, the protocol of downregulation was not standardized between both groups. Luteal E2 pre-treatment was included in clomiphene citrate protocol. Luteal E2 pre-treatment in non-downregulation protocols helps to abolish corpus luteum rescue and synchronize follicular development during IVF and also used to lower the serum FSH to restore FSH receptors in granulose theca cells preparing for the new cycle. Improvement in stimulation and pregnancy outcomes has been reported in poor responders with luteal E2 pre-treatment in various non-downregulation protocols including those with no pituitary suppression and GnRH antagonist protocols [25-27,15]. Although, this study offers promising results in that a trend toward shorter duration, lower amount and cost of medication, the study was limited by a small patient population and a power analysis may be helpful to determine sample size that would be needed to add evidence to this observation. A two-treatment parallel study design would require a total of 432 patients (216 patients in each arm) to detect a clinically relevant difference in clinical pregnancy rate per woman randomized of 12%, with specified power of 80%, a Type I error probability of 0.05, and a control/study group ratio of 1, using an uncorrected χ^2–test. Previous cycle cancellation due to poor response and high basal FSH levels are two of the most commonly used selection criteria for poor responder patients [28]. Both criteria were adopted in the present study to increase the recruitment rate but, conversely, this might lead to a heterogeneous study population with significant cost reduction [29].

Conclusion

In conclusion, modified mild ovarian stimulation approach in the form of GnRH antagonist plus clomiphene citrate and lower dose of HMG preceeded with luteal E2 supplementation is as effective as the conventional ovarian stimulation in poor responder women undergoing ICSI treatment and offers a patient friendly protocol, being associated with a shorter duration of gonadotropin injection, lower medication amount and cost and comparable cycle outcomes.

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Disclosure Statement

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