Arch Gynecol Obstet (2011) 283:1159–1164
DOI 10.1007/s00404-010-1828-z

REPRODUCTIVE MEDICINE

Comparison of mild and microdose GnRH agonist flare protocols on IVF outcome in poor responders

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Received: 10 July 2010 / Accepted: 21 December 2010 / Published online: 9 January 2011

Abstract
Purpose To compare the IVF outcome of clomiphene citrate/gonadotropin/antagonist (mild protocol) and microdose GnRH agonist flare protocols for poor responders undergoing in vitro fertilization.
Methods 159 poor responder patients were randomized and ovarian stimulation was performed with clomiphene citrate, gonadotropin and antagonist (group I) or microdose GnRH agonist flare (group II) protocols. Main outcome was clinical pregnancy rate and secondary outcomes were doses of gonadotropin administration and duration of stimulation.
Results There were no significant differences in age, causes of infertility, basal FSH, BMI, duration of infertility, E_2 level on the day of hCG injection in both groups. Although the cancellation, fertilization, and clinical pregnancy rates were similar in both groups, the endometrial thickness, number of retrieved oocytes, mature oocytes and implantation rate were significantly higher in mild protocol. The doses of gonadotropin administration and duration of stimulation were significantly lower in mild protocol.
Conclusion We recommend mild protocol in assisted reproductive technology cycles for poor responders based on our results regarding less doses of used gonadotropin and a shorter duration of stimulation.

Keywords Poor responders · GnRH agonist · GnRH antagonist · Clomiphene citrate · IVF outcome

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Introduction

Despite the progression in assisted reproductive technology (ART), the preferred protocol for poor responders is still controversial [1–3]. The management of poor responders consists of 10% of ART cycles [4, 5].

The response to controlled ovarian hyperstimulation (COH) is lower regarding estradiol (E_2) level, number of obtained oocytes, and fertilization, implantation and pregnancy rates in patients with low ovarian reserve [6, 7]. Furthermore, bad quality embryos are observed in these women more than normoresponders [6] and the increase of cancellation rate and doses of gonadotropin administration are remarkable results in poor responders [8, 9].

Even though several criteria have been introduced for poor responders, the main defect in their management is the lack of specific definition [10, 11]. Several strategies are available to improve ART cycle outcome in poor responders. These modalities include using high FSH dose [12], stop GnRH agonist protocol [7], addition of growth hormone [13], transdermal testosterone [14], aromatase inhibitor [15], GnRH antagonist [2, 4] and recombinant

FSH (r-FSH) [16], while the improvement of pregnancy rate has been quite low.

The most common used protocol for ovarian stimulation is microdose GnRH agonist flare in poor responders [10]. Some investigators concluded that the use of GnRH agonist, even in lower doses, led to prolonged stimulation and increased the cost without improving IVF outcome [4]. Furthermore, this method increased LH, progesterone and androgen of serum in follicular phase, which caused deleterious effect on follicular growth and oocyte quality [17, 18].

Clomiphene citrate co-treatment with gonadotropin and antagonist is one of the recommended protocols in poor responders. Clomiphene citrate increases endogenous FSH versus agonist in microdose protocol [19]. Decreasing the doses of used gonadotropin and duration of stimulation are its beneficial effects in COH cycle [20–22].

The aim of this study was to compare CC/gonadotropin/antagonist and GnRH agonist flare protocols on IVF outcome in poor responders.

Materials and methods

Study design

This study was a prospective randomized controlled trial including 159 poor responder patients who were candidate for IVF between March 2008 and May 2010. The study was approved by ethics committee of Research and Clinical Center for Infertility, Yazd University of Medical Sciences. A written informed consent was obtained from all patients. Women $\geq$38 years old who had one or more previous failed IVF cycles in which three or fewer oocytes were been retrieved and/or serum E_2 level $\leq$500 pg/ml on the day of hCG administration were enrolled in this study. Patients with BMI >30 kg/m^2, endocrine or metabolic disorders, history of ovarian surgery, severe endometriosis and severe male factor (patients with azoospermia, normal morphology of sperm <4%, immotile sperm and frozen-thawed sperms) were excluded from the study. Patients were divided into two groups, 79 women in group I received CC/gonadotropin/antagonist (mild protocol) and 80 women in group II received microdose GnRH agonist flare (microdose protocol). A method of computer-generated randomization was used. The primary outcome was clinical pregnancy rate. Doses of used gonadotropin, the duration of stimulation, the number of retrieved oocytes, obtained embryos, endometrial thickness and implantation rate were considered as secondary outcomes.

Treatment protocols

All women received oral contraceptive for 21 days which started on the first day of previous cycle. In group I, stimulation was started by administration of clomiphene citrate (Iran Hormone, Tehran, Iran) 100 mg from day 3 of menstruation cycle until day 7 of cycle and gonadotropin stimulation with 225–300 IU daily, r-FSH (Gonal-F, Serono, Aubonne, Switzerland) SC or hMG (Merional, IBSA, Lugano, Switzerland) IM was started from day 5 of cycle. In group II, ovarian stimulation was initiated with GnRH agonist, buserelin (Suprefact, Aventis Pharma, Frankfurt, Germany) 50 μg SC twice a day from day 2 of cycle of withdrawal bleeding. After 2 days, 225–300 IU/day r-FSH SC or hMG IM was administered.

Ovarian response was monitored by serial ultrasound examinations and evaluation of serum E_2 levels, then doses of gonadotropin were adjusted as required in both groups.

In group I, when at least one follicle $\geq$14 mm in mean diameter was observed, 0.25 mg GnRH antagonist (Ganirelex, Organon, the Netherlands) SC daily was started and continued until hCG injection. Urinary human chorionic gonadotropin (pregnyl, Organon, Oss, the Netherlands) 10,000 IU was administered intramuscular when at least two follicles reached a mean diameter of 18 mm in both groups. Also, endometrial thickness and serum E_2 level were measured on the day of hCG injection. Oocyte retrieval was performed 34–36 h after hCG injection and conventional IVF or intracytoplasmic sperm injection (ICSI) was done as appropriately. All embryos were scored by the number, size, shape, symmetry and cytoplasmic appearance of blastomeres, and the presence of anucleate cytoplasmic fragmentation [23].

Based on the number and quality of available embryos and patient's age, one to five embryos were transferred on the day 2 or 3 after oocyte retrieval under ultrasound guidance with a CCD embryo transfer catheter (Laboratory C.C.D., Paris, France). Luteal support with progesterone in oil (Progesterone, Aburaihan Co., Tehran, Iran) 100 mg daily IM was started on the day of oocyte retrieval and was continued until the documentation of fetal heart activity on ultrasound. Pregnancy was identified by measuring serum β-hCG level 14 days after embryo transfer. Clinical pregnancy was considered as the presence of gestational sac with fetal heart activity by transvaginal ultrasonography that was performed 3 weeks after positive β-hCG.

Cycle cancellation was defined as three groups [1]: poor ovarian response: fewer than two growing follicles on transvaginal ultrasound, and an E_2 level <200 pg/ml on the day 7 of stimulation [2]; failed oocyte retrieval: no obtained oocyte on the day of ovarian puncture [3]; failed fertilization: no fertilized oocyte after IVF/ICSI.

Statistical analysis

Data were expressed as mean ± SD and median. The Statistical Package for Social Science (SPSS, version 15.0

for windows; SPSS Inc., Chicago. IL) was used for data analysis. Normality was evaluated using Kolmogorov–Smirnov test. *t* test, Mann–Whitney and Chi-square test were used for analysis as needed. *P* value of less than 0.05 was considered statistically significant.

Results

The results were reported in accordance with the Consort statement (Fig. 1). 159 patients were enrolled in this study and none of them lost to follow up; therefore, final analysis was done on 79 patients in group I and 80 patients in group II. 18 women in each group did not transfer embryo: in group I, seven patients because of poor ovarian response, five because of failed oocyte retrieval and six because of failed fertilization; in group II; six patients because of poor ovarian response, five because of failed oocyte retrieval and seven because of failed fertilization. But they were included in the final analysis in accordance with the intention-to-treat method.

Demographic and infertility characteristics for both groups are presented in Table 1. Age, BMI, basal FSH, basal E_2, duration of infertility and causes of infertility were comparable in both groups.

The results of the ovarian stimulation are shown in Table 2. The number of stimulation days (7.91 ± 1.8 vs. 8.82 ± 1.7; 95% CI −1.000, 0.000) and the doses of used gonadotropins (1,791.50 ± 774.50 vs. 3,161.20 ± 886.05; 95% CI −1,630.61, −1,108.97) were significantly lower in group I than group II. The endometrial thickness (8.70 ± 1.4 vs. 8.02 ± 1.08; 95% CI 0.28, 1.13), the number of follicle ≥17 mm on the day of hCG injection (6.21 ± 4.3 vs. 4.85 ± 3.6; 95% CI 0.000, 2.000), retrieved oocytes (6.34 ± 5.4 vs. 4.10 ± 3.3; 95% CI 1.001, 3.001), and mature oocytes (5.59 ± 5.0 vs. 3.48 ± 2.9; 95% CI 0.001, 3.00) were higher in group I than group II. The cancellation rate and E_2 peak level on the day of hCG injection were statistically similar in both groups.

The results of oocytes insemination and embryological characteristics are shown in Table 3. The percentage of conventional IVF and ICSI was similar in two groups. The number of obtained and transferred embryos was comparable in two groups. The percentage of good quality embryos was 39.3% in group I and 40.3% in group II.

The implantation rate was significantly higher in group I than group II (16.38 vs. 7.26%; 95% CI 0.012, 0.170); however, no significant differences were observed in fertilization rates in two groups (58.74 vs. 62.61%; 95% CI −0.14, 0.06; Table 3). No significant statistically differences existed in clinical pregnancy rates per cycle (24.1 vs. 16.2%; OR 0.163; 95% CI 0.279, 1.346) and per transfer (31.1 vs. 21%; OR 0.586; 95% CI 0.259, 1.328; Table 4).

Discussion

There were many attempts to improve IVF outcome in poor responders. However, the best protocol is unknown. The aim of this study was to improve ART outcome by using CC/gonadotropin/antagonist protocol in poor responders.

The results of this prospective randomized trial showed that the mild protocol did not improve the fertilization and clinical pregnancy rates in poor responders compared to

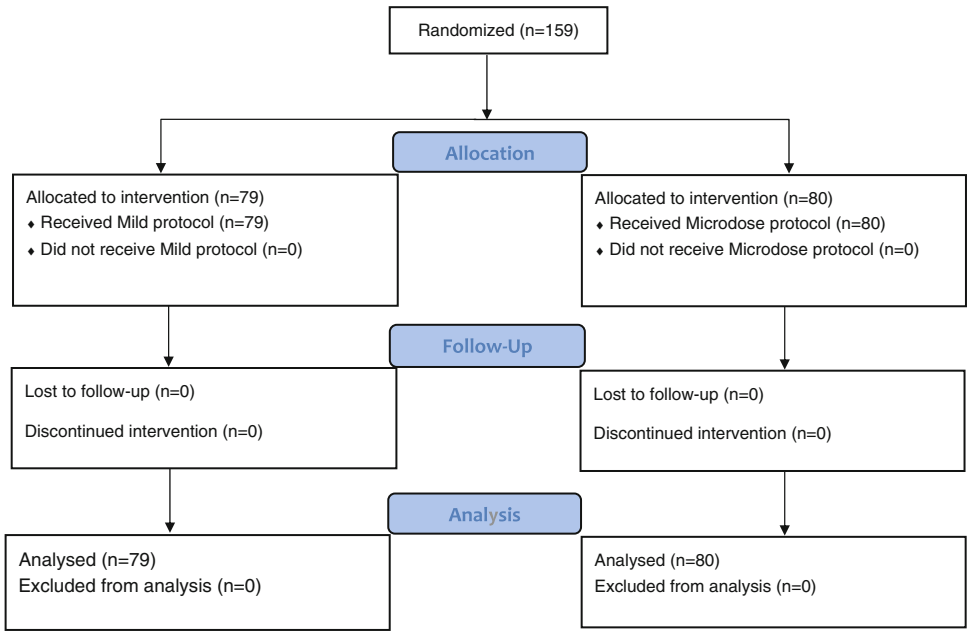

Fig. 1 Consort statement flow diagram

Table 1 Demographic and infertility characteristic of patients

Variables	Group I (mild)	Group II (microdose)	*P* value
Age (years)	39.44 ± 1.40	39.67 ± 1.60	0.486
BMI (kg/m^2)	24.56 ± 2.50	25.20 ± 2.30	0.099
Basal FSH (IU/l)	9.89 ± 3.50	10.02 ± 2.90	0.760
Basal E_2 (pg/ml)	63.41 ± 5.10	62.09 ± 3.20	0.284
Duration of infertility (years)	14.30 ± 6.10	13.30 ± 5.00	0.279
Infertility causes			0.982
Male factor	40 (50.60%)	42 (52.50%)	
Unexplained factor	20 (25.30%)	19 (23.80%)	
Tubal factor	9 (11.40%)	10 (12.50%)	
Mild endometriosis	10 (12.70%)	9 (11.20%)	

BMI body mass index, *FSH* follicular stimulating hormone, E_2 estradiol

Table 2 Results of ovarian stimulation of the two different groups

Variables	Group I (mild)	Group II (microdose)	*P* value	95% CI
Total ampoule of gonadotropin (IU)	1,791.50 ± 774.50	3,161.20 ± 886.05	0.000	−1,630.61, −1,108.97
Days of stimulation	7.91 ± 1.80	8.82 ± 1.70	0.003	−1.000, 0.000
	8[a] (IQ = 2)	9[a] (IQ = 2.25)		
Endometrial thickness day hCG (mm)	8.70 ± 1.40	8.02 ± 1.08	0.001	0.28, 1.13
E_2 day hCG (pg/ml)	1,509.20 ± 299	921.80 ± 572	0.078	
No. of follicle ≥17 mm day hCG	6.21 ± 4.30	4.85 ± 3.60	0.025	0.000, 2.000
	6.50[a] (IQ = 5)	4[a] (IQ = 4)		
No. of retrieved oocytes	6.34 ± 5.40	4.10 ± 3.30	0.005	1.001, 3.001
	6.50[a] (IQ = 5)	4[a] (IQ = 3)		
No. of MII oocytes	5.59 ± 5.00	3.48 ± 2.90	0.005	0.001, 3.00
	6[a] (IQ = 5)	4[a] (IQ = 2.50)		
Cycle cancellation			0.984	
Poor ovarian response	7[b] (8.90%)	6 (7.50%)		
Failed oocyte retrieval	5 (6.30%)	5 (6.20%)		
Failed fertilization	6 (7.60%)	7 (8.80%)		

E_2 estradiol, *hCG* human chorionic gonadotropin, *MII* metaphase 2, *ET* embryo transfer

[a] Median (interquartile range)

[b] Number (%)

Table 3 Results of the insemination, embryological characteristic in two groups

Variable	Group I (mild)	Group II (microdose)	*P* value
Conventional IVF (%)	34.30%	27.50%	0.459
ICSI (%)	65.70%	72.50%	0.459
No. of obtained embryos	3.87 ± 2.70	2.61 ± 1.60	0.055
	3[a] (IQ = 3)	2[a] (IQ = 2.25)	
No. of transferred embryos	2.31 ± 0.77	2.01 ± 0.81	0.318
	2[a] (IQ = 1)	2[a] (IQ = 2)	
Good quality embryo (%)	39.30%	40.30%	0.262
Fertilization rate (%)	58.74%	62.61 (95% CI −0.14, 0.06)	0.482
Implantation rate (%)	16.38%	7.26% (95% CI 0.012, 0.170)	0.024

IVF in vitro fertilization, *ICSI* intracytoplasmic sperm injection

[a] Median (interquartile range)

Table 4 Outcome of cycle

Variable	Group I	Group II	Odds ratio (95% CI)	*P* value
Clinical pregnancy rate/cycle	24.10%	16.20%	0.613 (0.279, 1.346)	0.241
Clinical pregnancy rate/transfer	31.10%	21%	0.586 (0.259, 1.328)	0.222

microdose protocol. However, the days of stimulation and doses of used gonadotropin were decreased in mild protocol. The cancellation rates were not significantly different in two groups, while implantation rate and number of retrieved oocyte were higher in mild group.

Lainas et al. showed lower ongoing pregnancy rate and higher E_2 level on the day of hCG injection in microdose protocol compared to antagonist protocol. They could not provide preferred protocol to improve IVF outcome in poor responders [2]. In 2005, it was reported that microdose protocol had no more advantages in terms of fertilization, implantation and pregnancy rates than antagonist protocol. However, cancellation rate was lower in microdose group [5]. In a research, the results of treatment in microdose and antagonist protocols were similar, except higher E_2 level in microdose protocol [6].

Recently, Demirol et al. in a prospective study showed that the used gonadotropin was reduced in microdose stimulation compared to antagonist protocol, although there were lower fertilization and clinical pregnancy rates in microdose protocol. They did not find a significant difference in cancellation rate [9]. In some studies, microdose protocol did not increase pregnancy rate compared with antagonist protocol, while in terms of fertilization and implantation rates led to different results [24, 25].

Yarali et al. evaluated microdose and letrozole/antagonist protocols outcomes in poor responders. They demonstrated that doses of gonadotropin, duration of stimulation and number of retrieved oocytes were significantly higher in microdose protocol. The clinical pregnancy rates were comparable between two groups [26]. Schoolcraft et al. conducted a similar study in poor responders. They found that the number of obtained oocytes, fertilization and ongoing pregnancy rates were higher in microdose than letrozole/gonadotropin protocols. There were no differences in implantation and cancellation rates in two groups [27].

D'Amato evaluated results of treatment in mild and long protocols and showed that the number of retrieved oocytes was higher with more doses of gonadotropin in mild stimulation. No differences were found in terms of fertilization and pregnancy rates in two protocols [28]. In Benadiva's study [29], in contrast to our results, the number of retrieved oocytes was lower in CC/gonadotropin protocol than the long one.

Nikolettos et al. [8] investigated IVF outcomes of mild and long protocols in women with low ovarian response. Similar to our results, they found that duration of stimulation and doses of gonadotropin administration were reduced in mild protocol. Pregnancy rates were similar in both groups in their study [8]. Also, we found that the high doses of gonadotropins are ineffective in poor responder patients.

Similar to our research, a retrospective study was conducted on 13 poor response patients. They did not find significant differences in fertilization rate and embryo quality in mild and microdose groups. Unlike our results, number of retrieved oocytes and endometrial thickness were similar in both groups [19]. The main point of this study was the small sample size of cases that limited statistical power of the study.

Some investigators reported adverse effects of clomiphene citrate on endometrial thickness [30, 31]. In present study, higher endometrial thickness in mild protocol may relieve this concern. This difference may be reflected by the progesterone level on the day of hCG administration that it was not measured in this study.

Few studies have been conducted on mild protocol regarding IVF outcome compared to other protocols in poor responders. According to our results, it seems that mild protocol did not increase clinical pregnancy statistically; however, considering the better results in this protocol, it can be a substitute for microdose protocol in poor patients.

Conclusion

According to our results, it seems that the high doses of gonadotropins are useless in poor responders. Although in our study fertilization and clinical pregnancy rates did not improve with CC/gonadotropin/antagonist, but considering shorter stimulation days, lower used gonadotropins and being more cost effectiveness, we recommend mild protocol in poor responders in ART cycles.

Conflict of interest None of the co-authors have any financial or other relevant conflict of interest in the material covered by the manuscript.

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