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Research Article

GnRH Agonist Stop Antagonist Protocol versus GnRH Antagonist Protocol for Expected Poor Ovarian Response in ICSI Cycles: a Randomized Comparative Study -

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ABSTRACT

Study design: A Randomized prospective comparable study.

Objective: To compare the efficacy of GnRH agonist stop antagonist and GnRH antagonist protocols in ICSI outcome for women who are expected to have poor ovarian response.

Setting: ART unit of Obstetrics and Gynecology Department of Qena University Hospital, South Valley University, Egypt.

Duration: From September 2016 to December 2017.

Patients and methods: 88 infertile women with expected poor ovarian response have been included in this study. Patients were randomly classified into 2 groups as regarding to the pituitary suppression protocol (Group I: included 44 women received GnRH agonist stop antagonist protocol and Group II: included 44 women received GnRH antagonist protocol).

Results: 9 cases (4 in group I and 5 in group II) were cancelled due to low follicular growth (< 2). There were no statistically significant differences between the two groups as regarding to the duration of stimulation, the total doses of gonadotrophins used, the number of mature follicles and the number of oocytes retrieved (p value > 0.05). There were mildly statistically significant differences between the 2 studied groups as regarding to endometrial thickness, E2 at date of HCG injection, the oocytes quality, the embryos quality, and in the clinically pregnancy rate per initiated cycles (p value < 0.05).

Conclusion: GnRH agonist stop antagonist protocol was slightly better than GnRH antagonist protocol in expected poor ovarian response infertile women in ICSI cycles, there were increase in (quality oocytes, quality embryos, endometrial thickness, E2 levels at time of HCG injection and in the clinical pregnancy rate.

Recommendation: A larger multicentric randomized trial with larger number of cases should be done to verify the actual benefits of GnRH agonist stop antagonist protocol in comparison to GnRH antagonist protocol in expected poor responders facing ICSI or IVF procedures. Also GnRH agonist stop antagonist protocol may need further many wide randomized trials to verify the precise effect on live birth rate and take home baby.

Keywords: Gonadotrophin Releasing Hormone (GnRH) agonist; GnRH antagonist; Intracytoplasmic Sperm Injection (ICSI) cycles; Poor Ovarian Response (POR)

INTRODUCTION

The success of Assisted Reproduction Technology (ART) is based on many factors including the total number of retrieved ova [1]. The Poor Ovarian Response (POR) incidence in the controlled ovarian hyperstimulation ranged between 9 and 24% as reported in literatures [2]. In PORs, FSH level becomes high in the end of luteal phase this allows the more sensitive and larger antral follicles develop more than the other small follicles and this leads to asynchronization in follicle diameters [3,4] and subsequently the number of follicles ready to be recruited and the number of retrieved oocytes will be decreased [5,6]. Inadequate development number of follicles with standardized doses of ovarian stimulation protocols and lower rates of pregnancy are considered the two main POR characteristics [7]. After 2011, a final homogenous definition was proposed by the ESHRE Working Group on Poor Ovarian Response definition called (Bologna Criteria), according to ESHRE new definition, the POR patient must has 2 of 3 following criteria: (a) age ≥ 40 years or presence of any risk factor for POR other than age as pelvic infection, ovarian surgery, short menstrual cycle, ovarian endometrioma, and or chemotherapy, (b) previous POR (3 or less oocytes) with conventional adequate stimulation protocol; or (c) presence of abnormal ovarian reserve tests as the number of basal antral follicles < 5-7 or AMH < 0.5-1.1 ng/mL) [8]. Various modalities have been suggested in treatment of poor responders in order to improve ovarian response and enhance ART success rate [9]. One of these various protocols (GnRH agonist stop GnRH antagonist protocol) which was introduced by Berger and his associates in 2004 for first time [10], as GnRH agonist used for a short period before gonadotrophins stimulation to ensure pituitary suppression and removal of any residual functional cyst and to prevent premature LH surge, hence decrease cycle cancellation rate [11,12], GnRH antagonist was introduced in assisted reproduction technologies because they were effective in prevention of premature LH surge and could allow a natural recruitment of follicles that developed in the follicular phase [13].

AIM OF WORK

To compare the efficacy of GnRH agonist stop antagonist and GnRH antagonist protocols in ICSI outcome for women who are expected to have poor ovarian response.

PATIENTS AND METHODS

This randomly prospective comparative study was conducted on 88 infertile couples with expected poor ovarian response according to presence of (Bologna criteria) from European Society of Human Reproduction and Embryology (ESHRE) [8]. Infertile women were defined as poor responders if they had at least 2 of the following 3 criteria: (a) advanced women age (≥ 40) or presence of any other risk factor for POR; (b) presence of previous Poor Ovarian Response (POR) (≤ 3 oocytes retrieved under a conventional stimulation protocol); (c) presence of any abnormalities in Ovarian Reserve Tests (ORT) (AFC < 5-7 or AMH < 0.5-1.1 ng/mL). The selected cases underwent ICSI procedure at assisted reproduction unit of Qena University Hospital, South Valley University, Egypt, from September 2016 to December 2017. Clear verbal counseling and informed written consent had obtained from all participants couples in this study according to the Medical Ethics committee of Faculty of Medicine, South Valley University.

METHODS

Patients were randomly (using a computer generated randomization method) classified into groups as regarding to pituitary suppression protocols (Group I: included 44 women received GnRH agonist hold antagonist protocol) and (Group II: included 44 women received GnRH antagonist protocol). All

cases had received combined contraceptive pills in the cycle prior to ICSI cycle. In group I (Agonist stop Antagonist group), GnRH agonist (decapeptyl; Ferring) 0.1 mg injected subcutaneously daily starting in midluteal phase in previous cycle and stopped at time of menstruation before starting gonadotrophins stimulation on day 2 of menstrual cycle (recombinant FSH; Gonal F pen; Serono, Aubonne, Switzerland) or hMG (Menogon; Ferring 75 iu) at 300-450 IU/day was initiated and careful monitoring was done for follicular growth by trans-vaginal ultrasound (every other day) till one follicle or more on both ovaries reached 14mm where GnRH antagonist (Cetrotide; Merck Serono 0.25mg daily) injected subcutaneously till the date of HCG trigger. In group II (Antagonist group) gonadotrophins stimulation started on day 2 of menstrual cycle (as in group I) and GnRH antagonist (Cetrotide 0.25 mg) injected subcutaneously daily when one follicle or more on both ovaries reached 14mm, Cetrotide injection continuous till the time of HCG trigger. In both groups when 2 follicles or more had 18 mm (mean diameter) recombinant HCG (Ovitrelle 500 IU) was injected subcutaneously for final follicular maturation. Cycle cancellation was considered if less than 2 follicles were achieved. Oocytes retrieval was done 36 hours post hCG triggering and ICSI procedure was performed for all cases. One to three good quality (A&B) day 3 and day 5 embryos were transferred. Outcome Measures: primary outcome was measuring the number and quality of retrieved oocytes, total doses and duration of gonadotrophins stimulation, E2 levels and endometrial thickness and its pattern on the day of hCG triggering and number of cycle cancellation. The secondary outcome assessed the fertilization rate, number and quality of embryos and pregnancy (chemical and clinical) rate. Serum β-hCG level was assayed 2 weeks post embryo transfer and trans-vaginal ultrasound assessment was done 3 weeks later for positive cases (chemical pregnancy) in order to confirm pregnancy by detection of gestational sac or sacs and fetal viability by observing fetal heart valve movements (clinical pregnancy). Luteal support was achieved with 400 mg Cyclogest administered vaginally twice daily for 2 weeks post fertilization for all cases had embryo or embryos transferred, the hormonal support continued in HCG positive cases to the end of first trimester.

STATISTICAL ANALYSIS

Results of this study were expressed as means ± Standard Deviation (SD), or number (%). Comparison between the 2 categorical data was performed using t test or and χ^2. The data was considered significant if p values was ≤ 0.05 and highly significant if $p < 0.01$. SPSS computer program (version 19 windows) was used in the statistical analysis.

RESULTS

9 cases (4 in group I and 5 in group II) were cancelled (less 2 follicles had developed during controlled ovarian stimulation). There were no statistically significant differences between group I and II in women age, BMI, AMH, basal AFC, day 2 FSH, day 2 E2, duration or causes of infertility (p value > 0.05 (table 1). Also there were no statistically significant differences between the 2 groups as regarding to the number of cancelled cycles, the duration or the total doses of gonadotrophins stimulation, the number of mature follicles and the number of retrieved oocytes (p value > 0.05). There were mildly statistically significant differences between group I and group II in the oocytes quality, endometrial thickness and E2 level at time of HCG injection (p value < 0.05) (table 2). There was no significance between the 2 studied groups in fertilization rate, number of transferred embryos and chemically positive pregnancy rate, but there was a mildly significant difference in the quality of embryos and in the clinically pregnancy rate per initiated cycle (p value < 0.05) (table 3).

DISCUSSION

Assisted reproduction techniques had helped millions of infertile and sub infertile couples all over the world to achieve the dream of the motherhood and fatherhood. Since the time of Louise Brown birth

Table 1: Patient characteristics.

	Group I (N = 44)	Group II (N = 44)	*p* value
Age in years (mean ± SD)	38.3 ± 3.6	39.1 ±3.4	NS
BMI Kg/m² (no %)			
< 25	9 (20.4)	10 (22.7)	
25 - <30	12 (27.3)	14 (31.8)	NS
≥ 30	23 (52.3)	20 (45.4)	
AMH ng/ml (mean ± SD)	1.0 ± 0.3	0.97 ± 0.2	NS
Basal AFC (mean ± SD)	4.6 ± 2.3	4.3 ± 2.1	NS
Day 2 FSH (mIU/mL) (mean ± SD)	9.3 ± 3.4	9.6 ± 3.2	NS
Day 2 E2 (pg/mL) (mean ± SD)	34.2 ± 16.2	35.6 ± 18.4	NS
Infertility Duration (yrs) (mean ± SD)	8.7 ± 4.6	8.6 ± 4.4	NS
Causes of infertility (%)			
Male factor	44.2	43.7	NS
Tubal factor	14.3	15.1	NS
Ovarian factor	10.5	10.7	NS
Endometriosis	7.9	8.1	NS
Unexplained	23.1	22.4	NS
Cycle cancellation (no %)	4 (9.09)	5 (11.36)	NS

NS = Non-Significant.

Table 2: Ovarian stimulation outcome in Group I and Group II.

	Group I (N = 40)	Group II (N = 39)	*p* value
Duration of gonadotrophins stimulation (days) (mean ± SD)	11.7 ± 1.6	11.3 ± 1.4	NS
Dose of gonadotrophins (IU) (mean ± SD)	4743.6 ± 1241.4	4675.1 ± 1220.4	NS
Number of mature follicles (mean ± SD)	6.1 ± 2.7	6.4 ± 2.4	NS
Number of oocyte retrieved (mean ± SD)	4.2 ± 2.0	3.9 ± 1.8	NS
Oocyte maturity (M2) (mean ± SD)	3.0 ± 0.9	2.2 ± 0.7	S
Endometrial thickness in mm (mean ± SD)	8.7 ± 2.3	6.8 ± 2.1	S
Estradiol (E2) in day of HCG triggering (mean ± SD)	1366.3 ± 743.2	1123.4 ± 691.3	S

NS = Non-Significant S = Significant.

Table 3: ICSI outcome in Group I and Group II.

	Group I (N = 40)	Group II (N = 39)	*p*-value
Fertilization rate (%)	71.5%	69.7%	NS
Embryo grades (%)			
A & B	65.3%	53.2%	S
C & D	34.7%	56.8%	
No. of embryos transferred (mean ± SD)	1.7 ± 0.6	1.8 ± 0.6	NS
Chemical pregnancy rate per initiated cycle (no %)	18/40 (45.0)	17/39 (43.0)	NS
Clinical pregnancy rate per initiated cycle (no %)	14/40 (35.0)	11/39(28.2)	S

NS = Non-Significant S = Significant.

in 1978, [14] assisted reproductive techniques have been evolved dramatically in a great effort in optimization in the probability of pregnancy for sub infertile couples. Although the numerous scientific and technological evolution, however, the poor ovarian response management for *in vitro* fertilization or intracytoplasmic sperm injection is still assessed to be one of the most hard task for the infertility specialists, [15,16] where small number of women gametes could be obtained in poor responders and associated with a significantly diminished pregnancy rate. Various modalities have been used over the past few years towards optimal management of poor responders and many modified controlled ovarian hyperstimulation protocols had been implemented without concreting evidence on the compelling advantages for one protocol over the other [2,9]. Poor ovarian response actually is a big challenge in assisted reproduction centers all over the world. In this study we aimed to compare the GnRH agonist stop antagonist and GnRH antagonist as pituitary suppression protocols in management of expected poor ovarian response ICSI cycles, GnRH agonist had known in its ability of suppression any residual ovarian cysts and decline the high basal LH which is associated with oocyte aneuploidy beside it increase the quality of retrieved oocytes but has disadvantages where a large number of gonadotrophins ampoules are needed besides an increase in the duration of gonadotrophins stimulation so in this study we had used GnRH agonist for short period in the luteal phase (to overcome the previous disadvantages) and had stopped immediately when menstruation occurred before starting stimulation with gonadotrophins, the GnRH antagonist was administered in group I later on when one follicle or more achieved 14 mm in mean diameter and compared with GnRH antagonist protocol (alone not proceeded with agonist) in group II. In this study GnRH agonist stop antagonist protocol was significantly better than GnRH antagonist protocol in the increased number good quality oocytes, enhanced endometrial thickness and its pattern and increased the levels of estradiol in the day of HCG injection also had statistically significant differences as regarding to quality of embryos and clinically pregnancy rate per initiated cycle, and these results agreed with many results had been reported in literature as Demirol et al. [17] and Yannis et al. [18], Demirol et al. had showed that a agonist microflare protocol had a highly significant rate of implantation in comparison with the antagonist protocol in women with poor ovarian response, in Yannis et al. had found no difference in the quality of oocyte in contrary to our results. Our study had demonstrated that the clinical pregnancy rate was mildly significantly higher in the GnRH agonist group than GnRH antagonist group and these results agreed with what had been reported by Yannis et al. [18] who showed clinical pregnancy rate (35.8% agonist versus 25.6% antagonist with $p = 0.03$). In contrary to our results what had been reported by Cheung et al. [19], in a prospective randomized trial that compared the long GnRH agonist to the antagonist protocol in poor responders IVF cycles and reported that there was no a statistically significant difference between the 2 groups as regard to stimulation or in the laboratory and the pregnancy outcomes with exception of the transferred embryos number that had a higher significance in the antagonist group (2.32 ± 0.58 versus 1.50 ± 0.83 with p value = 0.01). In our study the cancellation rate was similar in both group but in Yannis et al. [18] reported a higher cancellation rate in GnRH antagonist group. In literature there are 2 RCTs had evaluated the effect of a standard nonstop long GnRH agonist protocol (started in luteal phase of previous cycle prior to ICSI cycle) versus a stop GnRH agonist protocol as regarding to pregnancy rate in poor responder infertile women [20, 21], the results of these 2 studies showed that there was no statistically significant difference between nonstop long GnRH agonist and stop GnRH agonist in the clinical pregnancy rate per initiated ICSI cycle (OR = 1.17,95% -CI: 0.42-3.24), but any way these two studies reported statistically significant differences in the duration of gonadotrophins stimulation (WMD: -0.4 days; 95% CI: -2.0 to +1.2) and in the total doses gonadotrophins drugs used for controlled ovarian stimulation (WMD: -3.6 ampoules, 95% CI: -18.8 to +11.6), with a similar number of retrieved oocytes in the 2 groups (WMD: +0.64 COCs, 95% CI: -3.1 to +4.3).

CONCLUSION

GnRH agonist stop antagonist protocol was superior to GnRH antagonist protocol in; increased number of good quality oocytes, enhancement of endometrial thickness and increased E2 at time of HCG injection, increased embryo quality and increased the clinical pregnancy rate in expected poor ovarian response infertile women.

RECOMMENDATIONS

(a) A larger multicenter randomized trial with larger number of cases should be done to verify the actual benefits of GnRH agonist stop antagonist protocol in comparison to GnRH antagonist protocol in expected poor responders facing ICSI or IVF procedures. (b) Also GnRH agonist stop antagonist protocol may need further many wide randomized trials to verify the precise effect on live birth rate and take home baby.

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