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Research Article

IVF Outcomes of Microdose Flare-up, GnRH Antagonist and Long Protocols in Patients Having a Poor Ovarian Response in the First Treatment Cycle

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Received Date: 05-04-2021; **Accepted Date:** 24-04-2021; **Published Date:** 30-04-2021

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Abstract

Objectives: To compare the outcome of patients assumed to be poor responders before their first cycle of IVF and treated either microdose flare-up or GnRH antagonist protocols with patients stimulated by long GnRH protocol and had a poor ovarian response with a low yield of the oocyte after their first IVF cycle.

Study Design: Retrospective cohort study.

Place and Duration of Study: Department of Obstetrics and Gynecology from September 2014 to February 2019.

Methodology: Patients treated with the first cycle of IVF and diagnosed as poor responders after ovarian stimulation were evaluated according to the treatment protocol, including microdose flare-up (Group 1: 136 patients), GnRH antagonist (Group 2: 105 patients), and long GnRH agonist (Group 3: 77 patients).

Mumtaz H | Volume 2; Issue 1 (2021) | JSRP-2(1)-017 | Research Article

Citation: Mumtaz H, et al. IVF Outcomes of Microdose Flare-up, GnRH antagonist and Long Protocols in Patients Having a Poor Ovarian Response in the First Treatment Cycle. J Surg Res Prac. 2021;2(1):1-11.

DOI: <http://dx.doi.org/10.46889/JSRP.2021.2107>

Results: Basal FSH level was significantly lower in group 3 compared to other groups ($p < 0.05$). The number of oocytes retrieved, the number of metaphase II oocytes were similar between groups, although the mean AFC was significantly higher in group 3 than in group 1 and 2 ($p < 0.05$). Clinical pregnancy rates per patient were higher in group 3 (22.9%) than in group 1 (13.7%) and group 2 (14.4%), but the difference was not statistically significant ($p = 0.214$). The live birth rate per patient was statistically higher in group 3 (21.4%) as compared to other groups (9.7%, 10.3%, respectively; $p < 0.05$).

Conclusion: Long protocol may be an option in poor responders undergoing IVF. Ovarian reserve markers are essential factors with stimulation protocol for the success of IVF in poor responder patients.

Keywords

Poor Responder; Microdose Flare-Up; GnRH Antagonist; Long Protocol; IVF; Pregnancy Outcomes

Introduction

The number of cycles with poor response to Ovarian Stimulation (OS) protocols has been increased with the widespread use of Assisted Reproductive Techniques (ART). Poor response to OS occurs in approximately 9 to 24% of all patients undergoing *In-vitro* Fertilization (IVF) [1]. In the literature, there are no precise criteria to define a Poor Ovarian Response (POR). ESHRE (European Society of Human Reproduction and Embryology) has recently described POR when at least two of the following three features should be present:

1. Advanced maternal age (≥ 40 years)
2. Any other risk factor for; a previous POR (≤ 3 oocytes by a conventional stimulation protocol)
3. An abnormal ovarian reserve test (i.e., AFC (Antral follicle count), 5-7 follicles or AMH (Anti-Mullerian Hormone), 0.5-1.1 ng/ml) [2].

A new approach for poor responders termed as "POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) stratification" has been indicated recently due to the heterogeneity in definitions. This classification consists of 4 groups according to age (< 35 or ≥ 35 years), ovarian reserve parameters ($AFC \geq 5$ or < 5 , $AMH \geq 1.2$ or < 1.2) and the number of retrieved oocytes after standard stimulation (< 4 or 4-9 oocytes) [3].

Several treatment protocols have been proposed to enhance POR in ART. Among many stimulation protocols (GnRH agonist, GnRH antagonist, microdose flare-up) and adjuncts (DHEA, Growth hormone, and others) for predicted poor responder, none is very effective or superior as evidence-based [4]. Main theoretical advantages of GnRH antagonist and microdose flare-up protocols in predicted poor responders are mild suppression of hypophysis and initial flare of endogen gonadotropins for microdose protocol and prevention of premature LH surge and luteinization without suppression of endogen gonadotropins resulting in more recruitment of follicles for antagonist protocol [5,6]. Besides this, some experts offer long protocol as the first option for poor responders due to better follicular synchronization [7].

Generally, GnRH antagonist protocol is the most preferred regimen for POR [8]. A Cochrane review comparing different OS protocols in poor responders stated that using antagonist protocol resulted in a higher Number of Oocytes Retrieved (NOR) compared to long protocol but a fewer NOR than flare-up protocol [9]. Another recent Cochrane review has shown higher Clinical Pregnancy Rates (CPR) and NOR in long protocol than short protocol [10]. Likewise, similar results have been found regarding the NOR between long and short regimens in a recent Randomized Controlled Trial (RCT) [11]. Thus, there is no robust data to determine the best of these regimens for starting the OS in poor responders [9]. Choosing one of these regimens is challenging because of the lack of sufficient evidence and the POR definition variations. Besides this, most of the previous reports were about binary comparisons of these three main treatment protocols in different patients.

So, we aimed to evaluate the outcome of patients who were assumed to be a poor responder before stimulation and treated in their first cycle with microdose or antagonist protocols and compare their outcomes with patients who were stimulated with long GnRH protocol in their first cycle and had a poor response to gonadotropins with low number oocytes retrieved after stimulation.

Materials and Methods

This study was conducted retrospectively at Department of Obstetrics and Gynecology from September 2014 to February 2019. It was approved by the Ethics Committee of the University. Patients applying to the IVF center with different etiologies of infertility and started IVF treatment were evaluated from the medical records of the hospital. Three groups were formed according to their IVF protocol as microdose GnRH agonist (Group 1), GnRH antagonist (Group 2) and long GnRH agonist (Group 3).

Patients stimulated by either microdose flare-up or GnRH antagonist protocol and anticipated as poor responders according to their age, basal FSH or AFC prior to stimulation were reviewed as poor responders study groups. All patients in the microdose (Group 1) and antagonist

protocol (Group 2) had the first cycle of IVF and had the Number of Oocytes Retrieved (NOR) ≤ 5 after ovarian stimulation. Patients treated by long luteal GnRH agonist according to their age, basal FSH, or AFC and diagnosed as poor responders after stimulation due to the low yield of oocytes in their first IVF cycle were evaluated as the control group. All patients in the long agonist group (Group 3) had NOR ≤ 5 after stimulation as in study groups. When patients had >5 oocytes after their cycle, they were excluded from the study. Patients with a diagnosis of endocrinological disorders, including polycystic ovary syndrome, hypothyroidism or hyperprolactinemia, endometriosis, and severe male factor infertility, were also excluded.

In group 1, low dose OC (Desolett; Organon, Netherlands) was started on day 1 of the previous cycle for 21 days. On the second day of menstruation, 40 μ g SC twice daily of leuprolide acetate (Lucrin; Abbott, France) (80 μ g/day) was initiated. Recombinant FSH (Gonal-F; Serono, Turkey) 300-450 IU/day was started on the 3rd day of the cycle. Leuprolide acetate and recombinant FSH were continued until the day of hCG administration.

In group 2, recombinant FSH 300-450 IU/day was commenced on the 3rd day of the cycle, and when the leading follicle reached 14 mm in diameter, 0.25 mg cetorelix (Cetrotide; Asta Medica, Germany) was administered daily until hCG injection.

In group 3, leuprolide acetate (1 mg) was started in the mid-luteal phase of the previous cycle and ceased when the pituitary suppression was confirmed (E2 level <50 pg/ml). Then recombinant FSH 300-450 IU/day was started, and leuprolide acetate was decreased to half of the initial dose (0.5 mg). Leuprolide acetate and recombinant FSH were maintained until the day of hCG administration.

Follicle growth was followed by serial ultrasound evaluation and serum E2 measurements to adjust the gonadotropin dose in compliance with the ovarian stimulation response. All the sonographic exams were performed by Voluson 730 Pro-machine (GE Healthcare Austria GmbH and Co OG). 250 mcg choriogonadotropin alfa (Ovitrelle, Merc Serono, Italy) were used to trigger ovulation when the mean diameter of the leading follicles was observed ≥ 17 -18 mm by ultrasonography. Transvaginal oocyte retrieval was performed 36 hours after hCG administration. ICSI procedure was carried out for all retrieved metaphase II oocytes. ET (Embryo transfer) was performed 2-3 days after oocytes retrieval for high or good-quality embryos (grade I [high-quality]: embryos with equal blastomere and no observed cytoplasmic fragmentation; grade II [good-quality]: embryos with equal blastomere and $<20\%$ fragmentation of the cytoplasm) under transabdominal ultrasound guidance by using a flexible catheter (Wallace; Irvine Scientific, Santa Ana, CA).

Vaginal Progesterone (P) supplementation (Crinone 8% gel, Serono) was started to all patients for luteal phase support after the transfer and continued until fetal heart activity was observed. Clinical pregnancy was diagnosed when a gestational sac or a fetus with cardiac activity was

followed by ultrasonography. The live birth was defined as the delivery of a viable fetus of ≥ 23 weeks' gestation.

Primary outcome measures were CPR and Live Birth Rates (LBR) per patient in this study. Secondary outcome measures were the NOR, the number of mature oocytes and estradiol levels on the day of hCG trigger. The fertilization rate was defined as the ratio of the total number of fertilized oocytes to the total number of mature oocytes retrieved.

Data were analyzed with Statistical Package for Social Sciences (SPSS, version 21.0, Statistics, 2013, Chicago, IBM, USA). Normality tests, including the Kolmogorov-Smirnov test, were used for data analyses concerning normal distribution. One-way analyses of variance (One-way ANOVA) with Bonferroni post hoc test was used to compare the mean values between stimulation protocol groups. Chi-square test was used to analyze the differences between evaluated categorical data. The fertilization rate was compared with the chi-square test. Continuous variables were presented as mean $\pm$ standard deviation, and categorical data were presented as percentages. Statistical significance was defined as $p < 0.05$.

Results

A total of 318 patients were evaluated in this study. Group 1 had 136 (42.8%) patients, Group 2 had 105 (33.0%) patients, and Group 3 had 77 (24.2%) patients. Basal characteristics of groups were shown in Table 1. The mean age was not different between groups. Also, there were no significant differences in BMI, duration of infertility, and causes of infertility between groups. The mean AFC was significantly higher in group 3 (5.5 ± 1.9) than group 1 (4.8 ± 1.7) and group 2 (4.7 ± 2.0) ($p < 0.05$), and the mean basal FSH level was significantly lower in group 3 (7.8 ± 2.7) as compared to group 1 and 2 (9.3 ± 3.9 , 9.7 ± 4.6 , respectively) ($p < 0.05$).

The comparison of ovarian stimulation parameters between groups was given in Table 2. The mean duration of stimulation, the mean progesterone, and LH levels on the day of the trigger were similar between groups. Patients in group 1 used a significantly higher total dose of gonadotropins (4189.5 ± 1252.7) as compared to group 3 (3714.7 ± 1120.7) ($p < 0.05$). The mean estradiol level on the day of hCG trigger was significantly higher in group 3 (1148.0 ± 546.9) as compared to only group 2 (933.9 ± 427.3) ($p < 0.05$). The mean endometrial thickness, the number of follicles ≥ 17 mm in diameter on the day of hCG injection, and cycle cancellation rates were not different between groups. Also, the mean total NOR, number of metaphase II oocytes, and the number of transferred embryos were similar among groups. There was not any complication during the ovum pick-up procedure in groups. Fertilization rates were not different between groups (70.6%, 69.1%, 67%, respectively) ($p = 0.645$).

Clinical pregnancy was achieved in 47 of 291 patients (16.2%) for all groups. In group 3, the CPR was higher than group 1 and 2, but the difference was not statistically significant (22.9%,

13.7%, 14.4%, respectively; $p=0.214$). Overall live birth was reported in 37 of 291 patients (12.7%). LBR per patient was statistically higher in group 3 as compared to group 1 and 2 (21.4%, 9.7%, 10.3%, respectively; $p<0.05$).

Variables (318 patients)	Group 1 (Microdose) ⁽¹⁾ (n=136)	Group 2 (Antagonist) ⁽²⁾ (n=105)	Group 3 (Long agonist) ⁽³⁾ (n=77)	p-value
Age (year)	36.4 ± 4.3	36.1 ± 5.3	35.1 ± 3.5	0.130
Duration of infertility (month)	107.7 ± 68.5	96.5 ± 71.3	100.2 ± 62.5	0.436
Basal FSH (mIU/ml)	9.3 ± 3.9 ⁽³⁾	9.7 ± 4.6 ⁽³⁾	7.8 ± 2.7 ^(1,2)	0.009
Antral follicle count	4.8 ± 1.7 ⁽³⁾	4.7 ± 2.0 ⁽³⁾	5.5 ± 1.9 ^(1,2)	0.005
BMI (kg/m ²)	23.1 ± 2.3	22.7 ± 2.7	23.2 ± 2.5	0.345
Causes of infertility n, (%)				0.214
Mild male factor	47 (34.6)	27 (25.7)	29 (37.7)	
unexplained	52 (38.2)	53 (50.5)	37 (48.1)	
tubal	22 (16.2)	16 (15.2)	7 (9.1)	
mixt	15 (11)	9 (8.6)	4 (5.2)	
Data were presented as mean ± SD and percentage (%). BMI: Body Mass Index; FSH: Follicle-Stimulating Hormone; Statistically significant differences between groups were presented with Superscript (n); $p < 0.05$ was considered significant.				

Table 1: Comparison of basal characteristics of patients between groups.

Variables (318 patients)	Group 1 (Microdose) ⁽¹⁾ (n=136)	Group 2 (Antagonist) ⁽²⁾ (n=105)	Group 3 (Long agonist) ⁽³⁾ (n=77)	p-value
Duration of stimulation (day)	11.5 ± 1.9	11.0 ± 2.5 ⁽¹⁾	10.8 ± 2.1	0.054
Total dose of gonadotropin(IU)	4189.5 ± 1252.7 ⁽³⁾	3994.1 ± 1397.9	3714.7 ± 1120.7 ⁽¹⁾	0.033
E2 level on hCG day (pg/ml)	1054.2 ± 506.0	933.9 ± 427.3 ⁽³⁾	1148.0 ± 546.9 ⁽²⁾	0.045
LH level on hCG day (IU/L)	3.0 ± 2.1	3.6 ± 3.2	3.3 ± 2.7	0.475
Progesteron level on hCG day (ng/ml)	0.8 ± 0.5	0.8 ± 0.6	1.0 ± 0.7	0.166
Number of follicle ≥17 mm on hCG day (mm)	2.1 ± 1.0	1.9 ± 1.0	2.0 ± 1.3	0.294
Endometrial thickness on hCG day (mm)	10.4 ± 2.3	10.1 ± 2.4	10.7 ± 2.0	0.179
Cycle cancellation rate, n (%)	12 (8.8)	8 (7.6)	7 (9.1)	0.924
Number of Oocytes retrieved	3.2 ± 1.3	3.1 ± 1.4	3.4 ± 1.9	0.410
Number of MII Oocytes	2.7 ± 1.2	2.5 ± 1.3	2.9 ± 1.4	0.138
Fertilization rates, n of PN (%)	262 (70.6)	183 (69.1)	150 (67)	0.645
Number of transferred embryos	1.8 ± 0.8	1.7 ± 0.7	1.6 ± 0.7	0.104

Clinical pregnancy rate, per patient, n (%)	17 (13.7)	14 (14.4)	16 (22.9)	0.214
Live birth rate, per patient, n (%)	12 (9.7)	10 (10.3)	15 (21.4)	0.042
Data were presented as mean $\pm$ SD, numbers and percentages. E2: Estradiol; LH: Luteinizing Hormone, hCG: Human Chorionic Gonadotropin. MII: Metaphase 2, PN: Pronucleus. Statistically significant differences between groups were presented with Superscript (n); $p < 0.05$ was considered significant.				

Table 2: Comparison of ovarian stimulation results and pregnancy outcomes between groups.

Discussion

In poor responder patients, GnRH antagonist and microdose flare-up protocols have been frequently used in recent years to avoid profound gonadotropin suppression seen in the long luteal protocol. In the literature, microdose flare-up and GnRH antagonist protocols were mostly compared with each other in patients with POR [5,12-14]. However, there is limited data, including one RCT that compares the IVF outcomes of these protocols concurrently with long protocol in poor responders [11]. In our study, we found that although the NOR and the number of metaphase II oocytes were comparable between groups, the LBR was statistically higher in the long luteal group than microdose flare-up and GnRH antagonist protocol.

In contradiction to our results, significantly increased Pregnancy Rates (PR) and decreased Cancellation Rates (CR) were reported in the microdose group as compared to the long agonist protocol in two studies [15,16]. However, Leondires et al. found no statistical difference in PR between groups with a significantly higher CR in the microdose group [17]. There were no differences concerning oocyte numbers and reproductive outcomes between two groups in one RCT [18]. Conversely, in a recent Cochrane review, significantly higher CPR and NOR have been found in long protocol than short flare-up protocol [10]. Indeed, short flare protocols did not reflect microdose flare protocols in this review, so the conclusion could not be used to compare microdose flare and long protocols.

In general, higher NOR, implantation, and PR were reported in the GnRH antagonist regimen compared to the long protocol [9,19]. In a recent RCT by Sunkara, et al., no difference has been shown in the NOR between these two groups, with a non-significantly higher Ongoing Pregnancy Rate (OPR) in the antagonist group [11]. However, Lambalk, et al., have reported similar NOR, CPR, OPR, and LBR among two groups in a recent meta-analysis [20]. On the other hand, one RCT found that long agonist protocol improved NOR and CPR compared to the GnRH antagonist group in poor responders [21].

Mumtaz H | Volume 2; Issue 1 (2021) | JSRP-2(1)-017 | Research Article

Citation: Mumtaz H, et al. IVF Outcomes of Microdose Flare-up, GnRH antagonist and Long Protocols in Patients Having a Poor Ovarian Response in the First Treatment Cycle. J Surg Res Prac. 2021;2(1):1-11.

DOI: <http://dx.doi.org/10.46889/JSRP.2021.2107>

Comparisons of the microdose flare-up and GnRH antagonist regimen are inconsistent in the literature. Kahraman, et al., found similar NOR and pregnancy rates in both groups, while higher E2 levels in the microdose group [5]. Schmidt, et al., stated no significant differences between both groups in terms of E2 levels on the day of hCG, NOR, and CPR [13]. In a recent RCT, Merviel, et al., also have reported similar NOR, OPR, and CPR among groups [22]. Boza, et al., found that peak E2 levels and CPR were not different between groups, although the number of metaphase II oocytes was significantly higher in the microdose group [23]. In a recent RCT, Ghaffari, et al., have reported similar NOR, CPR between two groups. However, they have found significantly higher LBR in the microdose group [24]. In another RCT, Davar, et al., reported that CPR and OPR were not different among groups, although NOR and the number of metaphase II oocytes were higher in the antagonist group. However, they administered a different antagonist treatment protocol in which GnRH antagonist was also used seven days before stimulation following estrogen priming [25]. On the other hand, Fasouliotis et al. reported a nonsignificant increase in CPR and a significant increase in OPR in the GnRH antagonist group [12]. Lainas, et al., also showed a significantly higher OPR in the antagonist group than in the microdose group, although E2 levels on the day of hCG were higher in the microdose group [14]. In our study, NOR, CPR, and LBR per patient were not different between these two groups, which was comparable with previous reports [5,13,22].

The LBR was significantly higher in the long agonist group as compared to others in our study. All these protocols have also been assessed recently by Sunkara, et al., and non-significantly higher OPR has been found in the GnRH antagonist group than in others [11]. The small sample size may lead to this nonsignificant difference, as stated by the authors. Our results may be explained by the retrospective design of the study. Another explanation of higher pregnancy rates in the long GnRH group could also be the relatively good prognosis of these patients, although the mean age was similar between groups. The long protocol group included patients with the lowest FSH level and the highest AFC on the 3rd day of the cycle, which may contribute to these good results. Also, the long agonist group may probably represent POSEIDON Group 1 or 2, which has been described in recent years for poor responder patients. In good prognosis poor responders like POSEIDON Group 1 and 2, prognostic factors such as ovarian reserve parameters seem crucial on IVF outcomes in addition to the stimulation protocol as in our study. Although the study population's homogeneity could not entirely be provided, three stimulation protocols were concurrently evaluated in our research. These results add evidence to the literature supporting the long agonist use in the poor responders.

Conclusion

In conclusion, in poor responders with relatively good ovarian reserve markers before stimulation, ovarian stimulation with long protocol might positively affect pregnancy outcomes in IVF cycles.

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