



Fixed Versus Flexible Antagonist Protocol in Reduced Ovarian Reserve Patients: A Historical Cohort Study

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Abstract

Objectives: The antagonist of gonadotropin-releasing hormone is proven to be effective and safe in preventing a surge in luteinizing hormone (LH) during in vitro fertilization (IVF) cycles. In addition, the differentiation of GnRH antagonist protocols is in timing the initiation of the GnRH antagonist. The present study aimed to compare fixed versus flexible antagonist regimens in patients with reduced ovarian reserve in order to identify a better regimen for these patients.

Materials and Methods: This study was of a historical cohort type. Totally, 129 patient files were investigated including 48 versus 66 files related to fixed or flexible protocols, respectively. The mean of age, body mass index (BMI), follicle stimulating hormone (FSH), and anti-Mullerian hormone (AMH), as well as the mean dose of gonadotropin, the mean length of IVF/ICSI cycles, and the mean counts of oocytes and embryos with grading including good, fair, and poor were compared between the 2 groups.

Results: The total and mean consumption of gonadotropin dose (recombinant FSH) in the flexible and fixed groups were significantly different ($P=0.05$). However, the mean antagonist (cetrotide) doses in the fixed and flexible groups were not significantly different while it was lower in the flexible group ($P=0.50$). Finally, the duration of gonadotropin consumption in IVF/ICSI period was not significantly different between the two groups.

Conclusions: In general, the fixed protocol is recommended in patients with reduced ovarian reserve since it is simple to use and more cost effective compared to the flexible protocol.

Keywords: Fixed, Flexible, Ovarian

Introduction

The antagonist of gonadotropin releasing hormone (GnRH) is effective and safe for preventing a luteinizing hormone (LH) surge during in vitro fertilization (IVF) cycles (1,2). During the past years, there has been a progressive shift away from GnRH agonist down-regulation toward the GnRH antagonist. In IVF/ICSI cycles, the GnRH antagonist competitively binds the GnRH receptor and yields a rapid onset and withdrawal of functions (3-6). In addition, the differentiation of GnRH antagonist protocols is believed to be in timing the initiation of the GnRH antagonist (6,7). In a fixed protocol, the GnRH antagonist is initiated in the sixth days of ovarian stimulation versus the flexible protocol follicular diameter as reference points for GnRh antagonist initiation (6,8,9).

Breakthrough LH surge during GnRH-antagonist is not frequently encountered in IVF cycles. These patients have a poorer ovarian reserve, increased age, and poor response to gonadotropins (3). In the Bologna criteria published by European Society of Human Reproduction and Embryology (ESHRE) in 2011, an abnormal ovarian reserve test is identified as antral follicle count (AFC) of less than 5-7 follicles or anti-Mullerian hormone (AMH)

< 0.5-1.1 ng/mL (10-13).

Tannus et al studied the effect of delayed initiation of gonadotropin-releasing hormone antagonist in a flexible protocol on IVF outcome. This study included patients aged ≤ 40 years. The antagonist was started when the leading follicle size was ≥ 13 mm or the serum E_2 level achieved ≥ 300 pg/mL (10).

Objectives

Few studies considered fixed versus flexible antagonist regimens in reduced ovarian reserved patients. Further, using the antagonist in reduced ovarian reserve patients is progressive. Therefore, the authors decided to design a study and compare the fixed versus flexible antagonist regimens in reduced ovarian reserve patients in order to identify a better regimen in these patients.

Design, Participants, and Data Collection Method

This study reviewed the IVF/ICSI files of the patients investigated in university-based tertiary hospitals in Tehran, Iran. Patients <41 years with reduced ovarian reserve, according to Bologna criteria, and those who received an antagonist protocol for IVF/ICSI cycles were included in this research conducted during (October)



2013-(September) 2017.

Incomplete patient files were excluded from the study. After the detailed study of the patients' files, the patients were again contacted and necessary information was obtained. Patients with reduced ovarian reserve in our center normally underwent treatment with an antagonist protocol and antagonist (cetrotide) 0.25 mg/d was initiated in 2 protocols. In one protocol, cetrotide was taken in a fixed protocol in sixth days after starting the gonadotropin. In a flexible protocol, cetrotide initiated to growth in ovarian follicle size. If the largest achieved follicle size was 13 mm, cetrotide was initiated. Each protocol for every patient was selected by a related doctor. A number of 129 patient files were investigated out of which 15 files were excluded as a result of incomplete information. Totally, less than half of the files (n=48) were related to a fixed protocol while the remaining files (n=66) were associated with a flexible protocol. A detailed history of all the patients was recorded. Then, the patients underwent a physical examination. Hormonal study (i.e., follicle stimulating hormone [FSH], LH, AMH, and E₂) in 2 or 3 days of menses was recorded. The hysterosalpingographic report, as well as the laparoscopic hysteroscopic surgical report of the patients was available. All the patients in 2 or three days of menstruation underwent transvaginal sonography. Furthermore, gonadotropin drugs (recombinant FSH [Gonal-F, Merk], HMG [Merional or Menogan, Ferring, IBSA], and urinary FSH [Fostimone, IBSA]) were initiated based on the age, AFC, and AMH. The patients had serially transvaginal sonography and the dose of gonadotropins was adjusted. In the fixed group, antagonist (cetrotide, Merk Serono) 0.25 mg/d was initiated in sixth days after starting the gonadotropin while in the flexible group, if the largest achieved follicle size was 13 mm, then, the cetrotide 0.25 mg/d was initiated. When the follicle size achieved 18 mm HCG 10000 IU (Darou Paksh or Organon) or recombinant HCG (Ovitrel) 250 µG (Merk Serono) was administered. After 36 hours, oocytes were retrieved. If in 11-13 days of menstruation the follicles failed to grow or the growth was stopped and the E₂ level reached <200 pg/mL, then, the cycle was canceled.

Two to three days after the oocytes were retrieved, the embryos were transferred. After fourteen days, B-HCG was checked. If the gestational sac was observed in the transvaginal sonography, clinical pregnancy was considered positive; however, if B-HCG was positive and the gestational sac was not represented by transvaginal sonography, then, chemical pregnancy was considered.

All patients received luteal phase support by cyclogest 400 mg vaginally twice daily at least 14 days until a pregnancy test was performed. If the pregnancy test was positive, cyclogest 400 mg was administered vaginally twice daily and continued until 10-12 weeks of pregnancy.

Data Analysis

The mean age, body mass index (BMI), FSH, and AMH

were calculated and the groups were compared. The mean dose of gonadotropin and the mean length of IVF/ICSI cycles were compared between the 2 groups. Moreover, the mean count of oocytes was retrieved and the mean count of embryos with grading including good, fair, and poor was compared between the 2 groups.

In this research, statistical analysis was conducted using the SPSS software, version 19. The continuous and categorical variables were employed in the present study. Descriptive statistics were reported as mean and SD for continuous variables and percentage for categorical variables. Additionally, a two-sample *t* test was used for continuous variables and χ^2 analysis or Chi-square test of independence was implemented for categorical variables for between-group comparisons. The odds ratio was estimated with 95% CI and the level of significance was considered at $P < 0.05$.

Results

The findings demonstrated no significant difference between the mean age of the patients between the fixed (35.8 years) and the flexible (38.2 years) groups. All patients were <41 years old. In addition, the mean BMI in the fixed and flexible groups were 25.19 and 25.95, respectively, and based on the result, no significant difference was observed between both groups in this respect.

The AMH of all the patients was <0.5-1.1 ng/mL and there was no significant difference between the 2 groups. Further, the mean of FSH in the fixed group was 7.45 while it was equal to 9.62 in the flexible group and no significant difference was found between the 2 groups in this regard (Table 1) (Figure 1). Other causes of infertility (i.e., mal, tubal, and endometriosis) were studied between the 2 groups; however, there was no statistically significant difference between both groups (Table 2).

The count of oocytes ($P=0.38$) and embryos ($P=0.51$), the number of embryos with different grades including the good ($P=0.12$), fair ($P=0.18$), and poor ($P=0.19$) were not significantly different between the fixed and flexible groups (Figure 1) (Table 3).

Furthermore, as shown in Table 3, endometrial thickness is not significantly different between the 2 groups ($P=0.26$).

The total and mean consumption of gonadotropin dose (recombinant FSH) in the flexible group was

Table 1. The Comparison of Clinical Characteristics Between the Fixed and Flexible Groups

Variables	Fix Group		Flexible Group		P Value
	Mean	SD	Mean	SD	
Age	35.87	3.76	38.42	5.07	0.24
BMI	25.19	1.93	25.95	5.29	0.35
FSH	7.45	3.97	9.62	5.36	0.38
AMH	0.70	0.33	0.52	0.36	0.29

Note. SD: standard deviation; BMI: body mass index; FSH: follicle stimulating hormone; AMH: anti-Mullerian hormone.

Table 2. The comparison of the Causes of Infertility Between the 2 Groups

Variables	Fixed	Flexible	P Value
Mal	25%	41%	0.44
Tubal	12%	17%	0.80
Endometriosis	12%	8%	0.76

Table 3. The Comparison of Oocyte Count and the Quality of Fetus Between the Fixed and Flexible Groups

Variables	Fixed Group		Flexible Group		P Value
	Mean	SD	Mean	SD	
Oocyte number	3.00	2.07	2.08	2.35	0.38
Embryo number	1.75	1.28	1.27	1.68	0.51
Good embryo	2.33	0.82	1.33	1.21	0.12
Fair embryo	1.98	0.96	1.00	1.41	0.19
Poor embryo	2.18	1.80	1.25	2.50	0.18
blastocyst	0.00	0.00	1.25	2.50	0.44
Endometrial thickness	7.71	1.70	5.71	4.19	0.26

higher compared to the fixed group and this finding was significantly different between the 2 groups ($P=0.05$). Although the mean of antagonist (cetrotide) doses in the fixed group was more than that of the flexible group, it was not significantly different ($P=0.50$).

Moreover, Table 4 demonstrates that the duration of gonadotropin consumption in IVF/ICSI between both groups is not significantly different ($P=0.3$). The comparison of gonadotropin consumption and length of treatment between the 2 groups is illustrated in Figure 2.

Based on the results represented in Table 5, the chemical and clinical pregnancy rate between the 2 groups are not significantly different ($P=0.23$). However, the rate of the cycle canceled in the flexible group is higher compared to the fixed group; however, it is not significantly different ($P=0.07$).

Discussion

The present study compared fixed and flexible antagonist protocols on reduced ovarian reserve patients. The age

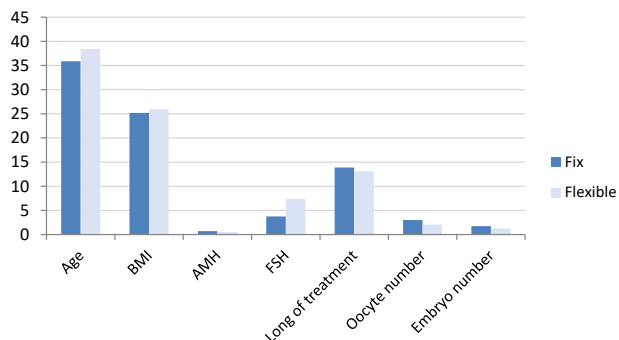


Figure 1. The Comparison of the Clinical Characteristics and Some IVF/ICSI Outcomes Between the Fixed and Flexible Groups.

Table 4. The Comparison of Gonadotropin and Antagonist (Cetrotide) Consumption Between the Fixed and Flexible Groups

Variables	Fixed		Flexible		P Value
	Mean	SD	Mean	SD	
Long of treatment	13.87	0.99	13.12	1.73	0.30
HMG	4.37	2.67	5.25	8.51	0.78
FSH recombinant	15.50	15.42	34.83	18.04	0.02
Urinary FSH	10.12	19.17	5.67	19.63	0.62
SUM1=HMG+FSH	30.00	15.16	45.75	17.31	0.05
recom+ urinary FSH					
Cetrotide	4.22	1.09	3.44	3.17	0.50

Note. SD: Standard deviation; HMG: Human menopausal gonadotropin; FSH: Follicle stimulating hormone.

and BMI of the patients in both groups represented no significant difference. Additionally, the FSH and AMH of the patients demonstrated no significant difference. In addition, the counts of oocytes ($P=0.38$), embryo ($P=0.51$), and embryo with good ($P=0.12$), fair ($P=0.18$), and poor ($P=0.19$) grades, along with endometrial thickness were not significantly different between both groups. However, the mean consumption of gonadotropin dose in the flexible group was more than that of the fixed group ($P=0.05$), indicating that there was a significant difference between the 2 groups in this respect.

Conversely, the length of the gonadotropin consumption was not significantly different in the fixed and flexible groups. Although the mean antagonist (cetrotide) doses in the fixed group were more than those of the flexible group, they were not significantly different ($P=0.50$). The chemical and clinical pregnancy rate indicated no significant difference between the fixed and flexible groups. However, the rate of the cycle cancelled in the flexible group was higher compared to the fixed group, however, it was not significantly different ($P=0.07$).

Tannus et al considered the effect of delayed starting of gonadotropin-releasing hormone antagonist in a flexible protocol on the IVF outcome. In this study, only the patients ≤ 40 years were included. The administration of the antagonist was started when the leading follicle size

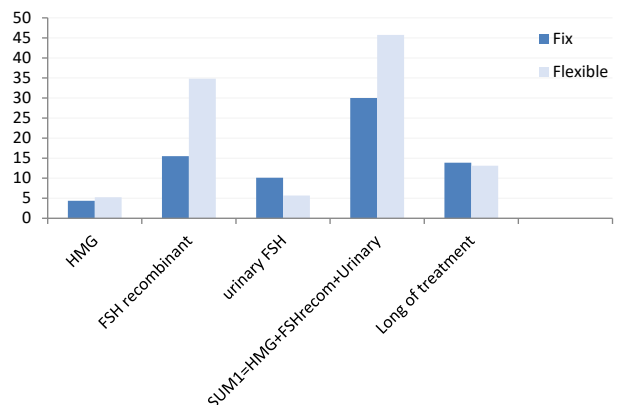


Figure 2. The Comparison of Gonadotropin Consumption and the Length of Treatment Between the Fixed and Flexible Groups

Table 5. The Comparison of Pregnancy Outcome and Cycle Canceled Between the Fixed and Flexible Groups

Variables	Fix Group	Flexible Group	P Value
Clinical pregnancy	10%	8%	0.23
Chemical pregnancy	12%	10%	0.23
Cycle cancel	22%	33%	0.07

was ≥ 13 mm or the serum E_2 level achieved ≥ 300 pg/mL (10). The patients were divided into 2 groups based on the day of starting the antagonist administration. As regards the time of starting GnRH antagonist administration, the results represented no difference in implantation, as well as clinical and ongoing pregnancy rate (10). These findings are in line with the results of the present study; however, the current study only investigated the reduced ovarian reserve patients while patients < 41 years were included. Further, in the above-mentioned study, a higher dose of gonadotropin was administered in the group receiving the antagonist, initiated later than sixth days after starting gonadotropin, and the time of gonadotropin administration was longer.

In the present research, the dose of gonadotropin was higher in the flexible group while the time of gonadotropin administration was not different between both groups although there was a difference in the definition of the flexible regimen and the method of separating both groups.

Estratios compared fixed and flexible antagonist protocols in IVF/ICSI cycles. In this study, 188 was included patients with age < 39 years while those patients who responded poorly were excluded from the study. The findings revealed that flexible antagonist administration failed to reduce the incidence of LH surge compared to the fixed antagonist protocol and that in the fixed group, antagonist consumption was lower. Then, cetrorelix was started on sixth days of rFSH stimulation in the fixed group whereas in the flexible group, cetrorelix was started when at least one of the following criteria were found: LH > 10 IU/L, presence of a follicle with mean diameter > 12 mm, and serum E_2 level > 150 pg/mL (14). Clinical and ongoing pregnancy rates were not significantly different between the 2 groups. This finding is in conformity with that of the present study; however, the included flexible criteria were different. Based on the results of the current study, the dose of gonadotropin consumption in the fixed group was lower. However, in this study, only reduced ovarian reserve patients were included while Estratios M (14) excluded this group of patients from the study.

Conclusions

The findings of the present study demonstrated that the flexible regimen in reduced ovarian reserve patients was not superior compared to the fixed regimen in terms of endometrial thickness and clinical pregnancy rate; however, the dose of gonadotropin administration in

the flexible group was higher. Furthermore, the mean antagonist (cetrotide) doses in the fixed group was higher than that of the flexible group; however, these findings were not significantly different. In general, the fixed protocol is recommended in reduced ovarian reserve patients since it is cost effective compared to the flexible protocol and simple to use because it requires fewer transvaginal sonography for determining the size of the follicle.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study, as a historical cohort, was confirmed by the Ethical Committee of Tehran University of Medical Sciences.

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