

## ART Outcomes in GnRH Antagonist Protocol (Flexible) and Long GnRH Agonist Protocol during Early Follicular Phase in Patients with Polycystic Ovary Syndrome: A Randomized Clinical Trial

Sara Mokhtar, Mohammad Reza Sadeghi, Mohammad Mehdi Akhondi, Simin Zafardoust, Bita Badenush, Farnaz Fatemi, Fattane Nazari, Koorosh Kamali, Afsaneh Mohammadzade \*

*1- Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran*

### Abstract

**Background:** Since increased LH in the early follicular phase in PCOS patients especially in GnRH antagonist protocol could be associated with reduced oocyte quality and pregnancy and impaired implantation. The current study was conducted to determine ART outcomes in GnRH antagonist protocol (flexible) and long GnRH agonist protocol and compare them with adding GnRH antagonist in GnRH antagonist (flexible) protocol during early follicular phase in patients with polycystic ovary syndrome undergoing ICSI.

**Methods:** In this randomized clinical trial, 150 patients with polycystic ovary syndrome undergoing ICSI were enrolled from 2012 to 2014 and randomly assigned to receive either GnRH antagonist protocol during early and late follicular phase or GnRH antagonist protocol (flexible) or long GnRH agonist protocol. The clinical and laboratory pregnancy in three groups was determined and compared. In this context, the chi-square and Fisher's exact test and ANOVA were used for data analysis. Statistical significance was defined as  $p < 0.05$ .

**Results:** There was no statistically significant difference with respect to chemical pregnancy and clinical pregnancy between the three groups. Also, other indices such as number and quality of oocytes and embryos were alike.

**Conclusion:** Totally, according to our results, GnRH antagonist protocol during early and late follicular phase and GnRH antagonist protocol (flexible) and long GnRH agonist protocol in patients with polycystic ovary syndrome undergoing ICSI are similarly effective and use of each one based on patients' condition and physicians' opinion could be considered.

**Keywords:** ART, GnRH agonist, GnRH antagonist, Infertility, PCOS.

**To cite this article:** Mokhtar S, Sadeghi MR, Akhondi MM, Zafardoust S, Badenush B, Fatemi F, et al. ART Outcomes in GnRH Antagonist Protocol (Flexible) and Long GnRH Agonist Protocol during Early Follicular Phase in Patients with Polycystic Ovary Syndrome: A Randomized Clinical Trial. *J Reprod Infertil.* 2015;16(3):148-154.

\* Corresponding Author:  
Afsaneh  
Mohammadzadeh,  
Reproductive  
Biotechnology Research  
Center, Avicenna  
Research Institute,  
ACECR, Tehran, Iran, P.O  
box: 19615-1177, Postal  
code: 1936773493  
E-mail:  
af85saf@yahoo.com

Received: Sept. 21, 2014  
Accepted: Jan. 6, 2015

### Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age (1). PCOS is associated with hyper androgenism, oligo/amenorrhea and infertility (2). PCOS patients, who are infertile encountered with many problems in a controlled ovarian hyperstimulation (COH). It seems hyper-secretion of LH and hyper-androgenemia are associated with reduced oocyte quality and impaired implant

tation and clinical pregnancy and increased abortion in these patients (3). In order to suppress LH before and during COH, GnRH agonists are important for PCOS patients in IVF protocols (4). GnRH agonists have disadvantages including the need for administration of the agents to induce pituitary desensitization for more than 2 weeks and multiple follicular growth and developing OHSS risks especially in patients with PCOS (5-

7). GnRH antagonists have several advantages over GnRH agonists. They decrease LH and FSH levels rapidly, without flare-up effect and according to previous studies, they reduce the incidence of OHSS and amount of used gonadotropins and the duration of stimulation as compared with GnRH agonist protocols (8). Studies on clinical pregnancy rate (CPR) and live birth rate (LB), presented different results; in a recent meta analysis, CPR was similar in GnRH agonists and GnRH antagonists groups (9). Meanwhile, some studies support earlier initiation of GnRH antagonists based on the observations that the exposure to LH and estradiol in the early follicular phase of a GnRH antagonist cycle was negatively associated with the probability of pregnancy (10, 11). On the other hand, there are limited studies that compare GnRH antagonist and GnRH agonist protocol on patients with PCOS.

The current study was conducted to determine and compare the GnRH antagonist protocol during early and late follicular phase with GnRH antagonist (flexible) and long GnRH agonist protocols in patients with PCOS undergoing ICSI.

This study was performed to answer the question that adding GnRH antagonist in the early follicular phase could improve pregnancy rate in comparison with other standard protocols since it suppresses the increased level of LH in PCOS patients, especially in GnRH antagonist protocol which can reduce oocytes quality and pregnancy.

### Methods

In this randomized clinical trial, 150 patients with PCOS undergoing ICSI were enrolled at Avicenna infertility clinic affiliated to Avicenna Research Institute (ARI) from 2012 to 2014. The project was approved by the ethical committee of Avicenna Research Institute and all of the participants, completed written consents form. PCOS diagnosis was according to Rotterdam criteria (12). The patients aged 20-38 years with normal prolactin and thyroid function tests and normal cardiac, hepatic and renal functions who had normal spontaneous onset of puberty and normal sexual development. The subjects with FSH > 12 or  $\geq 2$  ART failure or  $\geq 2$  first trimester abortion were excluded. None of the selected cases had ovarian cyst or anatomical abnormality in uterus and cervix or hydrosalpinx. ICSI was considered for the patients after six cycles of induction ovulation and three IUI cycles which failed to achieve pregnancy. Each participant was randomly allo-

cated to either GnRH antagonist protocol during early and late follicular phase group or GnRH antagonist protocol (flexible) group or long GnRH agonist protocol group. Randomization was performed according to computer generated random letters. For preventing of severe OHSS, 12 women did not have embryo transfer due to high risk of OHSS. Three cycles from GnRH antagonist during early and late follicular phase group, three cycles from GnRH antagonist (flexible) group and six cycles from GnRH agonist group were cancelled after oocyte retrieval.

All patients received oral contraceptive (ovocept LD, Abureihan, Iran) pretreatment for 21 days in the cycle preceding ovarian stimulation. On day 3 of the cycle after discontinuation of oral contraceptive (OC), ovarian stimulation was initiated when pituitary desensitization was achieved (absence follicle diameter > 10 mm and estradiol level < 40 pg/ml), using 150 to 225 IU of recombinant human FSH (Gonal-F; Merck Serono SA, Switzerland). rhFSH was administered in a step up fashion and the dose of rhFSH was adjusted every 3 to 4 days according to ovarian response. In GnRH agonist (long protocol) group, 0.5 mg of GnRH agonist (Buserelin acetate, superfact, Sanofi-Aventis, Germany) was commenced from day 21 prior to menstrual cycle and was reduced to 0.25 mg with gonadotropin stimulation and continued until HCG (choriomon, IBSA, Switzerland) administration. In GnRH antagonist (flexible) group, 0.25 mg of GnRH antagonist (cetorelix acetate, Cetrotide; Merck Serono SA, Switzerland) was started when at least 2 follicles reached 13-14 mm and continued until HCG administration. In GnRH antagonist group with early and late follicular phase, 0.25 mg of cetorelix was administered on days 1, 2 of gonadotropin stimulation and when at least 2 follicles reached 13-14 mm, it was started again and continued until HCG administration. In all groups, 10000 IU HCG was administered as an intramuscular injection for final oocyte maturation, when at least 2 follicles with diameter of at least 17 mm were observed. Transvaginal ultrasound (Honda 2000 HS, Japan) guided oocyte collection was performed 36 hr after HCG injection. Following ICSI and embryo culture, cleavage embryos were transferred into the uterus on the 3rd day after oocyte retrieval. Luteal phase support was obtained with progesterone (Progesterone in Oil 50 mg/mL, Iran Hormone, Iran) as an intramuscular injection from the day after ovum pick up and 100 mg after embryo

transfer. Chemical pregnancy was detected by serum hCG determination 14 days after embryo transfer (ET) and was confirmed with second HCG determination on 16 days after ET and transvaginal ultrasound scan was scheduled 2 weeks later to detect the gestational sac of pregnancy.

Primary outcome measure was clinical pregnancy, defined as the presence of a gestational sac by transvaginal ultrasonography. Secondary outcome measure included total amount and days of rhFSH administered, the numbers of retrieved, mature, and fertilized oocytes, good quality embryos, embryo implantation rate and the incidence of severe OHSS according to OHSS classification of Golan (13).

The collected data was analyzed using SPSS version 18 frequency for qualitative variables and mean and standard deviation were calculated for quantitative variables. In this context, the chi-square and Fisher's exact test, ANOVA and Bonferroni Post HOC test were considered. For variables which were not normally distributed, nonparametric test (kruskal-wallis) was used. Statistical significance was defined as  $p < 0.05$ . Clinical trial registration number was IRCT2012120311653N1 (www.irct.ir).

**Results**

All demographic variables included age, BMI, duration of infertility, type of infertility, FSH, and LH were compared between groups. The distribution of these variables in the three groups was similar (Table 1). Total dose of rFSH required was lower in GnRH antagonist during early and late follicular phase in comparison with other groups but statistically was not significant. There were no significant differences between the three groups on days of rhFSH administration. Number

of retrieved oocytes, mature oocytes, fertilized oocytes in GnRH antagonist during early and late follicular phase was more than the other groups but there were no significant differences between the three groups. Number of embryo transfer was similar in three groups (Fisher's exact test  $p$ -value=0.196). There were no significant differences between the three groups in embryos with good quality, cryopreserved embryos, follicles  $> 12$  mm, and endometrial thickness on the day of HCG injection (Table 2). There was significant difference in level of E2 on the day of HCG injection ( $p$ -value=0.015). In GnRH agonist long protocol group, level of E2 on the day of HCG injection was more than GnRH antagonist flexible protocol group (ANOVA-Post Hoc Test, Bonferroni,  $p = 0.012$ ). Cancellation rate for prevention of severe OHSS in GnRH agonist group was more than the other groups, but it was not statistically significant and severe OHSS was not seen in three groups. All groups were similar in multiple pregnancy. Chemical and clinical pregnancy rate and implantation rate in GnRH antagonist during early and late follicular phase were more than the other groups, although there was no significant difference between the three groups.

**Discussion**

The administration of GnRH-antagonist from the first day of stimulation did not appear to improve pregnancy rates in one IVF study (14). Earlier initiation of GnRH antagonist comes from potential disadvantages of using GnRH antagonist protocol in women with PCOS. Elevated LH levels will remain high until antagonist treatment begins. Consequently, LH levels may rise prematurely, particularly if antagonist treatment is withheld until the lead follicle diameter reaches 14 mm or

**Table 1.** Demographic characteristics of patients with PCOS undergoing ICSI were enrolled at Avicenna infertility clinic, 2012-2014

Demographic variables	GnRH agonist (long) (n=50)	GnRH antagonist (flexible) (n=50)	GnRH antagonist (early and late follicular phase) (n=50)	P-value
Age (year)	27.64±3.65	28.84±4.44	28.96±4.31	0.217 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	25.40±4.08	26.71±3.82	25.99±3.82	0.244 <sup>a</sup>
Duration of infertility (year)	4.87±3.03	4.45±3.82	3.96±3.11	0.398 <sup>a</sup>
<b>Type of infertility</b>				
Primary	96%	96%	92%	0.701 <sup>b</sup>
Secondary	4%	6%	8%	
FSH (IU/L)	6.70±2.22	6.44±1.62	5.82±1.89	0.066 <sup>a</sup>
LH (IU/L)	7.20±4.29	6.59±4.23	7.29±4.77	0.692 <sup>a</sup>

a: One way ANOVA, b: Chi-square test  
Values are presented as mean±SD or number (%)

**Table 2.** Comparison of COH results and ICSI outcome in patients with PCOS undergoing ICSI were enrolled at Avicenna infertility clinic, 2012-2014

Variables	GnRH agonist (long)	GnRH antagonist (flexible)	GnRH antagonist(early and late follicular phase)	P-value
Total dose of rhFSH (IU)	2206.5±684.55	5098.5±17317.3	2038.5±571.52	0.232 <sup>c</sup>
Days of rhFSH	10.64± 2.40	10.16± 4.48	10.18± 1.13	0.667 <sup>c</sup>
<b>On the day of hCG injection</b>				
Follicles>12 mm	23.30± 35.56	16.64± 5.65	18.34± 6.0	0.264 <sup>c</sup>
Estradiol (pg/ml)	4424.43±3117.72	2884.18± 2041.8	3787.33± 2635.15	0.015 <sup>c</sup>
Endometrial thickness (mm)	11.20± 14.28	9.12± 3.35	8.98± 1.70	0.348 <sup>c</sup>
Retrieved oocytes (No)	16.28± 9.71	14.96± 6.63	16.44± 7.67	0.607 <sup>c</sup>
Mature oocytes <sup>a</sup> (No)	13.92± 8.2	12.92± 6.14	14.78± 7.23	0.440 <sup>c</sup>
Fertilized oocytes (No)	10.7± 6.31	8.58± 5.518	12.78± 19.79	0.242 <sup>c</sup>
Grade A, B embryos <sup>b</sup> (M)	10.52± 6.15	7.88± 5.31	9.92± 6.2	0.067 <sup>c</sup>
Embryos cryopreserved (No)	6.4(1.5-10)	4.9(0-7)	6.06(0-8)	0.141 <sup>d</sup>
Chemical PR (%)	34.1%(15/44)	34%(16/47)	38.3%(18/47)	0.886 <sup>e</sup>
Implantation rate	0.11(0-0.33)	0.09(0-0.33)	0.12(0-0.33)	0.801 <sup>d</sup>
Clinical PR (%)	34.1%(15/44)	29.8%(14/47)	36.2%(17/47)	0.800 <sup>e</sup>
Multiple PR (%)	2.3%(1/44)	6.4%(3/47)	4.3%(2/47)	0.871 <sup>f</sup>
Cancellation rate for preventing severe OHSS (%)	12%(6/50)	6%(3/50)	6%(3/50)	0.596 <sup>e</sup>

a: Oocytes in metaphase II, b: Blastomers with equal sizes and surface fragmentation≤10%, c: One way ANOVA, d: Kruskal-wallis, e: Chi-square, f: Fisher's exact test  
Values are presented as mean±SD or mean (interquartile range 25-75) or % (number)

more. Moreover, evidence indicates that increased LH exposure during early follicular development may be detrimental and predispose to lower pregnancy rates (15). In this study, an attempt was made to compare GnRH antagonist protocol during early and late follicular phase and GnRH antagonist protocol (flexible) and long GnRH agonist protocol in patients with polycystic ovary syndrome undergoing ICSI and cetorelix 0.25 mg/day was administered in early follicular phase. This study has shown no statistical difference with respect to chemical pregnancy and clinical pregnancy between three groups.

Currently, administration of GnRH antagonist in early and late follicular phase has been performed (16). Kim et al. concluded GnRH antagonist in early and late follicular phase is at least as effective as GnRH agonist long protocol, in controlled ovarian stimulation for PCOS patients undergoing IVF, independent of body mass index. In our study, total dose of gonadotropin administration in GnRH antagonist protocol during early and late follicular phase was lower than antagonist GnRH (flexible) and GnRH agonist protocol and embryo transfer cancellation in GnRH agonist group was higher than the antagonist groups but statistically not significant and duration of stimulation was similar in three groups. In Kim et al.'s study, total

doses and days of gonadotropin administration were significantly lower in the antagonist group than in the agonist group and also the incidence of OHSS was lower. They used dose of 0.125 mg/day cetorelix in early follicular phase has been compared only with GnRH agonist protocol. The significant difference between the groups in Kim et al.'s study could be due to different sample size of two studies.

In our study, duration of stimulation in GnRH antagonist (flexible) was lower than the other groups and statistically was not significant. Kdous et al. in 2009 compared standard long GnRH agonist protocol and GnRH antagonist regimens in PCOS patients undergoing ICSI and showed GnRH antagonist protocol was a short and simple protocol. However, GnRH antagonist protocol provides a lower live birth rate with increased risk of early pregnancy loss compared to GnRH agonist long protocol (17). Our study differed with Kdous et al.'s in the third protocol in terms of GnRH antagonist during early and late follicular phase. In our study similar to Minaretzis et al., Kdous et al., and Xiao et al. studies, estradiol level on the day of HCG administration was significantly higher in GnRH agonist group than the other groups (17-19). Minaretzis et al. in 1995 demonstrated that GnRH antagonist administration

resulted in lower serum luteinizing hormone and estradiol levels and more mature oocytes and good quality embryos compared with GnRH agonist administration. This finding may be related to gonadotropin-releasing hormone analogs which may have direct action on ovarian function with differential effects on granulosa-lutein cell aromatase activity. Although in our study there was no significant difference between three groups in number of mature oocytes and good quality embryos, but the effectiveness of each method was determined. In our study, unlike to Kdous et al.'s, Lainas et al.'s, and Kim et al.'s, studies, total amount of gonadotropin administration in GnRH antagonist (flexible) group was higher than GnRH agonist group (5, 16, 17), but in GnRH antagonist during early and late follicular phase was lower than the other groups. Similar to Minaretzis et al.'s and Ashrafi et al.'s studies, there was statistically no significant difference between groups (18, 20). In our study, endometrial thickness on the day of HCG administration was higher in GnRH agonist group than the other groups and it could be due to higher estradiol level in this group. Also like our finding, Xiao et al. showed there was no statistically significant difference between GnRH antagonist and GnRH agonist groups in endometrial thickness on the day of HCG administration (19). However, the optimal time for GnRH antagonist initiation is still debatable. Lainas et al. in 2007 announced that initiation of GnRH antagonist on day one of gonadotropin stimulation is associated with an earlier follicular growth and a different hormonal environment during the follicular phase when compared with the long agonist protocol (11). In our study, clinical pregnancy and implantation rate was higher in GnRH antagonist during early and late follicular phase than the others, although this difference was not statistically significant. Abuzeid et al. in 2012 compared initiation of GnRH antagonist on day one of gonadotropin stimulation with day five of gonadotropin stimulation in PCOS patients undergoing ICSI. They suggest that early initiation of GnRH antagonist on day 1 of ovarian stimulation may improve implantation rates, especially after blastocyst transfer, although it was not statistically significant (21). In our study, implantation rate and clinical pregnancy rate in GnRH antagonist during early and late follicular phase were higher than other groups although it was not statistically significant. Lainas et al. in 2010 concluded ongoing pregnancy rates

(50.9% versus 47.3%) in the agonist and antagonist protocols in PCOS patients and our results confirm the finding (5). Kurzawa et al. in 2008 similar to our study concluded GnRH antagonist and agonist protocols in non-obese PCOS patients yielded similar embryological and clinical outcomes (6). Xiao et al. in the meta-analysis which included twenty-three RCTs evaluated the effectiveness of GnRH antagonist and GnRH agonist in normal ovarian responders undergoing IVF, showed that the clinical pregnancy rate was lower in the GnRH antagonist group than in the GnRH agonist group, and this difference was statistically significant. They concluded ongoing pregnancy and live birth rates were similar in the GnRH antagonist compared with the standard long GnRH agonist protocols (19). In our study, the number of mature oocytes was higher in GnRH antagonist during early and late follicular phase than the other groups, although it was not statistically significant. This finding is similar to Kdous et al.'s study but Minaretzis et al. and Ashrafi et al. showed the number of mature oocytes was significantly higher in GnRH antagonist group (17, 18, 20). In this study, embryo transfer cancellation rate for prevention of severe OHSS in GnRH agonist group was higher than the other groups. However it was not statistically significant in Ashrafi et al.'s study. Number of patients at risk of developing OHSS was higher in GnRH antagonist group (20). A meta-analysis of nine RCTs examining PCOS patients undergoing IVF/ICSI including 588 women who underwent long agonist protocols and 554 women who underwent GnRH antagonist protocols was performed by Lin et al. in 2014 (22). It was concluded that GnRH antagonist protocol is better than agonist long protocol to reduce the rate of severe OHSS; in the same vein, in our study, clinical pregnancy rate was similar in two groups. Choi et al. in 2012 compared ART outcomes through a prospective study which included 61 infertile women with PCOS treated with IVM, conventional IVF, GnRH agonist, and GnRH antagonist cycles, and concluded that clinical pregnancy rate per embryo transfer showed no differences among the three groups and OHSS was lower in GnRH antagonist group than GnRH agonist group. Moreover, there was no incidence of ovarian hyper stimulation syndrome in PCOS patients treated with IVM (23). In our study, embryo transfer cancellation rate for prevention of severe OHSS was similar in three groups. Recently, Singh et al. in 2014 through retrospective analysis

of collected data during 4 years compared conventional long agonist protocol with fixed antagonist protocol in PCOS patients undergoing IVF cycle. There was no significant difference in pregnancy rate or incidence of OHSS between two groups which confirms our findings. Cycle cancellation due to arrest of follicular growth was significantly higher in the antagonist group in that study (9).

### Conclusion

According to previous studies, high levels of LH during early follicular phase in PCOS patients especially in GnRH antagonist protocol lead to decreased egg quality, lower implantation, and increased miscarriage rates, so it seems that adding GnRH antagonist in early follicular phase in GnRH antagonist (flexible protocol) could increase pregnancy rate. This study showed GnRH antagonist protocol during early and late follicular phase and GnRH antagonist protocol (flexible) and long GnRH agonist protocol in patients with polycystic ovary syndrome undergoing ICSI are similarly effective and the use of each one based on the patients' condition and physicians' opinion could be considered. Further studies with large sample size are needed to confirm our findings, and live birth rates should be included in large-scale studies. Administration of GnRH antagonist with longer duration in future evaluations is recommended measurement of LH level before and after GnRH antagonist in comparison with GnRH antagonist (flexible) protocol during early follicular phase is recommended as well. Also, adding GnRH antagonist in early follicular phase in GnRH antagonist (flexible) protocol in non-PCOS patients is another suggestion.

### Acknowledgement

We are grateful to all of the colleagues at the Avicenna Infertility Clinic (AIC) for their inspiration and contribution. We would like to thank the patients for their kind help in this research.

### Conflict of Interest

Authors declare no conflict of interest.

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