DOI: 10.7860/JCDR/2018/37230.12193

Original Article

Obstetrics and Gynaecology Section

# Gonadotropin Releasing Hormone Agonists versus Antagonists in Women with Polycystic Ovary Disease Undergoing Intracytoplasmic Sperm Injection

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## ABSTRACT

**Introduction:** Polycystic ovary syndrome (PCOS) is one of the most important endocrine disorders that cause infertility in young women. Recent meta-analyses have reported that treatment success with GnRH antagonists and GnRH agonists was similar. But no studies are available to determine which protocol is the best in the PCOS patient group.

**Aim:** To compare the Intracytoplasmic Sperm Injection (ICSI) outcome of Gonadotropin Releasing Hormone Agonists (GnRHa) to antagonists (GnRHant) in women with polycystic ovary disease.

**Materials and Methods:** In this retrospective cohort study; out of 3000 patients, 144 women were enrolled who met the inclusion criteria for polycystic ovary disease, according to the Rotterdam criteria at the In-Vitro Fertilization Unit. Cases with GnRHa used for controlled ovarian hyperstimulation (n=95) were compared to cases with GnRHant use (n=49). All analyses were performed using the Statistical Package for Social Sciences software, version 15.0 for Windows. The variables were compared to Pearson Chi-Square and Fisher's-Exact Tests in 2×2 eyes. Normally distributed (parametric) variables were evaluated between groups, whereas Independent groups were compared using t-test.

**Results:** The mean age, infertility period, FSH level, body mass index and the mean number of embryos transferred were similar in both groups (p>0.05). The average dose of FSH was significantly lower in Group 2 (1765±624 IU) compared to Group 1 (2535±838 IU, p<0.001). The rate of cycle cancellation due to ovarian hyperstimulation risk was 6.4% in group 2, which was similar to the 15.2% in group 1 (p=0.13). The cleavage rate (Group 2; 49.1±22.2%, Group 1; 64.2±24.4%, p=0.001), fertilization rate (Group 2; 48.7±21.5%, Group 1; 63.2±21.5%, p=0.001) and the mean number of good quality embryos transferred (Group 2; 2.5±0.2, Group 1; 2.9±0.8, p=0.02) was significantly lower in group 2 compared to group 1. The clinical pregnancy rate was 30% in group 2 compared to 34.1% in group 1 (p=0.6). The live birth rate was 22.5% in group 2 and 25% in group 1 (p=0.7).

**Conclusion:** Similar clinical pregnancy outcomes can be achieved in GnRH antagonist cycles using lower gonadotropin doses compared to GnRH agonist cycles.


**Keywords:** GnRH antagonist, GnRH agonists, Polycystic ovary syndrome, Pregnancy outcome

## INTRODUCTION

PCOS is one of the most important endocrine disorders that cause infertility in young women [1]. Affecting 5-10% of women in their reproductive age, the syndrome has no definitive treatment [2]. The Ovarian Hyperstimulation Syndrome (OHSS) represents one of the most important complications of infertility treatments, and many different strategies have been described to avoid it [3]. It is now known that GnRH antagonists are effective in preventing OHSS in ovulation induction therapies [4,5].

It can sometimes be difficult to have adequate response to infertility treatment in PCOS patients, and thus different drug combinations may be needed. Low or no response can be seen, which may require substantial increases in the dose of drugs. Long treatment duration and increased cost due to excessive drug use can be notable, particularly in this group of patients [6-9].

Recent meta-analyses have reported that treatment success with GnRH antagonists (GnRHant) and GnRH agonists (GnRHa) was similar [10-12]. And, it has been observed that antagonist medications reduce the dose of gonadotropin used in patients with PCOS [13-15].

In the most recent meta-analysis, Lin H et al., studied nine clinical trials that were conducted before 2014. They indicated that no studies are available to determine which protocol is the best in the PCOS patient group. They argued that there has been conflicting evidence on Clinical Pregnancy Rate (CPR), Ongoing Pregnancy Rate (OPR) and Live Birth Rate (LBR), and that there is lack of data in some cases, as well as statistical heterogeneity, therefore further research is needed [10].

The aim of the study was to assess which of these treatment protocols are more effective, and which protocol provides better live birth rates.

## MATERIALS AND METHODS

This was a retrospective research study on patients who received treatment before 2007. No randomisation was performed between the groups. Differences between treatments were assessed. Step-up protocols were included in the study. Step down protocols were not examined.

### Selection of Cases

Out of 3000 patients, 144 women were enrolled who met the exclusion and inclusion criteria for polycystic ovary disease according to the Rotterdam criteria at the In Vitro Fertilization Unit of Maternity Hospital, Istanbul, Turkey. The Rotterdam criteria require the presence of two of the following: oligo/anovulation, hyperandrogenism or polycystic ovaries on ultrasound. All patients who had no PCOS history and received treatment other than the accepted protocols were excluded.

The total sample size was calculated as 87 when the power of the study (power=1-ß) was taken as 0.80 and the type 1 error (alpha) was taken as 0.05, assuming a 15% difference in the fertility

change among the drug groups. In view of the possible wastes, 144 participants were deemed sufficient.

The study was approved by the local Ethics Committee, and an informed consent was obtained from all patients prior to the study. Each couple underwent a standard infertility evaluation, including basal day three hormonal status, hysterosalpingography or hysteroscopy in women and semen analysis in men. The patients had intrauterine insemination three times with gonadotropins, but failed to obtain pregnancy. The demographic characteristics of our female patients are provided in [Table/Fig-1]. The couples with endometriosis and severe male factor infertility were excluded.

| Variable | Group 1 (agonist) (n=95) | Group 2 (antagonist) (n=49) | p-value |
|---|---|---|---|
| Age (year) | 29.1±1.1 | 28.2±4.7 | 0.1[a] |
| Body mass index (kg/m$^2$) | 25.2±4 | 25.8±3.6 | 0.6[a] |
| Duration of infertility (month) | 92±4±60 | 83.2±46 | 0.4[a] |
| Secondary infertility number | 19 (20) | 4 (8.2) | 0.06[b] |
| Tubal factor infertility number | 16 (16.9) | 7 (14.2) | 0.2[b] |
| Basal FSH (mIU/mL) | 5.5±1.6 | 5.6±1.5 | 0.7[a] |
| Basal LH (mIU/mL) | 5±2.4 | 5.8±2.9 | 0.1[a] |
| Basal Estradiol (pg/mL) | 40.9±18.5 | 47.8±21.3 | 0.07[a] |
| Spermiogram | | | |
| Normal | 47 (50) | 16 (32.7) | 0.2[b] |
| Oligospermia | 15 (16) | 8 (16.3) | |
| Azoospermia | 14 (14.9) | 15 (30.6) | |
| Oligoastheroteratospermia | 19 (19.2) | 10 (20.4) | |

**[Table/Fig-1]:** Demographic variables and laboratory results of the study population. Data are given as the mean±standard deviation, number and percentage
[a]Student's t-test, [b]Chi-square test

## Hyperstimulation Protocols

**Agonist protocol:** The cycle began with follitropin alpha or follitropin beta (150-300 units) on the twenty-first day after baseline ultrasonography. If bleeding occured in the form of spotting within ten days, or if the endometrial thickness was less than 5 mm or if the estradiol level was less than 100 pg/mL in the last ten days, the menstruation was accepted. Gonadotropin treatment was started on the 2$^{nd}$ or 3$^{rd}$ day of menstruation. The dosage ranged between 150 and 300 units based on patient's age, body mass index and previous experience of treatment. If there was insufficient growth in the follicle size, a 50% dose increase was made. The daily dose did not exceed 450 units and the treatment duration was not exceeded for four weeks.

Follitropin alpha (Gonal F®, Merck Serono SA, Switzerland.) or follitropin beta (Puregon®, Organon, Netherlands) injections were given as once-daily subcutaneous self-administered injections via a pen device. To prevent premature LH surge, a daily injection of GnRH agonist leuprolide acetate (Lucrin®, Abbott, France) was administered subcutaneously to the first group of patients (Group agonist; n=95), starting in the mid-luteal phase of the cycle.

**GnRH antagonist protocol:** Basal hormone profile and ultrasound evaluations were performed on the second day of menstruation. Gonadotropin treatment was not initiated in patients with a cystic formation larger than 20 mm. GnRH antagonist therapies were initiated on a daily basis when follicles were 14 mm and above (flexible protocol). A GnRH antagonist, cetrorelix (Cetrotide®, Merck Serono SA, Switzerland) or ganirelix (Orgalutran®, Organon, Netherlands) was administered. Treatment with GnRH antagonists continued until the day of HCG (Pregnyl®, Organon, Netherlands) administration.

In both protocols (agonist protocol and GnRH antagonist protocol), an ultrasound examination was performed six days after the treatment, and the estradiol value was checked. If the estradiol level was above 100 pg/mL or if the follicle size was over 10 mm, the dose was adequate. The treatment continued until at least 3 follicles reached 17 mm or more. Oocyte Pick Up (OPU) was performed 35-36 hours after administration of human chorionic gonadotropin. Sixteen hours after intracytoplasmic sperm injection, embryo formation was examined. After 2-3 days of oocyte pick-up, embryo transfer was performed in 4-8 blastomere phase under ultrasound guidance. Embryos with a fragmentation rate of 10 percent or less were accepted as good quality embryos. Twelve days after transfer, a pregnancy test (beta-HCG) was performed. Ultrasonography was performed for foetal cardiac activity two weeks after the positive pregnancy test. Only those with a positive pregnancy test were included in the calculation of Preclinical Pregnancy (PR) (biochemical pregnancy) rates. The OPR were calculated in patients who had positive foetal cardiac activity by the ultrasound findings, and completed the 9$^{th}$ gestational week. Live births were also accepted in LBR.

Any patient in the younger age group, lower body weight, older OHSS history, more follicular development, more than 20 oocyte accumulation, estradiol levels higher than 4000 pg/mL was considered at risk of developing OHSS.

When the patient was at risk for ovarian hyperstimulation syndrome as determined by the investigator, no HCG was administered, and coasting procedure or even cancellation of the stimulated cycle was considered.

After the embryo transfer, luteal phase support was performed via vaginal route with micronized progesterone 90 mg (Crinone gel® 8%, Merck Serono SA, Switzerland).

## Clinical Outcome

Parameters included cycle cancellations, total dose of gonadotropin, total number and M2 oocytes retrieved fertilization rate, number and quality of embryos, biochemical pregnancy rate, clinical pregnancy rate and live birth rate.

# STATISTICAL ANALYSIS

All analyses were performed using the Statistical Package for Social Sciences software, version 15.0 for Windows (SPSS, 15.0; Chicago, IL). Normal distribution of variables was examined by histogram graphs and Kolmogorov-Smirnov test. Mean, standard deviation, median and minimum-maximum values were used when descriptive analyses were presented. The variables were compared to Pearson Chi-Square and Fisher's-Exact Tests in 2×2 eyes. Normally distributed (parametric) variables were evaluated between groups, whereas independent groups were evaluated using t-test. Statistically significant results were obtained when the p-value was below 0.05.

# RESULTS

A total of 144 women were assessed for eligibility. Leuprolide acetate daily injection was subcutaneously administered to the first group (Group 1) of patients (Group agonist; n=95), starting in the mid-luteal phase of the cycle, and gonadotropin antagonist was started on Day two of menstrual cycle with recombinant FSH in the second group (Group 2) patients (Group antagonist; n=49).

The mean age, infertility period, FSH level, body mass index and the mean number of embryos transferred were similar in both groups (p>0.05) [Table/Fig-1].

The average dose of FSH was significantly lower in Group 2 (1765±624 IU) compared to Group 1 (2535±838 IU, p<0.001). The rate of cycle cancellation due to ovarian hyperstimulation risk was 6.4% in group 2, which was similar to the 15.2% in group 1 (p=0.13). The cleavage rate (Group 2; 49.1±22.2%, Group 1; 64.2±24.4%, p=0.001), fertilization rate (Group 2; 48.7±21.5%, Group 1; 63.2±21.5%, p=0.001) and the mean number of good quality embryos transferred (Group 2; 2.5±0.2, Group 1; 2.9±0.8, p=0.02) was significantly lower in group 2 compared to group 1.

| Outcome | Group 1 (agonist) (n=95) | Group 2 (antagonist) (n=49) | p-value |
|---|---|---|---|
| Duration of gonadotropin use (day) | 9.1±1.3 | 8.3±1.1 | <0.001[a] |
| Total FSH used (units) | 2535±838 | 1765±624 | <0.001[a] |
| Endometrial thickness on the day of hCG (millimeter) | 10.3±1.9 | 10.6±2.2 | 0.4[a] |
| Estradiol on the day of hCG (pg/mL) | 2835±1132 | 2595±1132 | 0.2[a] |
| Number of oocytes retrieved | 16.1±11.3 | 16.5±7.2 | 0.8[a] |
| Cleavage rate (%) | 64.2±24.4 | 49.1±22.2 | 0.001[b] |
| Fertilization rate (%) | 63.2±21.5 | 48.7±21.5 | 0.001[b] |
| Number of good quality embryos | 2.9±0.8 | 2.5±0.2 | 0.02[a] |
| The rate of cycle cancellation due to risk of OHSS (%) | 15.2 | 6.4 | 0.13[b] |
| Clinical pregnancy rate (%) | 34.1 | 30 | 0.6[b] |
| Live birth rate (%) | 25 | 22.5 | 0.7[b] |

**[Table/Fig-2]:** Outcome of controlled ovarian hyperstimulation and intracytoplasmic sperm injection.
Data are given as the mean±standard deviation, number and percentage
[a]Student's t-test, [b]Chi-square test

The clinical pregnancy rate was 30% in group 2 compared to 34.1% in group 1 (p=0.6). The live birth rate was 22.5% in group 2 and 25% in group 1 (p=0.7) [Table/Fig-2].

## DISCUSSION

In this retrospective cohort study, the efficacy of two regimens of ovarian stimulation in patients undergoing COH and ICSI for PCOS was evaluated. This study shows that there were no differences in the fecundity per cycle, pregnancy rate, live birth rate, transferred embryo numbers and cycle cancellation rates using either protocol.

It was found that the dose of rFSH used was significantly lower in the GnRHant group. Lambalk CB et al., reported similar results in their meta-analysis in 2017. Transferred embryo counts and cycle cancellation rates were similar in the GnRHa and GnRHant groups. The amount of rFSH used was 2206.5±684.55 in the GnRHa group, and 2038.5±571.52 in the GnRHant group. A numerical reduction was observed, but it was statistically not significant (p=0.232) [13].

In patients with PCOS, Ganor-Paz Y et al., found similar pregnancy rates in their treatments with GnRHa and GnRHant (p=0.5). The embryo transfer numbers were also similar [12].

Haydardedeoglu B et al., examined the differences between GnRHa and GnRHant plus oral contraceptives. The total gonadotropin dose was 1388.71±48.39 IU in the GnRHa group and 1253.25±415.81 IU in the GnRHant group, indicating a statistically significant difference (p=0.016) [14].

A study by Tehraninejad ES et al., showed that the number of HMG ampoules used in PCOS was significantly lower in GnRHant group. They used 24.28±5.02 ampoules in the GnRHant group, and 37.8±7.93 ampoules in the GnRHa group (p <0.001). Clinical pregnancy rates were similar in the GnRHant and GnRHa groups (40% and 33.3%, p=0.51, respectively) [15].

Lainas TG et al., studied the stimulation duration and total gonadotropin amount required in PCOS, and showed that both parameters were significantly reduced in the GnRHant group. Total FSH dose was 1850 IU (1370-1480 IU) in the GnRHant group and 1575 IU (1306-2212 IU) in the GnRHa group (p=0.019) [16].

Based on this literature, GnRH antagonists seem to be quite advantageous in PCOS patients both in terms of pregnancy outcomes and low drug use, and in preventing risk of OHSS.

## CONCLUSION

In conclusion, our results indicate that similar clinical pregnancy outcomes can be achieved in GnRH antagonist cycles using lower gonadotropin doses compared to the GnRH agonist cycles.

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**FINANCIAL OR OTHER COMPETING INTERESTS:** None.

Date of Submission: **May 22, 2018**
Date of Peer Review: **Jul 07, 2018**
Date of Acceptance: **Jul 19, 2018**
Date of Publishing: **Nov 01, 2018**