Taiwanese Journal of Obstetrics & Gynecology 58 (2019) 234–238

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

# Gonadotropin releasing hormone antagonist use in controlled ovarian stimulation and intrauterine insemination cycles in women with polycystic ovary syndrome

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ARTICLE INFO

*Article history:*
Accepted 5 July 2018

*Keywords:*
Controlled ovarian hyperstimulation
GnRH antagonist
In vitro fertilization
PCOS
Premature luteinization

ABSTRACT

*Objective:* To evaluate the effect of the GnRH antagonist on gonadotropin ovulation induction in women with PCOS.

*Materials and methods:* A total of 175 intrauterine insemination (IUI) cycles in women with polycystic ovary syndrome (PCOS) were included in the study. Women in the control group (n = 87) underwent controlled ovarian stimulation (COS) with recombinant follicle stimulating hormone (r-FSH) only, while women in the study group (n = 88) were administered r-FSH plus cetrorelix.

*Results:* As expected, the mean value of luteinizing hormone and progesterone, on the day of human chorionic gonadotropin administration were statistically significantly lower in patients receiving GnRH antagonist than the control group (p = 0.002). Premature luteinization occurred in only one of the patients in the GnRH antagonist group (1.1%) and in 15 of the 88 cycles in the control group (17.2%), showing a significant difference between the two groups (P = 0.001). The clinical pregnancy rate per cycle was higher in GnRH-antagonist group compared to the control group but the difference did not reach to a statistical significance (25% vs 14.9%, P = 0.096).

*Conclusions:* Adding GnRH-antagonist in COS/IUI cycles in women with PCOS resulted in a lower incidence of premature luteinization but did not improve pregnancy rates. However, owing to some benefits, antagonist therapy could be considered as a reasonable alternative to IVF in order to reduce PCOS patients'emotional distress.

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## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder leading to anovulatory infertility in young women. It effects approximately 5%–10% of women of reproductive age. Gonadotropin treatment has been recognised as an effective alternative treatment for clomiphene citrate (CC)-resistant anovulatory PCOS women. Problems related to the use of gonadotrophin therapy in PCOS women include the need for closer monitoring due to the increased risk of multifollicular development and relatively low fecundity [1,2]. The low pregnancy rates are suggested to be related to the hypersecretion of luteinizing hormone (LH) or premature LH surges. In women with PCOS, approximately 20%–26% of the controlled ovarian stimulation cycles have been reported to suffer from premature LH surge [3,4]. It has been demonstrated that elevated LH levels in the follicular phase affect oocyte quality by the early resumption of meiosis and premature oocyte maturation and ovulation, causing either lower implantation or increased miscarriage rates [5].

Although, some studies have shown that premature luteinization does not affect pregnancy rates, elevated follicular LH levels have a detrimental effect on pregnancy rates in vitro fertilization (IVF) cycles [6]. Therefore, the addition of gonadotropin-releasing hormone antagonists (GnRH-ant) in ovulation induction (OI) protocols may have a possible benefit in patients with PCOS.

GnRH-antagonists competitively inhibit endogenous GnRH, suppress the pituitary gonadotropin output, and produce an immediate and rapid decrease in FSH and LH levels without a flare effect. Administration of GnRH-ant in the late follicular phase prevents premature LH surge and premature luteinization.

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https://doi.org/10.1016/j.tjog.2019.01.012
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However, though these compounds have been used successfully in IVF clinics, their use in OI protocols is still controversial. The place of GnRH-ant in COS and intrauterine insemination (IUI) cycles in non-PCOS patients has been studied extensively [7–12]; however, there is limited number of publications on the use of GnRH-ant, especially cetrorelix, in OI cycles in the treatment of women with PCOS [3,4,13].

Therefore, we aimed to evaluate the efficacy of cetrorelix, a GnRH-ant, when used as an adjuvant to gonadotropins in the OI/IUI cycles of patients with PCOS.

## Material and methods

Following institutional ethical committee (17.09.2015/number 199) approval of the present study, the medical records of 175 consecutive women with PCOS who visited the Etlik Zübeyde Hanım Women's Health Teaching and Training Hospital Infertility Clinics were reviewed between January 2014 and October 2015. All subjects provided their written informed consent before participating in this retrospective cohort study. Subjects were excluded from the study if they had significant systemic disease such as congenital adrenal hyperplasia, androgen-secreting tumors, thyroid dysfunction, or Cushing's syndrome and/or had male factor (abnormal sperimogram according to the World Health Organization criteria) [14].The inclusion criteria were as follows: (1) age between 18 years and 38 years; (2) infertility duration >12 months; (3) body mass index of 18–38 kg/m2; (4) normal thyroid function and normal prolactin levels; (5) normal hysterosalpingography findings. All included patients with PCOS had previously experienced three unsuccessful cycles of CC/IUI therapy and had undergone their first gonadotropin OI with recombinant FSH. The diagnosis of PCOS was made on the basis of the Rotterdam Consensus Conference 2003 criteria [15].

All of the women underwent an ultrasound scan, and blood samples were taken on the third day of their menstrual cycle for the measurement of: FSH, LH, estradiol (E2), prolactin, and thyroid stimulating hormone (Advia Centaur; Siemens, Munich, Germany). None of the women were on metformin. The 87 patients with PCOS who received OI + IUI during the first seven months of the study period were designated as the control group, while and the 88 patients with PCOS who received OI + IUI and GnRH-ant were chosen as the study group.

Subjects in the control group were treated with r-FSH (Gonal-F; Merck Serono, Darmstadt, Germany or Puregon; Organon, Oss, the Netherlands), a subcutaneous injection of 50 IU–75 IU of r-FSH per day, starting on the third day of the menstrual cycle to induce follicular recruitment for five days. From the sixth day since the start of the menstrual cycle onwards, the dosage of gonadotropin was adjusted by the investigator, depending on the follicular growth evaluated by transvaginal ultrasonography (TVS) (Logiq A5; General Electric, Boston, MA, USA). The r-FSH administration was similar in both groups. Cetrorelix 0.25 mg (Cetrotide; Merck-Serono, Darmstadt, Germany) per day was added to the r-FSH in the study group when a leading follicle with a diameter >13 mm was measured during TVS and the serum estradiol was ≥250 pg/mL, LH <10 mIU/mL, and progesterone <1 ng/mL.

Subjects were monitored every two days to four days via TVS by a physician, and the diameter of the ovarian follicles and endometrial thickness were recorded. Blood samples were taken at the time of ultrasonography and LH, progesterone, and E2 were measured until the human chorionic gonadotropin (hCG) day. In the study group, hormonal levels were taken in an attempt to determine the correct timing of GnRH- administration so that progesterone, E2, and LH levels could also be measured on the first day of GnRH-ant administration. Premature LH rise was defined as LH >10IU/L, and the combination of a LH level >10 IU and a progesterone level >1 ng/mL was accepted as premature luteinization (PL). The cycles were not cancelled due to PL; instead, in the case of premature luteinization, hCG was administered immediately and IUI was performed 12 h–18 h later. The cycle was cancelled if E2 levels >1500 pg/mL or if there were more than three follicles >16 mm in diameter, in order to reduce the risk of ovarian hyperstimulation and multiple pregnancy. Recombinant hCG (r-hCG) (Ovitrelle; Merck-Serono, Darmstadt, Germany) was administered to induce ovulation when the leading follicle reached a mean diameter of at least 18 mm. IUI was planned 36 h–38 h after hCG administration in both groups using an IUI catheter (Wallace; Smiths Medical International, Walport, UK). Fourteen days after insemination, serum β-hCG levels were measured and repeated two days to four days later if positive (β-hCG >10 IU/L). Identification of embryonic heartbeat at TVS was defined as a clinical pregnancy. One positive β-hCG result was accepted as a biochemical pregnancy. All of the subjects received luteal phase support daily the day after IUI with vaginal progesterone (Crinone 8% gel, Darmstadt, Germany). Luteal support was continued until the pregnancy test was performed and in the case of a positive pregnancy up to 10 weeks–12 weeks' gestation. The diagnosis of ovarian hyperstimulation syndrome (OHSS) was based on the recommendations of the Practice Committee of the American Society of Reproductive Medicine [16]. Statistical analyses were performed using the Statistical Package for the Social Sciences (version 22.0; IBM Corp., Armonk, NY, USA) software program. Baseline demographic data as well as hormonal levels were compared in each treatment group by use of the Mann–Whitney U test, and median values were reported. Continuous variables were compared using the Student's t-test. The chi-squared test, Mann–Whitney U test, and Fisher's exact test were used to compare clinical outcomes between the two groups. A p value of <0.05 was considered to be statistically significant.

## Results

Data from the 88 women in the GnRH-ant study group and the 87 women in the control group were analyzed. Body mass index was significantly higher in the control group than in the antagonist group ($p = 0.001$).The baseline characteristics of the study cohorts are detailed in Table 1.

As expected, the mean values of LH, E2, and progesterone on the day of hCG administration were statistically significantly lower in patients who received GnRH-ant than in those who did not (4.09 mIU/mL ± 3.13 mIU/mL vs. 7.83 mIU/mL ± 4.28 mIU/mL, $p = 0.001$; 593.07 pg/mL ± 458.43 pg/mL vs. 758.15 pg/mL ± 595.89 pg/mL, $p = 0.004$; and 0.67 ng/mL ± 0.45 ng/mL vs. 1.26 ng/mL ± 1.51 ng/mL, $p = 0.002$, respectively). Table 2 summarizes the stimulation characteristics of the patients. The mean duration of cetrotide acetate treatment was 2.97 days ± 1.31 days. Premature luteinization occurred in one of the patients in the GnRH-ant group (1.1%) and in 15 cycles of the 88 patients in the control group (17.2%), revealing a significant difference between the two groups ($p = 0.001$).

The mean serum values of LH and progesterone on the day of hCG administration in pregnant and nonpregnant cycles were compared in order to determine the role of serum LH and progesterone levels in the prediction of IUI cycle outcomes. Although no statistically significant difference was found in both LH and progesterone mean values in pregnant and in nonpregnant cycles in the GnRH-ant group ($p = 0.63$ and $p = 0.89$), in the control group, LH and progesterone levels were significantly lower in the pregnant cycles as compared with in the nonpregnant cycles ($p = 0.011$ and $p = 0.045$).

**Table 1**
Comparision of baseline characteristics of the patients (n = 175).

| | r-FSH + antagonist n = 88 median (range) | r-FSH n = 87 median (range) | p |
|---|---|---|---|
| Age, years | 29.5 (19–38) | 29 (22–38) | 0.636 |
| BMI, (kg/m$^2$) | 27.0 (18.0–36.9) | 28.0 (20.2–36.3) | **0.001*** |
| Baseline FSH, (IU/L) | 6.20 (3.06–9.80) | 6.10 (3.30–9.93) | 0.523 |
| Baseline LH, (IU/L) | 6.3 (2.1–21.1) | 6.9 (1.5–16.5) | 0.715 |
| Baseline Estradiol, (pg/mL) | 39.52 (20–80) | 43.00 (20–67) | 0.760 |
| r-FSH dose,(U) | 750 (325–1625) | 650 (250–1800) | 0.074 |
| Duration of stimulation, (day) | 9 (4–18) | 9 (6–16) | 0.563 |
| Endometrium thickness on hCG day, (mm) | 9 (4.9–13.0) | 8 (6.0–16.0) | 0.153 |
| Peak LH (IU/L; day of hCG) | 3.18 (0.59–13.70) | 7.20 (0.68–16.30) | **0.001*** |
| Peak P (ng/mL; day of hCG) | 0.60 (0.10–2.01) | 0.89 (0.13–8.10) | **0.002*** |
| Peak E2 (pg/mL; day of hCG) | 588 (181–3500) | 450 (139–2503) | **0.004*** |

BMI: body mass index. r-FSH: recombinant follicle stimulating hormone, *p values with statistical significance (p < 0.05) are shown in bold, data analyzed using Mann–Whitney U tests, values are medians (25%–75% interquartile range).

**Table 2**
Cycle characteristics of the patients per cycle (n = 175)[a].

| | r-FSH + Antagonist n = 88 n (%) | r-FSH n = 87 n (%) | p |
|---|---|---|---|
| LH surge | 6 (6.9) | 20 (27.8) | **0.001*** |
| Premature progesterone rise | 10 (11.5) | 19 (26.4) | **0.015*** |
| Premature luteinization | 1 (1.1) | 15 (17.2) | **0.001*** |
| OHSS | 1 (1.1) | 0 | 1 |
| Canceled cycle | 3 (3.4) | 4 (4.6) | 0.72 |
| Clinical pregnancy | 16 (18.1) | 11 (12.6) | 0.096 |
| Monofollicular cycles | 61 (72.6) | 43 (51.8) | **0.006*** |
| Mean number of follicles | mean ± SD | mean ± SD | p |
| Follicle>16 mm | 1.37 ± 0.69 | 1.64 ± 0.77 | **0.008*** |
| Follicle 11–15.9 mm | 0.99 ± 1.46 | 0.90 ± 1.01 | 0.393 |

OHSS: ovarian hyperstimulation syndrome.
*p values with statistical significance (p < 0.05) are shown in bold.
[a] values are given as mean ± SD or number/number available for analysis (percentage).

Distribution of LH surge, premature progesterone rise, and premature luteinizing conditions according to clinical pregnancy status of treatment groups are shown in Table 3. The clinical pregnancy rate per cycle was higher in the GnRH-ant group than in the control group, but the difference did not reach a statistical significance (25% vs. 14.9%, p = 0.096).

There were a total of seen cycle cancellations because of hyperresponse, specifically three (3.4%) in the study group and four (4.5%) in the control group. Additionally, none of the patients experienced severe OHSS, and there was only one mild OHSS in the control group [16].

## Discussion

The aim of the present study was to determine the clinical benefits of GnRH-ant administration in COS/IUI cycles in infertile women with PCOS. Adding GnRH-ant to r-FSH treatment in a group of CC-resistant women with PCOS resulted in a lower incidence of premature luteinization at the day of HCG administration, but the use of GnRH-ant in OI did not improve pregnancy rates.

Although the administration of GnRH-ant in women undergoing IVF cycles has been studied extensively, there are only a few studies in existence that have compared the impact of GnRH-ant in COS/IUI cycles in women with PCOS [7–12]. Due to the heterogeneous nature of PCOS, it is import to evaluate the incidence and possible impact of premature luteinization and elevated LH and P levels on the cycle outcome.

There have been several conflicting views expressed in previously published studies regarding the effect of GnRH-ant on the duration of ovarian stimulation and the total dose of r-FSH. In most of the studies [3,17–19] no difference in the duration of stimulation was reported. However, Crosignani et al. [20] found that the duration of ovarian stimulation was prolonged in the group receiving GnRH-ant. In our study, we found that there was no significant difference in the duration of stimulation between the two groups.

As more FSH would be needed in antagonist cycles, owing to the suppression of endogen gonadotrophin production, in accordance with other studies [17,20], the total r-FSH dose required was higher in the GnRH-ant group, but the difference was not statistically significant. Interestingly, Allegra et al. [21] and Lambalk et al. [18] reported a lower total r-FSH dose used in women receiving

**Table 3**
Distribution of LH surge. Premature progesterone rise and Premature luteinizing conditions according to clinical pregnancy status of treatment groups.

| | r-FSH + Antagonist | | | FSH | | |
|---|---|---|---|---|---|---|
| | Clinic pregnancy yes (n = 22) n (%) | Clinic pregnancy. no (n = 66) n (%) | $p^a$ | Clinic pregnancy yes (n = 13) n (%) | Clinic pregnancy. no (n = 74) n (%) | $p^a$ |
| LH surge | | | | | | |
| yes | 0 | 6 (9.1) | 0.330 | 0 | 25 (33.7) | **0.014*** |
| no | 22 (100) | 60 (90.9) | | 13 (100) | 49 (66.2) | |
| Premature progesterone rise | | | | | | |
| yes | 1 (4.5) | 9 (13.8) | 0.441 | 0 | 24 (32.4) | **0.015*** |
| no | 21 (95.5) | 56 (86.2) | | 13 (100) | 50 (67.5) | |
| Premature luteinization | | | | | | |
| yes | 0 | 1 (1.5) | 1.000 | 0 | 15 (20.2) | 0.113 |
| no | 22 (100) | 65 (98.5) | | 13 (100) | 59 (79.7) | |

*p values with statistical significance (p < 0.05) are shown in bold.
[a] Fisher test.

antagonists, but the authors stated that the explanation of the reasoning for this observation was difficult.

Gomez–Palomeres et al. [22] reported a significantly higher number of mature follicles in the GnRH-ant group, and this was a pioneering study that showed a significant improvement in pregnancy outcome in the GnRH-ant group. On the contrary, some of the other published studies have reported no difference in the mean numbers of 11 mm–16 mm and >16 mm follicles in GnRH-ant groups [3,19]. Similar to the results of Ertunç et al., we found a significantly higher number of follicles with a diameter of 11 mm–16 mm and >16 mm in patients treated with r-FSH alone as well as a higher incidence of monofolliclar growth in the GnRH-ant treated group. To the best of our knowledge, endogenous LH has a very important role on follicular growth; therefore, we took into account the hormone levels in order to determine the exact timing of GnRH-ant administration. The mean estradiol, progesterone, and LH levels at the day of hCG administration were significantly lower in the group receiving GnRH-ant. In the presented study, when the serum mean values of progesterone and LH were compared among the two groups and between pregnant and nonpregnant subjects, no statistical difference was found in the mean progesterone and LH values between the pregnant and nonpregnant cycles in the study group. However, serum progesterone and LH levels were significantly lower in the pregnant cycles than in the nonpregnant cycles ($p = 0.045$ and $p = 0.011$ for progesterone and LH, respectively) in the control group.

The premature LH rise may lead to lower oocyte quality, reduced fertilization rates, and poor embryo quality [23]. Therefore, premature LH rise could also be related to lower pregnancy rates in COS/IUI cycles. In our study, pregnancy was not observed when the LH serum level on the day of hCG administration was >10 mIU/mL—as indicative of a premature LH rise—in both groups. In contrast to the study by Allegra et al. [21], better clinical pregnancy rates were not obtained in the GnRH-ant cycles in our study group.

Approximately 21%–26% of women with PCOS undergoing COS with gonadotropin are at risk for premature luteinization [3,4]. In our study, the incidence of premature luteinization was higher in the control group versus in the GnRH-ant group (19.5% vs. 1.1%, respectively), which is consistent with the study by Cardones et al. [24]. Similarly, Bakas et al. [25] found that there was a statistically significant reduction of premature luteinization risk in COS cycles treated with cetrorelix when compared with the control group (1.7% vs. 17.5%), and this finding is in accordance with those of other studies [3,21].

On the other hand, the reported effect of premature luteinization on clinical pregnancy outcome has been controversial [13]. Gomez–Palomeres et al. [11] showed a significant improvement in pregnancy outcome when a GnRH-ant was added to the COS protocol. On the contrary, most of the studies involving non-PCOS women reported a reduction of premature luteinization provided by the addition of GnRH-ant to the COS protocols, but this reduction was not found to lead to a significant increase in pregnancy rates [10,11,18,25]. In our study, we found that the pregnancy rates were similar between the two groups. Adding cetrorelix slightly improved the pregnancy rates of women with PCOS, but the difference did not reach a level of a statistical significance (25% vs. 14.9%, $p = 0.96$).

Premature luteinization was considered to be a cycle-cancellation criterion in several studies [26]. On the other hand, Ertunc et al. reported five patients who achieved pregnancy at the end of cycles with premature luteinization in the control group and two in the cetrorelix group [3]. Due to the abnormal follicular environment, the physiology and the response to r-FSH treatment are generally different for patients with PCOS such that the findings based on non-PCOS women may not be reproducible in women with PCOS. In a study by Bosch et al. [12], the authors explained the increase in progesterone levels without elevation of LH to be a result of the initial intense r-FSH dose, which increases granulosa cell steroidogenic activity. Another explanation for this finding may be the consequence of the activation of other pathways by FSH. In line with these findings, Segal et al. reported that women with PCOS with premature luteinization had similar pregnancy rates to those of women with PCOS without premature luteinization in IVF cycles [13]. In contrast to the above-mentioned study, however, we found that patients with premature luteinization did not become pregnant, both in the control and antagonist groups. In accordance with previous studies [25,27,28], our results showed an overall cycle cancellation rate of 3.9%.

Finally, the impact of adding GnRH-ant to the cost of COS protocols and the additional costs related to it are important issues to consider, but, notably, the present study is a retrospective study not designed to analyze cost-effectiveness. The completion of future studies with higher number of participants might give a clearer view about the effects of adding GnRH-ant to COS cycles in patients with PCOS.

In conclusion, adding GnRH-ant to r-FSH treatment in a group of CC-resistant women with PCOS resulted in more frequent monofollicular development, an improvement in the hormone profile, and a lower incidence of premature luteinization at the day of HCG administration. Adding GnRH-ant also slightly improved pregnancy rates, but the difference did not reach a level of statistical difference, and these favorable changes did not lead to an occurrence of clinical significance such as a decreased prevalence of OHSS, multiple pregnancy, or cancellation cycles.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

## Acknowledgments

None.

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