

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20260534>

Original Research Article

A prospective randomized pilot study comparing the short protocol with gonadotropin and gonadotropin-releasing hormone agonist to the combination of gonadotropin and gonadotropin-releasing hormone antagonist for ovulation stimulation in poor responder patients undergoing in vitro fertilization treatments

Keziban Saylam Dönmez^{1*}, Anne Delbaere²

¹Department of Obstetrics and Gynecology, Eskisehir City Hospital, Eskisehir, Turkey

²Department of Obstetrics and Gynecology, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), CUB Hôpital Erasme, Route de Lennik, Brussels, Belgium

Received: 14 January 2026

Revised: 11 February 2026

Accepted: 12 February 2026

*Correspondence:

Dr. Keziban Saylam Dönmez,
E-mail: kezibansaylam@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: This study aimed to evaluate the effect of gonadotropin-releasing hormone antagonist for ovulation stimulation in poor responder patients undergoing in vitro fertilization treatments.

Methods: Patients who had previously undergone two IVF cycles and had collected fewer than 5 oocytes in their last attempt, with a baseline FSH value below 15 IU/L, were selected to be included to the study. The patients were randomly included to one of the treatment groups. Before treatment, patients used oral contraceptive pills for 21 days. In Group A, recombinant gonadotropin was used with GnRH agonist in a short protocol. In Group B, recombinant gonadotropin was used with GnRH antagonist cetrorelix.

Results: A total of 24 patients were included in the study. In Group A (11 patients), recombinant gonadotropin was used with GnRH agonist in a short protocol. In Group B (13 patients), recombinant gonadotropin was used with GnRH antagonist cetrorelix. The characteristics of the previous cycles for patients were also similar in both groups. Statistically, it was observed that the estradiol values in Group A were higher during ovulation induction. No significant difference was observed in the amount of gonadotropin used and stimulation durations in both groups. No significant difference was found in the number of oocytes collected. One pregnancy occurred in Group A, while 2 pregnancies occurred in Group B. A positive correlation was found between the baseline FSH value and the amount of gonadotropin used in Group B.

Conclusions: There was no statistically significant difference in term of oocytes, embryo and pregnancy in the two groups. Larger-scale studies are needed to obtain definitive results.

Keywords: Cetrorelix, GnRH agonist, GnRH antagonist, IVF, Poor responders

INTRODUCTION

In recent years, women in developed countries have married at an older age. With the increase in fertility age, there has been a rise in infertility rates. Studies conducted with in vitro fertilization have shown that advanced age is

directly related to poor ovarian response, low estradiol levels, low oocyte collection, and low fertilization rates.¹

Approximately 20% of women who begin IVF treatment experience poor ovarian response, resulting in cycle cancellations or a low retrieval of oocytes.^{2,3}

There are many reasons for the reduction of the ovarian reserve, including advanced age, previous ovarian surgery, chemotherapy and pelvic radiotherapy.

When investigating the causes of infertility, ovarian reserve is always evaluated. For this, criteria have been developed. The Bologna criteria are based on three conditions: advanced maternal age (>40 years) or any other POR risk factor; a previous incident of POR during COH; and a low ovarian reserve test in terms of anti-mullerian hormone or antral follicle count. Two of these three criteria are required for a POR diagnosis according to the Bologna criteria. In addition, two cycles with POR after maximal stimulation are sufficient to classify a patient as a poor responder even in the absence of the other criteria mentioned.^{4,5} Furthermore, the Poseidon Group proposed a different stratification to personalize treatment according to the patients characteristics.^{6,7}

In standard controlled ovarian hyperstimulation (COH) cycles (luteal long protocol) with GnRH agonists, treatment is started on day 21 of the previous cycle and continued until ovulation. This practice leads to pituitary desensitization, suppressing the early luteinizing hormone (LH surge) release by administering only gonadotropin, and increasing the number and synchronization of developing follicles. However, it also results in decreased sensitivity to gonadotropin for follicle development, requiring increased dosages. While the exact reason is not fully understood, modification of paracrine ovarian factors and ovarian gonadotropin receptors is considered a contributing factor.

For these reasons, alternative stimulation methods have been sought for patients with poor ovarian response. The most commonly used methods include increasing gonadotropin doses, decreasing GnRH analog doses, the short protocol use (simultaneous initiation of gonadotropin and GnRH analog), pre-cycle oral contraceptives use and growth hormone use.

Because GnRH antagonist inhibits LH release, they do not cause a decrease in gonadotropin sensitivity in the ovaries as GnRH agonists do. Since treatment is initiated at the end of the critical follicular phase for these patients, the use of GnRH antagonist seems logical.⁸

The objective of this study is based on the consideration that a COH protocol containing GnRH antagonist may be beneficial for the poor responder patient group in IVF treatments, we wanted to evaluate the treatment protocol containing cetrotirelix. In a prospective randomized study, 2 different COH protocols were compared in the poor responder patient group. In one arm, recombinant gonadotropin (Gonal-f®) and GnRH analogue (Busereline, Suprefact®) were used as a short protocol, and in the other arm, recombinant gonadotropin (Gonal-f®) and GnRH antagonist cetrotirelix (cetrotide®) were used. Patients in both groups used oral contraceptive pills for one month before treatment.

METHODS

The study was conducted between Oct-2002 and Feb-2004 at the Fertility Clinic, Department of Obstetrics and Gynecology, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), CUB Hôpital Erasme. The study was approved by the ethics committee.

Inclusion criteria

Patients with retrieval of less than 5 oocytes in the previous 2 IVF cycles and FSH <15 IU/L in the follicular phase. IVF or ICI cycles may be included. Informed consent was obtained from the patients. FSH values of the patients were checked on 3 days of menstruation during 2 cycles.

Ovulation induction and working protocol

Patients used oral contraceptives (Microgynon 30®, Bayer SA-NV Kouterveldstraat 7A 301 B-1831 Diegem, Machelen, Belgium) for 21 days before stimulation and were randomized into two separate groups.

In group A GnRH agonist (buserelin, Suprefact®, Bachem Holding AG Hauptstrasse 1444416 Bubendorf, Switzerland) and recombinant gonadotropin (Gonal-f®, Merck Europe B.V. Gustav Mahlerplein 102.1082 MA Amsterdam, Netherlands) was used as a short protocol. The first day of menstruation after the use of oral contraceptive pills (OCP), patients began to use buserelin (Suprefact® 6 x100 µg/day). Day 5 of cycles COH started with recombinant gonadotropin (Gonal-f® 4 X75IU/day). After three days if no response is received (in case of an increased of estradiol value less than 30 pg/ml), the dose was increased to 150 IU.

In Group B cetrotirelix as GnRH antagonist (Cetrotide®, Merck Europe B.V. Gustav Mahlerplein 102.1082 MA Amsterdam, Netherlands) and recombinant gonadotropin (Gonal-f®) were used. Patients on the second day of menstruation after the use of OCP started with recombinant gonadotropin (Gonal-f® 4 x75IU/day). After three days, if no response is received (in case of an increase of estradiol value less than 30 pg/ml), the dose of gonadotropin was increased to 150 UI. On the seventh day of the stimulation, 14 mm of follicle is observed 0.25 mg per day cetrotirelix was added to the treatment in the form of subcutaneous injection. In the presence of a dominant follicle reaching 20 mm in both groups 10.000 UI hCG (Pregnyl®, Organon Belgium Rue de La Loi 34, Bruxelles, Belgium) was used for ovulation induction. Stimulation follow-up, oocyte collection and embryo culture techniques were done in both groups in the same way according to the routine practice of the center. Embryo transfer was performed 2 days ovum pick up (OPU). In both groups, 1 day after OPU vaginal progesterone (3 x 100 mg/day, Utrogestan®, Delpharm Drogenbos SA Groot-Bijgaardenstraat, 128 1620 Drogenbos Belgium) for luteal phase support is provided. After 14 days of OPU, pregnancy was investigated by looking at the value of

blood human chorionic gonadotropin (βhCG). If pregnancy occurred, the formation of the pregnancy sac at 4-5 weeks with vaginal ultrasound was evaluated.

Outcome measures

We evaluated stimulation characteristics (doses of gonadotropin used, stimulation time, estradiol values and collected oocyte numbers), fecundation, implantation and pregnancy rates for both groups.

Statistical analysis

The statistical analysis was performed with SPSS 10 program, Student’s t- test, Fisher’s exact test and linear

regression were performed. p<0.05 was found to be significant.

RESULTS

A total of 24 patients were included in the study, 11 patients were in group A, and 13 patients were in group B. The characteristics of the patients are given in Table 1. In both groups, the patients' ages, duration of infertility, previous IVF treatments, and OPU numbers were observed to be statistically similar.

No significant difference was observed in the causes of infertility in the 2 groups (Table 2).

Table 1: Clinical characteristics of patients.

	Group A	Group B	P value
Number of patients	11	13	
Age (years)	35.27±4.9	36.62±4.6	0.496
Infertility period (month)	59.73±43	34.58±37	0.133
Number of previous IVF cycles	3.3±1	3.6±1.3	0.476
Previously validated OPU	2.8±1.1	3±0.9	0.659

Values are means values ± standard deviation. Student’s t- test, p<0.05 is significant

Table 2: Causes of infertility.

	Group A, N (%)	Group B, N (%)	P value
Tubal factor	7 (0.64)	6 (0.46)	0.444
endometriosis	4 (0.36)	3 (0.23)	0.659
Cervical	1 (0.09)	2 (0.15)	1.000
Male factor	7 (0.64)	7 (0.54)	0.697

Fisher’s exact test, p<0.05 is significant

The previous IVF cycles were examined in the included patients, and no significant differences were observed (Table 3).

The average duration of cetorelix use in Group B was calculated as 5.3 days. The distribution of IVF or ICSI was

observed to be equal in both groups. No significant difference was observed between the FSH values of the patients on the 3rd day of menstruation and the FSH values before the start of OCS, which were measured during 2 cycles. 3341 UI of gonadotropin was used in group A (short protocol), and 4119 UI of gonadotropin was used in group B. Stimulation lasted an average of 10.7 days in group A and 11.9 days in group B. Differences were not statistically significant. During ovulation induction, estradiol values were 1324 pg/ml in group A and 939 pg/ml in group B, and this difference was found to be statistically significant (Table 4). There was no cycle cancellation. There was no significant difference in the number of oocytes collected between the groups. No embryo transfer was performed on three patients (2 ICSI and 1 IVF) due to failed fertilization.

Table 3: The previous cyclical characteristics.

	Group A	Group B	P value
Cycle 1			
Used FSH doses (IU)	3998±1796	3831±1153	0.823
Stimulation duration (day)	12.1±3.6	11.4±2.9	0.605
Estradiol (pg/ml)	1435±602	1615±1032	0.617
Oocyte count	4.2±2.4	5.1±2.9	0.419
Cycle 2			
Used FSH doses (IU)	4820±1965	3840±1248	0.159
Stimulation time (day)	11.5±4.7	11.2±2.9	0.830
Estradiol (pg/ml)	1081±429	720±444)	0.064
Oocyte count	2.4±1.1	1.6±1.5	0.177

References to means values ± standard deviation. Student’s t- test, p <0.05 is significant

There were 3 pregnancies in total. One pregnancy (5.8%) occurred in group A and resulted in biochemical

pregnancy. Two pregnancies (9%) occurred in group B and resulted in early abortion.

Table 4: Features of the cycles in the study.

	Group A	Group B	P value
FSH 1 (mIU/l)	8.4±2.3	9.33±3	0.437
FSH 2 (mIU/l)	9.64±3.5	9.31±2.6	0.794
FSH before OCP (mIU/l)	9.90±1.9	10.54±4.7	0.694
Used gonadotropin dose (IU)	3341±844	4119±1344	0.111
Stimulation duration (day)	10.7±2.2	11.9±2.1	0.187
estradiol (pg/ml)	1323.9±458	938.8±325	0.025
Oocyte count	3.45±2.3	4.85±2.8	0.199

References to means values ± standard deviation. Student’s t- test, p<0.05 is significant.

In Group B, correlation was observed between the FSH value before OCP and the dose of gonadotropin used. In both groups, no correlation between the FSH value before OCP and the stimulation duration, estradiol value, the collected oocyte number (Table 5, Figure 1).

Table 5: Correlation between the FSH value before OCP use and the dose of gonadotropin used.

	P value	
	Group A	Group B
Used gonadotropin dose (UI)	0.137	0.043
Stimulation duration (day)	0.357	0.130
estradiol (pg/ml)	0.086	0.163
Oocytes count	0.149	0.117

References to means values ± standard deviation. Student’s t- test, p<0.05 is significant.

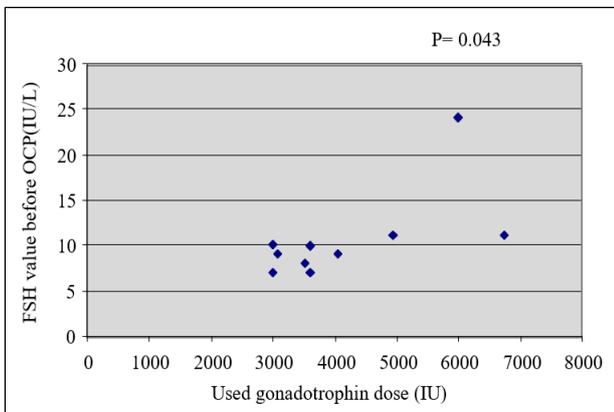


Figure 1: Group B: Correlation between the FSH value before OCP use and the dose of gonadotropin used correlation (linear, p<0.05 was found to be significant.)

Table 6: Group B Between FSH value after OKS use and cyclical criteria correlation.

	P value
Used gonadotropin dose (IU)	0.739
Stimulation duration (day)	0.722
estradiol (pg/ml)	0.761
Oocytes count	0.779

p<0.05 is significant

However, there was no significant correlation between the FSH value after the use of OCP and the gonadotropin dose used, stimulation duration, estradiol values, collected oocyte number (Table 6).

DISCUSSION

The management of patients with poor ovarian response (POR) remains a controversial and complex clinical challenge in reproductive medicine. If patients undergo IVF treatment for the first time, it is recommended to assess ovarian reserve with antral follicle count, anti-Müllerian hormone.⁹ Poor response to a previous treatment is also a diagnostic criterion for POR.⁴ In our study, we selected patients who had already tried IVF treatment and resulted in a poor response.

Generally, IVF treatments are conducted by the combined use of COH GnRH agonist and gonadotropin. It is usually applied in the form of a long protocol. However, prolonged use of GnRH agonists can cause a flare-up effect and ovarian desensitization, necessitating the initiation of gonadotropin treatment. This type of protocol may also reduce responses to gonadotropin in the ovaries, and it is important, especially for patients with POR. When GnRH antagonists are used in the follicular phase, desensitization of the ovary develops and prevents early LH release. Spontaneous ovulation is thus prevented and it allows to continue the stimulation and ensure the development of more follicles. GnRH antagonists can be favorable for POR.

Our study is a prospective randomized study on the one hand analogue of GnRH with recombinant gonadotropin (Gonal-f[®]) and as a short protocol (busereline, Suprefact[®]) on the other hand, the GnRH antagonist cetrorelix (Cetrotide[®]) with recombinant gonadotropin (Gonal-f[®]) using it, two different treatment protocols were compared. In our study, the quantity of gonadotropin used, stimulation duration and collected oocyte count were similar in both groups. Estradiol value at ovulation induction used was significantly lower in the GnRH antagonist group. Also, in the cetrorelix group, there was a correlation between the FSH value before use of OCP and the dose of gonadotropin used. It is useful to be careful here because in this group, there was a patient who had a very high FSH level. Figure 1 shows that if the patient is

excluded, it is believed that there will be no correlation. In our study, there was no significant difference regarding oocyte count and pregnancy rates.

The use of GnRH antagonists and GnRH agonists in IVF treatments for normal responders has shown similar results for fertilization and pregnancy rates.^{10,11}

In a meta-analysis and a review realized by Xiao et al, antagonist protocol was associated with fewer oocytes retrieved, lower E2 levels, and thinner endometrium compared with GnRH agonist protocols in poor responder patients.¹² But the clinical pregnancy and cycle cancellation rates were similar in both treatments. A randomized study with 111 patients showed that fewer eggs were retrieved in the agonist regimen and suggest that the antagonist regimen may be favorable for POR.¹³

GnRH antagonist can be used in two ways. Dose used daily or long-acting (4 days) single dose. There was no significant difference between them.¹⁴

Recently, a retrospective study with 190 patients don't find differences in the uses of GnRH agonist for POR.¹⁵

The present study has certain limitations. The number of patients included was relatively small, which may limit the generalizability and statistical strength of the findings. Therefore, larger studies with a greater sample size are required to validate the results.

CONCLUSION

In conclusion, we wanted to share our experience. It is important to check ovarian reserve of infertile patients to plan COH correctly. In our study, there were no significant differences between GnRH agonist and GnRH antagonist protocols in POR patients.

ACKNOWLEDGEMENTS

Authors would like to thank fertility clinic of the CUB Erasme Hospital for their support during study. Authors would like to thank Ms. Viviane DeMaertelaere for her invaluable assistance in performing the statistical analyses.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of Hospital Erasme, Université Libre de Bruxelles

REFERENCES

1. Sharma V, Riddle A, Mason BA, Pampiglione J, Campbell S. An analysis of factors influencing the establishment of a clinical pregnancy in an ultrasound-based ambulatory in vitro fertilization program. *Fertil Steril.* 1988;49(3):468-78.

2. Jones HW Jr, Acosta A, Andrews MC, Garcia JE, Jones GS, Mantzavinos T, et al. The importance of follicular phase to success and failure in in vitro fertilization. *Fertil Steril.* 1983;40(3):317-21.
3. Scott RT, Hofmann GE. Prognostic assessment of ovarian reserve. *Fertil Steril.* 1995;63(1):1-11.
4. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod.* 2011;26(7):1616-24.
5. Younis JS, Ben-Ami M, Ben-Shlomo I. The Bologna criteria for poor ovarian response: a contemporary appraisal. *J Ovarian Res.* 2015;8(1):76.
6. Poseidon Group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number); Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, Esteves SC, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril.* 2016;105(6):1452-3.
7. Drakopoulos P, Bardhi E, Boudry L, Vaiarelli A, Makrigiannakis A, Esteves SC, et al. Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept. *Ther Adv Reprod Health.* 2020;14:1-11.
8. Reissmann T, Schally AV, Bouchard P, Riethmüller H, Engel J. The LHRH antagonist Cetrorelix: a review. *Hum Reprod Update.* 2000;6(4):322-31.
9. Ovarian Stimulation TEGGO, Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. *Hum Reprod Open.* 2020;2020(2):hoaa009.
10. Albano C, Felberbaum RE, Smits J, Riethmüller-Winzen H, Engel J, Diedrich K, et al. Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. *Hum Reprod.* 2000;15(3):526-31.
11. Olivennes F, Belaisch-Allart J, Emperaire JC, Dechaud H, Alvarez S, Moreau L, et al. Prospective randomized, controlled study in in vitro fertilization-embryo transfer with a single dose of a LHRH antagonist (cetrorelix) or a depot formula of an LHRH agonist (Triptorelin). *Fertile Steril.* 2000;73(2):314-20.
12. Xiao J, Chang S, Chen S. The effectiveness of gonadotropin-releasing hormone antagonist in poor ovarian responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertil Steril.* 2013;100(6):1594-601.
13. Sunkara SK, Coomarasamy A, Faris R, Braude P, Khalaf Y. Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. *Fertil Steril.* 2014;101(1):147-53.

14. Olivennes F, Diedrich K, Frydman R, Felberbaum RE, Howles CM. Safety and efficacy of a 3 mg dose of the GnRH antagonist cetrorelix in preventing premature LH surges: report of two large multicentre, multinational, phase IIIb clinical experiences. *Reproductive BioMedicine Online*. 2003;6(4):432-8.
15. Al Hussaini TK, Mohamed AA, Askar A, Abden AA, Othman YM, Hussein RS. Ovarian stimulation in patient oriented strategies encompassing individualised oocyte number 4 category; Antagonist versus short agonist protocols. *J Hum Reprod Sci*. 2023;16(3):212-7.

Cite this article as: Dönmez KS, Delbaere A. A prospective randomized pilot study comparing the short protocol with gonadotropin and gonadotropin-releasing hormone agonist to the combination of gonadotropin and gonadotropin-releasing hormone antagonist for ovulation stimulation in poor responder patients undergoing in vitro fertilization treatments. *Int J Reprod Contracept Obstet Gynecol* 2026;15:821-6.