

Original article

Comparative Study of Agonist *versus* Antagonist Protocols in Patients with Polycystic Ovary Syndrome: A Cross-Sectional Study

Huda Alsharief^{*}, Amira Alorify, Amal Sultan, Mona Alkawafy

Department of Gynecology and Obstetrics, Medicine Faculty, Benghazi University

Corresponding email. hudaalshrief@gmail.com

Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrinopathy affecting 5–10% of reproductive-age women, frequently necessitating controlled ovarian stimulation via GnRH analogues to mitigate the risk of premature luteinizing hormone surges. The study aims to compare the efficacy of the fixed Gonadotropin-Releasing hormone (GnRH) antagonist protocol vs. the GnRH agonist protocol in patients with polycystic ovary syndrome undergoing ICSI. A cross-sectional study was conducted among 158 PCOS patients at the Benghazi Teaching Hospital for Fertility and Assisted Reproduction. A statistically significant difference was observed in the duration of stimulation, which was found to be significantly longer in the agonist protocol compared to the antagonist protocol (10±2 vs 9.3±1.6, $p = 0.0005$). There is no significant difference between both groups in view of the dose of gonadotropin drugs (26.7 ± 8.5 in agonist group vs. 25.3 ± 10 in antagonist group), pregnancy outcome (17% agonist group vs. 14.3% antagonist group with $p = 0.403$). A statistically significant difference was observed in the number of MII oocytes; the agonist protocol had a higher number ($p = 0.028$). The antagonist protocol was associated with a significantly higher incidence of empty follicles compared to the agonist protocol ($p = 0.032$). While both protocols yielded identical pregnancy rates and similar safety profiles regarding OHSS, the GnRH Agonist protocol appeared more favorable in this specific study due to lower cancellation rates and fewer empty follicles.

Keywords. Polycystic Ovarian Syndrome, GnRH Agonist, GnRH Antagonist, ICSI, OHSS.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy among reproductive-age women [1]. In the 1990s, the diagnosis of PCOS was entirely clinical and required the presence of menstrual irregularity and hyperandrogenism after exclusion of other causes [2]. In 2001, a consensus meeting was held in the National Institutes of Health, and more importance was given to the presence of polycystic ovarian morphology [3]. Epidemiological studies suggest that approximately 5-10% of reproductive-age women have PCOS, and 16-25% of an otherwise normal population have isolated polycystic ovarian morphology (PCO) on ultrasound [4]. The primary oocyte quality has a significant impact on the survival of the embryo, as well as on the establishment and maintenance of pregnancy and fetal growth. Furthermore, abnormalities such as endocrine/paracrine, metabolic activity disorder, and intrafollicular changes during the folliculogenesis and follicle maturation can lead to incomplete maturation of the embryo and its ability to grow in PCOS patients.

Low-quality oocyte cells in such cases can reduce the pregnancy rate, the splitting, and implantation, and thus increase the likelihood of miscarriage. PCOS is believed to be a leading factor in the deterioration of oocyte quality. It is generally accepted that PCOS is not a specific endocrine disease, but a syndrome represented by a collection of signs and symptoms, and that no one sign, symptom, or test is diagnostic. The diagnostic criterion most commonly utilized in clinical practice for diagnosing PCOS is the "Rotterdam" criterion [5]. The diagnosis of PCOS should be based on at least two of the three major criteria: oligoanovulation, clinical or biochemical signs of hyperandrogenism, and polycystic-appearing ovary(s) (assessed by ultrasonography, described as an ovarian volume of more than 10 mL³ and/or more than 12 follicles measuring between 2 and 9 mm in size in at least one ovary), also excluding other endocrinopathies having a similar clinical presentation [6,7].

Compared to normally cycling women, those with PCOS generally exhibit increased serum LH concentrations, low-normal FSH levels, and increased LH to FSH ratios [7,8]. The increase in serum LH levels results from abnormal LH secretory dynamics, characterized by an increase in LH pulse frequency and, also, in pulse amplitude [9,10]. LH pulse frequency in women with PCOS does not exhibit the normal cyclic variation seen in ovulatory women and is relatively constant, at approximately one pulse per hour. This pattern presumably reflects a similar increase in hypothalamic GnRH pulse frequency, which favors secretion of LH more than FSH [11-13]. Insulin resistance is a common feature in obese and, to a lesser extent, lean women with PCOS; the overall prevalence ranges between 50% and 75% [14]. Up to 35% of women with PCOS exhibit impaired glucose tolerance, and 7- 10% meet the criteria for type 2 diabetes mellitus. [15]. The combined actions of insulin and androgens lower SHBG concentrations, yielding increased free androgen levels, which aggravate the underlying insulin resistance [16]. Hyperandrogenism is the key feature of PCOS, resulting primarily from excess androgen production in the ovaries and, to a lesser extent, in the adrenals as well as in excess body fat [17]. In women with PCOS, approximately 60% of circulating androstenedione derives directly from the ovaries and the remainder from the adrenals [18]. Obesity in

women with PCOS is typically distributed centrally, with a greater increase in visceral than in subcutaneous fat. However, even lean women with PCOS have an increased percentage of body fat, a higher waist-hip ratio, and greater intra-abdominal, peritoneal, and visceral fat, compared to normal women matched for Body Mass Index (BMI) [19].

The antagonist protocol may be the preferred stimulation protocol for PCOS patients treated by ICSI in view of the reduction of OHSS incidence rates, the shorter duration of treatment, and less gonadotropin requirement. Our findings indicate that administration of GnRH antagonists in PCOS patients undergoing IVF may lead to superior results.[20]. The GnRH agonist (GnRH-a) protocol is a conventional protocol, probably the most widely used throughout the world even now, allows a quite good predictability of the work in ART units, implies a low cancellation rate, and allows to get a relatively high number of pre-ovulatory follicles of retrieved oocytes and, as a consequence, of embryos available for transfer, thus leading to a satisfactory pregnancy rate [21]. The relatively recent introduction of GnRH antagonists in clinical practice has provided another option for ovarian stimulation in ART [21]. The introduction of GnRH antagonists (GnRH-ant) in assisted reproductive technologies (ART) to prevent LH surge seemed to open up a new way towards a more "friendly In Vitro Fertilization (IVF). Unlike the indirect pituitary suppression induced by GnRH-a, GnRH-ant administration causes immediate and dose-related inhibition of gonadotropin release by competitive occupancy of the GnRH receptors in the pituitary [22]. In "in vitro" fertilization and embryo transfer, the majority of randomized clinical trials unequivocally demonstrate that the use of exogenous gonadotropin in conjunction with a gonadotropin-releasing hormone (GnRH) agonist, which can suppress pituitary FSH and LH secretion, is linked to a higher pregnancy rate when compared to the use of gonadotropins alone.

Compared to the lengthy agonist protocol, GnRH antagonist protocols are more efficient in preventing an early rise in LH and cause a shorter and more economical ovarian stimulation. [23]. In the current study, we tried to clarify the efficacy of two commonly used protocols prescribed for PCOS patients in the Benghazi Teaching Hospital for Fertility and Assisted Reproduction, that less studies conducted in this hospital.

Methodology

Study Design and Setting

A cross-sectional study was conducted in the Benghazi Teaching Hospital for Fertility and Assisted Reproduction.

Study Population

A total of 158 PCOS patients' files were revised, who were subdivided into two groups according to the prescribed protocols: group 1 (n = 88) was stimulated by a GnRH agonist, and group 2 (n = 70) was stimulated by a fixed (day 7) antagonist protocol.

Treatment Protocols

In the GnRH agonist protocol (agonist group), triptorelin 0.1mg (Decapeptyl 0.1) is administered daily subcutaneous injection, and gonadotropin was started on the second day of cycle I/m (the dose was modified according to the response), and both the agonist and gonadotropin were continued until the day of triggering. In the fixed GnRH antagonist protocol (antagonist group), gonadotropin was given starting from cycle day 2 in a dose of 150 IU daily (the dose was modified according to the response). day 7 (Cetrotide,0.25mg) subcutaneous injection daily injection was started, and both gonadotropin and antagonist were continued until the day of triggering.

Coasting was decided in patients showing hyper response (> 20 follicles in each ovary and or E2 > 3500 pg./ml). As soon as three follicles with a mean diameter of ≥ 17 mm were reached, 5000 IU of Human Chorionic Gonadotropin (HCG) was administered intramuscularly once, 36 h before oocyte pickup. Oocyte retrieval was performed assisted by transvaginal ultrasound-guided aspiration. All embryos were transferred under abdominal ultrasound guidance. Luteal phase support with progesterone was initiated for 14 days after the embryo transfer.

Outcome Measures

Outcome measures were the clinical pregnancy rate (CPR), duration of stimulation, total dose of stimulation, and E2 concentration on the day of HCG administration, number of oocytes retrieved, number of embryos transferred, fertilization rate, and cancellation rate. Clinical pregnancy is defined as the presence of a gestational sac with a fetal heartbeat detected in 6–7weeks of gestation.

Data Management

The patients' data were analyzed using SPSS version 25. Descriptive statistics, including frequency and percentage, were performed, and inferential statistics were used to analyze the differences between the two protocols using the chi-square crosstabulation test. A p-value less than 0.05 is considered significant.

Ethical Consideration

The Benghazi Teaching Hospital for Fertility and Assisted Reproduction Ethics Committee granted ethical permission, and patient information is kept confidential.

Result

A total of 158 PCOS patients were included in this study, with the main age group being (31-41), representing 63.3% of the sample. The majority of cases (71%) were with the primary type of infertility. The mean \pm standard deviation of the infertility duration was 5 ± 2.8 years, with 62.7% having a range of 1 - 5 years. 98.7% of them had previous ICSI, and 56% had agonist protocol (Table 1).

Table 1. Distribution of patients according to personal characteristics

Variable	No.	%
Age/Years		
20-30	53	33.5
31-41	100	63.3
>41	5	3.2
Infertility type		
Primary	112	70.9
Secondary	46	29.1
Infertility Duration		
1-5	99	62.7
6-10	52	32.9
> 10	7	4.4
Previous ICSI		
0-3	156	98.7
4-6	2	1.3
Protocol Type		
GnRH Agonist	88	55.7
GnRH Antagonist	70	44.3

The study revealed statistically significant differences between the two protocols (GnRH Agonist, GnRH Antagonist) for women's body mass index (BMI) (p-value = 0.004) (Table 2).

Table 2. Comparison of different BMIs in both groups

BMI	GnRH Agonist	GnRH Antagonist
	No. (%)	No. (%)
< 30	30 (34.9%)	41 (56.9%)
\geq 30	56 (65.1%)	31 (43.1%)
Total	86 (100%)	72 (100%)

The study revealed no statistically significant differences between the two protocols (Agonist, Antagonist) in patient age (years), total dose, E2 level on HCG day, and endometrial thickness. In contrast, the duration of stimulation had a statistically significant difference between agonist and antagonist protocol longer duration for stimulation with agonist (p-value = .005) (Table 3).

Table 3. The baseline characteristics of the studied cases

Parameters	GnRH Agonist	GnRH Antagonist	P value
Age /years	32.4 \pm 5	33.3 \pm 4.4	0.248
Total dose	26.7 \pm 8.5	25.3 \pm 10	0.320
Duration of Stimulation	10 \pm 2	9.3 \pm 1.6	0.005
E2 at HCG day	2219 \pm 1063	2061 \pm 1127	0.367
End. Thickness	9.7 \pm 2	9.5 \pm 1.9	0.702

Our study showed that there were no statistically significant differences between the two protocols (Agonist, Antagonist); about poor response or failed fertilization and OHSS (p value > 0.05), while about Empty follicles had a statistically significant difference (p value = .032), cancellation rate (18.6%) with Antagonist protocol, and (6.8%) with Agonist protocol, revealed that more empty follicles and a high cancellation rate were associated with the antagonist protocol (Table 4).

Table 4. Comparison of differences between the two protocol groups

Parameter	GnRH Agonist	GnRH Antagonist	P-value
Cancellation Rate	6/88 (6.8%)	13/70 (18.6%)	–
Causes			
Empty Follicles	4/88 (4.5%)	10/70 (14.3%)	0.032
Poor Response	1/88 (1.1%)	0/70 (0%)	1.000
Failed Fertilization	1/88 (1.1%)	1/70 (1.4%)	0.961
OHSS	0/88 (0%)	2/70 (2.9%)	0.515

In this current study, there were no statistically significant differences between the two protocols (GnRH Agonist, GnRH Antagonist) in terms of the number of oocytes retrieved, number of embryos transferred, number of GI and pregnancy rate; (p value >0.05). However, there was a significant statistical difference in the number of MII (p-value = 0.028) (Table 5).

Table 5. Comparison of different ICSI outcomes in both groups

Parameters	GnRH Agonist	GnRH Antagonist	P value
No. of Oocytes Retrieved	5.6±2.9	4.9±2.9	0.314
No. of MII	3±2	2.4±1.9	0.028
No. of Embryo Transferred	2.2±0.9	2±0.9	0.127
No. of GI	1.8±0.9	1.6±0.8	0.144
Pregnancy Rate	15/88(17%) 15 / 158 (9.5%)	10/70(14.3%) 10/158(6.3%)	0.403

Discussion

The study was conducted at the Benghazi Teaching Hospital for Fertility and Assisted Reproduction and included a total of 158 patients diagnosed with polycystic ovary syndrome (PCOS). These patients were analyzed to compare the outcomes of two stimulation protocols—GnRH agonist and GnRH antagonist—undergoing IVF/ICSI. A statistically significant difference was observed between the two protocols with respect to women's body mass index (BMI) (p = 0.004). This finding is consistent with the study by Zhang J. et al. [24], which also reported differences in BMI between the two groups. In contrast, another study found no significant differences in BMI [25].

Regarding patient age, the present study revealed no statistically significant differences between the two protocols. This result aligns with the findings of Mahnaz Ashrafi et al. [28]. However, Zhang J. et al. [24] reported a significant difference in age between the groups. Our study reported that there was no statistical difference between the two groups in terms of estradiol levels, that similar to that of Mahnaz Ashrafi et al [25], while the study by Kaur H. et al the levels were higher in the agonist group [26,27]. In this study, the duration of stimulation had a statistically significant difference between the two protocol longer duration for stimulation with the antagonist (p-value = .005), which is consistent with other previous studies [25,28]. However, a study by Kadoura S, et al. reported a shorter duration of stimulation when using an antagonist protocol[27].

The GnRH-ant protocol has better clinical pregnancy outcomes when the endometrial thickness is in the medium thickness range of 7–10 mm [24]. The study revealed that there were no statistically significant differences between the two protocols regarding endometrial thickness that inconsistent with Kadoura S et al.'s study. There was a significant difference between the two protocols, with thinner endometrial thickness using the antagonist protocol [27].

In terms of the total dose of gonadotropin, the study revealed no statistically significant difference between the two protocols. This finding is consistent with the study by Mahnaz Ashrafi et al. [25]. However, it contrasts with the results reported by Behery et al., who found a statistically significant reduction in the total gonadotropin dose with the antagonist protocol [24,27,28]. Our study demonstrated a statistically significant difference in the cancellation rate (p = 0.032), with the antagonist protocol showing a higher rate of cancellation compared to the agonist protocol. This finding is in agreement with the study by Daniel Growa et al., which reported that the GnRH agonist group had a lower risk of cancellation before oocyte retrieval (4.3% versus 5.2%; p < 0.05) [29]. Conversely, Kadoura S. et al. reported no significant differences in cycle cancellation rates between the two groups [27].

The current study showed that there were no statistically significant differences between the two protocols regarding OHSS, similar to another study where no significant differences in the incidence of OHSS were found [30]. However, a study conducted by Behery et al and by Kaur H et al reported that there was a difference between the two groups in terms of ovarian hyperstimulation syndrome (OHSS) incidence. It was higher in the agonist group [25, 29,31]. In this current study, there were no statistically significant differences between the two protocols in terms of the mean number of oocytes retrieved (mean ± SD, 5.6 ± 2.9 vs. 4.9 ± 2.9, with p = 0.314), which coincides with the results of the studies of Minaretzis et al. and Hwang et al. [25, 32, 33]. However, there were significant differences between the two groups in terms of the

number of oocytes retrieved, which was significantly higher in the agonist group [26, 27]. The findings showed no statistical significance in terms of pregnancy rate; these findings were similar to the previous studies [24,26, 27,28]. However was significant in another study that the pregnancy rate was significantly lower in the antagonist group compared with the agonist group [31]. Our findings showed a significant statistical difference in the number of MII oocytes with the agonist protocol, that having a larger number of MII, similar to Mahnaz et al, there were significant differences regarding the number of Metaphase II oocytes between the two groups [25].

Conclusion

The study concluded that the GnRH Agonist protocol provided a more stable stimulation cycle with a significantly lower risk of cancellation and fewer empty follicles. However, since the final pregnancy rates and embryo quality remained comparable between the two, the choice of protocol may depend more on individual patient factors rather than the likelihood of a positive pregnancy test alone. However, the GnRH Agonist protocol appeared more favorable in this specific study due to lower cancellation rates and fewer empty follicles.

Recommendation

A subsequent prospective randomized controlled study is needed to confirm these results.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

References

1. Carmina E, Lobo RA. Polycystic ovary syndrome: arguably, the most common endocrinopathy is associated with significant morbidity in women. *J Clin Endocrinol Metab.* 1999;84(6):1897-9.
2. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. *Polycystic Ovary Syndrome.* Boston: Blackwell; 1992. p. 377-84.
3. Chang RJ. Polycystic ovary syndrome: diagnostic criteria. In: Chang RJ, Heinder J, Dunaif A, editors. *Polycystic Ovary Syndrome.* New York: Marcel Dekker; 2002. p. 361-5.
4. Polson DW, Wadsworth J, Adams J, Franks S. Polycystic ovaries: a common finding in normal women. *Lancet.* 1988;1(8582):870-2.
5. Abbott DH, Bacha F. Ontogeny of polycystic ovary syndrome and insulin resistance in utero and early childhood. *Fertil Steril.* 2013;100(2):2-3.
6. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19-25.
7. Rebar R, Judd HL, Yen SS, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J Clin Invest.* 1976;57(5):1320-9.
8. Balen AH. Hypersecretion of luteinizing hormone and the polycystic ovary syndrome. *Hum Reprod.* 1993;8(Suppl 2):123-8.
9. Kazer RR, Kessel B, Yen SS. Circulating luteinizing hormone pulse frequency in women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 1987;65(2):233-6.
10. Imse V, Holzapfel G, Hinney B, Kuhn W, Wuttke W. Comparison of luteinizing hormone pulsatility in the serum of women suffering from polycystic ovarian disease using a bioassay and five different immunoassays. *J Clin Endocrinol Metab.* 1992;74(5):1053-60.
11. Wildt L, Häusler A, Marshall G, et al. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. *Endocrinology.* 1981;109(2):376-85.
12. Gross KM, Matsumoto AM, Bremner WJ. Differential control of luteinizing hormone and follicle-stimulating hormone secretion by luteinizing hormone-releasing hormone pulse frequency in man. *J Clin Endocrinol Metab.* 1987;64(4):675-80.
13. Spratt DI, Finkelstein JS, Butler JP, Badger TM, Crowley WF. Effects of increasing the frequency of low doses of gonadotropin-releasing hormone (GnRH) on gonadotropin secretion in GnRH-deficient men. *J Clin Endocrinol Metab.* 1987;64(6):1179-86.
14. Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? *Am J Obstet Gynecol.* 1992;167(6):1807-12.
15. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab.* 1999;84(1):165-9.
16. Moller DE, Vidal-Puig A, Azziz R. Severe Insulin-Resistance Hyperandrogenic Syndromes. In: *Contemporary Endocrinology.* Totowa (NJ): Humana Press; [year unknown]. p. 129-307.
17. Kumar A, Woods KS, Bartolucci AA, Azziz R. Prevalence of adrenal androgen excess in patients with the polycystic ovary syndrome (PCOS). *Clin Endocrinol (Oxf).* 2005;62(6):644-9.
18. Cedars MI, Steingold KA, de Ziegler D, Lapolt PS, Chang RJ, Judd HL. Long-term administration of gonadotropin-releasing hormone agonist and dexamethasone: assessment of the adrenal role in ovarian dysfunction. *Fertil Steril.* 1992;57(3):495-500.

19. Goyal M, Dawood AS. Debates regarding lean patients with polycystic ovary syndrome: a narrative review. *J Hum Reprod Sci.* 2017;10(3):154-9.
20. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, Kolibianakis EM. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Hum Reprod.* 2010;25(3):683-9.
21. Ye H, Huang G, Pei L. A prospective, randomized controlled study comparing the effects of gonadotropin-releasing hormone agonist long and short protocols for in vitro fertilization. *Zhonghua Fu Chan Ke Za Zhi.* 2008;36(4):222-5.
22. Olivennes F, Belaisch-Allart J, Emperaire JC, Dechaud H, Alvarez S, Moreau L. Prospective, randomized, controlled study of in vitro fertilization. *Reprod Biomed Online.* 2004;8(4):419-30.
23. Depalo R, Jayakrishan K, Garruti G, Totaro I, Panzarino M, Giorgino F, Selvaggi LE. GnRH agonist versus GnRH antagonist in in vitro fertilization and embryo transfer (IVF/ET). *Reprod Biol Endocrinol.* 2012;10:26.
24. Zhang J, Sun YF, Xu YM, Shi BJ, Han Y, Luo ZY, Zhao ZM, Hao GM, Gao BL. Effect of endometrium thickness on clinical outcomes in luteal phase short-acting GnRH-a long protocol and GnRH-ant protocol. *Front Endocrinol (Lausanne).* 2021;12:578783.
25. Ashrafi M, Moini A, Mohammadzadeh A, Ezabadi Z, Zafarani F, Baghestani AR. A comparative study of GnRH antagonist and GnRH agonist in PCO patients undergoing IVF/ICSI cycles. *Iran J Reprod Med.* 2005;3(1):14-8.
26. Kaur H, Krishna D, Shetty N, Krishnan S, Srinivas M, Rao KA. A prospective study of GnRH long agonist versus flexible GnRH antagonist protocol in PCOS: Indian experience. *J Hum Reprod Sci.* 2012;5(2):181-6.
27. Kadoura S, Alhalabi M, Nattouf AH. Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/ICSI cycles of polycystic ovary syndrome women: a systematic review and meta-analysis. *Sci Rep.* 2022;12(1):4456.
28. Behery MA, Hasan EA, Ali EA, Eltabakh AA. Comparative study between agonist and antagonist protocols in PCOS patients undergoing ICSI: a cross-sectional study. *Middle East Fertil Soc J.* 2019;24:2.
29. Grow D, Kawwass JF, Kulkarni AD, Durant T, Jamieson DJ, Macaluso M. GnRH agonist and GnRH antagonist protocols: comparison of outcomes among good-prognosis patients using national surveillance data. *Reprod Biomed Online.* 2014;29(3):299-304.
30. Xia L, Tian L, Tan J, Zhang S, Wu Q. GnRH antagonist versus depot GnRH agonist protocol in polycystic ovary syndrome (PCOS): analysis using propensity score matching. *Arch Med Sci.* 2021. doi:10.5114/aoms/133574
31. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, van der Veen F, van Wely M. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. *Hum Reprod Update.* 2017;23(5):560-79.
32. Minaretzis D, Alper MM, Oskowitz SP, Lobel SM, Mortola JF, Pavlou SN. Gonadotropin-releasing hormone antagonist versus agonist administration in women undergoing controlled ovarian hyperstimulation: cycle performance and in vitro steroidogenesis of granulosa-lutein cells. *Am J Obstet Gynecol.* 1995;172(5):1518-25.
33. Hwang JL, Seow KM, Lin YH, Huang LW, Hsieh BC, Tsai YL, et al. Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pretreatment for patients with polycystic ovary syndrome: a prospective randomized study. *Hum Reprod.* 2004;19(9):1993-2000.