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Classical Antagonist Protocol in Comparison With Agonist Stop Protocol in Polycystic Ovary Syndrome Women Undergoing ICSI Trial: A Randomized Controlled Trial

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Abstract

Background and aim: Polycystic ovary syndrome (PCOS) is distinguished by hyperandrogenism, oligomenorrhea, and a cystic ovarian morphology. Ovarian hyperstimulation syndrome (OHSS) is more likely to occur in women with PCOS who undergo In vitro fertilization (IVF). The utilization of human chorionic gonadotropin (hCG) to begin the ovum's ultimate maturation is a significant mechanism in OHSS. The *ESHRE* guidelines recommend that in women with PCOS undergoing intracytoplasmic sperm injection (ICSI)/IVF treatment the gonadotrophin releasing hormone antagonist protocol is optimal or superior to gonadotrophin releasing agonist long protocol. In this study we aimed to compare pregnancy rate between classical (standard) antagonist protocol to agonist stop/antagonist protocol in women with PCOS undergoing ICSI as a primary outcome.

Patients and methods: It was an open randomized, parallel treatment clinical trial comparing classical antagonist protocol to agonist stop/antagonist protocol in PCOS women undergoing ICSI cycles. A total number of 150 participants divided randomly into two groups, group (A): 'classical antagonist protocol' group ($n = 75$) while group (B): 'agonist stop/antagonist protocol' group ($n = 75$).

Results: There was no significant variation in the pregnancy rate between the two groups. Duration of stimulation was also significantly longer among group B than group A. There was not a statistically significant distinction in OHSS amongst both groups, number of oocytes collected, number of embryos transferred, and fertilization rate.

Conclusion: In PCOS women undergoing ICSI/IVF treatment, the gonadotropin-releasing hormone (GnRH) antagonist protocol is equally effective as or more so than the gonadotrophin releasing agonist stop protocol. The benefits of both procedures can still be utilized.

Keywords: ICSI, Ovarian hyperstimulation syndrome, Polycystic ovary syndrome, Pregnancy

1. Introduction

Lack of menstrual cycles characterizes polycystic ovary syndrome (PCOS), the most frequent endocrinopathy affecting females of reproductive age, increased androgen levels and the development of cysts on the ovaries. In the 1980s, researchers first revealed the use of gonadotropin-releasing hormone

(GnRH) agonists in vitro fertilization (IVF).¹ The ideal timing of human chorionic gonadotropin (hCG) administration and ovum collection was made possible by GnRH agonists' capacity to block luteinizing hormone (LH) and stop premature LH surges, which raised IVF success rates. Long-term GnRH agonist therapies have since become standard practice and are most usually used.²

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In PCOS, excessive androgen levels, which have a detrimental effect on follicle production, are thought to be caused by elevated LH levels. Theoretically, greater follicular development could result from antagonist-mediated suppression of endogenous LH secretion and ovulation stimulation.³ There is an increased risk of ovarian hyperstimulation syndrome (OHSS) for females with PCOS who undergo IVF. An important mechanism in OHSS is the use of hCG to kick-start the ovum's final maturation. GnRH antagonist therapies, which employ GnRH agonist activation, have been created as a work-around for this issue.⁴

We hypothesized that luteal phase agonist will add value in PCOS women undergoing intracytoplasmic sperm injection (ICSI) regarding synchronization of both ovaries, more control or suppress of LH, so more improvement in embryo implantation and pregnancy outcome besides benefits of antagonist in preventing OHSS.

The Objective of this work was to evaluate pregnancy rate among classical antagonist protocols to agonist stop/antagonist protocol in females with PCOS undertaking ICSI.

2. Patients and methods

It was an open randomized, parallel treatment clinical trial comparing classical antagonist protocol to agonist stop/antagonist protocol in PCOS women undergoing ICSI cycles. Recruitment of participating women had been from the Infertility Outpatient Clinics of International Islamic Centre for Population Studies and Research at Azahar University, Cairo, Egypt from January 2021 to December 2022. A total number of 150 participants divided randomly into two groups, group (A): 'classical antagonist protocol' group ($n = 75$) while group (B): 'agonist stop/antagonist protocol' group ($n = 75$).

Prior to taking part in the study, all participants were asked to provide informed and written permission. The study includes two PCOS treatment groups: group I 'the antagonist protocol group' where they will do ICSI using classical antagonist protocol as follow:

Starting from cycle day 2, where trans vaginal ultrasound were done, serum follicle-stimulating hormone (FSH)/E2 will be checked, the starting dose adjusted according to age, BMI, anti-müllerian hormone (AMH) or number of antral follicles noted by trans vaginal ultrasound, then, follow-up of the response with adjustment of dose, then the antagonist will be added when main follicle cohort greater than or = 14 mm or serum E2 greater than or = 350 pg/ml, then trigger when follicles reaching

maturity. Group II 'agonist stop/antagonist protocol group' where they will receive mid luteal agonist in the preceding ICSI cycle before starting classical antagonist protocol.

2.1. Inclusion criteria

Only women under 35 years with PCOS criteria according to ESHRE RO. TERDAM 2003, with normal tubes either by H.S.G and/or laparoscopy, with partners having normal male semen parameters and free from other endocrine abnormalities were involved in the research.

2.2. Exclusion criteria

Cases not fulfilling the previously mentioned criteria or refusing to share in the study were excluded.

In group (A), starting from cycle day 2, where serum E2 was checked to be less than 50 pg/ml the starting dose adjusted according to age, BMI, AMH and number of antral follicles, then, follow-up of the response with adjustment of dose, then the antagonist was added when main follicle cohort greater than or = 14 mm or serum E2 greater than or = 350 pg/ml, then trigger when follicles reaching maturity. On the other hand, group II received mid luteal agonist in the preceding ICSI cycle before starting classical antagonist protocol.

2.3. Sample size

The sample size was determined utilizing the following assumptions and a research based on work by Prapas *et al.*⁵: Confidence at the 95% level, with 80% power, and 5% margin of error. In the end, the largest possible output sample size was 227.45. As a result, the number of individuals was raised to 250 to account for potential dropouts during the follow-up phase of the research.

$$\left(\frac{Z_{a/2} + Z_B}{P_1 - P_2}\right)^2 (p_1q_1 + p_2q_2)$$

Takazawa and Morita.⁶

n = sample size.

$Z_{a/2}$ (The critical value that divides the central 95% of the Z distribution).

Z_B (The critical value that divides the central 20% of the Z distribution).

p_1 = Accuracy prevalence in group A.

p_2 = Accuracy prevalence in group B.

2.4. Statistics/data analysis

All collected data was inputted into a computer and analyzed statistically utilizing SPSS (Statistical Package for the Social Sciences) version 26. The data were tested for normalcy with the help of the Shapiro-Wilks method. Numbers and percentages were utilized to illustrate the qualitative information. The χ^2 and Fisher exact tests were utilized to determine statistical significance between the indicated differences in qualitative variables. Quantitative information was summarized by means \pm SD. A Student *t*-test and a Mann Whitney test were utilized to match the two groups' means on parametric and nonparametric quantitative variables, respectively. Statistical significance is estimated by a *P* value less than 0.05.

3. Results

Table 1.

Table 1. Infertility data amongst the examined groups.

Variable	Group A <i>n</i> = 75	Group B <i>n</i> = 75	<i>P</i> value
Type of infertility			
Primary, <i>n</i> (%)	42 (56)	36 (48)	0.414
Secondary, <i>n</i> (%)	33 (44)	39 (52)	
Duration of infertility			
Mean \pm SD	3.9 \pm 2.1	4.5 \pm 1.9	0.105
Median (Range)	4 (1, 7)	5 (1, 7)	

χ^2 , Chi square test; Mann–Whitney *U* test.

^a*P* is significant at less than 0.05.

Table 2. Comparing the ovulation and pregnancy rates of the two groups.

Variable	Group A <i>n</i> = 75	Group B <i>n</i> = 75	<i>P</i> value
Ovulation rate			
Yes, <i>n</i> (%)	39 (52)	37 (49.3)	0.870
No, <i>n</i> (%)	36 (48)	38 (50.7)	
Pregnancy rate			
Yes, <i>n</i> (%)	30 (40)	40 (53.3)	0.141
No, <i>n</i> (%)	45 (60)	35 (46.7)	

This table shows:

Primary infertility was reported in our patients 56% and 48% among group A and B correspondingly with no significant variation. There was no significant distinction between the examined groups concerning duration of infertility (Fig. 1, Table 2).

This table shows:

There was no significant distinction amongst the examined groups as regard ovulation rate and pregnancy rate (Table 3).

This table shows:

There was a statistically significant distinction amongst the investigated groups concerning Stimulation duration. There was no significant variation among the examined groups regarding OHSS, NO. of oocyte retrieved, NO. of embryo transferred and Fertilization rate (Fig. 2).

4. Discussion

All previous studies used the OHSS rate as their primary indicator of success, however the validity of

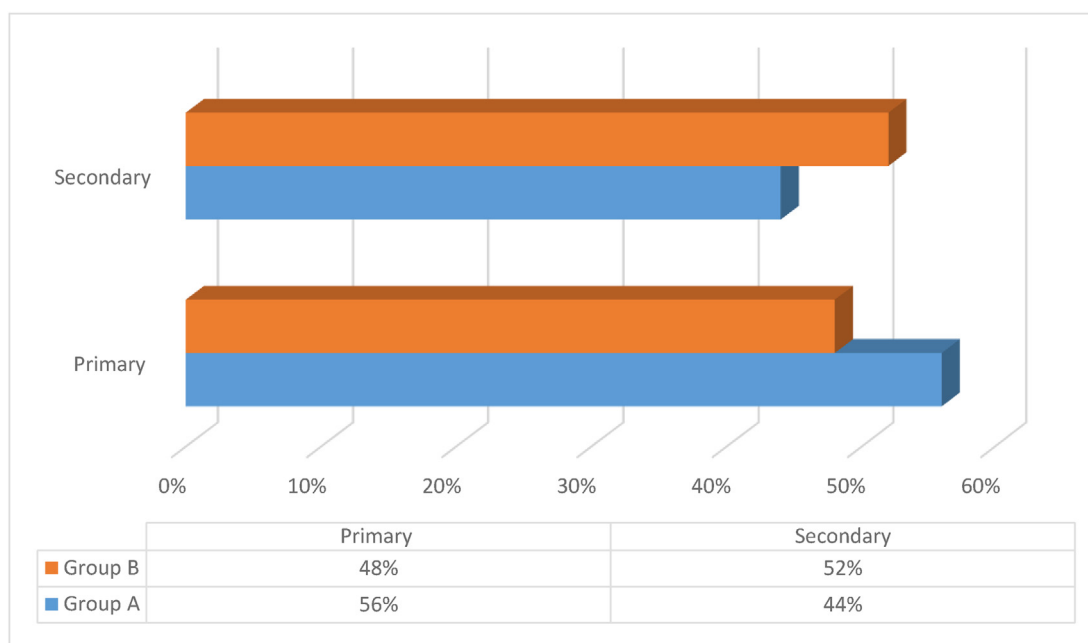


Fig. 1. Type of infertility amongst the two investigated groups.

Table 3. Comparing outcome measures amongst the two groups.

Variable	Group A n = 30	Group B n = 30	P value
Stimulation duration			
Mean \pm SD	10.4 \pm 1.2	10.8 \pm 1.1	0.035*
Median (Range)	10 (9, 12)	11 (9, 12)	
OHSS			
Mild, n (%)	43 (57.3)	45 (60)	0.891
Moderate, n (%)	23 (30.7)	20 (26.7)	
Severe, n (%)	9 (12)	10 (13.3)	
No. of oocyte retrieved			
Mean \pm SD	14.1 \pm 3.2	13.6 \pm 3.3	0.504
Median (Range)	14 (9, 19)	13 (9, 19)	
No. of embryo transferred			
Mean \pm SD	2.9 \pm 1.4	2.9 \pm 1.4	0.849
Median (Range)	3 (1, 5)	3 (1, 5)	
Fertilization rate			
Yes, n (%)	36 (48)	38 (50.7)	0.870
No, n (%)	39 (52)	37 (49.3)	

the meta-analysis was limited because the study locations used various OHSS classification schemes. Theoretically, a GnRH antagonist therapy could decrease the OHSS rate. Also, it is feasible that it is not required to use OHSS rates as the major outcome measurement.⁷ According to the suggestions stated in the guidelines, the gonadotrophin releasing hormone antagonist protocol is optimal or preferable to the gonadotrophin releasing agonist long protocol for PCOS-affected women getting ICSI/IVF treatment. For PCOS patients having ICSI,

Matteo believes that luteal phase agonists will be helpful in terms of synchronizing the two ovaries and improving control over or lowering LH. As a result, improvements in embryo implantation and pregnancy outcomes will emerge along with the benefits of antagonist in lowering OHSS.⁸

Our study was aiming to compare pregnancy rate between classical antagonist protocols to agonist stop/antagonist protocol in cases with PCOS undergoing ICSI. It was an open randomized, parallel treatment clinical trial comparing classical antagonist protocol to agonist stop/antagonist protocol in PCOS women undergoing ICSI cycles. Primary infertility was reported in our patients 56% and 48% among group A and B correspondingly with no significant variation. There was not a significant distinction among the two distinct groups in terms of infertility duration or ovulation rate. There was no a significant distinction in the pregnancy rate amongst the two groups analyzed. Period of stimulation was also significantly longer among group B than group A. No significant difference among the two investigated groups concerning OHSS, number of oocyte retrieved, number of embryo transferred and fertilization rate.

Research comparing agonist and antagonist methods has yielded conflicting results. The fixed GnRH-ant treatment was linked with a 5% lower pregnancy rate matched to the usual GnRH-a long

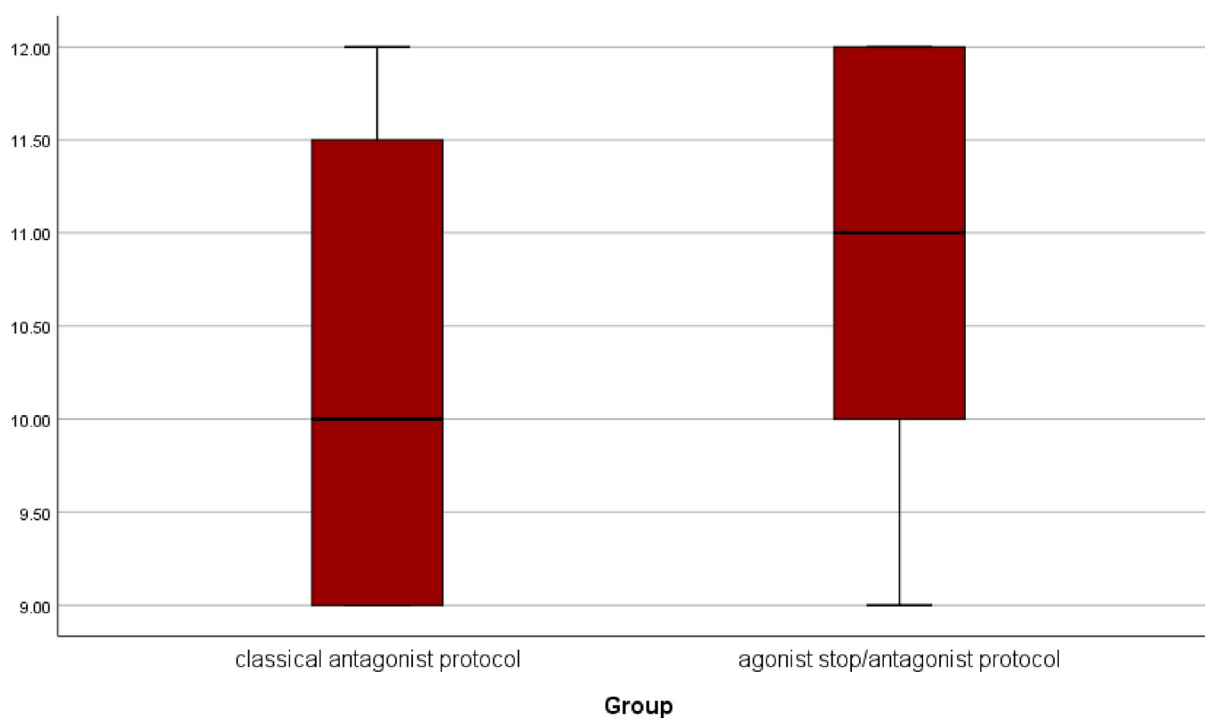


Fig. 2. Stimulation duration among the two groups.

strategy, according to a meta-analysis conducted by Al-Inany.⁹ However, a second research by Kolibianakis *et al.*¹⁰ found no significant variation in the likelihood of a live birth among GnRH-ant and GnRH-a by conducting a meta-analytic evaluation of 22 randomized controlled trials (RCTs) published as full articles in peer-reviewed journals. Thirdly, a revised meta-analysis by Al-Inany *et al.* found no significant distinction in pregnancy rates among GnRH agonist and GnRH ant regimens.¹¹ According to Singh *et al.*, the antagonist group required a significantly lower dose of gonadotropin. The total number of retrieved oocytes, the proportion of M2 oocytes, the rate of fertilization, the rate of cleavage and the proportion of Grade 1 embryos were comparable among the two subgroups. There were no appreciable differences in the pregnancy rate either. Moderate OHSS was present in two individuals on the agonist regimen and none on the antagonist regimen; however, there was no statistically significant variation.¹²

Individuals with PCOS have been the subject of several research evaluating agonist and antagonist treatments, with wildly varying outcomes. In a randomized prospective pilot research conducted by Bahçeci *et al.* in 2005, it was discovered that the antagonist group had considerably less M2 oocytes than the agonist group did in terms of both the number of days of stimulation and the total gonadotropin dose administered. Moreover, they discovered no discernible difference in OHSS incidence between these two groups.¹³ Additionally, Ashrafi *et al.* discovered that the number of recovered oocytes and M2 oocytes were considerably higher in the antagonist group in their RCT. The overall dose of gonadotropins, the rate of fertilization and the number of pregnancies all showed no statistically significant differences. The number of cases in danger of OHSS (E2>3000 pg/ml) was unexpectedly greater in the antagonist group.¹⁴

4.1. Conclusion

In PCOS women undergoing ICSI/IVF treatment, the GnRH antagonist protocol is equally effective as or more so than the gonadotrophin releasing agonist stop protocol. The benefits of both procedures can still be utilized.

Authorship

All authors have a substantial contribution to the article.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Conflicts of interest

The authors declared that there were no conflicts of interest.

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