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Comparative study between fixed and flexible GnRH antagonist protocol versus GnRH agonist long protocol in polycystic ovarian disease patients treated with IVF

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Abstract:

The objective of the present study was to compare and evaluate the effectiveness and safety of GnRH agonist long protocol compared with the GnRH antagonist (fixed and flexible) protocols in polycystic ovary syndrome (PCOS) patients undergoing in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) cycles. This study was carried out on 60 patients with polycystic ovarian disease undergoing ICSI, their age ranged from (20 to 40 years). The cases were selected from The International Center for Population Study and Research (ICPS), Al-Azhar University. Eligible patients who accepted to take part in the study were randomized into 3 study group: Group A: 20 patients were included in agonist protocol, Group B: 20 patients were included in fixed antagonist protocol and Group C: 20 patients were included in flexible antagonist protocol. The results obtained from this study indicated no statistically significant differences regarding the pregnancy rates or regarding the developing of ovarian hyperstimulation syndrome (OHSS) complication in the studied population; so larger studies with larger sample size and longer duration are needed to clarify the roles of different IVF protocols.

Keywords:

Gonadotropin-releasing hormone agonist, gonadotropin-releasing hormone antagonist, *in vitro* fertilization, polycystic ovarian syndrome

Introduction:

Polycystic ovary syndrome (PCOS) is a common endocrinal disorder affecting 6.6-8% of women in childbearing period **(1)**. It is associated with 75% of the causes of anovulatory infertility (2).

The polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that, gathered together, form a spectrum of a disorder with a mild presentation in some and in others a severe disturbance of reproductive, endocrine and metabolic function.The definition of the syndrome has been much debated. Key features include menstrual cycle disturbance, hyperandrogenism and obesity.There are many extra-ovarian aspects to the pathophysiology of PCOS, yet ovarian dysfunction is central. At a joint consensus meeting of the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology (ASRM/ESHRE) a refined definition of the PCOS was agreed,namely the presence of two out of the following three criteria: oligo- and/or anovulation, hyperandrogenism (clinical and/or biochemical), polycystic ovaries with the exclusion of other etiologies. The morphology of the polycystic ovary has been redefined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (> 10 cm3)(3).

The pathophysiology of PCOS is likely to be multifactorial and polygenic. There is a significant body of evidence suggesting that excess ovarian androgen production is central in the pathogenesis of PCOS **(4)**.

One of the main problems occurring in patients with PCOS undergoing IVF / ICSI is developing ovarian hyperstimulation syndrome (OHSS); a serious iatrogenic complication of ovarian stimulation induced and triggered by exogenous and/or endogenous HCG which varies from mild to severe and critical forms **(5)**.

The long GnRH agonist protocol has been used for pituitary desensitization in patients with PCOS undergoing IVF / ICSI with the benefit of significant reduction in the occurring of premature LH surges and the frequency of cycle cancellation **(6).**

GnRH antagonist down-regulation protocol in IVF / ICSI has gained much popularity over the last few years **(7).** It acts by competitive inhibition of GnRH receptors in pituitary, and produce an immediate and rapid reduction in LH and FSH levels without GnRH receptor

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desensitization as well as flare-up effect. Previous studies have shown that GnRH antagonist protocols decrease the incidence of OHSS as well as the amount of gonadotropins used and the duration of stimulation as compared with GnRH agonist protocols in the general population [8].

In the last years, there was more interest in using GnRH antagonist protocol in patients with PCOS treated with IVF with the aim of reducing the incidence of OHSS in this vulnerable group of patients. Recent studies showed that GnRH antagonist protocol to be as effective as the GnRH agonist LP in PCOS patients with lower rates of OHSS [9].

Patients and Methods

This study was carried out on 60 patients with polycystic ovarian disease undergoing ICSI. The cases was selected from The International Center for Population Study and Research (ICPS), Al-Azhar University. **The study was approved by the Ethics Board of Al-Azhar University.**

Inclusion criteria

- Age group between 20-40 years.
- Normal prolactin and thyroid function tests.
- Normal cardiac, hepatic and renal functions.
- Normal spontaneous onset of puberty and normal sexual development.
- Normogonadotrophic females.
- Day 2 FSH level below 10 IU/L.
- PCOS patients (fulfilling Rotterdam criteria of PCOS)[3].
- Body mass index (BMI) <35kg/m2.

Exclusion criteria

Poor response in previous intracytoplasmic sperm injection (ICSI) cycles.

- History of previous ovarian surgery.
- Uterine factor infertility.
- Severe male factor infertility.
- Patients with endometriosis or ovarian cyst.
- Thyroid and prolactin disorders.
- Anatomical abnormality in uterus or cervix or hydrosalpinx.
- Disorders in cardiac, hepatic and renal functions.

Randomization:

Eligible patients who accepted to take part in the study were randomized into 3 study group
Group A: 20 patients were included in agonist protocol.
Group B: 20 patients were included in fixed antagonist protocol.
Group C: 20 patients were included in flexible antagonist protocol.

Ovarian stimulation

All patients received oral contraceptive pills starting on day 4 of spontaneous menses of the cycle prior to the treatment cycle for 21 days pretreatment in the cycle preceding ovarian stimulation.

Ovarian stimulation was commenced on day 2 of spontaneous or progesterone withdrawal bleeding. The starting dose was adjusted according to patient's age, antral follicle count (AFC) and prior response to gonadotropin stimulation as per unit protocol. We used step up protocol of gonadotropin stimulation and the dose was adjusted every 3-4 days according to ovarian response. The gonadotropin preparations used were highly purified FSH (Fostimone (IBSA, Switzerland) and highly purified hMG (Merional, IBSA, Switzerland).

In Group A: GnRH agonist (long protocol) group, GnRH agonist, lucrine (Abbott Cedex, Istanbul, Turkey) 0.1 mg / day was started on day 21 of the pre-treatment cycle. When pituitary desensitization was achieved, ovarian stimulation was started and the GnRH agonist was decreased to 0.05 mg / day till day of HCG. Down regulation was confirmed by biochemical markers (LH <5 IU/ml, E2 <50 pg/ml and progesterone <1 ng/ml) and transvaginal ultrasound (TVS) assessment of endometrial thickness (ET) and ovarian status (ET <3 mm, no ovarian cyst >2 cm).

In Group B: (fixed antagonist protocol), we started the gonadotrophin on cycle day 2 when ovarian suppression is assured. Then GnRH antagonist 0.25 mg cetrorelix; cetrotide (Serono) was given daily on stimulation day 6 of menstrual cycle and was continued till the day of hCG.

In Group C (flexible antagonist protocol), Ovarian stimulation was commenced on day 2 of the cycle , daily intramuscular injection of gonadotrophin was started, 0.25 *mg* of GnRH antagonist (cetrorelix acetate, Cetrotide; Merck Serono SA, Switzerland) was started when a leading follicle reached 14 mm and continued till the day of HCG.

Ovarian triggering

Ovarian follicular response was monitored with transvaginal ultrasound. Ultrasound scanning was started on stimulation day 7 then every other day. HCG injection was given (Choriomone 10,000 IU im, Choriomone, IBSA, Switzerland) when at least 3 follicles greater than 16 mm in diameter were detected on transvaginal ultrasound scan with the leading follicle reached 18-20 mm in diameter.

Oocyte retrieval was performed under anesthesia 36 hours after HCG administration. Fertilization was performed by standard IVF or ICSI. Cleavage stage embryo transfer (ET) was performed on day 2 or day 3.

Embryo transfer was performed under abdominal ultrasound guide for proper embryo placement to the mid-uterine cavity. Two to five grade A or B embryos were transferred as per unit protocol. Embryo transfer was performed with a Wallace catheter (Smith Medical International Ltd, Hythe, Kent, UK).

Progesterone support of luteal phase was commenced on the day of ET with 800 mg micronized progesterone vaginally till 12 weeks of pregnancy.

A serum HCG pregnancy test was performed 14 days after ET. Clinical pregnancies were confirmed by at least one ultrasonographically confirmed viable fetus within the uterus 4 weeks after ET.

Statistical methodology:

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc, Chicago) version 17 for Microsoft Windows. Data were described in terms of mean $\pm$ SD (standard deviation) for continuous variables and frequencies (number of cases) and percentages for categorical data. A one-way analysis of variance (ANOVA) was used when comparing between more than two means, kruskall Wallis test for multiple group comparisons in non-parametric data and Chi square test was used to compare categorical data.

P value <0.05% was considered significant.

Results:

This study was carried out on 60 patients with polycystic ovarian disease undergoing ICSI, they then divided into three protocols; 20 patients for each one; (20 patient for long agonist protocol, 20 patients for fixed antagonist protocol and 20 patients for flexible antagonist protocol).

Table (1): Baseline characteristics of the studied population; (N=60):

Characteristics	Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*P value*
Age (years)	32.55±3.634	31.75±3.447	30.75±3.972	NS
BMI (kg/m2)	24.85±2.183	24.25±1.372	24.75±1.970	NS
FSH (m IU/ml)	6.05±0.887	6.45±0.945	5.90±0.852	NS
E2 (pg/ml)	42.20±6.818	42.00±1.522	43.80±6.118	NS

P value≤ .05 significant (S), P value≥.05 Non significant (NS

Table (1) summarized the baseline characteristics of patients enrolled in the three protocol groups. There was no significant difference in mean age, BMI, day 2 FSH, and E2 level

Table (2): Causes of infertility in the studied population; (N=60):

Causes of infertility	N (%) Group (A)	Group (B)	Group (C)	*P value*

	N= 20	N= 20	N= 20	
Tubal	8(40%)	7(35%)	9(45%)	NS
Unexplained	6(30%)	6(30%)	5(25%)	NS
Male	4(20%)	5(25%)	4(20%)	NS
Male and female	2(10%)	2(10%)	2 (10%)	NS

P value≤ .05 significant (S). P value≥.05 Non significant (NS)

Table (2) illustrated the causes of infertility among the studied groups; the different causes of infertility were nearly equally distributed among the studied groups with no statistically significant difference. Tubal factor was highest in group (C) while unexplained infertility was lowest in the same group. Male infertility was highest among group (B) and mixed (male and female) infertility was highest in group (C); however all differences were not significant statistically *(p-values >0.05).*

Table (3): Hormonal data of the studied 3 groups; (N=60):

Data	Mean ±SD Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*P value*
Days of HMG	13.55±1.356	9.85±1.424	8.15±.875	S
Doses of HMG	2369.50±738.580	1690±197.084	1502.50±788.482	NS
Endometrial thickness	13.05±1.395	9.90±1.832	11.05±1.468	S
E2 level at HCG	2727.50±363.273	2965.00±318.343	1450.00±280.507	S

As summarized in table (3); the days of HMG was significantly highest among the group (A) with a mean of 13.55 ±1.356 as compared with group (B) and group (C) where the mean was 9.85 ±1.424 and 8.15 ±.875 days for groups (B) and (C) respectively with p-value <0.05.
Regarding the dose of HMG; no statistically significant difference was detected between the three groups.
The endometrial thickness was significantly highest among the group (A) with a mean of 13.05 ±1.395 (mm) as compared with group (B) and group (C) where the mean was 9.90 ±1.832 and 11.05 ±1.468 (mm) for groups (B) and (C) respectively with p-value <0.05.
E2 level at HCG was significantly lowest among the group (C) with a mean of 1450.00 ±280.507 as compared with group (A) and group (B) where the mean was 2727.50 ±363.273 and 2965.00 ±318.343 for groups (A) and (B) respectively with p-value <0.05.

Table (4): Clinical data of the studied 3 groups; (N=60):

Data	Mean ±SD Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*P value*
N. of oocytes retrieved	12.55±1.317	11.35±1.899	10.55±1.395	NS
N. of MII oocyte	8.30±1.261	7.30±1.418	5.90±.912	S
N. of MI oocyte	2.90±788	2.15±.875	2.00±.858	NS
N. of degenerate oocyte	2.30±0.865	2.90±.788	2.05±.826	NS

As regard the number of oocytes retrieved; no statistically significant difference was detected between the three groups.
Number of MII oocyte was significantly lowest among the group (C) with a mean of 5.90 ±.912 as compared with group (A) and group (B) where the mean was 8.30 ±1.261 and 7.30 ±1.418 for groups (A) and (B) respectively with p-value <0.05. However; no statistically significant difference was detected between the three groups regarding the number of MI oocyte. The same finding was observed

regarding the number of degenerate oocyte where no statistically significant difference was detected between the three groups.

Table (5): Number of embryos between studied 3 groups; (N=60):

Data	Mean ±SD Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*P value*
Number of embryos	7.15±1.182	6.20±1.105	4.80±1.105	S
Number of ET	2.85±.813	2.90±.788	2.80±.834	NS

As regard the number of embryos; the number was significantly lowest among the group (C) with a mean of 4.80 ±1.105 embryos as compared with group (A) and group (B) where the mean was 7.15 ±1.182 and 6.20 ±1.105 for groups (A) and (B) respectively with p-value <0.05.
Regarding the number of ET; no statistically significant difference was detected between the three groups.

Table (6): Pregnancy rates of ICSI cycles between 3 groups; (N=60):

		N (%) Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*p-value*
Pregnancy	Yes	9(45%)	10(50%)	7(35%)	NS
	No	11(55%)	10(50%)	13(65%)	

As demonstrated in table (6); pregnancy was confirmed in 9 cases (45%) of group (A), 10 cases (50%) of group (B) and 7 cases (35%) of group (C) with no statistically significant difference between the studied 3 groups p-value >0.05

Table (7): Cycle cancellation rate among the 3 groups; (N=60)

		N (%) Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*p-value*
Cancellation	Cancelled	2(10%)	2(10%)	1(5%)	NS
	Not cancelled	18(90%)	18(90%)	19(95%)	

As mentioned in table (7); protocol cancelation was done for 5 cases; 2 cases (10%) of group (A), 2 cases (10%) of group (B) and only one case (5%) of group (C) with no statistically significant difference between the studied 3 groups (p-value >0.05).

Table (8): Causes of Cycle cancellation among the 3 groups; (N=5):

		N (%) Group (A) N= 2	Group (B) N= 2	Group (C) N= 1	*p-value*
Causes	Poor responder	1(5%)	1(5%)	1(5%)	NS
	Negative fertilization	1(5%)	1(5%)	0(0%)	

An regarding the causes of cancellation in the 5 cancelled cases; as mentioned in table (8)
Three cases were cancelled due to poor response (one case in each group of the three studied groups) and 2 cases were cancelled due to negative fertilization [1 case from group (A) and the other case from group (B)] with no statistically significant difference between the studied 3 groups (p-value >0.05).

Table (9): Moderate ovarian hyperstimulation syndrome (OHSS) rates in the studied 3 groups; (N=60):

		N (%)			
		Group (A) N= 20	Group (B) N= 20	Group (C) N= 20	*p-value*
Moderate OHSS	Yes	2(10%)	0	0	NS
	No	18(90%)	20(100%)	20(100%)	

As mentioned above; 2 patients (10%) of group (A) developed moderate OHSS, but none of the patients in group (B) and group (C) had this complication with no statistically significant difference between the studied 3 groups p-value >0.05

Discussion

The present study aimed to compare between GnRH agonist long protocol and GnRH antagonist protocols (fixed and flexible) in cases of polycystic ovarian diseases (PCO) treated by in vitro fertilization (IVF). The study was carried out on 60 patients with PCOS undergoing ICSI, 20 patients for each protocol where the cases were selected from The International Center for Population Study and Research (ICPS), Al-Azhar University.

In our study; the patients' age ranged from 20 – 40 years old with no statistically significant differences between the three studied groups. By including only patients with BMI <35, we excluded the possibility of the negative effect of high BMI on LH surge[(10)], the three studied groups had no significant differences regarding BMI. The distribution of causes of infertility in our studied population was similar among the three studied groups with no statistically significant difference between them.

Regarding the duration of administration of HMG to attain ovarian stimulation for IVF; there was a significant difference in the duration length were it was longest among the agonist protocol (Group A) with a mean duration of (13.55 ±1.356 days), while in the fixed antagonist protocol and the flexible antagonist protocol, the duration was shorter. Our finding was matched with many other studies as the reported by **Bahçeci *et al.*** where they reported a significantly lower duration in antagonist group [(11)]. However; no difference in days of stimulation between two groups were reported by **Kaur *et al.***, in their published prospective controlled study comparing long agonist protocol with flexible antagonist protocol [(12)].

Regarding the total gonadotrophin units required for stimulation; our results revealed no statistically significant difference in the required dose between the three studied groups which was opposite to the reported in a similar study in this regard where total dose of gonadotrophins was significantly lower in antagonist group[(12)]; however **Ashrafi and his colleges** reported no statistically significant decrease in amount of total gonadotrophin units required although it was very near to significant level[(13)]. The endometrial thickness was significantly highest among agonist protocol (Group A) with a mean thickness of (13.05 ±1.395 mm) followed by flexible antagonist protocol. Endometrial thickness was significantly smallest among females in fixed antagonist protocol as compared to other two groups with a mean of (9.90 ±1.832). Our results were similar to the results of ***Huang et al.*** [(14)], whose study included patients undergoing IVF and embryo transfer [(14)]. We have not been able to prove that the reduced endometrial thickness has any impact on the CPR. The fertilization rate showed no differences between the groups.

According to serum E2 level on day of hCG injection, females in fixed antagonist protocol group had significantly lower E2 level as compared to other two groups with a mean of (1450.00 ±280.507). On the contrary, **Ashrafi and his colleges** reported no statistically significant difference of E2 level between the two groups in their study [(13)].

The total number of retrieved oocytes were higher in agonist protocol (Group A) but without statistically significant difference between the studied groups. Although it was not statistically significant difference but it is opposite to the reported in many other studies that reported decrease in number of oocytes and other embryological data in the antagonist group than the agonist group[(15-17)], but most of these studies was done on general populations (PCO and non PCO patients).

The pregnancy rates in the present study was not significantly different between the studied three groups (45%, 50% and 35%) in the agonist, fixed antagonist and flexible antagonist protocols respectively. Our findings were different than the reported in many other studies where; **Orvieto and his colleges**found significant higher pregnancy rate in long agonist protocol compared with the GnRH antagonist protocol (36% vs. 19%) while two other similar studies showed no difference in pregnancy rate between two regimens[18-20].

Lainas and his colleges compared flexible GnRH antagonist protocol with long agonist protocol in PCOS patients and found that there was no difference in ongoing pregnancy rate. They concluded that, antagonist protocol should be the treatment of choice in PCOS patients [21]. More other studies also reflected the same view [22-23].

In this present study; protocol cancelation was done for 5 cases only; 2 cases of group (A), 2 cases of group (B) and only one case of group (C) with no statistically significant difference between the studied 3 groups. This finding was comparable with many other studies in this regard as the reported in a similar study to compare different protocols of GnRH where the cancellation rate was higher than the reported in our study but did not significantly differ between the studied groups [24].

Moderate ovarian hyperstimulation syndrome (OHSS) in the present study developed only in 2 cases from the studied population and both cases belonged to the GnRH agonist protocol group; but without statistically significant difference between the studied groups. This statistically insignificant difference may be because of the number of patients included in the study. A similar study in an Indian experience in 2012 of GnRH long agonist versus flexible GnRH antagonist protocol in PCOS reported 16 cases with OHSS in the agonist protocol which was significantly higher than the 2 cases reported in the antagonist protocol [12].

Pundir *et al.* [25] in a meta-analysis, which included 9RCTS with 966 women, tried to find whether GnRH antagonist protocol reduces the risk of OHSS in PCOS patients. There was no difference in severe OHSS rate but when moderate and severe OHSS cases were pooled, there was significant lower incidence in antagonist group [25].

Conclusion:

The results obtained from this study indicated no statistically significant differences regarding the pregnancy rates or regarding the developing of OHSS complication in the studied population; so larger studies with larger sample size and longer duration is needed to clarify the roles of different IVF protocols.

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