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Research Article

Fixed gonadotropin-releasing hormone antagonist protocol versus gonadotropin-releasing hormone agonist long protocol in patients with polycystic ovary syndrome treated for intracytoplasmic sperm injection cycles

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ABSTRACT

Background: Women with polycystic ovary syndrome (PCOS) are at risk of developing ovarian hyperstimulation syndrome (OHSS) during ovarian stimulation. Use of GnRH antagonist in the general sub fertile population is associated with lower incidence of (OHSS) than agonists and similar probability of live birth but it is unclear. Our Objective was to compare the fixed GnRH antagonist and GnRH agonist long protocols in patients with PCOS undergoing IVF.
Methods: In this randomized controlled trial (RCT), 200 patients with PCOS were randomly allocated in two groups: long GnRH (n = 100) and fixed GnRH antagonist protocol (n = 100).
Results: There is significant difference was observed in chemical pregnancy rate (46.0% versus 31.0%), and clinical pregnancy rate (43.0% versus 29.0%) in agonist and antagonist protocols, respectively. Duration of stimulation was significantly higher in agonist group (13.58 versus 12.381 days), respectively. Total number of ampoules of gonadotrophin is comparable in both groups (t=1.914, p=0.057).
Conclusions: The use of GnRH antagonists is more advantageous than GnRH agonists in relation to shorter duration of stimulation thus allowing a reduction in the treatment time that makes COS less costly and better patient compliance. In this study GnRH agonist shows higher pregnancy rate than antagonist, so larger studies needed to clarify their roles.

Keywords: Gonadotrophin-releasing hormone agonist, Gonadotrophin-releasing hormone antagonist, In-vitro fertilization, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of an ovulatory infertility characterized by chronic anovulation and hyperandrogenism.[1] The current diagnosis of PCOS is defined according to Rotterdam criteria. Diagnosis depends on two of the following criteria only; (1) clinical and/or biochemical evidence of hyperandrogenism with exclusion of other causes of androgen excess; (2) oligo or anovulation; (3) polycystic ovaries by ultrasound (ovarian volume >12cc with 10 or more follicles 2-8mm in diameter, arranged around echodense stroma).[2] PCOS is also reported to be associated with obesity, insulin resistance and type 2 diabetes, dyslipidaemia, hypertension, cardiovascular disease and late menopause endometrial carcinoma.[6-10] Frequently encountered endocrine features are hypersecretion of LH, hyperandrogenemia and compensatory hyperinsulinaemia.[3,4] The optimal infertility treatment for PCOS women is still a matter of

controversy. Recently, a consensus was reached on treatment for PCOS patients that includes the use of clomiphene citrate, exogenous gonadotrophins, laparoscopic ovarian surgery and IVF.[5] IVF is an effective treatment after repeated failure of ovulation induction by clomiphene citrate and gonadotrophins.[3,4] Tonic hypersecretion of LH is thought to be one of the major factors responsible for a high miscarriage rate, poor oocyte quality and low fertilization and cleavage rate in PCOS patients.[11-15] In patients undergoing IVF treatment, the elevated mean follicular phase serum LH level has adetrimental effect on the fertilization rate, cleavage rate and pregnancy outcome.[16] To reduce LH concentrations throughout the follicular phase and to prevent a premature LH surge, controlled ovarian stimulation (COS) with gonadotrophin after down regulation with GnRH agonist, the GnRH agonist long protocol is the most frequently used protocol for PCOS patients.[4,12-14]

Several studies have suggested that the duration of GnRH agonist administration needed to achieve pituitary suppression for PCOS patients is usually longer than that for normal ovulatory patients.[4,17,18] PCOS patients undergoing IVF have a high risk of developing ovarian hyperstimulation syndrome (OHSS), a serious iatrogenic complication of ovarian stimulation triggered by exogenous and/or endogenous hCG.[19] The introduction of GnRH antagonists in recent years with an established decrease in the incidence of OHSS as compared with GnRH agonists in the general population, might offer a new safer treatment option for these patients.[20,21] Gonadotrophin-releasing hormone (GnRH) antagonist is being increasingly used in COS for IVF from late 1990s.[22,23]

GnRH antagonists do not require long desensitization as in agonist protocol and induce rapid reduction in the level of follicle stimulating hormone (FSH) and luteinizing hormone (LH) without initial flair up thus ensuring a short and simple IVF cycle and better patient compliance. Although there was initial reports that antagonist cycles were associated with lower on-going pregnancy rate when compared to long agonist cycles.[22-23]

In our study we use fixed antagonist protocol as there was a trend toward a higher pregnancy rate with fixed antagonist protocol compared with the flexible antagonist protocol.[24]

METHODS

Patients

This study will be carried out on 200 females attending ElShatby university maternity hospital, Egypt. All cases will be recruited after fulfilling criteria of inclusion into the study. Inclusion criteria included age group between 20-40 years, normogonadotrophic females, PCOS patients (fulfilling Rotterdam criteria of PCOS); (2) body mass index (BMI) <35kg/m^2. While exclusion criteria included poor response in previous intracytoplasmic sperm injection (ICSI) cycles, history of previous ovarian surgery, uterine factor infertility, endometriosis, severe male factor infertility.

After approval of local ethics committee, a written informed consent will be taken from each patient and selected patients will be subjected to detailed history taking, clinical examination including general & gynecological examination, investigations for initial assessment included serum prolactin level, serum TSH level, baseline serum estradiol, total & free testosterone level, fasting insulin level and insulin resistance and baseline trans-vaginal ultrasound examination. Ovarian stimulation: All patients will receive oral contraceptive pills starting on day 4 of spontaneous menses of the cycle prior to the treatment cycle for 21 days. Patients will be subdivided into 2 groups by computer randomization. Group I: 100 patients will be included in agonist group. All patients will receive subcutaneous injection of GnRH agonist 0.1mg triptorelin; decapeptyl (Ferring) 6 days before discontinuation of COCs. When desensitization occurs, daily intramuscular injection of gonadotrophin starts. At that day the dose of GnRH agonist decreased to 0.05mg and continued until the day of hCG. Group II**:** 100 patients will be included in antagonist group they will start the gonadotrophin on cycle day 3 when ovarian suppression is assured. Then GnRH antagonist 0.25mg cetrorelix; cetrotide (Serono) will be given daily on stimulation day 5 and continue till the day of hCG. The starting dose of gonadotrophin is 150-225 IU/day for all patients in both groups and will be modified according to patient's response hCG; Choriomon (IBSA) is given in both groups in a dose of 10,000 IU intramuscular when 3 or more follicles reach a mean diameter of ≥18 mm in agonist protocol and ≥17mm in antagonist protocol. The main outcome measures were 1- The primary outcome measures include total number of oocytes, the number of mature oocytes per cycle of induction, serum estradiol and progesterone level on the day of hCG administration, implantation rate (number of sacs per number of embryo transfer), the grading of embryos obtained, the secondary outcome measure is the pregnancy rate which will be diagnosed by serum B-hCG assay 14 days after embryo transfer while clinical pregnancy which will be confirmed by observing fetal cardiac pulsation 2 weeks after positive pregnancy test by transvaginal ultrasound.

Statistical analysis of the data[25]

Statistical assessment was carried out with SPSS (Statistical Package for social Sciences) version 17. Exploration of the data: This yielded complete descriptive statistics including the minimum and maximum, range, mean, median and inter-quartile range for each variable. 2-Data were described using minimum, maximum, mean and standard deviation. 3-Comparisons were carried out for comparison between the two groups using student's test. 4-Box and Whiskers graph was used

in all variables regardless of normality. In the present study an alpha level was designed to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

RESULTS

The estrogen level in hCG day (pmol/l) in long agonist group ranged from 776 to 16722 with a mean value of 4912.40±2934.571, while in antagonist group it ranged from 152 to 10305 with a mean value 2926.75 ±2110.384. Estrogen level in hCG day was significantly higher in agonist group (Table 1). The progesterone level (ng/ml) in long agonist group ranged from 0.19 to 2.30 with a mean value 0.98±0.425, while in antagonist group it ranged from 0.15 to 2.80 with a mean value 0.87± 0.525. Using independent sample t test, there was no significant difference between the 2 studied groups. (Table 1). As regard the number of ampoules of gonadotrophins in the long agonist group it ranged from 15.0-79.0 with a mean value of 48.84±17.404 ampoules, while in the antagonist group it ranged from15.0-78.0 with a mean value of 53.31 ± 15.574 ampoules. Using independent sample t test, there was no significant difference between the 2 studied groups (Table 1). As regard the number of stimulation days in the long agonist group it ranged from 7 to 18 days with a mean value of 13.58±2.248 days, while in the antagonist group it ranged from 7 to 18 days with a mean value of 12.87±2.381 days. Using independent sample t test, the number of days in agonist group was significantly higher than in antagonist group (Table 1). As regard the number of retrieved oocytes in the long agonist it ranged from 0-41 with a mean value of 15.04±8.363 while in the antagonist group it ranged from 0 to 34 with a mean value of 9.42± 6.812. Using independent sample t test, the number of oocyte retrieved was significantly higher in the agonist group (Table 1). As regard the embryos transferred the number of embryo transferred in the agonist group ranged from 1 to 9 with a mean value of 4.63±1.474, while in the antagonist group it ranged from 1 to 9 with a mean value of 4.39±1.774. Using independent sample t test, there was no significant difference regarding the number of embryo transferred between the two studied groups (t=0.893, p=0.373). As regard the endometrial thickness in the long agonist group it ranged from 7.40 to 14.50mm with a mean value of 10.29±1.723mm while in the antagonist group it ranged from 7.20 to 14.00 mm with a mean value 10.01±1.334mm. Using independent sample t test, there was no significant difference in the endometrial thickness between both groups (Table 1). As regard the fertilization rate in the agonist group it ranged from 12.5 to 100.0% with a mean value of 58.79±20.482, while in the antagonist group it ranged from 7.69 to 100.0% with a mean value of 56.13±24.081. Using independent sample t test, there was no significant difference regarding the fertilization rate between the two studied groups (t=0.704, p=0.483).

As regard the ICSI cycle cancellation, in the long agonist group there were (3.0%) patients with cancelled cycles (2 with no response to stimulation and 1 with no fertilization),while in the antagonist group, there were (15.0%) patients with cancelled cycles (6 with no response to stimulation, 4 no oocyte retrieved, 5 no fertilization). Using Pearson Chi – square the cycle cancellation rate was significantly higher in antagonist group. The results showed that the chemical pregnancy rate was higher in the agonist group when compared with antagonist group, (46.0%), (31.0) (Table 2, Figure 1) respectively, clinical pregnancy rate, was higher in the agonist group when compared with antagonist group, (43.0%), (29.0%) respectively (Table 3, Figure 2).

Table 1: Ovarian stimulation characteristics, hormonal data on the day of hCG.

	Agonist group (n=100)	Antagonist group (n=100)	Test of significance (*p* value)
Number of ampoules			
Min-Max	15.0-79.0	15.0-78.0	t=1.914
Mean±S.D	48.84±17.404	53.31±15.574	*p*=0.057NS
Number of stimulation days			
Min-Max	7-18	7-18	t=2.168
Mean±S.D	13.58± 2.248	12.87± 2.381	*p*=0.031*
Estrogen level at hCG day			
Min-Max	776-16722	152-10305	t=5.493
Mean±S.D	4912.40± 2934.581	2926.75± 2110.384	*p*=0.000*
Progesterone level at hCG day			
Min-Max	0.19-2.30	0.15-2.80	t=1.521
Mean±S.D	0.98±0.425	0.87±0.525	*p*=0.130 NS
Endometrial thickness			
Min-Max	7.40-14.50	7.20-14.00	t=1.266
Mean±S.D	10.29±1.723	10.01±1.334	*p*=0.207 NS
Number of oocyte retrieved			
Min-Max	0-41	0-34	t=5.210
Mean±S.D	15.04± 8.363	9.42±6.812	*p*=0.000*

Table 2: Chemical pregnancy in the two studied groups.

	Group		
	Long-agonist group (n, %)	Antagonist group (n, %)	Total (n, %)
Pregnancy	46 (46.0%)	31(31.0%)	77 (38.5%)
No-pregnancy	54 (54.0%)	69 (69.0%)	123 (61.5%)
Total	100 (100%)	100 (100%)	

X^2=4.751; p=0.029*

Table 3: Clinical pregnancy in the two studied groups.

	Group		
	Long-agonist group (n, %)	Antagonist group (n, %)	Total (n, %)
Pregnancy	43 (43.0%)	29(29.0%)	72 (36.0%)
No-pregnancy	57 (57.0%)	71 (71.0%)	128 (64.0%)
Total	100 (100%)	100 (100%)	

X^2=4.253; p=0.039*.

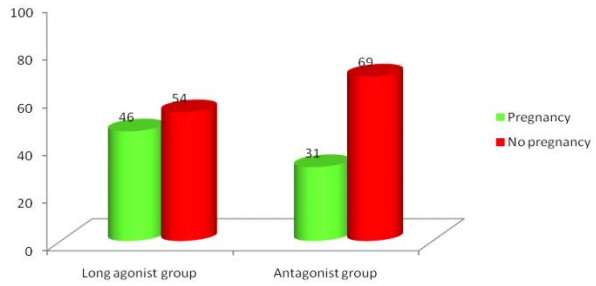

Figure 1: Chemical pregnancy in the two studied groups.

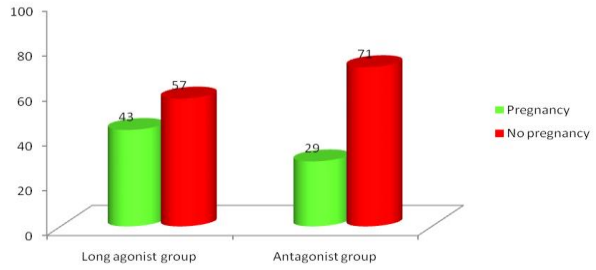

Figure 2: Clinical pregnancy in the two studied groups.

DISCUSSION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy that affects 5-7% of reproductive age group females. First described by Irving Fstain and Michael Leventhal in 1935.[1] Common clinical features include irregular menstruation, hirsutism, acne and infertility. Anovulation/oligo-ovulation is responsible for 40% of female infertility and PCOS accounts for 80% of these cases.[3,4] In vitro fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI) is the final step of treatment for PCOS patients with infertility.[5] However, controlled ovarian stimulation (COS) in these patients remains a challenge till date because of risk of potentially lethal complication like ovarian hyperstimulation syndrome (OHSS). Different stimulation protocols have been suggested as GnRH agonist and GnRH antagonist but still there is no consensus as to which protocol is best for patients with PCOS.[22,23] The objective of the current study was to compare fixed GnRH antagonist protocol in relation to GnRH agonist long luteal protocol in PCO infertile patients undergoing ICSI.

The present study was conducted on 2 groups of PCO females group I: included 100 patients received subcutaneous injection of GnRH agonist, 0.1mg triptorelin (decapeptyl; Ferring) 6 days before discontinuation of COCs. Group II: included 100 patients received GnRH antagonist 0.25mg cetrorelix (cetrotide; Serono) subcutaneously daily on stimulation day 5 and continued till the day of hCG.

Regarding the duration of stimulation in the 2 studied groups it was significantly higher in agonist group. As GnRH antagonist protocol achieves rapid and reversible suppression of LH without a flare-up effect which eliminates the need for prolonged treatment to achieve pituitary suppression, so fewer days of stimulation may be required ensuring better patient compliance. This agrees with the work of Lainas et al.[26]

On the other hand, a study done by Kaur et al comparing long agonist protocol with flexible antagonist protocol in PCOS infertile women, 60 cases received GnRH agonist long protocol and 40 received flexible GnRH antagonist protocol, demonstrated that there was no difference in days of stimulation between two groups.[27] This difference may be due to small sample size and different antagonist protocol used.

In the present study, there was no significant difference in the number of ampoules between the two studied groups (t=1.914, p=0.057). This agrees with the work of Hosseini et al compared GnRH antagonist and GnRH agonist protocols during COH of 112 infertile PCOS patients.[28]

On the contrary, a study done by Singh et al (a retrospective analysis of 4 years data of a single center among 117 patients of PCOS, 81 patients had long agonist protocol (leuprolide acetate) and 36 had fixed antagonist protocol (cetrorelix), demonstrated that total dose of gonadotrophin was significantly lower in antagonist group.[29] This difference may be due to small number of cases in antagonist group.

In the current study, the estrogen level in hCG day was significantly higher in agonist group (4912.40±2934.571 pmol/l) compared to antagonist group (2926.75± 2110.384 pmol/l).This is due to higher number of mature oocytes in agonist group.

In agreement, a study done by Orvieto et al comparing GnRH agonist with GnRH antagonist, 226 patient in the agonist group and 261 in the antagonist group, demonstrated that estrogen level in hCG day was higher in agonist group.[30]

In contrast, Singh et al demonstrated that there was no significant difference in the estrogen level in hCG day.[29] This difference may be due to small number of cases in antagonist group.

High level of E2 in hCG day could be associated with OHSS but in our study there was no cases of OHSS, this could be easily attributed to careful assessment of patients before stimulation and careful monitoring of follicular growth with adjustment of dose of gonadotrophin.

Regarding the number of retrieved oocytes in both groups; it was significantly higher in the long agonist

group. This agrees with the work of by Kaur et al and could be easily attributed to the higher number of mature oocytes obtained in agonist group.[27]

In contrast, study done by Lin H et al (9 RCTs examining PCOS patients undergoing IVF/ICSI including 588 women who underwent long agonist protocols, 554 women who underwent antagonist protocols), demonstrated that there was no significant difference in number of retrieved oocytes between both groups.[31] The difference may be due to different antagonist protocols used.

As concerned the pregnancy rates, chemical and clinical pregnancy rates were significantly higher in the agonist group. This is one of the main points aimed at studying in our research. This may be explained by better quality embryos in agonist group. This agrees with the work of Orvieto et al.[30]

On the contrary, a study done by Al-Inany et al (28 RCTs involving 5014 women) compared GnRH agonist and GnRH antagonist showed that there was no significant difference in pregnancy rate between the two regimens.[32] The difference between this study and the current study may be due to the different antagonist protocols used and different patient characteristics (PCOS and poor responders).

CONCLUSION

The use of GnRH antagonists is more advantageous than GnRH agonists in relation to shorter duration of stimulation thus allowing a reduction in the treatment time that makes COS less costly and better patient compliance. In this study GnRH agonist shows higher pregnancy rate than antagonist, so larger studies needed to clarify their roles.

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