Comparison of gonadotropin-releasing hormone agonist with GnRH antagonist in polycystic ovary syndrome patients undergoing *in vitro* fertilization cycle: Retrospective analysis from a tertiary center and review of literature

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ABSTRACT

INTRODUCTION: Polycystic ovary syndrome (PCOS) is one of the most common infertility factor for which women are enrolled in *in vitro* fertilization (IVF) technique. In the recent years, gonadotropin releasing hormone antagonist protocol has emerged as the protocol of choice for controlled ovarian hyperstimulation in these patients. **OBJECTIVES:** The objective of the present study is to compare conventional long agonist protocol with fixed antagonist protocol in PCOS patients undergoing IVF cycle. **MATERIALS AND METHODS:** Retrospective analysis of 4 years data of a single center from northern India. Totally 81 patients who had long agonist protocol were compared with 36 patients with similar baseline characteristics who had antagonist protocol. **RESULT:** Total dose of gonadotropin required was significantly lower (*P* - 0.004) in the antagonist group. There was no significant difference in pregnancy rate or incidence of ovarian hyperstimulation syndrome between two groups. Cycle cancellation due to arrest of follicular growth was significantly higher in the antagonist group (*P* - 0.027). **CONCLUSION:** More randomized control trials and meta-analysis are required before replacing conventional long agonist protocol with antagonist protocol in patients with polycystic ovary syndrome.

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

INTRODUCTION

First described by Irving Fstain and Michael Leventhal in 1935, polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy that affects 5-7% of reproductive age group females.[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.[2,3] *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) is the final step of treatment for PCOS patients with infertility.[4] 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).[5] Different stimulation protocols have been suggested, but still there is no consensus as to which protocol is best for patients with PCOS.

Gonadotropin-releasing hormone (GnRH) antagonist is being increasingly used in COS for IVF from late 1990s. 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 ongoing pregnancy rate when compared to long agonist cycles,[6,7] recent randomized control trials (RCT) show that there is no significant difference in fertilization rate and pregnancy outcome.[8-10] Three recent meta-analysis pointed out certain advantages of antagonist cycles like shorter period of gonadotropin stimulation, smaller dose of gonadotropin required and reduced incidence of OHSS.[11,12]

There are only limited number of studies in literature comparing GnRH agonist and antagonist protocol in PCOS patients[13-15] and we are yet to reach a final conclusion regarding the best IVF protocol in PCOS population. Hence the aim of the present study was to compare GnRH agonist and antagonist protocols in PCOS patients by retrospective analysis of data of 4 years from a single IVF center of Northern India.

MATERIALS AND METHODS

A retrospective analysis of records of PCOS patients who entered assisted reproductive technology program in All India Institute of Medical Sciences, New Delhi, India, from January 2007 to December 2012 (6 years) was performed. The diagnosis of PCOS was based on Rotterdam criteria.[16] Even though it was a retrospective study, we tried to omit the confounding factors by setting an inclusion criteria which include age between 20 and 35, body mass index (BMI) between 20 and 30, day 2 FSH level below 10 IU/L, no past history of genital tuberculosis, first IVF cycle, no documented evidence of hypothyroidism or hyper-prolactinemia and no other associated infertility factors except for tubal factor. Couples with male factor infertility were barred however those who underwent donor semen IVF were included into the analysis. Out of 944 patients who underwent IVF cycles in this time period, 153 had PCOS out of which 117 met the inclusion criteria and complete case record of these patients were reviewed thoroughly. Among 117 patients of PCOS, 81 patients had conventional long agonist protocol and 36 had fixed antagonist protocol.

In agonist group, patients were given 1 mg injection of leuprolide acetate (Injection Lupride, Sun Pharmaceutical Industries Ltd., Mumbai) starting from day 21 of menstruation for 14 days. Down regulation was confirmed by biochemical markers (LH <5 IU/ml, E2 <50 pg/ml and progesterone <1 ngm/ml) and trans vaginal ultrasound (TVS) assessment of endometrial thickness (ET) and ovarian status (ET <3 mm, no ovarian cyst >2 cm). After down-regulation, dose of leuprolide was reduced to 0.5 mg/day and patients were started on recombinant FSH (Injection Gonal-f, Merck Serono Specialties Pvt. Ltd., Italy). The starting dose was between 150 IU/day to 225 IU/day depending upon patient's characteristics. In antagonist group, patients were scanned for any ovarian cyst on the first day of the menstrual cycle and were started on injection gonal f (150 IU to 225 IU) from day 2. GnRH antagonist cetrorelix acetate (Injection Cetrotide, AEterna Zentaris, Canada). 25 mg was added on 6th day of the menstrual cycle (fixed dose regime). Follicular monitoring was done in both groups using TVS and dose of gonadotrophin was adjusted accordingly. The cycles were cancelled in patients with no follicle more than 10 mm after 10 days of gonadotropin stimulation. Ovulation was triggered when leading follicle reached 18 mm along with at least two follicles >16 mm, using 250 mg of recombinant human chorionic gonadotropin (HCG) (Injection Ovitrelle, Marck Serono, UK). Serum estrogen (E2) and ET were measured on the day of trigger. Embryo transfer was done between day 2 to day 5 depending upon the number of good quality embryo. All patients were given luteal phase support by i. m injection progesterone 100 mg/day. On the 6th day of embryo transfer, pregnancy was assessed by serum beta HCG assay and confirmed by the presence of the gestational sac on TVS after another 2 weeks. Biochemical pregnancies were not included in our analysis.

Statistical analysis

Data were computerized and analyzed using the statistical package IBM SPSS version 16.0. Descriptive statistics were computed for base-line characteristics of patients, ovarian stimulation factors, hormonal profile, ET on the day of HCG trigger and embryological variables for each study group. After determining whether the data met the normality assumption, Student *t*-independent two-tailed test was conducted to test whether the means of continuous variables were significantly different between the two study groups. Nominal or frequency data were analyzed using Chi-square test or Fishers's exact test as appropriate. For the entire statistical tests $P < 0.05$ was considered to be statistically significant.

RESULT

Among 944 patients enrolled in the given time period, 153 (16.2%) patients had PCOS and 117 patients met our inclusion criteria. Out of these 117, 81 (69.2%) patients had long agonist protocol and 36 (30.8%) patients had antagonist protocol. The baseline characteristics of patients enrolled in two protocol groups are summarized in Table 1. There was no significant difference in mean age, BMI, percentage of patient with primary infertility, day 2 FSH, LH, anti-Mullerian hormone, antral follicle count, combined

ovarian volume, percentage of patients with pre-menstrual proliferative or hyperplastic endometrium between two groups.

Ovarian stimulation characteristics, serum estrogen (E2) level and ET on the day of HCG trigger in two study groups are compared as shown in Table 2. In antagonist group, three patients were cancelled after 10 days of gonadotropin stimulation as no dominant follicle > 10 mm was seen on TVS. Total dose of gonadotropin was significantly lower in antagonist group however, no significant difference was found in total days of stimulation, number of follicles, E2 level and ET on the day of HCG trigger between two groups. Two patients in agonist group developed moderate OHSS after triggering for which embryo transfer was cancelled and all embryos were cryopreserved. Number of embryo transferred was between 2 and 4.

During analysis of embryological data [Table 3], we could not find any significant difference in number of oocyte retrieved, percentage of metaphage ll (M2) oocyte, fertilization rate, cleavage rate, percentage of grade 1 embryo formed between two groups. Mean number of embryo transferred was also not different in two groups. Table 4 shows number of clinical pregnancy and OHSS in two groups. Pregnancy was confirmed by USG in 21 patients (26.6%) of agonist group and in 10 patients (30.3%) of antagonist group but the difference was not significant statistically. As mentioned above 2 patients of agonist group developed moderate OHSS, but none of the patients in antagonist group had this complication.

DISCUSSION

GnRH agonist protocol is still considered as the gold-standard protocol in IVF/ICSI cycles for COH. In the recent years however, antagonist protocol is gaining popularity because of short and simple cycle and lower incidence of OHSS. Comparative studies of agonist and antagonist protocols yield conflicting results.[6-10] The meta-analysis by Al-Inany *et al*. in 2007[17] examined the first five comparative studies of fixed GnRH-ant protocol with the standard GnRH-a long protocol and showed 5% lower pregnancy rate with GnRH-ant regimen. Later, a second study by Kolibianakis *et al*.,[11] a meta-analytic review of 22 RCTs published as full papers in peer reviewed journals, showed that the probability of live birth between GnRH-ant and GnRH-a was not significantly different. A third study, which was an additional updated meta-analysis by Al-Inany *et al*.[12] also showed that there was no significant difference in pregnancy rate following GnRH ant compared with GnRH agonist regimens.

The objective of the present study was to compare the outcome of IVF cycles of PCOS patients in GnRH agonist and fixed antagonist protocol. We found significant lower dose of gonadotropin required in antagonist group. Total days of stimulation, number of follicles and E2 level on the day of triggering, total number of oocytes retrieved, percentage of M2 oocytes, fertilization rate, cleavage rate,

Table 1: Baseline characteristics

	Agonist group (*N*=81)	Antagonist group (*N*=36)	*P* value
Age	30.9±3.7	30.7±3.5	0.746
BMI	25.7±3.6	25.8±3.5	0.898
Primary infertility[a]	87.7	77.8	0.172
D2 FSH	5.4±1.5	5.4±1.6	0.945
D2 LH	7±3.5	7.3±4.1	0.691
AMH[b]	5.7±3.2 (*N*=55)	5.6±2.9 (*N*=19)	0.859
AFC	18.4±4.9	19.9±4.5	0.100
Combined ovarian volume	15.6±4.5	14.9±3.9	0.463
Proliferative/hyperplastic endometrium*	48.1	58.3	0.309

[a]Percentage, [b]Value not available in all cases. BMI=Body mass index; FSH=Follicle-stimulating hormone; LH=Luteinizing hormone; AMH=Anti mullerian hormone; AFC=Antral follicle count

Table 2: Ovarian stimulation characteristics, E2 level and ET on the day of trigger

	Agonist (*N*=81)	Antagonist (*N*=33)	*P* value
Total dose of gonadotropin	2728±1135.5	2073.1±915.5	0.004[a]
Days of stimulation	9.7±1.7	9.5±1.8	0.429
No. of follicles on the day of HCG	16.5±8.2	14.7±6.5	0.227
E2 on day of HCG	3630.2±2392.9	3205.8±2661.7	0.408
ET on day of HCG	8.73±1.8	8.5±1.4	0.228
Cycle cancellation due to arrest of follicular growth	0 (0/81)	3 (3/36)	0.027[a,b]

[a]Statistically significant; [b]Fisher's exact test. ET=Endometrial thickness; HCG=Human chorionic gonadotropin

Table 3: Embryology data of two groups

	Agonist group (*N*=81)	Antagonist group (*N*=33)	*P* value
Oocyte retrieved	13.6±7.1	11.5±5.5	0.122
M2 oocyte[a]	78.2±18.3	81.2±14.1	0.397
Fertilization rate	77.9±18.1	78.5±16.9	0.892
Cleavage rate	92.1±15.9	95.5±9.8	0.251
Grade 1 embryo[a]	81.1±21.5	74.1±27.3	0.150
No. of embryo transferred	2.8±0.7	2.69±0.6	0.676

[a]Percentage

Table 4: Clinical pregnancy and OHSS

	Agonist group (*N*=81)	Antagonist group (*N*=33)	*P* value
Clinical pregnancy	21 (21/79)[a]	10 (10/33)	0.817
Moderate OHSS	2 (2/81)	0 (0/33)	1.00[b]

[a]Embryo transfer not done in 2 cases, [b]Fisher's exact test. OHSS=Ovarian hyperstimulation syndrome

percentage of Grade 1 embryo, all were comparable between two groups. The pregnancy rate was also not significantly different. Two patients of agonist regime and none of antagonist regime had moderate OHSS, but the difference was not statistically significant.

In literature, there are a number of studies comparing agonist and antagonist protocol in PCOS patients with highly variable results [Table 5]. Bahçeci *et al*. in 2005[18] did a randomized prospective pilot study which showed no difference in total dose of gonadotropin used, number of oocyte retrieved and pregnancy rate between agonist and antagonist group but the number of days of stimulation, number of M2 oocytes were significantly lower in antagonist group. They also found no significant difference in incidence of OHSS between these two groups. In the same year, Ashrafi *et al*.,[13] in their RCT, found that number of retrieved oocytes and M2 oocytes were significantly higher in antagonist group. There was no statistically significant difference in total dose of gonadotropin, fertilization or pregnancy rate. Interestingly, number of patients with risk of OHSS (E2 > 3000 pg/ml) was significantly higher in antagonist group (*P* - 0.004). Ragni *et al*., (2005) on the other hand, showed significant lower risk of OHSS in antagonist group.[14]

Orvieto *et al*. in 2009[15] found significant higher pregnancy rate in long agonist protocol (36% vs. 19%) while Hosseini *et al*.[19] and Kim *et al*.[20] in 2010, showed no difference in pregnancy rate between two regimens. Lainas *et al*.[21] in 2010 compared flexible GnRH antagonist protocol with long agonist protocol in PCOS patients. They found that, the total dose of gonadotropin, number of days of stimulation, incidence of OHSS were significantly lower in antagonist group but there was no difference in ongoing pregnancy rate. They concluded that, antagonist protocol should be the treatment of choice in PCOS patients. More recent studies (Haydardedeoglu *et al*. 2012, Onofriescu *et al*. 2013)[22,23] also reflect the same view.

From India, Kaur *et al*.[24] in 2012, published their prospective controlled study comparing long agonist protocol with flexible antagonist protocol. They found no difference in days of stimulation between two groups, but total dose of gonadotropin was significantly lower in antagonist group. We also found the same. Number of oocyte retrieved, number of mature oocyte, fertilization rate were higher in agonist group but there was no difference in clinical pregnancy rate and life birth rate. The incidence of OHSS was lower in antagonist group. We also found no difference in pregnancy rate but unlike this study, we couldn't find any difference in number of retrieved oocytes, number of mature oocytes, fertilization rate between two groups. These findings were similar to study of Lainas *et al*. We had two patients in agonist group and none in antagonist group with moderate OHSS, the difference being insignificant. Though this insignificant difference may be because of smaller no of patients in antagonist group, Bahçeci *et al*.[18] in their pilot study also found no difference in OHSS rate in two regimen. So, in our opinion, careful assessment of patients before stimulation, low starting dose of gonadotropin and careful monitoring of follicular growth with adjustment of dose of gonadotropin can reduce the incidence of OHSS in PCOS patients undergoing COH with long agonist regimen.

In our study, we also had 3 patients in antagonist group in whom no dominant follicle was formed after 10 days of stimulation. None of the patients in agonist group had follicular growth arrest, the difference being statistically significant. In the study of Bahçeci *et al*.[18] 3 of 27 patients (11%) in antagonist group and 1 of 25 patients (4%) in agonist group had arrest of follicular development. Though we can't draw any conclusion from two studies, these findings do evoke the old debate regarding the role of LH in follicular development. GnRH antagonist can induce a sharp decrease in serum LH level which may be detrimental if the level falls below a "threshold." In fact, minimum threshold of LH has to be maintained for adequate steroidogenesis and folliculogenesis (European recombinant human LH

Table 5: Previous comparative studies of GnRH agonist and antagonist in PCO patients undergoing IVF cycles

Year	Author	Agonist group	Antagonist group	Outcome	Remarks
2004	Hwang *et al.*	25	24	Duration of stimulation is significantly reduced in favor of GnRH-ant when GnRH-ant multiple dose and GnRHa long protocol are compared (OR: −0.86, 95% CI: −1.14-−0.59, *P*<0.01), although this was not associated with a significant reduction in gonadotropin consumption. No significant difference was found regarding the number of cumulus−oocyte complexes retrieved and the likelihood of clinical pregnancy. No severe OHSS occurred in the studies reporting OHSS (Hwang *et al.*, 2004; Bahçeci *et al.*, 2005). No significant difference in the incidence of OHSS (grades I-II) was present	Limited evidence from the literature suggests that in PCOS patients duration of stimulation is shorter using GnRH-ant and that GnRH-ant are associated with a non-significant lower consumption of gonadotropins, as compared with treatment with the GnRHa long protocol
2004	Asharfi *et al.*	23	24		
2004	Kim *et al.*	21	20		
2005	Bahceci *et al.*	70	59		
2012	Kaur *et al.*	60	40	No significant difference was seen in clinical pregnancy and implantation rate but OHSS rate was significantly lower in antagonist group	GnRH antagonist protocol is equally effective and safer in women with PCOS

GnRH=Gonadotropin; OR=Odds ratio; CI=Confidence interval; PCOS=Polycystic ovary syndrome; GnRHa=GnRH analogue; OHSS=Ovarian hyperstimulation syndrome

study group 1998). In antagonist regimen, abrupt fall of LH at a critical stage of folliculogenesis when follicles become more and more sensitive to LH due to increased LH receptor on granulose cells hinders the combined attempt of FSH and LH to achieve complete follicular maturity and oocyte competence.[25] Another problem with antagonist regime is that, pre-existing follicle size discrepancies may hinder coordinated follicular growth during ovarian stimulation, thereby reducing the number of follicles that reach maturation.[26] Luteal phase suppression of endogenous FSH in long agonist protocol can trim down this discrepancy. Increase no of mature oocyte retrieved in patients undergoing long agonist protocol (Bahçeci *et al*., Kaur *et al*.) can be explained by these theories.

We found two meta-analysis comparing agonist and antagonist protocol in OHSS patients. The meta-analysis of Griesinger *et al*.[27] in 2006, compared agonist and antagonist protocol in a total of 305 patients with PCOS, and included four studies. Pregnancy rates were not significantly different in the agonist and antagonist groups but the incidence of severe OHSS was significantly lower in the antagonist group. Pundir *et al*.,[28] in a recent meta-analysis which included 9 RCTS 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 ($P < 0.0001$) lower incidence in antagonist group.

The present study analyzed a single center data of 4 years. We found comparable pregnancy rate in two regimen and lower dose of gonadotropin in antagonist group. Of importance is the fact that follicular growth arrest was significantly higher in antagonist group while OHSS rate was similar. With the limits of the retrospective study, we can still conclude that it is not the time to replace long agonist protocol with antagonist protocol in PCOS patients enrolled for IVF. In our opinion, larger RCTs with adequate sample size and more meta-analysis are required to reach a final conclusion.

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