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Comparison of ovarian response between PCOS and Non-PCOS patients undergoing ICSI with antagonist protocol

Krishnapillai Jayakrishnan[1*], Divya Nambiar[1], Jesin Leo Fency[1]

1. KJK Hospital, Trivandrum, Kerala, India

Abstract

Antagonists have been shown to be better than agonists in general and in the PCOS infertility with lower rate of OHSS. This study is a retrospective observational study and patient record review of PCOS and Non-PCOS groups of patients who entered ART over a duration of 3 years. On comparison of ovarian response in both groups, the mean number of oocytes obtained was more in the PCOS group but the number of mature oocytes obtained was significantly less. A higher fertilization rate and cleavage rate was observed in the non- PCOS patients i.e. 82.3% and 73.2% respectively versus 71% and 58.7% in the PCOS group which was statistically significant. There were no patients with OHSS in the non- PCOS group, whereas in the PCOS group we had 10 patients with mild OHSS, 4 (6%) patients with moderate OHSS and only 1 (1%) patient with severe OHSS. In conclusion the pregnancy rate was comparable in patients with PCOS undergoing GnRH antagonist ovarian stimulation compared with non-PCOS patients in whom the same controlled ovarian stimulation was used. Of importance is the fact that there was only one case of severe ovarian hyperstimulation syndrome in the PCOS group, making the use of the GnRH antagonist an attractive option in this high-risk group of patients.

Keywords: GnRH antagonist, PCOS, Ovarian response, Cleavage rate, OHSS

1. Introduction

Gonadotropin-releasing hormone (GnRH) antagonists can be used to prevent a luteinizing hormone (LH) surge during controlled ovarian hyperstimulation (COH) without the hypo-estrogenic side-effects, flare-up, or long down-regulation period associated with agonists. The antagonists directly and rapidly inhibit gonadotropin release within several hours through competitive binding to pituitary GnRH receptors. This property allows their use at any time during the follicular phase. Several different regimes have been described including multiple-dose fixed (0.25 mg daily from day six to seven of stimulation), multiple-dose flexible (0.25 mg daily when leading follicle is 14 to 15 mm), and single-dose (single administration of 3 mg on day 7 to 8 of stimulation) protocols, with or without the addition of an oral contraceptive pill.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that affects 5–10% of women of the reproductive age group (1). The clinical presentation varies from oligomenorrhea and a sonographic picture of polycystic ovaries with subtle phenotypic abnormalities or signs of hyperandrogenism to advanced polycystic ovarian syndrome and its associated long-term sequelae like Type 2 diabetes, cardiovascular disease, hypertension, endometrial cancer, breast cancer and ovarian cancer (2). The criteria for diagnosis of PCOS has been universally accepted as per the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group 2004 (3). The optimal infertility treatment for PCOS is still a controversy. These controversies surrounding the treatment have led to the recently published ESHRE/ASRM consensus that adhered to the therapeutic challenges raised in women with infertility and PCOS, the various treatments available and their efficacy as well as safety (4).

In vitro fertilization (IVF) remains a reasonable option in PCOS women who are refractory to conventional infertility treatment modalities or who

[*]**Corresponding address:** Dr. Jesin Leo Fency. KJK Hospital, Trivandrum, Kerala, India, Email: jesintyj@yahoo.co.in

have coexisting infertility factors (5). Many controlled ovarian stimulation (COS) strategies have been offered for the treatment of patients with PCOS undergoing IVF. However, there is no compelling evidence for the advantage of one stimulation protocol over the other. PCOS patients undergoing COS have a high risk of developing ovarian hyperstimulation syndrome (OHSS), a serious iatrogenic complication of ovarian stimulation (6). The initial gonadotrophin-releasing hormone (GnRH) analogues used in controlled ovarian stimulation were the GnRH agonists. Problems caused by GnRH agonists were mid-cycle gonadotrophin flares, a high incidence of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (7). Gonadotropin releasing hormone antagonists have been shown to offer an advantage over standard long agonist protocol in terms of decreasing incidence of OHSS, short duration of treatment, lower cost, lesser dose of gonadotropins required and being more patient friendly (8).

The introduction of newer GnRH analogues, the GnRH antagonists, created the potential for milder stimulation protocols that are better tolerated and less costly, have a quicker onset of action, result in a lower incidence of luteinising hormone (LH) surge, and are associated with a lower multiple pregnancy rate (9-12). Reviews and meta-analyses have recently compared the two GnRH analogues –the agonists with the antagonists – and have found no significant difference in fertilization rate and pregnancy outcome (13, 14).

It has been proposed that the newer GnRH antagonists may even be better for COS in the difficult patient subgroup (15).

Antagonists have been shown to be better than agonists in general and PCOS infertility patients in that antagonists require the use of less gonadotropin, result in better patient compliance and are associated with a lower rate of OHSS (16, 17). Therefore the aim of the study was to compare ovarian response between PCOS and Non-PCOS patients undergoing ICSI with antagonist protocol.

2. Meaterials and methods

2.1. Study design and patient characteristics

This study was a retrospective observational study and patient record review of two groups of patients who entered an ART program between January 2011 and December 2013 (3 years).

The entire data set available was collected for both groups. Only patients less than 35 years were included in the study. They were divided into 2 groups. The first group included all patients, who were diagnosed as having PCOS. The diagnosis of PCOS was made based on the Rotterdam criteria of the consensus conference of the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Health (ASRM) Rotterdam 2003(3). According to this, to diagnose a patient as PCOS, the presence of atleast two criteria of the following three: 1) A clinical or biochemical hyperandrogenism; 2) Oligo-or anovulation; 3) A ultrasound polycystic ovary appearance determined by an increase in ovarian volume (greater than 10 cm^3 per ovary) and / or containing more than 12 of 2-8 mm anechoic (follicles) for each ovary.

Also, other causes of hirsutism/anovulation were excluded.

The second group (*N*= 64) included all non PCOS patients during the same period who did not have a diagnosis of PCOS. Other contributory factors like male factor, endometriosis, tubal factor, uterine fibroids, postmyomectomy and low AFC (antral follicle count) leading to infertility were excluded from the study.

All patients were initially given oral contraceptive pills for 14 days for cycle regulation, then on Day 2 of period stimulation was started using 150 IU of human recombinant FSH(rhFSH, Gonal-F; Merck Serono SA, Geneva, Switzerland) after doing a vaginal ultrasound and measuring plasma E2 levels. Stimulation started only if E2 level was less than 50 pg/ml. This dose was adjusted by 50 to 100 IU after day 5 of stimulation depending on ovarian response, as assessed by the E2 levels and ultrasound. On day 6 of stimulation TVS repeated and E2 levels measured and if 1 follicle was > 13 mm in size antagonist cetrolix (Cetrotide; Serono International, Geneva, Switzerland) was started and stimulation continued. The trigger with recombinant HCG (Ovitrelle) of 250 mcg was given, when the leading follicle achieved 18 mm and at least 3 other follicle achieved 17mm or more. Embryo transfer was performed on day 3 following pickup and micronized progesterone 600mg/day and estradiol valerate 6 mg /day was given for luteal support after transfer for 15 days.

On day 14 after embryo transfer a blood sample was taken to assess the β- HCG values. If this was > 25 IU/L the test was considered positive and repeated 4 days later to look for rising values to confirm pregnancy.

A 66% rise in β- HCG value in 48 hrs was suggestive of healthy intrauterine pregnancy. Ultrasound was done when β- HCG level was > 2000 IU /L to assess the number of gestational sacs and site of gestation.

2.2. Outcome measurement

The following variables were analysed in PCOS and non PCOS patients - number of follicles, days of stimulation, peak estradiol levels on day of hCG, progesterone level on the day of hCG, fertilization rate of the oocytes, cleavage rate of the embryos, implantation rate, miscarriage rate, number of mature oocytes, fertilization rate, cleavage rate, endometrial thickness on the day of transfer, number of patients with excess embryos that were frozen and the rate of OHSS.

Pregnancy rate was defined as percentage of patients who tested βHCG positive. Ongoing pregnancy was defined as positive cardiac activity at a gestational age of 12 weeks. In this study we report the ongoing pregnancy rate. Implantation rate was calculated by dividing the number of gestational sacs seen on transvaginal sonography by number of embryos transferred.

Ectopic pregnancy was described as presence of extrauterine gestational sac and βHCG >1500 IU/L in the absence of intrauterine gestational sac. Miscarriage was defined as discontinuation/failure to grow of a pregnancy before 12 weeks of gestation. Biochemical pregnancy defined as positive serum β-HCG level which subsequently fell before reaching the ultrasound discriminatory zone for visualization of pregnancy by TVS.

Embryology details included the mean number of mature oocytes retrieved per patient, fertilization rate [the numerator was the number of two pronuclear oocytes, with the number of cumulus-oocyte-complexes retrieved as the denominator], cleavage rate, and endometrial thickness on day of embryo transfer and number of cases where embryos were frozen.

2.2.1. Grading of embryo quality

The Bolton classification, 1989, was used for grading of embryo quality. Three major components considered were blastomere regularity, speed of cleavage and degree of fragmentation. There are three grades of which grade 3 embryo are the best quality(18).

2.2.2. OHSS grading

Grading of OHSS was based on Mathur et al(19), and were grouped under Mild, moderate, severe and critical OHSS**.**

2.3. Statistical methods

Descriptive statistical analysis has been carried out in the present study. This study was exempt from the institutional ethics and review committee because of its retrospective, non-interventional nature, and the maintenance of total confidentiality. The statistical software, SAS (Statistical Analysis System) 9.3, were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables.

3. Results

Baseline characteristics and hormonal profile of the patients analyzed are shown in the Table 1.

Table 1. Baseline characteristics and hormonal profile of the patients

Variable	PCOS (N-71) Mean (±SD)	Non- PCOS (N-64) Mean (±SD)	Z score	P value
Age	30.6(2.8)	32.0(2)	3.0367	0.0029
BMI	24.4(3.6)	25.0(4.4)	0.5285	0.5980
Duration of infertility (years)	3(2-5)	3(2-5)		
E2 concentration on the day of trigger(pg/mL)	4265.7 (2358.8)	2479.9 (1306.6)	4.8103	.0001
Progesterone concentration on the day of trigger(ng/mL)	1.1(0.4)	1.2(0.5)	.8693	.3862
Endometrial Thickness on day of trigger	10(±1.2)	10.6(±1.3)	3.0574	.0029

There were total 71 patients in PCOS group and 64 patients in the Non- PCOS group. The mean age of patients in both groups was comparable. No significant difference was seen in BMI in both groups. E2 level on the day of trigger was higher in the PCOS group compared to the Non –PCOS group. This result was statistically significant (p<.0001) which is as expected owing to larger number of follicles recruited in PCOS patients as compared to the Non- PCOS patients. Duration of infertility was similar in both groups.

Progesterone level measured on the day of trigger was comparable in the two groups. Endometrial thickness measured on the day of trigger was slightly

reduced in the PCOS group, compared to the Non-PCOS group.

On comparison of ovarian response in both groups, the mean days of stimulation was slightly less in the PCOS group compared to the non PCOS group. This difference was not however statistically significant. The mean number of oocytes aspirated and matured was more in the PCOS group, compared to the non PCO group and this difference was found to be statistically significant. However, it was noted that the mean number of matured oocytes was the same as the mean number of aspirated oocytes in the non PCO group as against the PCO group where the matured oocytes were less than the aspirated oocytes. Also the percentage of mature oocytes obtained was significantly less in the PCO group as compared with the non-PCOS group.

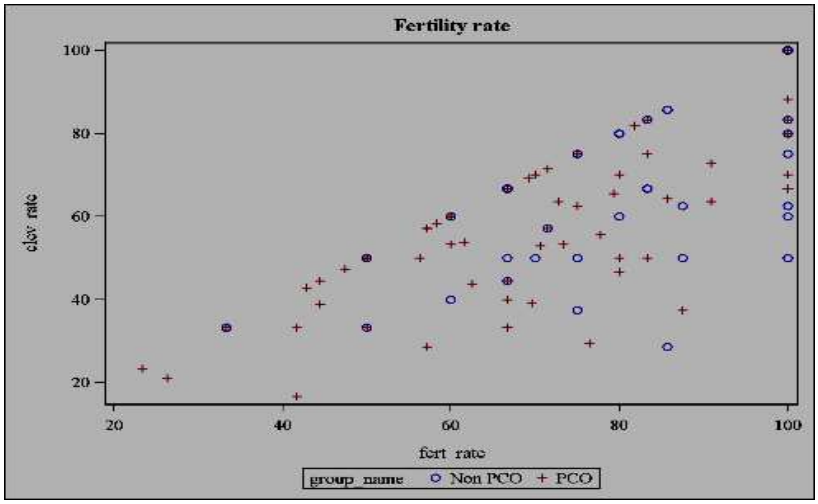

Figure 1. Comparison on the fertilization and cleavage rate between the PCOS and non PCOS group

Similarly the mean number of embryos fertilized, cleaved, and embryos frozen were more in PCOS group as expected as more eggs were aspirated. The fertilization rate and cleavage rates were higher in the non- PCOS group compared to the PCOS group which was also statistically significant (Table 2, Figure 1).

Table 2. Comparison of the ovarian response: Follicles, oocytes number, embryos fertilised and cleaved

Variable	PCOS(N=71)	Non-PCOS(N=64)	Z- score	P value
Days of stimulation [Mean(±SD)]	9.8(1.2)	10 (1.4)	0.4618	0.6442
No:of oocytes aspirated[Mean(±SD)]	14.5(6.6)	5.9(2.2)	8.2761	<.0001
No: of matured oocytes[Mean(±SD)]	12.3 (6.4)	5.9 (2.5)	7.5538	<.0001
% of matured oocytes-recovery rate	85.7 (17.2)	89.9 (18.5)	2.3919	0.0168
No: of oocytes fertilised[Mean(±SD)]	8.4(4.4)	4.3(2.2)	6.2998	<.0001
Fertilisation rate (%)	71 (19.7)	82.3 (20.2)	3.4104	0.0006
No; of embryos cleaved[Mean(±SD)]	6.9(3.9)	3.8(2)	5.6031	<.0001
Cleavage rate (%)	58.7 (20.4)	73.2 (23.7)	3.4282	0.0006
No: of embryos frozen[Mean(±SD]	3.1 (3.7)	0.6 (1.3)	5.4493	<.0001

We have used Bolton's criteria according to which, grade 3 embryos are the top quality embryos. In our study, (Table 3) we compared the grade 3 embryos with respect to the total embryos in each group and found that, the ratio of grade 3 embryos and total embryos was significantly less in the PCOS group. Embryos with higher cell number, regular appearing cells, and little or no fragmentation have a

higher overall chance of implantation. In our study we found that in the PCOS group, the ratio of top quality embryos was less as compared to the non PCO group.

Table 3. Oocytes number, matured number, recovery and top quality embryos

Variable	PCOS	Non-PCOS
Total number of oocytes	1028	380
Total number of matured oocytes	872	346
Recovery rate of matured oocytes	84.8%	91%
Total number of fertilised oocytes- embryos	596	278
Recovery rate of fertilised oocytes	68.3%	80.3%
Total No: of Grade 3 embryos(top quality)	401(67.2%)	191(70.8%)

The two groups were compared to assess the incidence of ovarian hyperstimulation syndrome which was found to be higher in the PCOS group. We had no patients with OHSS in the non- PCOS group, whereas in the PCOS group we had 10 patients with mild OHSS requiring supportive care only, and 4 (6%) patients with moderate OHSS requiring blood products transfusion and hospital admission and 1 (1%) patient with severe OHSS in whom the embryo transfer was cancelled and required ascitic fluid tapping with albumin infusion and HDU care. Transfer was deferred in two patients in the PCOS group as one patient had severe OHSS and the other patient had elevated serum progesterone. Embryo transfer is deferred when the serum progesterone level is more than 3 ng/ml(19-21) on the day of hCG trigger.

The implantation rates were comparable in the two groups. The ongoing pregnancy rate and the miscarriage rate were higher in the non PCO group. There was no ectopic pregnancy in the non- PCOS group while in the PCOS group 1 patient had an ectopic pregnancy that was treated successfully with medical management. The rate of biochemical pregnancy was found to be more in the PCO group.

Table 4. Comparison of Pregnancy parameters

Variable	PCOS	NON-PCOS
Beta-HCG positive rates(pregnancy rate)	28.2%	28.1%
Implantation rate	28.1%	28.1%
Biochemical pregnancy rate	20%	16%
Ongoing pregnancy rate	65%	72.2%
Miscarriage Rate	10%	16%

4. Discussion

PCOS patients have the propensity to develop a higher number of follicles during stimulation, which puts them at risk of OHSS (22). In our series, the number of oocytes collected from PCOS patients was significantly higher which was similar to the study by Pratap Kumar et al. (23) who also reported higher number of follicles in the PCOS group. However, the recovery rate of mature oocytes was more in the non PCOS group which was similar to our study. The study (23) mentioned above also has a higher OHSS rate in the PCOS group similar to the finding in our study. A lower incidence of OHSS is reported in the non PCO group. In our study no OHSS occurred in the non-PCOS group. One explanation for this higher rate of OHSS in PCOS group is probably the use of a starting dose of FSH (150 IU FSH) which is same in the two groups. Mulders et al. (24) reported more cancellations of cycles in the PCOS group. We had only one cycle that was cancelled due to OHSS. Heijnen et al. (25) in a meta-analysis of nine retrospective studies comparing the results of IVF, found that PCOS patients with normal ovulation, reported twice as high cycle cancellation risk.

A meta-analysis of nine studies (26) compared conventional IVF outcomes in PCOS patients with matched controls. The analysis reported significantly more oocytes per oocyte retrieval in PCOS group when compared with controls as in our study and higher fertilization rate in the control group which resulted in an equal number of fertilized oocytes in

both studied groups. In our study we report a higher recovery rate of fertilised oocytes (total fertilized oocytes/total matured oocytes x 100) in the non PCOS group vs PCOS group (Table 3).

In the context of conventional IVF and based on morphological study of cumulus-oophorus, some authors have reported a higher rate of immature oocytes in patients with PCOS (27-29). Several theories have been proposed to explain this phenomenon. The first theory is that of inadequate hormonal environment in connection with a high LH level, an insulin resistance, and abnormal secretion of *insulin-like growth factor* or androgens. Other authors have hypothesized a lower oocyte quality in relation to intrinsic defects rather than inadequate hormonal environment. Indeed, it has been shown that the expression of VEGF 9 (a major factor in the first phase of follicular growth) was abnormal in patients with PCOS (30). Indeed, nuclear immaturity does not seem to be the only possible mechanism of fertilization altered. The possibility of cytoplasmic immaturity as well as the possibility of the PCOS population specific chromosomal abnormalities have been also discussed (31).

Several authors using only ICSI showed that patients with PCOS produce many mature oocytes (metaphase II) than controls (32-34). In our study, ICSI was done for all patients and the mean number of oocytes fertilized was higher in the PCO group. This difference between the two groups was statistically significant. The number of embryos cleaved was also more in the PCOS group than the in the non PCOS group. The results obtained in the studies (32-34) using ICSI reported a rate of fertilization similar between PCOS patients and controls. Hwang (35) in a study of 60 patients with PCOS , comparing the fertilization rate obtained in a group of oocytes undergoing IVF and ICSI showed that the fertilization rate obtained by ICSI to be significantly higher.

The embryo quality to a great extent depends on the quality of oocyte from which it was obtained. Embryos with higher cell numbers, regular appearing cells, and little or no fragmentation have a higher overall chance of implantation. In our study, the total number of top quality embryos obtained was relatively more in the non-PCOS group as mature oocytes obtained were higher in this group. Similar results were obtained by Pratap Kumar et al. (23) study.

The results in terms of embryo quality are at least in favour of a similar embryo quality between PCOS patients and normal-ovulating patients (32, 33, 36). In our study, we obtained significantly higher embryo quality in non - PCOS group compared with PCO group.

In our study as well as those of Ludwig et al. (33), Mendes-Pereira et al. (34), the implantation rate was comparable between PCOS patients and controls. In our series, the implantation rate per transfer was similar between PCOS patients and Non- PCOS patients. Whereas the ongoing pregnancy rate was more in the non PCOS group vs the PCOS group (Table 4). Indeed in a vast majority of studies using conventional IVF ICSI have found similar results (26, 28-34). Two recent meta-analyses of pregnancy and neonatal outcome after ART in PCOS patients versus non-PCOS patients have shown an increased cycle cancellation rate, more oocytes retrieved per retrieval, a lower fertilisation rate, and increased pregnancy and neonatal complications in patients with PCOS (12, 14).

In two recent meta-analysis comparing the outcome of GnRH agonist versus antagonist, both showed that the incidence of OHSS was significantly reduced in the antagonist protocol without compromising the pregnancy rates (37,38). It seems logical that the patients with a history of OHSS & who are considered at high risk of developing OHSS should be treated by GnRH antagonist protocol (39). Recent Cochrane review has shown 50% reduction in the incidence of OHSS in antagonist group compared to long agonist protocol (40).

The total OHSS incidence (mild, moderate and severe) in a high-risk population, mainly consisting of PCOS patients, undergoing ovarian stimulation for in vitro fertilization (IVF) after either a long pituitary suppression with Gn-RHa or co- treatment with a GnRH antagonist and having final oocyte maturation triggered with hCG has been reported to be as high as 17–31% (41, 42), whereas the incidence of severe OHSS has been reported to be 15% in the PCOS IVF patient [40]. This number should be compared with the general IVF population, in which the incidence of moderate OHSS has been described to be ~5% and the severe cases in need of hospitalization ~2% (43).The PCOS group in our study has rates of moderate and severe OHSS which is comparable to the general IVF population.

The endpoint of this study was a successful ongoing pregnancy. Table IV summarises the success rates in the two main groups. The pregnancy rates achieved in our treatment protocols are similar to those achieved in published fertility programmes (35). The ongoing pregnancy rate was slightly more in the non PCOS group versus the PCOS group. The miscarriage rates in the non-PCOS group was slightly higher than the PCOS group whereas there was a

slight increase in the biochemical pregnancy in the PCOS group compared to the non PCOS group .

5. Conclusion

In PCOS women though the number of follicles was more, recovery rate of mature oocytes and top-quality embryos was less. Pregnancy rates however were comparable in both groups. OHSS remains a major concern before starting ovarian stimulation in these patients. Finally, several other research topics remain, such as defining the best stimulation protocol and the problem of spontaneous miscarriages often reported in these patients. With the limits of a retrospective study, our analysis still enables us to conclude that there were no significant differences in procedural and pregnancy success in patients with PCOS undergoing GnRH antagonist ovarian stimulation compared with non-PCOS patients in whom the same controlled ovarian stimulation was used. Of importance is the fact that there was only one case of severe hyperstimulation syndrome in the PCOS group, making the use of the GnRH antagonist an attractive option in this high-risk group of patients.

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