The Gonadotropin Releasing Hormone Antagonist Protocol for Superovulation in Polycystic Ovarian Disease during Assisted Reproduction

Adel Elsayed Ibrahim

Assisted Reproductive Unit, Azhar University- Cairo- Egypt
Adel.sayed29@gmail.com

Abstract: Background: The assisted reproductive technology is the last option in the treatment of Polycystic ovarian disease after failure of conventional treatment. The main problem with superovulation in PCOD in long agonist protocols is a high incidence of ovarian hyper stimulation syndrome. The use of GnRh antagonist protocol in PCOD was in an attempt to decrease incidence of OHSS without compromising pregnancy outcome. **Sitting**: Azhar ART unit. **Aim of the work**; to comparethe GnRh antagonist protocol with long agonist protocol for superovulation in PCOS patients. **Material and methods**; This a retrospective studies carried out in Azhar ART unit in the period from June 2011 to March 2013, in which 150 patients with PCOD were classified into; 80 patients were received GnRh antagonist protocols and 70 patients were received long GnRh agonist protocol. The outcome measures were pregnancy outcome, incidence of ovarian hyper stimulation syndrome, the duration of stimulation and total dose of HMG needed for ovarian stimulation. **Results:** The duration of stimulation was significantly shorter in the antagonist group (10.475), in addition the number of HMG ampules was significantly lower in the antagonist group (25.149±10.18 vs 35. 126±8.23). Furthermore the incidence of OHSS was significantly lower in the antagonist group (8 %, 0.2% vs 15%, 3.2%) for moderate and severe cases respectively. On the other hand the clinical pregnancy outcome was significantly lower in the antagonist group (25.36 % vs. 40.56). **Conclusions:** The GnRh antagonist protocol for superovulation in polycystic ovary disease decreases the duration of stimulation as well as number of HMG ampules, furthermore it decreases the incidence of ovarian hyper stimulation syndrome. But unfortunately it decreases the clinical pregnancy outcome if compared with the long GnRh agonist protocol.
[Adel Elsayed Ibrahim. **The Gonadotropin Releasing Hormone Antagonist Protocol for Superovulation in Polycystic Ovarian Disease during Assisted Reproduction.** *Nat Sci* 2014;12(1):96-99]. (ISSN: 1545-0740). http://www.sciencepub.net/nature. 15

Key words; GnRh antagonist, GnRH agonist, PCOD, Ovarianhyper stimulationsyndrome,ICSI.

1.Introduction

The polycystic ovarian disease is one of the most common endocrine disorders in female (5-10 %) and constitutes one of the most common causes of female infertility [1-3]. The Rotterdam ESHRE/ASRAM sponsored consensus workshop group 2004, has defined the PCOS as a presence of the 2 criteria out of three criteria; oligoamenorrhoea or anovulation, an evidence of hyperandrogenism whether clinical or laboratory, picture of PCO with U/S according Adams criteria [4-6].

The main lines of treatment of PCOS are weight reduction, insulin sensitizing agent, ovulation induction, laparoscopic ovarian drilling, and finally assisted reproduction in the form of IVF and ICSI if the previous measures have been filed.

The main problems during superovulation in polycystic ovary syndrome

Is the higher incidence of ovarian hyper stimulation syndrome which occur in about 8- 23 % of cases[(7)], which characterize by hyperestrogenism, increased capillary permeability and shift of fluid from the intracellular compartment to extracellular compartment. The ovarian hyper stimulation syndrome has been graded from mild to critical grade which need admission to the ICU and manifested by renal impairment, respiratory compromise, water and electrolyte imbalance, embolic manifestation and liver impairment.[7]

The antagonist protocols characterized by lower incidence of ovarian hyper stimulation syndrome if compared with agonist protocols[8-11]. However the published articles regarding pregnancy outcome are scarce and conflicting, some article reported lower pregnancy outcome with antagonist protocols, [12] .other investigators found comparable pregnancy outcome. [8-10]. We aim to compare the antagonist protocol vs. agonist protocol in PCOS, in an attempt to find the ideal protocol for superovulation for PCO.

2.Patients and methods

This retrospective study carried out at Azhar ART unit, in the period from June 2011 to March 2013. In which 150 patients with PCOS according Rotterdam criteria (presence of two of the following three features; oligo and or anovulation, PCO picture by U/S, clinical and Lab evidence of hyperandrogenism), were recruited for this study. The patients age was between 20-38 yrs.old, the FSH level was less than 10 iu/ml, BMI was less than 30.The exclusion criteria were azospermic men, FSH more

than 10 IU/L, BMI was more than 30, uterine abnormalities (myoma, synechia and a polyp), poor response in the previous ICSI cycle. The patients were classified into two groups; 70 patients were received standard GnRh long agonist protocol, 80 patients were received the GnRh antagonist protocol.

In the long GnRh agonist protocol, The patients were received down regulation started on the day 21 of the cycle, in the form of Decapeptyl CR single injection or Decapeptyl 0.1 daily subcutaneous injections until the time of HCG administration. After complete down regulation as proved by the E2 level less than 50 pg/ml, thin endometrium, absence of follicular cyst. The ovarian superovulation was started with HMG 150-225 IU/day according the age and BMI. Monitoring by u/s was carried out at day 6th of superovulation and then repeated day after day until at least 3 follicles reached 18 mm in the diameter. At this time triggering by HCG 10,000 unit was done followed by ovumpickup 36 hours later.

In the antagonist protocols, the HMG was started in the 2nd day of menses, 150-225IU/day was given according the age, BMI and pattern of ovarian response during the previous cycle. The monitoring was started on the 6th day of the cycle, and the antagonist was given in the form of cetrotide 0.25 mg SC, daily injection, when dominant follicle was reached 14 mm in diameter and was continued until the triggering of ovulation. The triggering of ovulation was achieved when at least 3 follicles reached 18 mm in diameter by human chorionic gonadotropin 10,000 I/IM injection

The ovum pickup was carried out under general anaesthesia 36 hours later by using single lumen needle. Oocyte assessment was performed by slandering morphology criteria (GV, M1, M2) and intracytoplasmic sperm injection was carried out in the ordinary manner, fertilization was defined as presence of pronuclei 16- 18 hrs. post injection. Embryo grading was done by slandered morphology criteria (Ga, GB, Gc). 2- 3 Ga embryo was transferred at day 3 post retrieval using a labotect catheter under ultrasonic guide.

Luteal phase support was started after ovum pickup in the form of natural progesterone 800mg/day, given vaginally in two divided doses, which was continued for 8 weeks. If the patient have got pregnancy, the clinical pregnancy was determined by the demonstration of fetal sac and fetal pulsation at 6th weeks gestation, while on-going pregnancy was determined by the demonstration of the fetal pulsation at 10th week Of gestation.

The outcome measures; The primary outcome measures ware, clinical pregnancy, while the 2nd outcome were duration of stimulation , number of HMG amp, number of follicles, the number of oocyteretrieved, present of fertilization, number of GA embryos, the number of embryos transferred.

Statistical methods

The statistical softwere SPSS 19.0 were used for statistical analysis, for continuous values, mean and SD was used while % was used for categorical values. For comparison between the results of the continuous scale, student` s t test was used while chi-square test and fisher extract was used to compare values on the categorical scale.

Table 1; Clinical characteristics of patients.

	Agonist	Antagonist	*P* value
Age	27±8.312	29 ± 7.965	Non-significant
Duration of infertility	8.234±6,345	6.21± 7.965	Non significant
Basal FSH	8.2±2.73	7.7±3.2	Non-significant
Basal LH	7.357±1.78	6.97±2.	Non-significant
BMI	29.5±5.82	28± 9.6	Not significant

The table 2 present; the stimulation outcome.

	Agonist	Antagonist	*P* value
Duration of stimulation	14.35±2.45	10.476±3.06	Significant
Dose of HMG	40.34±8.35	30.05±5,23	Significant
Total number of follicles	9.23±4.345	6.148±4.12	Non significant
Number of oocyte retrieved	6.275±4.234	5.234 ± 3.462	Non significant
Number of metaphase 1	1.71±0,234	1.26±0.679	Not significant
Number of metaphase 2	3.1±1.234	2.89±1.884	Not significant
Percent of fertilization	78 %	75 %	Not significant
Number of GA embryos	3.9 ±1.17	4.5±1.56	Not significant
Number of ET	2.8±1,980	3.2±1.25	Not significant
Duration of coasting	5.3±1.4	3.4±1.8	Significant
Incidence of moderate OHSS	15 %	8 present	Significant
Incidence of severe OHSS	3.2%	0.2 %	Significant
E2 (pg/ml)at time of HCG	2634±923	1900±340	Significant

Table (3): Clinical and on-going pregnancy outcome.....?

	Antagonist	Agonist	*P* value
Clinical pregnancy	25.35 %	40,56 %	Significant
On-going pregnancy	23%	31 %	Not significant

3.Results

The table 1 reveals; the clinical characteristics of patients, there were no significant differencesbetween antagonist and agonist regarding age, duration of infertility, BMI, basal FSH and basal LH.

Stimulation outcomes:

Which presented in the table 2; the duration of stimulation was significantly shorter in the antagonist group (10.476 ±3. 06) versus (14.35±2.45) for long agonist protocol. In the same way the number of HMG ampules required for ovarian stimulation was significantly lower in the GnRh antagonist protocol (25,149± 10.18) versus (35.126±8.23 for agonist).

There were no significant differences between antagonist group and agonist group regarding, total number of follicles (6.148 ± 3.06 versus9. 23 ±4. 345), number of oocyte retrieved (5.234 ± 3.462 versus 6.275±4.234), number of metaphase 1 oocytes (1.71±0,234 versus 1.26±0.679), number of metaphase 2 oocytes (2.89±1.884 versus 3.1±1.234), the present of fertilization (78 % versus 75 % for antagonist), number of grade A embryos and number of embryo transfer (4.5±1,56, 3.2±1.25, versus 3.9 ±1. 17, 2.8±1,980

The E2 level at time of HCG administration was significantly lower in the antagonist group (1931±847, if compared with agonist group, also there was a significant difference regarding the duration of coastine which was significantly shorter in the antagonist group (3.4±1.8) versus (5.3±1.4 for agonist group). As regards OHSS, the incidence of OHSS in moderate and severe degree were significantly lower in the antagonist group (8 %, 0.2 %, if compared with agonist group (15%, 3.2%)

Pregnancy outcome.

Which presented in the table 3; the clinical pregnancy outcome was significantly lower in the antagonist protocol (25 % versus 40.56% for the long agonist group, also the on-going pregnancy outcome was significantly lower in the antagonist protocol if compared with the agonist long protocol.

4.Discussion

This a retrospective study, carried out at Azhar ART unit in the period from June 2011 to March 2013, to compare antagonist protocol and agonist protocol for ovarian stimulation in the PCOS during intracytoplasmic sperm injection. We recruited 150 patients with PCOS according Rotterdam criteria; 80 patients were received antagonist protocol and 70 patients were received long agonist protocol. We found that, the duration of stimulation was significantly shorter in the antagonist group (10.476 ±3.06) if compared with long agonist protocol (14.35±2.45). Also we found that, the total dose of HMG ampules needed for ovarian stimulation was significantly lower in the antagonist protocol (30.05±5.23) if compared with long agonist protocol (40.34±8.35).As in agonist protocols, the ovarian stimulation was started after pituitary and ovarian suppression, asconsequences larger dose and longer duration of stimulation will be needed to overcome the ovarian suppression. The our findings are in agreement with many articles published in literature, [8,10,11].

The OHSS is the one of the main problems during ovarian stimulation in PCOD patients during assisted reproductive technology. The our results revealed significantly decreased incidence of OHSS in the antagonist protocol(8% in the moderate degree and 0.2% in the severe degree) if compared with agonist protocol(15%) in the moderate degree and 3.5 % in the severe degree).The decreased incidence of ovarian hyper stimulation syndrome in the antagonist protocol could be explained by immediate suppression of LH at mid follicular phase whish affecting the growth of smaller follicles which the main source of E2 which has a main role in the pathogenesis of ovarian hyper stimulationsyndrome. Furthermore the use of antagonist protocols, allow trigger of ovulation by GnRh agonist which result in the marked reduction in the OHSS.These findings are in agreement with, a meta-analysis, in which 966 women included in nine randomized trial, they found significant lower risk of ovarian hyper stimulationsyndrome in the antagonist protocol if compared with agonist group[10].In the same way other investigator examined 50 patients with PCOS, they found decreased incidence of OHSS in the antagonist group if compared with agonist protocol([8]),. In other hand other published article, has not agree with our findings, they examined 129 PCOS patients for antagonist and agonist protocol, they found no differences in the incidence of OHSS between agonist and antagonist protocols[13]. Also we found that, the clinical pregnancy rate was lower in the antagonist protocol (25.35%) if compared with agonist protocol (40.56%).The decreased pregnancy rate in the antagonist protocol, could be attributed to lower

cumulative experience as antagonist has been recently introduced to ART, also the lower pregnancy outcome could be attributed to possible effects on the endometrial receptivity and ovarian tissue which need to be clarified. The our findings were in agreement with other investigator,who studied 152 patients with PCOS, they found, significantly lower pregnancy rate in the antagonist group(19 %) if compared with agonist group(36 %)[12].In the other hand many published articles found no significant differences in the pregnancy outcome in the antagonist and agonist protocol [13, 8,14,11].

In conclusion, the antagonist protocol has many advantages in the PCOS during ovarian stimulation for ICSI, which included; shorter duration of stimulation and a smaller dose of HMG ampules which make antagonist protocol more convenient to patient. Also lower incidence of OHSS which make this protocol safer for patients. The significant decreased in the pregnancy outcome in the our findings must be explained with caution, also the similar pregnancy rate in the agonist and the antagonist protocols documented in many articles,mustbe explained with caution, as antagonist has been recently introduced more work with huge number of cases must be accumulated to address this dilemma. Finally the antagonist protocol could be the right option in patient highly susceptible for OHSS.

References

1. Goldenberg N,Glueck C. Medical therapy in women with PCO before and during pregnancy and lactation. Minerva Ginicol 2008 ;60(1): 63-75.
2. Boomsma GM, Faucer BC, Macklon NS (2008) Pregnancy complications in women with PCO Semin. Reprod. Med 2008;26(1):72-84.
3. Azziz R, Woods KS, Reyna R . The prevalence and feature of PCO in an unselected population. Journal of Clinical Endocrinol and Metabolism 2004; 89(6):2754-9.
4. AzzizR(2006) Diagnosis of PCOS: The Rotterdam criteria are premature. Journal of Clinical Endocrinol and Metabolism.2006 ; 91(3): 781-785.
5. The Rotterdam ESHRE/ASRM sponsored PCOS concensus workshop group 2004 Hum Reprod. 2004 :19(1):41-47.
6. BalenAH, LavenJ S, Tan SL. Ultrasonic assessment of the PCO: consensus definition. Human Reprod update 2003(9); 505-514.
7. Brinsden PR, WadaI,Tan SL(1995) Diagnosis , prevention and management of ovarian hyperstimulation syndrome. Br J of Obstet and Gynecol.1995;102(10):767-72.
8. Alina Onofriescu, Adrian Bors, Alexenderluca, Holicov M. Home GnRh antagonist IVF protocol in the PCOS(2013) Current Health Science Journal, volme39(2)2013
9. Xiao J,Chen S, Zhang C, Chang S. Effectiveness of GnRh antagonist in the treatment of patients with polycystic ovary syndrome undergoing IVF: a systemic review and meta-analyis .Gynecol Endocrinol 2013;(29(3): 178-91.
10. Pundir J, Sunkara SK, Eltokhy T, Khalaf Y. Meta-analysis on the GnRh antagonist protocols; Do they reduce the risk of OHSS in PCOS. Reprod Biomed online. 2012 24(1);6-22.
11. Mahnazashrafi Ashrafmoin i, Afsanehmohammadzadeh. A comparative study of GnRh antagonist and GnRh agonist in PCO patients undergoing IVF-ICSI cycles. SAJOG. January 2012.
12. Oriveto R, Melcers S, Homburg R, Nahum R. What is the preferred GnRh analogue for polycystic ovary syndrome patients undergoing controlled ovarian hyperstimulation for *in vitro* fertilization. Fertil Steril 2009,91(4); 1466-8)
13. Bahceci , ulugU, Ben-sholomoI. Use of GnRH antagonist in controlled ovarian hyperstimulation in women with polycystic ovary disease; a prospective ,pilot study. J Reprod Med 2005,50(2) 84-90
14. Lains TG, Sfontouris IA, Zorzovilis IZ. Flexible GnRh antagonist versus GnRh agonist long protocol in patients with polycystic ovary syndrome treated for IVF; A prospective randomized controlled trial. Hum Reprod 2010;25:683- 693.

1/2/2014