Journal of Fertilization : In Vitro, IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology

Abdelmeged, JFIV Reprod Med Genet 2014, 3:1
DOI: 10.4172/2375-4508.1000137

Research Article

A Comparative Study between GnRH Antagonist and Long Agonist Protocols in Patients with Polycystic Ovarian Syndrome (PCOS) Undergoing *in vitro* Fertilization

Ayman Abdelmeged, Amer Abdalah, Ahmad Mahran*, Alaa Gamal and Esam Elgendy

Department of Obstetrics and Gynaecology, Faculty of Medicine, Minia University, Minia, Egypt

Abstract

We compared the efficacy and safety of GnRH antagonist protocol and GnRH long agonist protocol in patients with PCOS undergoing IVF/ICSI. A total of 100 patients with PCOS candidate for IVF/ICSI were prospectively studied. Patients were randomly allocated to either antagonist or agonist groups. There was no significant difference between the two groups as regards the clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate per clinical pregnancy and multiple pregnancy rates. However, there was a significantly lower dose and shorter duration of gonadotropin stimulation and lower incidence of severe ovarian hyperstimulation syndrome (OHSS) in the antagonist group (P = 0.001, 0.001 and 0.01 respectively). GnRH antagonist protocol may be the protocol of choice in PCOS patients undergoing IVF / ICSI.

Keywords: GnRH antagonist; GnRH agnonist; Polycystic ovary syndrome; Ovarian hyperstimulation syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinal disorder affecting 6.6-8% of women of reproductive age [1]. It is associated with 75% of the causes of anovulatory infertility [2]. There has been much debate about the definition of PCOS. A refined definition was agreed at a recent joint European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus meeting [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 facing patients with PCOS undergoing IVF / ICSI is developing ovarian hyperstimulation syndrome (OHSS); a serious iatrogenic complication of ovarian stimulation triggered by exogenous and/or endogenous hCG which varies from mild to severe and critical forms [5-7]. 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 incidence of premature LH surges and the frequency of cycle cancellation [8,9]. However, it has the disadvantages of long duration of GnRH agonist administration, increased dose and duration of gonadotropin stimulation with subsequent higher cost. Moreover, it does not reduce the incidence of OHSS [10].

GnRH antagonist down-regulation protocol in IVF / ICSI has gained much popularity over the last few years [11]. It acts by competitive inhibition of GnRH receptors in pituitary, and produce an immediate and rapid decrease in LH and FSH levels without GnRH receptor desensitization as well as flare-up effect. Previous studies have shown that GnRH antagonist protocolsreduce 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 [12-14]. In the last few years, there was more interest in using GnRH antagonist protocol in patients with PCOS undergoing 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 [15-18]. This study was performed to evaluate the effectiveness and safety of GnRH antagonist protocol compared with the standard long agonist protocol in patients with PCOS undergoing IVF / ICSI.

Patients and Methods

This study was a prospective randomized controlled trial involving 100 patients with PCOS undergoing IVF / ICSI at Minia infertility research unit, Minia, Egypt in the period from June 2012 to May 2014. The Ethical approval for the study was obtained from the local ethical committee of Faculty of Medicine, Minia University, Egypt. All the patients signed written informed consents before inclusion in the study.

Inclusion criteria for the study were: a) age between 18 – 39 years, b) baseline FSH ≥ 10 c) diagnosis of PCOS based on the Rotterdam criteria, in which at least two of the following three criteria were met: (1) oligo or an ovulation, (2) clinical or biochemical hyper androgenaemia, (3) polycytic ovaries (> 12 follicles <10 mm and/or ovarian volume >10 ml per ovary by vaginal ultrasound). Hyperprolactinaemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, an adrenal or ovarian tumour were excluded before enrolment in the study. We excluded patients with: a) previous poor response to ovarian stimulation. b) endometriotic cyst c) uterine abnormality diagnosed with ultrasound, hysterosalpingography (HSG) or hysteroscopy. d) any hormonal therapy taken within 3 cycles prior to the study. We performed intention to treat analysis.

Randomization

Eligible patients who accepted to take part in the study were randomized into either study group (antagonist group, n = 50) or control group (GnRH agonist group, n = 50). Randomization was

***Corresponding author:** Ahmad Mahran, Department of Obstetrics and Gynaecology, Minia University, Minia61111, Egypt, E-mail: ezzeldin_ahmad@yahoo.com

Received October 25, 2014; **Accepted** November 05, 2014; **Published** November 12, 2014

Citation: Abdelmeged A, Abdalah A, Mahran A, Gamal A, Elgendy E (2014) A Comparative Study between GnRH Antagonist and Long Agonist Protocols in Patients with Polycystic Ovarian Syndrome (PCOS) Undergoing *in vitro* Fertilization. JFIV Reprod Med Genet 3: 137. doi:10.4172/2375-4508.1000137

done simply using sealed envelopes.Neither patients nor doctors were blinded to the treatment assigned.

Ovarian stimulation

In the antagonist group, 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. GnRH antagonist, ganirelix (Orgalutran, Organon, The Netherlands) 0.25 mg / day was started when a leading follicle reached 14 mm and continued till the day of HCG. In the agonist 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 continued with the same dose till day of HCG. Ovarian stimulation was performed in the same way as in the antagonist group. The gonadotropin preparations used were highly purified FSH (Fostimone, IBSA, Switzerland) and highly purified hMG (Merional, IBSA, Switzerland).

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 5,000 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 anaesthesia 36 hours after HCG administration. Fertilization was performed by standard IVF or ICSI.

Cleavage- stage embryo transfer (ET) was performed on day 2 or 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.

Outcome measures

The Primary outcome measure of the study was:

- Ongoing pregnancy, defined as a clinical pregnancy of 12 or more weeks of gestation, per allocated woman.

The secondary outcome measures of the study were:

-Clinical pregnancy rate; calculated as the number of patients with clinical pregnancy divided by the number of patients who had embryo transfer.

-Incidence of OHSS. We used the modified classification system suggested by Mathur et al., 2005 [19].

- Total dose and duration of gonadotropin stimulation.

-Miscarriage rate per clinical pregnancy; calculated as the number of patients who had miscarriage divided by the number of patients who had clinical pregnancies.

-Multiple gestations rate; calculated as the number of patients who had multiple gestation divided by the number of patients who had clinical pregnancies.

	Antagonist group (n = 50)	Agonist group (n = 50)	P value
Age (years)	30.4 ± 5.3	29.6 ± 5.3	0.4
BMI (Kg/m^2)	28.2 ± 3.1	27.9 ± 3.6	0.2
Duration of infertility (years)	7.5 ± 1.3	7.6 ±0.7	0.9
Infertility type Primary secondary	 42 (84%) 8 (16%)	 38 (76%) 12 (24%)	0.1
Basal FSH (IU/L)	5.9 ± 1.2	5.2 ± 1.3	0.6
Basal LH (IU/L)	7.2 ± 1.3	7.7 ± 1.5	0.4
Testosterone (ng/ml)	2.2 ± 0.4	1.7± 0.5	0.7
SHBG (ng/ml)	40.4 ± 5.6	37.9± 4.9	0.8
FAI	6.6 ± 2.2	6.3± 2.1	0.8
Prolactin (ng/ml)	8.9 ± 2.1	8.4 ± 2.8	0.3
AFC	27.3 ± 3.4	29.1 ± 3.1	0.5
Ovarian volume (ml)	12.3± 2.4	13.1 ± 2.2	0.6

Data are presented as mean ± SD or number (%)
(BMI = body mass index, FSH = follicle stimulating hormone, LH = luteinizing hormone, SHBG = sex hormone binding globulin, FAI = free androgen index, AFC = antral follicle count)

Table 1: Characteristics of the study population.

- Total number of retrieved oocytes and mature oocytes.

- Total number of embryos and grade A embryos.

Embryos were classified according to Veeck's grading [20] as follow:

Grade 1: preembryos with blastomeres of equal size and no cytoplasmic fragnmentaions;

Grade 2; preembryos with blastomeres of equal size with cytoplasmic fragnmentaions equal to 15% of the total embryo volume;

Grade 3: uneven blastomeres with no fragmentations;

Grade 4: uneven blastomeres with gross fragmentation (≥ 20% fragments).

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 ± SEM (standard deviation) for continuous variables and frequencies (number of cases) and percentages for categorical data. Independent Student's t-test was used to compare quantitative variables and Chi square test was used to compare categorical data. A P value <0.05% was considered significant.

Results

There was no significant difference in the demographic, hormonal or sonographic features between the two groups. Characteristics of the study population are summarized in Table 1.

Fifty cycles were initiated in each group. In the agonist group, 3 cycles were cancelled after oocyte retrieval due to high risk of OHSS. Frozen embryos were transferred later in non stimulated cycles. No cycles were cancelled in the antagonist group. This difference in the cycle cancellation rate was statistically significant (P = 0.01). The dose and duration of gonadotropin stimulation were significantly lower in the antagonist group as compared with the agonist group (P = 0.001). There were no significant differences between the two groups regarding the total number of retrieved oocytes, mature oocytes, total number of embryos, grade A embryos, fertilization and cleavage rates. The characteristics of ovarian stimulation in both groups are summarized in Table 2.

	Antagonist group (n = 50)	Agonist group (n = 50)	P value
No. of cycles initiated	50	50	
No. of ET cycles	50	47	
Cancellation rate	0%	6%	0.01*
Total HMG dose (IU)	2049.5 ± 396.2	2702.2 ± 618.9	0.001*
Duration of stimulation (days)	11 ± 1.5	20.1 ± 2.6	0.001*
Pre-ovulatory follicle (n)	13.1 ± 2.6	13.3 ± 2.5	0.9
Retrieved oocytes (n)	12.6 ± 5.3	10.9 ± 5.1	0.1
Mature oocytes (n)	7.3 ± 3.3	6.5 ± 2.6	01
Total no. of embryos	4.2 ± 2.4	4.4 ± 1.8	0.5
Embryo transferred (n)	3.3 ± 1.3	3.3 ± 0.9	0.8
Grade A embryo transferred (n)	2.3± 0.8	2.4 ± 0.7	0.3
Fertilization rate (%)	64.4 ± 9.2	68.1 ± 9.3	0.1
Cleavage rate (%)	94.5±0.6	94.7±0.5	0.6
OHSS Mild Moderate Severe	 3 2 3	 4 1 0	 0.5 0.3 0.01

Data are presented as mean ± SD or number (%)
*Statistically significant difference

Table 2: Characteristics of ovarian stimulation in both groups.

	Antagonist group (n =5 0)	Agonist group (n = 50)	P value
Clinical pregnancy rate (%)	24/50 (48%)	22/50 (44%)	0.8
Ongonig pregnancy rate (%)	20/50 (40%)	19/50 (38%)	0.9
Miscarriage rate (%)	4/ 24 (16.7%)	3 / 22 (13.6%)	0.7
Multiple pregnancy rate (%)	2/24 (8.3%)	4/22 (18.2%)	0.2

Table 3: The outcome measures in both groups.

There was no statistically significant difference between the two groups regarding to the clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate per clinical pregnancy and multiple pregnancy rate. The outcome measures of the two groups are shown in Table 3.

Discussion

Over the past few years, GnRH antagonist protocols have been more frequently used in IVF / ICSI in a wide range of patients including patients with expected high response. This last group includes PCOS patients who are at higher risk of developing OHSS during ovarian stimulation. Theoretically, GnRH antagonist protocols can reduce the OHSS rate. There is limited number of published studies evaluating the use of GnRH protocol in PCOS patients undergoing IVF/ICSI.

In this study, we evaluated the efficacy, safety of GnRH antagonist protocol in PCOS patients undergoing IVF/ ICSI as compared with the traditional GnRH agonist long protocol. We used the ongoing pregnancy rate as the primary outcome. Incidence of OHSS, clinical pregnancy rate, , total dose and duration of gonadotropin stimulation, miscarriage rate per clinical pregnancy and multiple pregnancy rates were used as the secondary outcome for the study.

In agreement with the results of the present study, Griesinger et al. (2006) in a meta-analysis including 305 patients from four studies found no significant difference in pregnancy rates in the agonist and antagonist groups, but a significantly higher incidence of severe OHSS in the agonist group [21]. Another meta analysis was done by Xio et al. (2013) including 1332 PCOS patients from 12 studies showed that GnRH antagonist protocol as compared to GnRH agonist protocols, is associated with fewer oocytes retrieved, lower E2 levels, and thinner endometrium whereas the clinical pregnancy and cycle cancellation rates are similar [22].

Results obtained from a recent meta-analysis done by lin et al. (2014) including1142 patients from nine studies that showed no difference between the use of GnRH antagonist protocol compared with the standard long protocol with respect to clinical pregnancy rate (CPR) and ongoing pregnancy rate (OPR) in patients with PCOS undergoing IVF while significantly reducing the rate of severe OHSS. That meta-analysis highlights the need for further RCTs to allow more solid conclusion [23].

The difference in the occurrence of OHSS observed in the current study does not appear to be associated with the number of retrieved oocytes as there was no significant difference between the two groups. However that may be related to the number of small follicles which were not retrieved and might be associated with the total dose and duration of gonadotropin stimulation which were significantly lower in the antagonist group.

One of the main advantages of the GnRH antagonist protocol that it is more patient friendly as the dose gonadotropin stimulation may be low and the duration of treatment is short by at least 14 days. If we take into consideration the cost of treatment per pregnancy including the working hours lost due to prolonged treatment and inconvenience of multiple injections for more days with the traditional long agonist protocol as well as the cost of hospitalization due to OHSS, the final cost may be considerably lower with the antagonist protocol. This economic comparison needs to be evaluated in further studies.

In conclusion, GnRH antagonist protocol can achieve a similar clinical pregnancy and ongoing pregnancy rates in patients with PCOS undergoing IVF / ICSI as compared with the traditional GnRH agonist long protocol with lower dose and shorter duration of gonadotrphin stimulation and less risk of severe OHSS. GnRH antagonist protocol may be the protocol of choice in PCOS patients undergoing IVF / ICSI.

Acknowledgment

The authors are quite grateful to the entire medical, laboratory and nursing staff of Minia infertility research unit for their kind help and cooperation throughout the research work.

References

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, et al. (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 89: 2745-2749.
2. Kousta E, White DM, Franks S (1997) Modern use of clomiphene citrate in induction of ovulation. Hum Reprod Update 3: 359-365.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 19: 41-47.
4. Franks S (2002) Adult polycystic ovary syndrome begins in childhood. Best Pract Res Clin Endocrinol Metab 16: 263-272.
5. Homburg R, Berkowitz D, Levy T, Feldberg D, Ashkenazi J, et al. (1993) In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. Fertil Steril 60: 858-863.
6. Delvigne A, Rozenberg S (2002) Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 8: 559-577.
7. Delvigne A, Rozenberg S (2003) Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update 9: 77-96.
8. Homburg R, Levy T, Berkovitz D, Farchi J, Feldberg D, et al. (1993) Gonadotropin-releasing hormone agonist reduces the miscarriage rate for pregnancies achieved in women with polycystic ovarian syndrome. Fertil Steril 59: 527-531.
9. Balen AH, Tan SL, MacDougall J, Jacobs HS (1993) Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum Reprod 8: 959-964.
10. Kolibianakis EM, Collins J, Tarlatzis BC, Devroey P, Diedrich K, et al. (2006)

Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update 12: 651-671.

11. Al-Inany HG, Abou-Setta AM, Aboulghar M (2007) Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. Cochrane Database Syst Rev 14:640-649.

12. Kolibianakis EM, Albano C, Kahn J, Camus M, Tournaye H, et al. (2003) Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotro¬pin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy. Fertil Steril 79: 873-880.

13. Aboulghar MA, Mansour RT, Amin YM, Al-Inany HG, Aboulghar MM, et al. (2007) A prospective randomized study comparing coasting with GnRH antagonist administration in patients at risk for severe OHSS. Reprod Biomed Online 15: 271-279.

14. Depalo R, Jayakrishan K, Garruti G, Totaro I, Panzarino M, et al. (2012) GnRH agonist versus GnRH antagonist in in vitro fertilization and embryo transfer (IVF/ET). Reprod Biol Endocrinol 10: 26.

15. Elkind-Hirsch KE1, Webster BW, Brown CP, Vernon MW (2003) Concurrent ganirelix and follitropin beta therapy is an effective and safe regimen for ovulation induction in women with polycystic ovary syndrome. Fertil Steril 79: 603-607.

16. Kim CH, Lee YJ, Hong SH, Kim SH, Chae HD (2004) Efficacy of a GnRH antagonist during early and late controlled ovarian hyperstimulation period in women with polycystic ovary syndrome undergoing IVF-ET. Hum Reprod 19: 104-105.

17. Hwang JL, Seow KM, Lin YH, Huang LW, Hsieh BC, et al. (2004) Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study. Hum Reprod 19: 1993-2000.

18. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, et al. (2010) Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). Hum Reprod 25:683-689.

19. Mathur R, Evbuomwan I, Jenkins J (2005) Prevention and management of ovarian hyperstimulation syndrome. Current Obstet Gynaecol 15: 132-138.

20. Veeck L (1990) The morphological assessment of human oocytes and early conception. In: Keel BA, Webster BW (Eds) Handbook of the laboratory diagnosis and treatment of infertility. CRC Press, Boca Raton, FL.

21. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM (2006) GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. Reprod Biomed Online 13: 628-638.

22. Xiao J, Chang S, Chen S (2013) The effectiveness of gonadotropin-releasing hormone antagonist in poor ovarian responders undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril 100: 1594-1601.

23. Lin H, Li Y, Li L, Wang W, Yang D, et al. (2014) Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. PLoS One 9: e91796.