

Research Article

Gnrh Antagonist versus GnRH Agonist Long Protocol in Overweight and Obese Women with Polycystic Ovary Syndrome Stimulated for IVF

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Submitted: 08 June 2015

Accepted: 22 June 2015

Published: 29 June 2015

ISSN: 2333-6439

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Keywords

- PCOS
- GnRH agonist
- GnRH antagonist
- IVF

Abstract

Objective: To compare the flexible GnRH antagonist GnRH agonist long protocol in overweight and obese patients with polycystic ovarian syndrome (PCOS) in terms of number of retrieved oocytes and clinical pregnancy rate.

Design: Prospective non-randomized controlled study.

Setting: University IVF Center in association with private IVF center

Patient(s): 69 overweight and obese women (BMI>24) with PCOS underwent their first cycle of IVF embryo transfer with intracytoplasmic sperm injection (ICSI).

Intervention(s): The patients were allocated in the flexible GnRH antagonist or GnRH agonist long protocol according to the physician preferences (none randomized).

Main Outcome Measure(s): The primary outcomes included the total retrieved oocytes and the clinical pregnancy rate.

Result(s): No differences were observed in clinical pregnancy rates in the agonist and antagonist protocols. There was higher number of retrieved oocytes in the antagonist group. Both groups were similar in fertilization, implantation and miscarriage rates.

Conclusion(s): The current study suggests that the flexible GnRH antagonist protocol is associated with a similar clinical pregnancy rate, higher number of retrieved oocytes, similar gonadotropin requirement and similar implantation and miscarriage rates compared with GnRH agonist. The simple flexible GnRH antagonist protocol may be the treatment of choice for PCOS women undergoing controlled ovarian hyperstimulation "COH".

ABBREVIATIONS

PCOS: Polycystic Ovarian Syndrome; **GnRH:** Gonadotropin Releasing Hormone; **IVF:** In vitro Fertilization, **COH:** Controlled Ovarian Hyperstimulation; **OCPs:** Oral Contraceptive Pills

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most prevalent cause of anovulatory infertility in women in the reproductive age with a prevalence rate of about 10% [1]. PCOS is characterized by both metabolic and reproductive abnormalities. According to Rotterdam criteria (2004), the patient should be diagnosed to have PCOS when two of the following are met: chronic oligoovulation or anovulation, clinical or biochemical hyperandrogenism and ultrasound polycystic ovaries [2]. The optimum infertility

treatment in PCOS is still controversial. However, IVF is considered a popular final infertility management option for the resistant cases [3,4].

Obesity and insulin resistance are common features in PCOS subjects. It is estimated that 50% of the PCOs women are overweight and obese [5,6]. Obesity in PCOS is usually central phenotype and almost always associated with insulin resistance [6,7].

Overweight and obese women with PCOS can be challenging during IVF cycles [8]. These women show slow initial response during controlled ovarian hyperstimulation followed by robust response with high incidence of developing ovarian hyperstimulation syndrome (OHSS) [9]. It is believed that GnRH antagonist cycles have been associated with lower risk of OHSS

especially with the introduction of GnRH agonist trigger in the high risk PCOS women [10].

However, there is no conclusive result about the impacts of the use of GnRH antagonist protocol during COH in the overweight and obese PCOS undergoing IVF.

We hypothesize that GnRH antagonist cycles can be associated with improved IVF outcomes. The objective of our study was to compare the flexible GnRH antagonist GnRH agonist long protocol in overweight and obese patients with polycystic ovarian syndrome (PCOS).

MATERIALS AND METHODS

Study population

The study subjects consisted of 68 overweight and obese PCOS women with BMI > 24 underwent first cycle fresh IVF performed during the period from June, 2014 to June, 2015 at University and private IVF centers. These patients were diagnosed as PCOS according to Rotterdam criteria (2004) by the presence of at least two of the following: basal ultrasound polycystic ovary (12 or more follicles ranging 2-9mm), hyperandrogenism (clinical and / or biochemical) and anovulation or oligoovulation (less than 9 ovulatory cycles per year). All patients had normal TSH, prolactin, and day 3 FSH levels. Only women less than 40 years old were included in the analysis.

Specific exclusion criteria were associated male factor, documented tubal factor or pelvic adhesions and FSH more than 10 IU/ml. Women who started program or drugs to reduce their weight were excluded. We also excluded the canceled cycles (cycles with no embryo transfer).

Recruitment

The patient with PCOS who have been allocated to the GnRH antagonist and GnRH agonist long protocol according to the preference of their health care provider. The women were classified into 2 groups according to the cycle protocol: Flexible GnRH antagonist protocol (n=47, antagonist group) and GnRH agonist long protocol (n=22, agonist group). We obtained an institutional approval from the ethical committee before starting the study.

IVF protocol

Patients were kept on oral contraceptive pills "OCPs" (0.25 mg of levonorgestrel plus 0.05 mg of ethinylestradiol; Organon Pharmaceuticals) for at least 2 weeks. Before starting OCPs, the patients were allocated to either agonist or antagonist group after proper patient counseling. On day 2 or 3 of the menstrual blood flow, we started COH using recombinant FSH "rFSH" (Gonal F®, serono Inc., Rockland, MA, USA) in combination with urinary gonadotropins "FSH and LH" (Fostimon, IBSA, Switzerland). The dose and type of gonadotropins had been tailored in each case by the supervising physician.

In the antagonist group, OCPs were discontinued after at least 2 week of OCPs intake. The COH was started on day 2 or 3 of the menstrual blood flow. GnRH antagonist was administered in a dose of 0.25 mg SC Ganirelix (ganirelix, Organon, USA Inc., Roseland, NJ, USA) when any one of the following criteria was

met: 1) day 6 of COH or 2) when the leading follicle >13 mm or 3) when the estradiol level > 600.

In the agonist group, GnRH agonist "leuprolide acetate" (Lupron®, TPA pharmaceutical, North Chicago, IL, USA) started during OCPs intake. After one week of GnRH agonist with OCPs, OCPs was discontinued. GnRH agonist dose was 10 IU per day which reduced to 5 IU with the start of COH.

In both groups, monitoring with ultrasound examination and E2 levels was initiated on day 5 of gonadotropins stimulation. According to the ovarian response, we started step up or step down of the gonadotropin dose. We monitored the patients using transvaginal ultrasound and estradiol level (E2). The final ovulation trigger was done using hCG (Profasi, Serono Inc., Randolph, MA, USA) at dose 5000 or 10000 IU.

Oocyte retrieval was performed 34-36 hours following hCG administration. ICSI were performed to all the mature oocytes 6 hours after the retrieval. The best quality cleavage stage embryos (day 2 or 3 embryos) were used for ET. The number of embryos transferred was individualized to the patient; three or four embryos was the most common number used.

The luteal phase was supported using intramuscular progesterone 25mg twice daily. Serum b-hCG were assessed 14 days after ET.

STATISTICAL ANALYSIS

Outcome measures

The main outcomes in our study were number of oocytes retrieved and clinical pregnancy rate (calculated by the number of clinical pregnancies diagnosed by the gestational sac on ultrasound examination divided by the embryo transfer cycles) and miscarriage rate (the number of the miscarriages per the number of the clinical pregnancies. Secondary outcomes include the total dose of gonadotropins, fertilization rates (the total number of fertilized oocytes divided by the total number of retrieved oocytes), number of embryos and implantation rate (number of sacs seen by ultrasound evaluation divided by the number of embryos transferred).

Statistical tests

Agonist and antagonist groups were compared using Microsoft Excel. The differences were analyzed using Student t test, or chi-square wherever indicated. A value of P < 0.05 was considered statistically significant. Fertilization rate was defined as the number of two pn oocytes divided by the total number of retrieved oocytes. The implantation rate was calculated as number of gestational sacs divided by number of embryos transferred. Clinical pregnancy rate was defined as number of clinical pregnancy divided by number of cycles transferred. Miscarriage rate was obtained by number of miscarriages (spontaneous pregnancy loss when the fetus <12 weeks) divided by number of clinical pregnancies.

RESULTS AND DISCUSSION

Patient baseline and cycle characteristics

The demographic and cycle characteristics of the study

population are summarized in Table 1. Agonist and antagonist groups were similar except for number of antral follicle count (AFC) which was significantly higher in the antagonist group treated (33 ± 14 vs 25 ± 13 , $p=0.03$). The decision to be allocated to agonist or antagonist groups was made by the supervising physician after patient counseling. There was no significant differences in the total gonadotropin doses used in stimulation in both groups (1892 ± 681 vs 1530 ± 694). Also, the triggering estradiol was similar in both groups.

Cycle outcomes

Table 2 summarizes cycle outcomes in the two groups of patients. The number of the retrieved oocytes was significantly higher in the antagonist treated group (17 ± 10 vs 10 ± 2 , $p<0.01$). The number of the fertilized oocytes (two pronuclear stage) was higher in the antagonist group (9.3 ± 5.3 vs 6.3 ± 2.2 , $p<0.01$). We did not find differences regarding fertilization, clinical pregnancy, implantation or miscarriage rates between both groups.

DISCUSSION

In our study, we compared the efficacy of flexible GnRH antagonist and the long GnRH agonist protocols for pituitary down regulation during IVF cycle treatment in PCOS patients. To our knowledge, our study is the first one which compare between both protocols in the overweight and obese PCOS subjects. We hypothesis that the antagonist protocol will be similar and more simple than long GnRH agonist protocol in the overweight and obese PCOS women undergoing COH during IVF cycles.

We found that clinical pregnancy, implantation and miscarriage rates were similar in the two protocols, although the GnRH antagonist protocol was associated with significantly higher number of retrieved oocytes. In addition, total amount of gonadotropin required were similar in both groups. We suggest that flexible GnRH antagonist is simple and appropriate protocol that can be used in the COH in the prospective hyper responders

Table 2: IVF cycle outcomes in both groups.

	antagonist group (n=47)	Agonist group (n=22)	P value
Retrieved oocytes (Mean \pm SD)	17 ± 10	10 ± 2	$< 0.01^*$
# 2pn (Mean \pm SD)	9.3 ± 5.3	6.3 ± 2.2	$< 0.01^*$
Fertilization rate (%)	(392/726)54	(140/236)59.3	0.15
Pregnancy rate %	(22/42)52	(14/22)63.6	0.39
Implantation rate%	(24/44)54.5	(16/28)57.14	0.83
Miscarriage rate(%)	(8/22)36.4	(2/14)14.3	0.15

*: statistically significant at P value < 0.05
Abbreviations: pn: pronucleate; ET: embryo transfer

especially the women with PCOS.

Long GnRH agonist protocol has been used for pituitary down regulation for a long time. This protocol is still prevalent. However, many studies recommended the use of the antagonist protocol [11,12].

Our finding demonstrates that there is no significant differences between the flexible GnRH antagonist and the long GnRH agonist protocols in the overweight and obese PCOS women regarding the total gonadotropins dose used in the stimulation, the clinical pregnancy, implantation and miscarriage rates. Lin et al (2014) used nine RCTs examining women with PCOS underwent IVF/ICSI and concluded that the clinical pregnancy rate in the antagonist protocol patients was similar to those with the agonist protocol and recommended the use of the antagonist protocol [12].

The significant high number of the retrieved oocytes in the antagonist group in our study can be related to the higher antral follicle count in this group and the preference of the working physician to allocate the patients in the antagonist protocol. We are looking to this as a weakness point in our study.

In conclusion, our study suggest that the overweight and obese PCOS women will benefit from the simple flexible GnRH antagonist protocol during COH.

CONCLUSION

Our study suggest that the overweight and obese PCOS women will benefit from the simple flexible GnRH antagonist protocol during COH.

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Table 1: Patient's baseline and cycle characters:

	antagonist group (n=47)	Agonist group (n=22)	P value
Age (years)	32.1 ± 3.3	32.4 ± 4.2	0.8
BMI (Kg/M ²)	32 ± 6	29 ± 6	0.13
Duration of infertility (years)	2.50 ± 1.14	2.79 ± 1.42	0.38
Basal estradiol (pg/mL)	25 ± 10	23.6 ± 8.8	0.43
Number of Antral follicle count	33 ± 14	25 ± 13	0.03*
AMH (ng/mL)	7.9 ± 6	5.6 ± 4.8	0.19
Basal FSH (IU/L)	6.6 ± 1.8	5.7 ± 2.8	0.14
Total gonadotropin doses (IU)	1892 ± 681	1530 ± 694	0.06
Triggering estradiol (pg/mL)	2856 ± 1476	2442 ± 994	0.18

-All values are expressed in (Mean \pm SD)
 - Statistical test: Student t-test
 - *: P value is statistically significant at < 0.05
Abbreviations: BMI: body mass index; AMH: Antimullarian hormone; FSH: Follicular stimulating hormone

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Cite this article

Abdalmageed OS, Ismail AM, Farghaly TA, Abdelaleem AA, Darwish AM, et al. (2015) GnRH Antagonist versus GnRH Agonist Long Protocol in Overweight and Obese Women with Polycystic Ovary Syndrome Stimulated for IVF. *Med J Obstet Gynecol* 3(4): 1063.