Al-Azhar International Medical Journal

Volume 1 | Issue 3 Article 10

3-1-2020

GnRH agonis short protocol versus GnRH antagonist flexible protocols in poor responder undergoing in vitro fertilization treatment.

Aly Elboghdady Adel
Obstetrics and Gynecology Department,Faculty of Medicine,Al-Azhar University,Cairo,Egypt.,
elboghdadyd8@gmail.com

How to Cite This Article

Adel, Aly Elboghdady (2020) "GnRH agonis short protocol versus GnRH antagonist flexible protocols in poor responder undergoing in vitro fertilization treatment.," *Al-Azhar International Medical Journal*: Vol. 1: Iss. 3, Article 10.
DOI: https://doi.org/10.21608/aimj.2020.26790.1185

OPEN AIMJ ORIGINAL ARTICLE

Obst. and Gyn.

(GnRH) Agonist (Short Protocol) Versus GnRH Antagonist (Flexible) Protocols in Poor Responder Undergoing In Vitro Fertilization Treatment

Adel Aly Elboghdady[1,*] MD and Amal Helmy Yassin[2] MSc

** Corresponding Author:*
Adel Aly Elboghdady
elboghdadyd8@gmail.com

Received *for publication March 28, 2020;* ***Accepted*** *April 21, 2020;* ***Published online*** *April 21, 2020.*

doi: 10.21608/aimj.2020.26790.1185

1 Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

2 Fertility Care Unit, Mansoura University

ABSTRACT

Background: poor response can be broadly defined as unsatisfactory ovarian response despite adequate ovarian stimulation.
Aim of the work: : To compare the short agonist and flexible antagonist protocols in the management of poor responders to standerd long down regulation protocol.
Design: Randomized prospective comparative study.
Setting: private IVF center (Engab).
Patients and methods: One hundred poor-responder (IVF) (ICSI), who responded poorly to the standerd long down- regulation protocol in their first treatment cycle.
Intervention(s): Peak serum E2 was assayed on the day of hCG administration.
Main Outcome Measure(s): primary outcome: number of gonadotropins ampoules used, peak E2 at the triggering day, number of oocytes retrieved, number of metaphase II oocytes, fertilization rate, embryo quality and number of embryos transferred.cycle cancellation. Secondary Outcome: pregnancy rate , miscarriage rate.
Results: GnRH-antagonist protocol shows increased – non significant- pregnancy rate and decreased - non significant - miscarriage rate than agonist short protocol, however agonist short protocol appears to be more effective than the GnRH-antagonist protocol in terms of number of gonadotropins ampules, peak E2 level, fertilization rate, and top-quality embryos transferred in poor-responder.
Conclusion: The probability of pregnancy might be better with the use of the antagonist protocol, also flexible antagonist protocol is a simpler and more patient friendly method of ovarian stimulation compared with the short agonist protocol.

Keywords: *Agonist; antagonist; short protocol; ICSI; poor responders.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Defining poor ovarian response (POR) has been a long standing challenge. Prompted by the call for a universally accepted definition, the European Society of Human Reproduction and Embryology organized a Campus Workshop in 2011 and published the ‘‘Bologna Criteria [BC] to Define Poor Responders’’ [1]. POR was defined as the collection of three or fewer oocytes in two prior ovarian stimulation cycles, or collection of three or fewer oocytes in a single stimulation cycle from a woman who is over 40 years of age, or collection of three or fewer oocytes in a single stimulation cycle and an abnormal ovarian reserve test (ORT: antral follicle count less than five to seven follicles or antimullerian hormone € < 0.5–1.1 ng/mL), or presence of an abnormal ORT in a woman over 40 years of age The treatment of poor responders has challenged many in the field of assisted reproduction. A variety of ovarian stimulation protocols have been tried with some degree of success indicating different reasons for poor response. Many clinicians simply increase the gonadotropin daily dose despite the lack of supporting evidence [2]. The short down-regulation protocol (flare-up) has been reported to successfully improve ovarian response in poor responders [3]. The initial agonistic flare-up that occurs with the short protocol may also aid follicular recruitment, which may theoretically reduce the gonadotropin requirements.

The use of GnRH antagonists in the stimulation protocol of poor responders would benefit from the endogenously produced gonadotropins as well as prevent premature LH surge. Therefore, it theoretically lends itself perfectly to the treatment of poor responders [4].

PATIENTS AND METHODS

A total of one hundred poor responder patients attended to the privet clinic (Engab) mansoura preparing for ICSI, from august 2018 to January 2020, were included in this study. Ethical approval was obtained for the study and informed consent was obtained from all patients before entry in the study.

Patient details were recorded according to age, menstrual history, baseline (day- 3) pelvic ultrasound finding, FSH, LH, E2 at the previous cycle of starting treatment. Recent semen analysis must be done not more than three months before starting stimulating cycle .

Inclusion criteria:

- A regular menstrual cycle (duration 21–35 days).
- Age up to 40 years.
- Basal FSH up to 13 IU/L.
- Body mass index (BMI) < 30 kg/m².

One or more previous IVF/ICSI cycles with poor ovarian response. Determination of "poor response"based on a combination of some of the following factor; estradiol level on the day of human chorionic gonadotropin (HCG) injection < 500 pg/ mL, failure in obtaining of at least three follicles > 16 mm in diameter, the number of mature oocytes retrieved less than four or had prior cancellation on a cycle used luteal long GnRH-a protocol. [5]

Exclusion criteria:

- Presence of a clinically significant systemic disease; diabetes mellitus.
- PCOS, hyperprolactinaemia or any other endocrine disorder.
- Submucosal polyp, leiomyoma or uterine septums which were detected on hysterescopy or hysterosalpingography.
- Patients with severe male factor or azospermia are also excluding from this study.

Intra-cytoplasmic Sperm Injection (ICSI) was performed for all cycles. The poor responders were randomized into two groups: Group 1: In which GnRH -a flare-up protocol were used for down-regulation (n=50). Group 2: In which the GnRH antagonist protocol were used for down regulation (n=50).

Stimulation Regimens

In the GnRH-a flare-up group, each patient started treatment with 0.1 IU Leuprolide acetate (Decapeptyl, Triptofem Ferring, Ibsa) subcutaneously per day from cycle day- one until the day of HCG administration, this dose were reduced to half to patients with delayed response to HMG during monitoring. The exogenous gonadotropin stimulation was started on day 2 of the cycle.

In the GnRH antagonist group, exogenous gonadotropins were started on cycle day 2, and 0.25 mg cetrorelix (Cetrotide; Serono) were added when the lead follicle reached 14 mm in diameter. Cetrorelix were continued until the day of HCG administration.

In both stimulation regimens, 375 - 450 IU of gonadotropin, were administered to all patients, with individual adjustments according to ovarian response as measured by serial ultrasound scans and serum E2 levels from day 6-8 of gonadotrophin stimulation.

Human chorionic gonadotrophin (HCG), (Choriomon, IBSA), at a dose of 10,000 IU were given when at least two follicles ≥18mm diameter. Peak E2 Level was measured on the same day.

Oocyte retrieval was performed 34-36 hours after hCG administration by ultrasound-guided transvaginal, pethidine were the sedative and analgesic used. follicular aspiration, mature (MII) oocytes were fertilized through intracytoplasmic sperm injection ICSI.

Oocytes were examined 16–18 hours after ICSI for pronuclei (PN). Normal fertilization defined as existence of two pronuclei (2PN). The embryos obtained will be categorized on day 2 or 3 into four categories depending on their morphologic appearance, zonal thickness, cytoplasmic fragmentation, and blastomere size:

Grade I [high quality]: embryos with equal blastomeres and no observed cytoplasmic fragmentation; grade II [good quality]: embryos with equal blastomeres and <20% fragmentation of the cytoplasm; grade III [fair quality]: embryos with unequal blastomers and 20%–50% fragmentation of the cytoplasm; grade IV [poor quality]: embryos with unequal blastomers and >50% fragmentation of the cytoplasm.[6]

Up to three embryos at 4- to 8-cell stage were replaced per patient under ultrasound scan guidance using a Labotect Embryo Transfer Catheter (Labotect GmbH, Labor- Technik-Gottingen, Germany).

Luteal phase support with 400 mg micronized progesterone (prontogest Ibsa) self-administered vaginally or rectally from the day of retrieval for 14 days and continued for another 6–8 weeks in cases in which a pregnancy was achieved.

Two weeks after embryo transfer, serum -hCG were measured for confirmation of pregnancy, and a diagnosis of clinical pregnancy after visualization of fetal heart pulsation four weeks later by transvaginal US.

RESULTS

Characteristic	GnRH-a	GnRH antagonist	*P value*
No. of patients	50	50	
Age (y)	35.33 ± 3,23	36.71 ± 4.18	NS
BMI	25.11 ± 2.11	25,71 ± 1.68	NS
No. of Gonadotropins ampoules	64.80 ± 22.59	76.40 ± 15.01	**0.017**
peak E2	1192.10	798.10	**0.009**
No. of oocytes retrieved	3 (0 – 5)	2 (0 – 4)	NS
No. of mature oocytes	2 (0 – 4)	2 (0 – 3)	NS
fertilization rate	88.89	78.14	**0.019**
No. of transferred embryos	1 (o -3)	1 (0 – 2)	NS
No. of top-quality embryos	52	33	**0.044**
Pregnancy rate	20%	18%	NS
Miscarriage rate	44.44%	**30%**	NS

GnRH-antagonist protocol shows increased – non significant- pregnancy rate and decreased - non significant - miscarriage rate than flare up protocol, however the flare-up protocol appears to be more effective than the GnRH-antagonist protocol in terms of number of FSH ampules, peak E2 level, fertilization rate, and top-quality embryos transferred in poor-responder patients.

DISCUSSION

In the present study, we observed that pregnancy rate was increased -but not significant- in the antagonist than in flare up group, However, the flare-up protocol appears to be better than antagonist protocol as regard to the number of FSH ampoules administered significantly (P<.005) higher in the GnRH antagonists than in the flare-up group), peak E2 level, fertilization rate and top quality embryos were significantly higher (P<.005) in the flare-up than the GnRH-antagonist groups.

Our data are in contrast with those of Akman et al.[7] who that found no significant differences in the number of FSH ampoules administered. In the last study, low-dose oral contraceptive was started on cycle day 1 of the previous cycle for 21 days, and on the 2nd day of menstruation, the GnRH-a was administered in a micro dose regimen (40 µg/d). It is probable that a flare-up regimen with GnRH-a (100 µg/d), as used in our study, induces a greater additional gonadotropin stimulus than a dose of 40 µg/d and, consequently, a reduction in the number of FSH ampoules.

Schmidt et al.[8] randomized 48 previously poor responder patients to either a GnRH antagonist protocol(ganirelix 0.25 mg daily in a flexible protocol) or a micro-dose flare regimen (LA, 40 µg bid, after OCP pretreatment). Ovarian stimulation consisted of 300 IU of recombinant FSH every morning and 150 IU of hMG every evening. Cancellation rates due to an inadequate response were equally high, close to 50% in both groups. While only 13 women in the antagonist group, and 11 women who received a micro-dose flare completed their cycle, no significant differences in oocyte yield (8.9 vs. 9), fertilization rate (69.1% vs63.5%), or clinical pregnancy rate (38.5% vs. 36.4%) were detected. It was concluded that the antagonist protocol appears to be as effective as the micro-dose flare protocol for COS in poor responders, but could be a superior choice in terms of cost and convenience for the patient.

Trifon G et al.[9] showed a significantly higher ongoing pregnancy rate observed with the use of the flexible antagonist compared with the short GnRH agonist protocol in poor responder patients treated by IVF, It is not clear what is the source of the difference observed in that study regarding ongoing pregnancy rates between the two compared groups. In contrast to our results, the total units of FSH administrated during stimulation as well as the number of oocytes retrieved, embryos transferred and the implantation and fertilization rate were similar between the two study groups. However, E2 levels on the day of HCG administration were significantly higher in the agonist [727(439–1029) pg/ml] versus

the antagonist group [572(325–838) pg/ml] which is consistent with our results.

Sunkara S K et al.[10] compared Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens and showed that Number of oocytes retrieved was significantly higher with long GnRH agonist compared with the short agonist regimen (4.42 _ 3.06 vs. 2.71 _ 1.60), while there was no significant difference between long agonist and antagonist regimens (4.42 _ 3.06 vs. 3.30 _ 2.91). Duration of stimulation and total gonadotropin dose were significantly higher with long agonist compared with short agonist and antagonist regimens. The ongoing pregnancy rate was 8.1% with long and short agonist regimens and 16.2% with the antagonist regimen

Kamel A.et al.[11] is Retrospective comparative study where One hundred thirty-four patients undergoing IVF/ intracytoplasmic sperm injection (ICSI) treatment, who responded poorly to the standard long down-regulation protocol in their first treatment cycle. In the second cycle, 77 received short flare-up agonist and 57 received antagonist protocol. He found that no cycle cancellation in the flare-up protocol and 7% cancellation rate in the antagonist protocol , a significantly higher number of patients had embryo transfer in the flare-up protocol and no difference in pregnancy rate (PR) between the two groups.

Davar R et al.[12] compared the efficacy of microdose gonadotropin-releasing hormone (GnRH) agonist flare (MF) and GnRH antagonist/letrozole protocols in poor responders undergoing *in vitro* fertilization ,and showed that the days of stimulation, mean gonadotropin dose, the number of mature follicles, and oocytes retrieved and metaphase II oocytes retrieved, serum estradiol level on the day of human chorionic gonadotropin administration, and the percentage of top and good quality embryos were significantly higher in the MF group. The endometrial thickness, fertilization rate, and the number of embryos transferred were similar in both groups. The implantation and clinical pregnancy rates were higher in the MF group and the total cancellation rate was higher in the GnRH antagonist/letrozole group, but these findings were not statistically significant.

Merviel et al.[13] studied Four hundred and forty poor responders during their second IVF cycle. all had failed to become pregnant during their first IVF cycle where the long GnRH-agonist stimulation protocol was used. Patients were prospectively randomly assigned to 2 protocol groups at the start of ovarian stimulation; group 1 was treated with a contraceptive pill + flare-up GnRH-agonist protocol and group 2 with the GnRH-antagonist protocol. the study showed no statistically significant differences as regard to duration of stimulation (11.8 ± 2.3 in flare-up GnRH-agonist protocol and 11.6 ± 2.7with the GnRH-antagonist protocol.), Total FSH/hMG dose (IU) (4664 ± 605 in flare-up GnRH-agonist protocol and 4680 ± 641 with the GnRH-antagonist protocol.), No of oocytes retrieved, No of M2 oocytes retrieved, Clinical pregnancy rate per transfer (%) (17.9 In flare-up، 15.9 with the GnRH-antagonist protocol) and ongoing pregnancy rate per transfer (%) (14.6 in flare-up and 14.2 in the GnRH-antagonist protocol).

Also Nabati A et al.[14] compared the efficacy of microdose gonadotropin-releasing hormone (GnRH) agonist flare (MF) and GnRH antagonist/letrozole protocols in poor responder patients and Concluded that MF method of pregnancy leads to more positive results in pregnancy based on chemical and clinical evaluation in comparison with AL and is advised for poor responder patients.

This inconsistency in the results could be attributed to heterogeneity in the definition of poor response among the studies, however, there is now evidence to suggest that the probability of pregnancy might be better with the use of the antagonist protocol, also flexible antagonist protocol is a simpler and more patient friendly method of ovarian stimulation compared with the short agonist protocol. Therefore, the GnRH antagonist protocol might represent the preferred way for stimulating poor responders for IVF.

CONCLUSION

There is now evidence to suggest that the probability of pregnancy might be better with the use of the antagonist protocol, also flexible antagonist protocol is a simpler and more patient friendly method of ovarian stimulation compared with the short agonist protocol.

Future more powerful randomized prospective studies, besides confirming the results reported here should also focus on the comparative use of a fixed versus a flexible protocol in patients with poor ovarian response.

REFERENCES

1. Ferraretti AP, La Marca A, Fauser BC, et al. ESHRE consensus on the definition of ‘‘poor response’’ to ovarian stimulation for in vitro fertilization: the Bologna criteria. *HuReprod* 2011;26:1616–24.

2. Polyzos NP and Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel? *Fertil Steril* 2011;96:1058–61.e7.

3. Surrey E, Bower J, Hill D, et al. Clinical and endocrine effects of a microdose GnRH agonist flare regimen administered to poor responders who are undergoing in vitro fertilization. *Fertil Steril* 2014;69:419 –24 .

4. Nikolettos N, Al-Hassani S, Felberbaum R, et al Gonadotrophin-releasing hormone antagonist protocol: a novel method of ovarian stimulation in poor responders. *Eur J Obstet Gyn Reprod Biol;* 2001; 97:202–7.

5. Marci R, Caserta D, Dolo V, et al. GnRH antagonist in IVF poor-responder patients:

results of a randomized trial. *Reprod Biomed Online*;2005; 11:189–193.

6. Staessen C, Camus M, Bollen N, et al. The relationship between embryo quality and the occurrence of multiple pregnancies. *Fertil Steril*; 1992; 3:626–630.

7. Akman MA, Erden HF, Tosun SB, et al. Comparison of agonistic flare-up-protocol and antagonistic multiple dose protocol in ovarian stimulation of poor responders: results of a prospective randomized trial. *Hum Reprod;* 2001;16:868–870.

8. Schmidt DW, Bremner T, Orris JJ, et al. randomized prospective study of microdose leuprolide versus ganirelix in invitro fertilization cycles for poor responders. *Fertil Steril*; 2005; 83:1568–1571.

9. Trifon G. Lainas1, Ioannis A. et al. Flexible GnRH antagonist versus flare-up GnRH agonist protocol in poor responders treated by IVF: a randomized controlled trial Human Reproduction. 2008; Vol.23, No.6 pp. 1355–1355.

10. Sunkara S K, Coomarasamy A, Faris R, et al. Long gonadotropin releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. *Fertil Steril*., 2014;101: 147–53.

11. Kamel A. Mohamed, W. A. R. Davies, Julian Allsopp, et al. Agonist "flare-up" versus antagonist in the management of poor responders undergoing in vitro fertilization treatment *Fertil Steril*. 2005;83:331–5.

12. Davar R, Oskouian H, Ahmadi S, et al. GnRHantagonist/letrozole versus microdose GnRH agonist flare protocol in poor responders undergoing in vitro fertilization. *Taiwan j obstet gynecol* ;2010; 49(3):297–301

13. Merviel P , Rosalie Cabry-Goubet, Emmanuelle Lourde, et al. Comparative prospective study of 2 ovarian stimulation protocols in poor responders: effect on implantation rate and ongoing pregnancy Reproductive Health 2015; 12:52. DOI 10.1186/s12978-015-0039-2.

14. Nabati A , Peivandi1 S, Khalilian A, et al. Comparison of GnRh Agonist Microdose Flare Up and GnRh Antagonist/Letrozole in Treatment of Poor Responder Patients in Intra Cytoplaspic Sperm Injection: Randomized Clinical Trial , *Global Journal of Health Science;* 2015; Vol. 8, No. 4.