Comparison of two ovarian stimulation protocols among women with poor response: A randomized clinical trial

Minoodokht Bavarsadkarimi (1), Sirous Omidi (2), Farinaz Shahmoradi (1), Zahra Heidar (1), Sahar Mirzaei (1)

(1) Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; (2) Abadan University of Medical Sciences and Health Services, Abadan, Iran.

Abstract

This is a randomized controlled trial conducted in a tertiary referral fertility department. Participants were women with previous poor ovarian response undergoing in vitro fertilization (IVF). One hundred and ninety-two women were randomized to the short GnRH agonist and antagonist regimens. The primary outcome was the number of oocytes retrieved. Secondary outcome measures were the number of embryos transferred, chemical and clinical pregnancy rate and live birth. The number of oocytes retrieved was higher with the gonadotrophin-releasing hormone (GnRH) antagonist regimen compared to the short agonist regimen (3.10 ± 2.70 vs. 2.99 ± 2.60), but there was no significant difference. The duration of stimulation and total gonadotropin dose were higher with short agonist regimens compared to antagonist regimens, with the latter being statistically significant (p < 0.001). The chemical pregnancy rate was 8.33 percent with the short agonist regimen and 7.29 percent with the antagonist regimen, with no statistically significant difference (p = 0.79). In terms of lower cycles cancellation and higher chemical pregnancy, short GnRH agonist regimen is an appropriate choice for poor responders.

Key Words: GnRH antagonist; short GnRH agonist; Bologna criteria; poor ovarian response; IVF; RCT.

The administration of poor responders in in vitro fertilization (IVF) cycles are highly contentious due to their inadequate response to controlled ovarian stimulation. A low ovarian response can be idiopathic or caused by a number of factors such as age, decreased ovarian reserve, endometriosis, and previous ovarian surgery. Poor ovarian response, defined as the development of an insufficient number of mature follicles after gonadotropin stimulation, resulting in cycle cancellation or the yield of only a few oocytes, occurs in 9% – 24% of women undergoing IVF treatment, and is becoming an increasing problem as women delay childbearing. The number of retrieved oocytes and available embryos for transfer have a significant impact on the likelihood of IVF treatment success. Poor ovarian response, on the other hand, is usually associated with low pregnancy rates, and many of these cycles are terminated before egg collection begins. Several strategies for preventing cycle cancellation have been proposed, including lowering the dosage and timing of gonadotrophin-releasing hormone agonists (GnRHa), or using GnRHa flare-up regimens. A retrospective analysis showed that the flexible short protocol may be a useful stimulation protocol in women with poor ovarian response over 40 years old. Compared with the routine short protocol, the flexible short protocol (FSP) delayed the start-up time of gonadotropin administration and reduced gonadotropin usage. These procedures should, in theory, eliminate excessive ovarian suppression while benefiting from the additional gonadotrophin stimulus provided by GnRHa's agonistic effect. The GnRHa method desensitizes the pituitary gland by administering a gonadotrophin releasing hormone (GnRH) agonist on a daily basis for a long period of time. The other approach is to block pituitary luteinizing hormone (LH) secretion immediately with a GnRH antagonist. The introduction of GnRH antagonists (GnRH-ant) into clinical practice may provide new hope for patients who have failed to respond to other treatments. GnRH-ant prevents the LH surge from occurring within a few hours, which is a common cause of cancellation in patients with poor ovarian response. GnRH-ant action does not result in early
Two ovarian stimulation protocols for women with poor response

Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

folliculogenesis inhibition, which is critical for patients with a limited number of follicles.13,14 There is currently insufficient evidence to support an ideal protocol for poor responders.15-22 Given the conflicting evidence and the growing need to clarify the effectiveness of the available ovarian stimulation protocols for poor responders, particularly in terms of ovarian hyperstimulation occurrence, our goal was to conduct a randomized controlled trial (RCT) to see if the two regimens, short agonist flare vs. antagonist regimens, differ in their effectiveness.

Materials and Methods

Study Design and description of procedure

A prospective randomized controlled trial conducted in poor responder IVF patients attending Mahdieh Hospital, a university-affiliated Infertility and IVF center between February 2021 and September 2021. The National Research Ethics Committee approved the study, and all participants provided written informed consent prior to participation.

Definition of poor ovarian response

Poor responders were defined as having at least two of the following three characteristics, according to the Bologna criteria:23

i) Advanced maternal age (≥40 years)
ii) Previous POR (≤3 oocytes with a conventional stimulation protocol); and
iii) Abnormal ovarian reserve test (Follicle Count ≤7 follicles or AMH ≤1.2 ng/mL corr. 7.85 pmol/L).

Patients were eligible to participate if they met two of the three criteria listed above. Patients were excluded from the study if they had at least one of the following criteria: 1) presence of a clinically significant systemic disease; diabetes mellitus 2) PCOS, hyperprolactinemia, or any other endocrine disorder 3) submucosal polyp, leiomyoma or uterine septum 3) patients with severe male factor or azoosperma.

Randomization and blinding

The statistician of Mahdieh Hospital provided a computer-generated randomization schedule in blocks of four. A third party randomly assigned eligible participants to one of two treatment arms: the first group (n = 96) underwent short GnRH agonist regimen. The second (n = 96) group was given a GnRH antagonist regimen. The doctor who performed the oocyte retrieval procedure and the embryologist who assisted in the procedure were both unaware of the treatment allocation. The hMG starting dose was disclosed to the treating physicians, but were blinded to the capsule content. Our statistician was also blinded from the allocated treatment while analyzing the data.

Outcomes and sample size calculation

The number of oocytes MII collected after ovarian stimulation was the primary outcomes. Other outcome measures included clinical pregnancy rate, live birth, the number of chemical pregnancies, the number of embryos transferred. The sample size was calculated using the observed effect size in number of oocytes retrieved from existing literature, which was 0.4 when comparing GnRH antagonist versus short GnRH agonist protocols.15 For this difference of two retrieved oocytes, with an SD of 1.6 (as observed in the existing literature), a power of 80%, and an alpha of 5%, 100 women were needed in each arm. To account for possible dropouts, we decided to include 105 participants per group, assuming and adjusting for a worst-case scenario of 5% attrition. GnRH agonist (Buserelin, CinnaFact®) was started on day 1 of the cycle after the ultrasound scan to confirm quiescence of the ovaries. Buserelin (CinnaFact®) was administered at a dose of 100 (IU), followed by follitropin alfa (Cinnal-F) injections and hMG (PD Homog) administration at a dose of 300 to 375 IU/day, began on the second day of the cycle, with the dose fluctuating based on ovarian response. From day 1 to day 5 of the cycle, the dose of Buserelin injected was 100 IU, 50 IU, 30 IU, 10 IU, and 5 IU, respectively. Both buserelin and gonadotropin injections were continued until hCG (Ovitrel, Merck, Italy) was administered; at this stage, at least two follicles 16 to 18 mm or a few follicles 14 to 16 mm were obtained. For GnRH antagonist regimen Gonadotropin injections were started at the same dose after an ultrasound scan on day 2 of the cycle to confirm quiescence of the ovaries, When the lead follicle reached a diameter of 12 mm, the GnRH antagonist cetrorelix (Cetrotide; Merck - Serono) was given at a dose of 0.25 mg daily. The gonadotropin and cetrorelix injections were both continued until the triggering. The study protocol allowed for the simultaneous use of two hCG (Ovitrel 250 µg; Merc) ampules. The hCG injection was followed by 36 hours of transvaginal ultrasound guided oocyte retrieval. Depending on the number and quality of available embryos, embryo transfer (ET) was performed under transabdominal ultrasound guidance 3 days after oocyte retrieval. The number of embryos implanted into the uterine cavity was determined by the Human Fertilization and Embryology Authority policy, as well as the woman's age, the quality and number of embryos available for transfer, and her medical history. Depending on the quality of the available embryos, the patient’s age and the ward protocol 1 to 3 embryo was transfered.Women below the age of 40 could have up to two embryos replaced, and women over the age of 40 could have up to three embryos replaced. Surplus 3-day embryos being frozen if they were freezeable. All women were given progesterone suppository 400 mg twice daily (Cyclogest, Actovere) starting on the day of oocyte retrieval and continuing until a negative pregnancy test or 8 weeks’ gestation. To confirm pregnancy, a serum beta human chorionic Gonadotropin (b-hCG) were performed approximately 2 weeks after transvaginal ultrasound guided embryo transfer. The detection of a fetal heartbeat on an ultrasound scan was used to define
Two ovarian stimulation protocols for women with poor response
Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

a clinical pregnancy. Between 7 and 8 weeks’ gestation, a pregnancy scan was performed to confirm viability and the continuation of the pregnancy. Data on patient age, infertility-related variables, ovarian stimulation characteristics, number of follicles >13 in diameter on the day of hCG administration, number of oocytes retrieved, embryo quality, and number of embryos transferred were collected and compared across the two study groups.

Statistical Analysis
The analysis was supposed to be done by intention to treat (ITT). The baseline and outcome data were separated and summarized separately. Continuous variables (for example, age and BMI) were summarized as mean with standard deviation (SD). The t-test with two independent samples was used to compare the means of continuous variables. The chi-square test was used to compare categorical data between the two intervention groups. When the count tables were less than 5, the Exact Fisher test was used. All of the alternative hypotheses were two-sided. Statistical significant was set to p < 0.05. Stata version 15 was used for all statistical analyses (Stata Corp., College Station, TX).

Results
The study recruited the participation of 220 women. Twenty women withdrew their consent, and 192 women were randomly assigned to one of two arms of the study, with 96 women in each. COS was performed on 96 women using the short GnRH agonist regimen and 96 women using the GnRH antagonist regimen. Three of the eight women who did not receive the allocated intervention became infected with COVID-19 while waiting to begin the IVF treatment cycle, and five women later decided not to pursue further IVF treatment. Figure 1 depicts the consolidated standards of reporting trials (CONSORT) flow diagram for this study.
Two ovarian stimulation protocols for women with poor response
Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

Table 1 shows the demographic characteristics of the women who were randomly assigned to one of the two regimens. The baseline characteristics of the two groups were comparable, including age on the first day of gonadotropin stimulation, body mass index (BMI), duration of infertility, type of infertility, endometriosis, previous IVF attempts with poor ovarian response, previous pregnancies, including previous IVF pregnancies, and previous live births. The two groups were also comparable in terms of baseline serum AMH, ovarian surgery history, and abortion history. The study's overall mean age was 37.39±4.52 years, the mean basal serum AMH level was 0.86±0.78 ng/mL, and the mean BMI was 25.80±3.89. The most common cause of infertility (46.43 %) was unexplained (91/196); 29.59 % (58/196) had a male factor, 14.79 % (29/196) had a tubal factor, and 9.19 % (18/196) had other factors such as endometriosis and fibroids as the sole cause of infertility.

Table 2 compares the stimulation characteristics of the two groups. The mean number of oocytes retrieved did not differ statistically significantly between the two groups (p=0.76). The chemical pregnancy rate did not differ significantly between the two regimens (p=0.79). The number of cycles cancelled prior to oocyte retrieval did not differ significantly between the two regimens (p=0.64). The mean duration of stimulation did not differ...
A meta-analysis conducted by Papamentzelopoulou M. et al.,24 revealed that GnRH antagonist protocols have a shorter duration of ovarian stimulation, whereas GnRH-agonist protocols have fewer cycle cancellation rates, more embryos transferred, and more clinical pregnancies. In a previous meta-analysis of fourteen studies conducted by Danhua Pu and his colleagues,22 a shorter duration of stimulation with GnRH antagonists was also observed. In the same study, no statistical difference in the number of oocytes and mature oocytes retrieved was found, which agrees with our findings. Furthermore, those authors found no statistical difference in cycle cancellation rates and clinical pregnancy rates, as we found in the present study.

Discussion

The purpose of this study was to compare the efficacy of short GnRH agonist and GnRH antagonist regimens in infertile women who had a poor response to ovarian stimulation during IVF. The number of oocytes retrieved was the study's primary outcome. The findings of this study show that the short GnRH agonist and GnRH antagonist regimens are equally effective in terms of clinical pregnancy and ongoing pregnancy rates were 5.21 % and 4.17 %, respectively. In both groups of GnRH agonist short and GnRH antagonist, the rate of ongoing pregnancy was 4.17 %.

In poor responders, RCTs comparing the short GnRH agonist and GnRH antagonist protocols have fewer cycle cancellation rates, and increased pregnancy rates.27,28 Indeed, the GnRH agonist regimen demonstrated in many trials of patients, who had failed to respond to gonadotropin alone. Generally they showed improved outcomes such as lower cancellation rates and higher pregnancy rates.16-20 The inconsistency in results could be attributed to differences in the definition of poor response across studies. Griesinger et al. conducted a meta-analysis on the use of GnRH agonist vs. antagonist in poor responders and discovered that the GnRH antagonist flexible dose regimen produced more oocytes than the long agonist regimen.21 Another meta-analysis comparing GnRH agonist vs. GnRH antagonist use in poor responders found no significant difference in efficacy between the two regimens.22 The definition of poor response in these two meta-analyses differed,21,22 which could explain the disparity in their results. While assisted reproduction techniques are becoming more advanced, with high success rates in terms of pregnancy and live birth rates, poor responders remain a research challenge for assisted reproduction experts. It wasn't until 2011 that the scientific community came to an agreement on poor responder definition, establishing the Bologna criteria,23 defining the inclusion of a specific group of patients in subsequent studies.

A meta-analysis conducted by Papamentzelopoulou M. et al.,24 revealed that GnRH antagonist protocols have a shorter duration of ovarian stimulation, whereas GnRH-agonist protocols have fewer cycle cancellation rates, more embryos transferred, and more clinical pregnancies. In a previous meta-analysis of fourteen studies conducted by Danhua Pu and his colleagues,22 a shorter duration of stimulation with GnRH antagonists was also observed. In the same study, no statistical difference in the number of embryos transferred and the number of cycles that had embryos frozen in the three regimens (p = 0.77). The overall sample's clinical pregnancy and ongoing pregnancy rates were 5.21 % and 4.17 %, respectively. In both groups of GnRH agonist short and GnRH antagonist, the rate of ongoing pregnancy was 4.17 %.

Two ovarian stimulation protocols for women with poor response

Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

- 5 -
Two ovarian stimulation protocols for women with poor response
Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

eggs were blinded to the study protocol, the clinicians involved in the decision-making for hCG administration to induce ovulation were not, which is a study weakness. Despite the fact that the majority of women had the long GnRH agonist regimen in the previous cycle, the randomization process was not stratified by previous regimen, which could be a confounder.

Based on previous RCTs, GnRH agonist protocols appear to be more efficient in terms of clinical pregnancy and cycle cancellation rates than GnRH antagonist protocols.\textsuperscript{16,17,31-35} though in a single-center RCT, the GnRH antagonist protocol was associated with higher pregnancy rates than the GnRH agonist regimen.\textsuperscript{36} For poor responder subgroup management, the European society of human reproduction and embryology (ESHRE) Guideline Group on Ovarian Stimulation currently recommends both GnRH antagonists and GnRH agonists.\textsuperscript{33} Despite the lack of evidence for or against either protocol, the guideline group does not recommend either hormone pre-treatment or adjuvant therapies, specifically growth hormone, testosterone, dehydroepiandrosterone, aspirin, and sildenafil,\textsuperscript{34–37} for increasing the effectiveness or safety of patients with poor ovarian response.

In conclusion, based on the current study and in terms of effectiveness, agonist protocol could be chosen as a first choice approach, while keeping in mind the higher duration of stimulation typically required in such protocol.

On the other hand, special attention should be paid to the high heterogeneity observed in the duration of ovarian stimulation, number of oocytes/mature oocytes retrieved, and embryos transferred, implying that variations in the study population, patients’ characteristics, and protocol implementation, including the type and doses of GnRH analogs, have an effect on the robustness of the respective results.

As a result, developing an ideal protocol for poor responders is a major issue in assisted reproduction that must be addressed, emphasizing the need for larger randomized well-designed cohort studies with low statistical errors to generate safer protocol conditions.

| List of acronyms |
|------------------|
| AMH - Anti Mullerian Hormone |
| b-hCG – Beta- Human Chorionic Gonadotropin |
| BMI - body mass index |
| CONSORT - consolidated standards of reporting trials (COS – Controlled Ovarian Stimulation) |
| ESHRE - European society of human reproduction and embryology |
| ET – Embryo transfer |
| GnRH: gonadotrophin-releasing hormone |
| GnRHa - gonadotrophin-releasing hormone agonists |
| GnRH-ant - GnRH antagonists |
| hMG – Human menopausal gonadotropine |
| ITT – intention to treat |
| IU – international units |

IVF - in vitro fertilization
LH: luteinizing hormone
MII - metaphase 2
RCT - randomized controlled trial
SD - standard deviation

Contributions of Authors
MB, SO, FS, ZH participated in conception and design of the study, acquisition, analysis and interpretation of data, wrote the manuscript, performed literature review, article drafting and revision, reviewed and edited the manuscript critically, all authors read and approved the final version.

Acknowledgments
None

Funding
None

Conflict of Interest
The authors declare no conflict of interests.

Ethical Publication Statement
We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author
Zahra Heidar, Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
ORCID iD:0000-0001-7071-1535
E-mail: dr_zheidar@yahoo.com

E-mails and ORCID ID of co-authors
Minoodokht Bavarsadkarimi: Minoo.karimij58@gmail.com
ORCID iD: 0000-0001-9539-1435
Sirous Omidi: omidisirous@gmail.com
ORCID iD: 0000-0003-3159-6209
Farinaz Shahmoradi: miss.shahmoradi@yahoo.com
ORCID iD: 0000-0002-8322-5162
Sahar Mirzaei: s.mirzaee@sbmu.ac.ir
ORCID iD: 0000-0002-6648-3004

References
1. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. BJOG An Int J Obstet Gynaecol. 1997;104:521–7. doi:10.1111/j.1471-0528.1997.tb11525.x.
2. Garcia JE, Jones GS, Acosta AA, Wright G. Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: Phase II. 1981. Fertil Steril. 1983;39:174–9.
3. Karande V, Gleicher N. A rational approach to the management of low responders in in-vitro

- 6 -
Two ovarian stimulation protocols for women with poor response

Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

fertilization. Hum Reprod. 1999;14:1744–8. doi:10.1093/humrep/14.7.1744.
4. Bewley S, Braude P, Davies M. Which career first? Bmj. 2005;331:588–9. doi:10.1136/bmj.331.7517.588.
5. Ulug U, Ben-Shlomo I, Turan E, Erden HF, Ali Akman M, Bahceci M. Conception rates following assisted reproduction in poor responder patients: A retrospective study in 300 consecutive cycles. Reprod Biomed Online. 2003;6:439–43.
6. Scott RT, Navot D. Enhancement of ovarian responsiveness with microdoses of gonadotropin-releasing hormone agonist during ovulation induction for in vitro fertilization. Fertil Steril. 1994;61:880–5. doi:10.1016/S0015-0282(16)36700-4.
7. Surrey ES, Bower J, Hill DM, Ramsey J, Surrey MW. Clinical and endocrine effects of a microdose GnRH agonist flare regimen administered to poor responders who are undergoing in vitro fertilization. Fertil Steril. 1998;69:3 SUPPL. 2:249–254. doi:10.1016/S0015-0282(97)00575-X.
8. Zhang X, Feng T, Yang J, Hao Y, Li S, Zhang Y, et al. A flexible short protocol in women with poor ovarian response over 40 years old. J Ovarian Res. 2021;14:3.
9. Huirne JAF, Lambalk CB. Gonadotropin-releasing hormone-receptor antagonists. Lancet. 2001;358:1793–803. doi:10.1016/S0140-6736(01)67977-6.
10. Huirne JAF, van Loenen ACD, Schats R, McDonnell J, Hompes PGA, Schoemaker J, et al. Dose-finding study of daily gonadotropin-releasing hormone (GnRH) antagonist for the prevention of premature luteinizing hormone surges in IVF/ICSI patients: Antide and hormone levels. Hum Reprod. 2004;19:2206–15. doi:10.1093/humrep/deh357.
11. Huirne JAF, Lambalk CB, Van Loenen ACD, Schats R, Hompes PGA, Fauser BCJM, et al. Contemporary Pharmacological Manipulation in Assisted Reproduction. Drugs. 2004;64:297–322. doi:10.2165/00003495-200406300-00005.
12. Kraft I, Gorgy A, Hill J, Menon D, Podsiadly B. Will GnRH antagonists provide new hope for patients considered “difficult responders” to GnRH agonist protocols? Hum Reprod. 1999;14:2959–62. doi:10.1093/humrep/14.12.2959.
13. Akman MA. Addition of GnRH antagonist in cycles of poor responders undergoing IVF. Hum Reprod. 2000;15:2145–7. doi:10.1093/humrep/15.10.2145.
14. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Comparison of agonistic flare-up-protocol and antagonist multiple dose protocol in ovarian stimulation of poor responders: Results of a prospective randomized trial. Hum Reprod. 2001;16:868–70. doi:10.1093/humrep/16.5.868.
15. Sunkara SK, Coomarasamy A, Faris R, Braude P, Khalaf Y. 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. doi:10.1016/j.fertnstert.2013.09.035.
16. Kahraman K, Berker B, Atabayoglu CS, Sonmez M, Cetinkaya E, Aytaç R, et al. Microdose gonadotropin-releasing hormone agonist flare-up protocol versus multiple dose gonadotropin-releasing hormone antagonist protocol in poor responders undergoing intracytoplasmic sperm injection-embryo transfer cycle. Fertil Steril. 2009;91:2437–44. doi:10.1016/j.fertnstert.2008.03.057.
17. Malmsuri S, La Marca A, Giulini S, Xella S, Tagliasacchi D, Marsella T, et al. Comparison of a gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist flare-up regimen in poor responders undergoing ovarian stimulation. Fertil Steril. 2005;84:402–6. doi:10.1016/j.fertnstert.2005.01.139.
18. Schmidt DW, Bremner T, Orris J, Maier DB, Benadiva CA, Nulsen JC. A randomized prospective study of microdose leuprolide versus ganirelix in in vitro fertilization cycles for poor responders. Fertil Steril. 2005;83:1568–71. doi:10.1016/j.fertnstert.2004.10.053.
19. Lainas TG, Sfountouris IA, Papanikolaou EG, Zorzovilis JZ, Petsas GK, Lainas GT, et al. Flexible GnRH antagonist versus flare-up GnRH agonist protocol in poor responders treated by IVF: A randomized controlled trial. Hum Reprod. 2008;23:1355–8. doi:10.1093/humrep/den107.
20. Aletebi F. Comparing gonadotrophin-releasing hormone agonists or gonadotrophin-releasing hormone antagonists in poor responder in IVF. Middle East Fertil Soc J. 2007;12:123.
21. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. 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. 2006;13:628–38. doi:10.1016/S1472-6483(10)60652-9.
22. Pu D, Wu J, Liu J. Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF. Hum Reprod. 2011;26:2742–9. doi:10.1093/humrep/der240.
23. Ferrariatti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of poor response to ovarian stimulation for in vitro fertilization: The Bologna criteria. Hum Reprod. 2011;26:1616–24. doi:10.1093/humrep/der092.
24. Papamentzelopoulou M, Stavros S, Mavrogianni D, Kalantzis C, Loutradis D, Drakakis P. Meta-
Two ovarian stimulation protocols for women with poor response
Eur J Transl Myol 32 (3): 10634, 2022 doi: 10.4081/ejtm.2022.10634

-8-

analysis of GnRH-antagonists versus GnRH-agonists in poor responder protocols. Arch Gynecol Obstet. 2021;304:547–57. doi:10.1007/s00404-020-05954-z.

25. Lambalk CB, Banga FR, Huirme JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: A systematic review and meta-analysis accounting for patient type. Hum Reprod Update. 2017;23:560–79. doi:10.1093/HUMUPD/DMX017.

26. Madani T, Ashrafi M, Yeganeh LM. Comparison of different stimulation protocols efficacy in poor responders undergoing IVF: A retrospective study. Gynecol Endocrinol. 2012;28:102–5. doi:10.3109/09513590.2011.579206.

27. Hugues JN, Durnerin IC. Revisiting gonadotrophin-releasing hormone agonist protocols and management of poor ovarian responses to gonadotrophins. Hum Reprod Update. 1998;4:83–101.

28. Cummins JM, Yovich JM, Edirisinghe WR, Yovich JL. Pituitary down-regulation using leuprolide for the intensive ovulation management of poor prognosis patients having in vitro fertilization (IVF)-related treatments. J Vitr Fertil Embryo Transf. 1989;6:345–52.

29. Kailasam C, Keay SD, Wilson P, Ford WCL, Jenkins JM. Defining poor ovarian response during IVF cycles, in women aged <40 years, and its relationship with treatment outcome. Hum Reprod. 2004;19:1544–7.

30. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: An analysis of 400 135 treatment cycles. Hum Reprod. 2011;26:1768–74.

31. Tazegül A, Görkemli H, Özdemir S, Aktan TM. Comparison of multiple dose GnRH antagonist and minidose long agonist protocols in poor responders undergoing in vitro fertilization: A randomized controlled trial. Arch Gynecol Obstet. 2008;278:467–72. doi:10.1007/s00404-008-0620-9.

32. Mohamed KA, Davies WAR, Alsoppe J, Lashen H. Agonist “flare-up” versus antagonist in the management of poor responders undergoing in vitro fertilization treatment. Fertil Steril. 2005;83:331–5. doi:10.1016/j.fertnstert.2004.07.963.

33. Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI†. Hum Reprod Open. 2020;2020. doi:10.1093/hroopen/hoa009.

34. Li XL, Wang L, Lv F, Huang XM, Wang LP, Pan Y, et al. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: A systematic review and meta-analysis. Med (United States). 2017;96. doi:10.1097/MD.0000000000006443.

35. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2015;2015:CD009749.

36. Siristatidis CS, Basios G, Pergialiotis V, Vogiatzi P. Aspirin for in vitro fertilisation. Cochrane Database Syst Rev. 2016;2016:CD004832–CD004832. doi:10.1002/14651858.CD004832.pub4.

37. Ataalla WM, Elhamid T, Elhalawy AE. Adjuvant sildenafil therapy in poor responders undergoing in vitro fertilization: A prospective, randomized, double-blind, placebo-controlled trial. Middle East Fertil Soc J. 2016;21:175–9. doi:10.1016/j.mefs.2015.12.004.

Disclaimer
All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher

Submission: May 23, 2022
Revision received: May 30, 2022
Accepted for publication: June 10, 2022