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. 2.992.60), 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 cancelation and higher chemical pregnancy, short GnRH agonist regim is appropriate choice for poor responders.

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

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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.[1] 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,[2,3] occurs in 9% –24% of women undergoing IVF treatment,[3] and is becoming an increasing problem as women delay childbearing.[4] The number of retrieved oocytes and available embryos for transfer have a significant impact on the likelihood of IVF treatment success.[5] 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.[1] Several strategies for preventing cycle cancellation have been proposed, including lowering the dosage and timing of gonadotrophin-releasing hormone agonists (GnRHa),[6] or using GnRHa flare-up regimens.[7] 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.[8]

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.[9–11] The introduction of GnRH antagonists (GnRH-ant) into clinical practice may provide new hope for patients who have failed to respond to other treatments.[12] 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

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 azoospermia.

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 regim 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, embrio 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 transferd.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 freezable. 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 embrio transfer. The detection of a fetal heartbeat on an ultrasound scan was used to define

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.

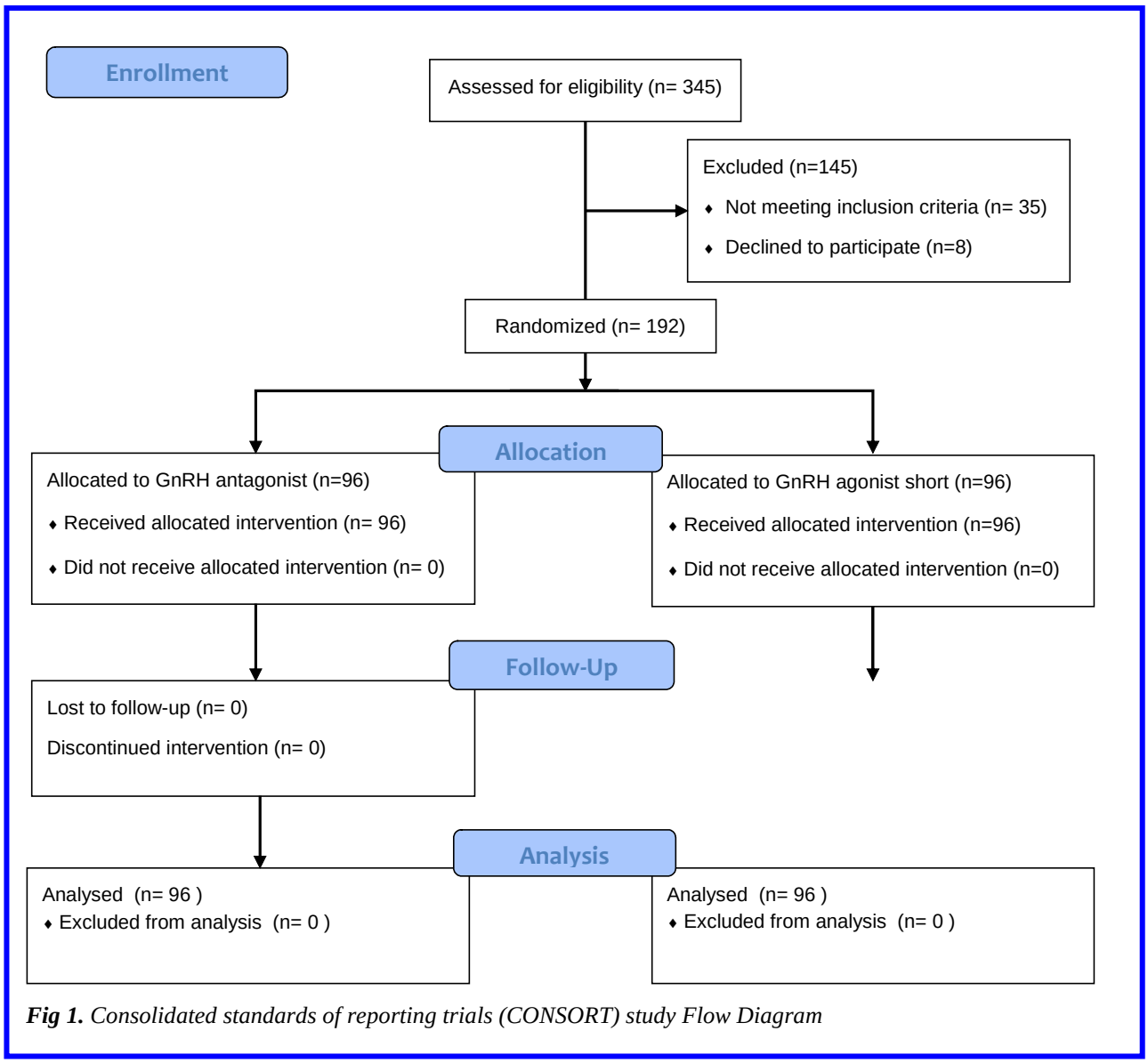

Fig 1. *Consolidated standards of reporting trials (CONSORT) study Flow Diagram*

Table 1. *Baseline characteristics of women undergone short GnRH agonist and antagonist protocols.*

	All (n=192)	GnRH agonist short (n=96)	GnRH antagonist (n=96)	p value
Age (year)	37.39±4.52	37.26±4.63	37.53±4.42	0.68
<35	46	24 (25%)	22 (22.92%)	
35-40	67	38 (39.58%)	29 (30.20%)	
>40	79	34 (35.42%)	45 (46.88%)	0.24
BMI	25.80±3.89	25.90±4.27	25.70±3.51	0.72
Type of infertility				
Primary	104	46 (47.92%)	58 (60.42%)	
Secondary	88	50 (52.08%)	38 (39.58%)	0.08
Cause of infertility				
History of POR, yes (%)	29	10 (10.42%)	19 (19.79%)	0.07
AMH (ng/ml)	0.86±0.78	0.69±0.47	1.01±0.96	0.004
History of ovarian surgery, yes (%)	12	6 (6.25%)	6 (6.25%)	1.00
Endometriosis, yes (%)	35	18 (18.75%)	17 (17.71%)	0.85
No. history of abortion	0.42±0.93	0.44±0.91	0.39±0.94	0.75
No. of parity				
0	158	81 (84.38%)	77 (80.21%)	
1	29	12 (12.50%)	17 (17.71%)	
2	3	3 (3.12%)	2 (2.08%)	0.56

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

Table 2. *Stimulation and study outcomes per treatment group (n=200).*

	All (n=192)	GnRH agonist short (n=96)	GnRH antagonist (n=96)	p value
Gonadotropin	3043.22±1178.06	3638.21±1181.82	2580.44±949.49	<0.001
Duration of stimulation (day)	8.97±2.20	9.10±2.72	8.89±1.79	0.56
Cycles cancelled before oocyte retrieval, yes (%)	20	9 (9.38)	11 (11.46%)	0.64
No. of oocytes retrieved	3.05±2.64	2.99±2.60	3.10±2.70	0.76
No. of Embryo transferred	1.56±1.52	1.59±1.61	1.53±1.43	0.77
Chemical Pregnancy, yes (%)	15	8 (8.33%)	7 (7.29%)	0.79
Clinical Pregnancy, yes (%)	10	5 (5.21%)	5 (5.21%)	1.00
Live Birth, yes (%)	8	4 (4.17%)	4 (4.17%)	1.00

significantly between the two regimens (p=0.56). Total gonadotropin consumption differed significantly between the three groups ($p < 0.001$; GnRH agonist short: 3638.21±1181.82; GnRH antagonist: 2580.44±949.49). There was no significant difference in the mean 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 %.

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 oocyte retrieval outcome, but the number of oocytes retrieved is lower with the short GnRH agonist regimen compared to the long GnRH agonist regimen. The study found that the short GnRH agonist regimen resulted in higher gonadotropin consumption and a longer duration of stimulation when compared to the antagonist regimens.

In poor responders, RCTs comparing the short GnRH agonist vs. the GnRH antagonist regimen yielded contradictory and variable results.[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 regimen.[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 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.. Interestingly, a recent meta-analysis of six poor responder-relative studies found no evidence of a difference in clinical pregnancy rate (RR 0.85, 95% CI 0.66–1.10).[25] Our study presents a the same clinical pregnancy rate upon use of short GnRH-agonist against GnRH-antagonist. In addition, there were no differences in oocyte yield in the aforementioned meta-analysis,[25] as we found in the present study. However, Pu et al. (2011)[22] combined GnRH agonist studies into one group, regardless of whether it was the long agonist or short agonist regimen. A retrospective study comparing the long GnRH agonist vs. the short GnRH agonist vs. the short GnRH agonist minidose vs. the GnRH antagonist regimens in poor responders found that the long GnRH agonist regimen produced significantly more oocytes and mature oocytes than the short GnRH agonist minidose regimen.[26] It is worth noting that the benefits of pituitary downregulation by GnRH agonists have been 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.[27,28] Indeed, the GnRH agonist long protocol is the most widely used protocol in the world. However, decreased sensitivity to gonadotropins with GnRH agonist long protocol administration has led some specialists to reduce the dose and duration of agonist in poor respond patients. Our objective criteria used to define poor ovarian response are the study's strength. We included women whose cycles were cancelled due to the production of three or fewer mature follicles or three or fewer eggs retrieved following maximal stimulation with at least 300 IU of gonadotropin per day, as Kailasam et al. demonstrated that low oocyte numbers ≤ 3 or cycle cancellation is detrimental to the outcome only after a gonadotropin dose of 300 IU/day.[29] The same study found that cycle cancellation after ovarian stimulation with 300 IU gonadotropin/day was associated with a significantly worse prognosis in the following IVF cycle, when compared to cycle cancellation with a lower gonadotropin dose, but a criticism of that study is that it was not powered to detect differences in the number of oocytes retrieved. However, due to the low pregnancy rates expected in those women, a large sample size would be required to power such a study in a group of poor responders. A study powered to detect differences in pregnancy rates in poor responders would necessitate nearly 200 women in each arm, rendering such a study impractical. The demonstration of a strong relationship, as well as an initial linear association, between egg number and live birth after IVF treatment,[30] justifies the use of egg number as a valid outcome variable in studies of poor ovarian response. Although the clinician performing the egg collection procedure and the embryologist assessing the number of

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,[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.[36] For poor responder subgroup management, the Eurpean society of human reproduction and embryology (ESHRE) Guideline Group on Ovarian Stimulation currently recommends both GnRH antagonists and GnRH agonists.[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,[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 - Eurpean society of human reproduction and embryology
ET – Embrio 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, ZHparticipated 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 readed and approved the final version.

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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.karimi58@gmail.com
ORCID iD: 0000-0001-9539-1435
Sirous Omidi: omidisiros@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

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