

Stop GnRH-agonist combined with multiple-dose GnRH-antagonist protocol for patients with IVF failures due to poor embryo quality-A proof of concept

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Abstract

Objective: To evaluate the role of the Stop GnRH-agonist combined with multiple-dose GnRH-antagonist protocol in improving IVF outcome in patients with repeated IVF failures and poor embryos quality.

Materials And methods: A proof of concept study consisting of 23 patients with IVF failures and poor embryos quality during conventional GnRH-antagonist protocol, who underwent a subsequent Stop GnRH-agonist combined with multiple-dose GnRH-antagonist ovarian stimulation (OS) protocol.

Results: During the Stop GnRH-agonist combined with multiple-dose GnRH-antagonist OS protocol, patients revealed significantly longer stimulation (10.7±2.3 vs 9.3±1.9 days, p<0.01, respectively), with no in-between group differences in the number of oocytes retrieved or the number of MII oocytes. Moreover, the number of TQE (2.8±2.2 vs 0.9±0.8, p<0.001, respectively) and the proportion of the number of TQE/number of MII oocytes retrieved (38±23 vs 14±13%, p<0.001) were significantly higher, as compared to their previous control cycles. Seven clinical pregnancies (30.4%) were recorded in the study group and none in the control group.

Conclusion: Patients with repeated IVF failures and poor embryos quality may benefit from the combined Stop GnRH-ag/ GnRH-ant OS protocol. Further large studies are required, aiming to validate our findings and to establish the appropriate patients' characteristics.

Introduction

Ovarian stimulation (OS) is a crucial step in the success of in vitro fertilization-embryo transfer (IVF-ET) because it allows the recruitment of multiple healthy fertilizable oocytes, correlating with cumulative live birth rate [1]. However, owing to the extreme variability in ovarian response to OS, it might yield either poor quality oocytes and embryos or a very small number of follicles [2].

While many OS protocols and various adjuvant treatment strategies are proposed to poor responder patients with no compelling advantage for one protocol over another [2-4], the hitherto published studies concerning OS protocols for repeated IVF failures due to poor quality embryos are scarce [5-6]. Moreover, most studies usually demonstrate an improved embryo quality as a secondary benefit, rather than directly confronting the problem of poor quality embryos.

Recently, while attempting to examine the appropriate OS protocol in poor-responder patients, we found that combining the Stop GnRH-agonist (-ag) protocol with GnRH-antagonist (-ant) protocols revealed significantly higher number of oocytes retrieved and top-quality embryos (TQE), with an acceptable clinical pregnancy rate [7]. The rationale behind the sequential treatment of the combined Stop GnRH-ag with multiple-dose GnRH-ant protocol stems from the advantages of its components. The mid-luteal GnRH-ag pre-treatment causes down regulation of the GnRH receptors with the consequent suppression of pituitary LH secretion for as long as 10 days after the last dose of the agonist. This effect, together with the immediate LH suppression

provided by the GnRH-ant, will eliminate premature LH surge and might improve the quality of the embryos generated.

Since its introduction to our COH armamentarium [7] we started offering the combined Stop GnRH-ag with multiple-dose GnRH-ant to patients with several unresolved infertility problems, including patients with repeated IVF failures and poor embryo quality. In the present study we aim to further assess the role of combined Stop GnRH-ag with multiple-dose GnRH-ant OS protocol in patients with repeated IVF failures in whom most, if not all, of their embryos were of poor quality.

Materials and methods

All consecutive patients with low proportion (<33%) of TQE per number mature (MII) oocytes retrieved, following standard multiple-dose GnRH-ant OS (control cycle), who were treated in our IVF unit during one-year period (2019) were evaluated. Of whom, only those who underwent a subsequent OS using the combined Stop GnRH-ag

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Key words: OS, flexible multidose GnRH-antagonist, IVF failures, IVF outcome, Poor-embryo quality, Stop GnRH-agonist

Received: October 10, 2020; **Accepted:** November 11, 2020; **Published:** November 17, 2020

with multiple-dose GnRH-ant protocol (study cycle), within 3 months of the previous IVF/ICSI cycle were included. The study was approved by the institutional research ethics board of Sheba Medical Center.

Embryos classification was based on the individual embryo scoring parameters according to pre-established definitions [5]. While a top quality embryo (TQE) was defined as seven or more blastomeres on day 3, equally-sized blastomeres and <15% fragmentation, poor quality embryos consist of all the rest.

The combined Stop GnRH-ag with multiple-dose GnRH-ant protocol was previously described [7]. It consisted of triptorelin (Lapidot, Netanya, Israel) 0.1 mg/day, starting in the midluteal phase. The GnRH-ag was discontinued with the onset of menses and after confirmation of down-regulation by serum E2 levels and vaginal ultrasound measurements, gonadotropins were initiated after two wash-out days. Patients were monitored by ultrasonography, serum estradiol and progesterone levels. Once the leading follicle had reached a size of 14 mm, or/and E2 levels exceeded 1200 pmol/L, co-treatment with the GnRH antagonist (cetorelix 0.25 mg/day), was initiated and continued up to and including the day of HCG administration.

Routine IVF or intracytoplasmic sperm injection (ICSI) was then performed, as appropriate. Transvaginal ET was performed 48-72 hours after ovum pick-up (OPU). All patients received luteal support with progesterone.

Data on patient age and infertility-treatment-related variables were collected from the files. OS characteristics, number of oocytes retrieved, embryo quality and number of embryos transferred were assessed and compared between the study cycles and the previous control cycles. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

Statistical analysis was performed with Student's paired t-test and Chi square, as appropriate. Results are presented as means + standard deviations; p value < 0.05 was considered significant.

Results

Twenty-three consecutive combined Stop GnRH-ag with multiple-dose GnRH-ant cycles in 23 patients were evaluated. Mean age during the study cycle was 38.6 ± 4.9 years.

While there were no differences between the groups in the peak estradiol, the number of follicles >13 mm on day of hCG trigger, number of oocytes retrieved, or the number of MII oocytes (Table 1). Patients who underwent the combined Stop GnRH-ag with multiple-dose GnRH-ant protocol had a significantly longer stimulation (10.7 ± 2.3 vs 9.3 ± 1.9 days, p<0.01, respectively) and higher number of TQE (2.8 ± 2.2 vs 0.9 ± 0.8, p<0.001, respectively), with a significantly higher proportion of the number of TQE/number of MII oocytes retrieved

Table 1. Clinical characteristics of the IVF cycles in the two study groups

	Control cycles	Study cycles	p values
Number of cycles	23	23	
Length of stimulation (days)	9.3 ± 1.9	10.7 ± 2.3	0.01
Peak E2 levels on day of hCG administration (pmol/L)	4151 ± 2744	5341 ± 3211	0.2
Number of follicles >13mm on day of hCG administration	5.2 ± 3.4	6.2 ± 3.5	0.12
Number of oocytes retrieved	6.4 ± 4.3	8.1 ± 5.4	0.08
Number of MII oocytes	5.4 ± 3.9	6.5 ± 4.0	0.2
Number of TQE	0.9 ± 0.8	2.8 ± 2.2	0.001
TQE/MIl oocytes (%)	14 ± 13%	38 ± 23%	0.001

(38 ± 23 vs 14 ± 13%, p<0.001), as compared to their previous control cycles.

Seven clinical pregnancies (30.4%) were recorded in the study group and none in the control group. However, it should be emphasized that the increased pregnancy rate in the combined Stop GnRH-ag with multiple-dose GnRH-ant protocol is biased due to the study design, which offered this protocol to patients with poor embryo quality who had failed a previous IVF attempt.

Discussion

In the present study, patients with IVF failure with poor embryo quality undergoing the combined Stop GnRH-ag with multiple-dose GnRH-ant protocol demonstrated a significantly higher number of TQE and an increased proportion of TQE, as compared to their previous IVF attempt, with the consequent improve in embryos implantation capacity.

In the present protocol, we combined the beneficial effects of mid-luteal GnRH-ag pretreatment together with that of the multidose GnRH-antagonist protocol: (a) The long GnRH-ag protocol pretreatment results in better synchronized response and a scheduled cycle [8,9]; (b) Cessation of GnRH-ag might improve ovarian response and avoids the need of increasing gonadotropin daily dose. GnRH-ag causes suppression of pituitary LH secretion for as long as 10 days after the last dose of the agonist [10]; (c) GnRH-ant provides immediate LH suppression that will eliminate premature LH surge and might improve the quality of the embryos generated [11].

Takahashi *et al.* [11] has studies the effect of GnRH-antagonist on embryo quality and pregnancy outcome of patients with a history of multiple IVF failures [11]. They found that with the GnRH-antagonist protocol, the number of patients whose embryos had developed to at least one expanded blastocyst on day 5 was significantly higher than with the GnRH-agonist protocol, resulting in improved pregnancy rate.

In previous studies, we have demonstrated that the combined Stop GnRH-ag with multiple-dose GnRH-ant protocols might be added to the treatment armamentarium of poor-responder patients [7] and those with elevated peak serum progesterone levels undergoing OS for IVF [12]. In the present proof of concept study, we also showed that patients suffering from repeated IVF failure and poor embryo quality might also benefit from this protocol.

Conclusion

Patients with repeated IVF failures and poor quality embryos produce a higher number of TQE, higher proportion of TQE with an improved pregnancy rate with the use of the combined Stop GnRH-ag with multiple-dose GnRH-ant protocol. This OS protocol is therefore suggested as a valuable new tool in the armamentarium for treating repeated IVF failures patients with poor embryo quality.

Further large prospective studies are needed to elucidate the role of the combined Stop GnRH-ag with multiple-dose GnRH-ant protocols in patients with repeated IVF failures patients and poor embryo quality and to identify the specific characteristics of women that will aid both fertility specialists' counselling and their patients in adjusting the appropriate OS protocol.

Declarations

The authors have nothing to declare.

Funding

This manuscript was not supported by specific funding.

Ethics approval and consent to participate

The study was approved by the institutional research ethics board of Sheba Medical Center.

Consent for publication

Not applicable (cohort historical).

Acknowledgements

NA.

Authors' contributions

RO was the principal investigator, designed the study, performed the statistical evaluations, assisted in writing the paper, and edited it in all its revisions. MK, AA, and JH participated in designing the study, assisted in writing the paper and edited it, proof read the paper, and took part in discussions regarding the results. VG retrieved the data, assisted in writing the paper and edited it, proof read the paper, and took part in discussions regarding the results. RN participated in designing the study, retrieved the data, assisted in writing the paper, and edited it in all its revisions. All authors read and approved the final manuscript.

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