Original Article

Assessment of The Results of Short Agonist Stop Ovarian Stimulation Protocol in Poor Responder Patients Undergoing ICSI Cycles

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ABSTRACT

Background: Poor ovarian response is 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. We aimed to determine if in poor responders' patients, the SAS stimulation protocol allows for a better number of oocytes, mature oocytes, total embryos at D2 and usable embryos in comparison with the last previous IVF attempt within the same patients.

Materials and Methods: We performed a prospective observational study on 56 women aged ≥ 18 and < 43 years who undergo an IVF protocol with the "short agonist stop" (SAS) protocol compared with the same patients' previous performance in their last IVF attempt. Enrolled patients were treated in two consecutive cycles. The first attempt was achieved with a standard protocol. Patients for whom the standard protocol has failed were treated in the subsequent cycle with the SAS protocol.

Results: Regarding the cumulative outcomes, ongoing pregnancy rate was significantly higher in SAS protocol compared to IVF protocol (0% vs. 12.5%, *P=0.026*). Number of cumulative ET, cancellation before oocyte pick, no usable embryo, biochemical pregnancy, and miscarriage rate were insignificantly different between both protocols.

Conclusion: The SAS stimulation protocol may offer promising results for poor responders with low prognosis and previous failed IVF.

Key Words: Embryo transfer, IVF protocol, poor ovarian response, SAS protocol.

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INTRODUCTION

Poor ovarian response (POR) is 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 anti-mullerian hormone (< 0.5–1.1 ng/mL), or presence of an abnormal ORT in a woman over 40 years of age[1, 2]. Patients identified as "poor responders" are an increasing population representing 10 to 24% of women involved in assisted reproductive technology (ART)[3].

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. The optimal treatment suited for poor responders is

not clearly established yet[4, 5]. Gonadotropin releasing hormone (GnRH) antagonists and GnRH agonists (GnRH-a) are equally recommended for predicted poor responders, according to ESHRE recommendations[6].

Also, consideration should be given to a mild ovarian-stimulation protocol and dual stimulation protocol in the same ovarian cycle, both offering encouraging results for POR[7]. The efficiency of adjuvant co-treatments has not yet been proven, although dehydroepiandrosterone (DHEA), LH or coenzyme Q10 supplementation seems promising[8, 9].

New hopes arise from ground breaking treatments in development such as autologous platelet-rich plasma intra ovarian injection or in vitro activation of follicles[10]. Finally, when ART is unsuccessful with autologous oocytes, egg donation, associated with a high live birth rate (LBR), remains the best option for poor responders. Their care in ART remains a challenge and the efficiency of their stimulation protocol is still being discussed[11].

Hazout *et al*.[12] and Schachter *et al*.[13] hypothesized that POR benefits from a double stimulation (flare up effect then gonadotropins) associated with a less strenuous

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blockage (discontinuation of GnRH-a) to favour follicular recruitment in order to obtain a better ovarian response and produce more oocytes and embryos, including more usable embryos, increasing chances of ongoing pregnancies (OP) in these low prognosis patients. Based on this data, "Short agonist stop" (SAS) protocol was proposed to poor responders patients that uses GnRH-a at first for the flare up effect at the beginning of the cycle for 7 days in total then stopped, enabling pituitary desensitization in order to prevent a premature LH surge, associated with a controlled ovarian stimulation with gonadotropins at maximum dosage (300IU/d)[14].

The SAS protocol is not mentioned in recent literature about stimulation protocols and management of poor responders in ART, nor in ESHRE's guidelines about ovarian stimulation for IVF/ICSI. This type of stimulation was studied more often in the 2000s, but still, only one randomized controlled trial (RCT) used this protocol[15, 16].

The aim of the present study is to determine if in poor responders' patients, the SAS stimulation protocol allows for a better number of oocytes, mature oocytes, total embryos at D2 and usable embryos in comparison with the last previous IVF attempt within the same patients.

PATIENTS AND METHODS

We performed a prospective observational case-control study on 56 women who underwent an IVF protocol with the "short agonist stop" (SAS) stimulation protocol compared with the same patients' previous performance in their last IVF attempt in a private IVF center after approval of the institutional ethical committee from Kafrelsheikh university. The informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were women aged ≥ 18 and < 43 years old with defined POR (low prognosis patients), according to POSEIDON stratification[17], and Underwent an IVF protocol with the "short agonist stop" (SAS) stimulation protocol.

Exclusion criteria were patient refusal, preimplantation genetic testing and fertility preservation cycles, non-compliance to the SAS protocol (modification of duration of GnRH-a).

Only the first cycle with SAS was included compared with the previous stimulation cycle.

IVF protocol group (control group):

Enrolled patients were treated in two consecutive cycles. The first attempt was achieved with a standard protocol for POR: antagonist protocol, long or short agonist protocol and mild stimulation. Ovulation triggering was performed with HCG (Choriomon,10.000IU, IBSA) when the leading follicles (at least 3 follicles, except for mild stimulation) reached a mean diameter of 17 mm and oocyte retrieval was performed 35 hours after. If less than 3 follicles were recruited, a conversion to ovulation induction or intra uterine insemination was performed, if possible (at least one patent tube and adequate semen parameters). Luteal phase was supported similarly by daily vaginal administration of 400 mg of micronized progesterone (Prontogest®,Marcyl), until the pregnancy test. Patients for whom the standard protocol has failed (no ongoing pregnancy, no remaining cryopreserved embryo) were treated in the subsequent cycle with the SAS protocol. Clinical and laboratory aspects of treatment were mainly done in a similar fashion in both cycles.

Case group:

Short agonists stop protocol (SAS group), for the SAS protocol, pre-treatment with estradiol valerate2mg (Cyclo-progynova®, Bayer Schering Phama, Germany), starting in the midluteal phase (D20) of the preceding cycle, was prescribed. After an ultrasound to confirm ovarian quiescence and a thin endometrium, associated with low P serum on day 2 of the cycle, 0.1 mg triptorelin (Decapeptyl® FERRING PHARMACEUTICALS GmbH- Germany) was initiated daily, for 7 days, then stopped. Controlled ovarian stimulation (COS) was initiated 2 days after the beginning of the GnRH-a, on day 4, with FSH or hMG at 300 IU as a starting dose. After 7 days without agonist, GnRH antagonist, cetrorelix 0.25 mg (Cetrotide®, Merck Serono, United Kingdom) was used daily until triggering. Triggering, oocyte retrieval and luteal phase support were all performed in a similar fashion to the previous IVF attempt.

IVF and embryo quality assessment:

Conventional IVF (cIVF) or intra cytoplasmic sperm injection (ICSI) technique were used as appropriate. IVF procedure was performed in our unit as previously described. At D3, embryo morphology was graded using a standard system including number, size and uniformity of blastomeres, degree of fragmentation and the presence of multinucleated blastomeres. Usable cleaved embryos were defined as embryos with at least 3 blastomeres at D2 and 7 at D3, blastomeres with relative uniformity and no multinucleation, with <30% of fragmentation.

At D5/6, blastocyst morphology was evaluated according to the Gardner and Schoolcraft grading system. 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 blastomeres and

20%-50% fragmentation of the cytoplasm; grade IV [poor quality]; embryos with unequal blastomeres and >50% fragmentation of the cytoplasm[18].

Thus, usable blastocysts were defined as full (grade 3), expanded (grade 4), partially hatched (grade 5), or fully hatched (grade 6) blastocysts with at least grade B trophectoderm quality. Usable blastocysts were freshly transferred at D5 or cryopreserved at D5/6 for subsequent transfers.

Embryo transfer and pregnancy outcome:

Fresh embryo transfers were performed either at the cleavage (D2-D3) or blastocyst stage (D5). Early blastocysts (grade 1 or 2) at D5 were kept in culture until D6 and cryopreserved if considered usable at that point. The surplus embryos (D2-D3 or D5-D6) that were considered usable according to morphologic criteria were cryopreserved for subsequent transfers. The embryo transfer strategy was determined by a multidisciplinary team. Embryos were cryopreserved by vitrification and thawed following the manufacturer's recommendations (Vit Kit-Freeze and Vit Kit-Thaw, FUJIFILM Irvine Scientific-BioCare Europe™). A maximum of two embryos were replaced.

All usable embryos were frozen (freeze all strategy) for subsequent frozen ET cycles if the circumstances were unsuitable for fresh ET, for instance in case of elevated P level, inadequate uterine cavity, prolonged ovarian stimulation (> 13 days) or accumulation of vitrified embryos for later transfer (desynchronization). FET (frozen embryo transfer) cycles were performed with natural cycle, hormonal replacement therapy or stimulated cycle regarding the ovulatory status.

Pregnancy was assessed by serum hCG assay after 15 days from oocyte retrieval. A biochemical pregnancy is characterized by the absence of an identifiable pregnancy on ultrasound examination despite a positive blood hCG pregnancy test (<100 IU/L). Clinical pregnancy was confirmed if a fetal heartbeat could be observed by transvaginal ultrasound. An ongoing pregnancy (OP) is defined as a pregnancy with a detectable heartbeat at 12 weeks of gestation or beyond. Live birth is defined as the birth of at least one living child, irrespective of the duration of gestation. Cumulative OP rate (cOPR) includes the outcomes from all fresh and frozen embryo transfers following an episode of ovarian stimulation.

The main outcome measure was the total number of oocytes obtained in poor responder patients after the SAS stimulation protocol. The secondary outcome were the total number of mature oocytes, embryos at day 2, usable embryos (cleaved embryos or blastocysts, eligible for transfer: either fresh or frozen, or surplus embryos, still frozen), cancellation and freeze all rates, and the outcome of IVF attempt: no pregnancy, biochemical pregnancy, miscarriage, ectopic pregnancy, ongoing pregnancy (rate per cycle, per oocyte pick up and per transfer) and live birth (if available), including cumulative outcomes

Statistical analysis:

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed *P value < 0.05* was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the overall population, 56 females were included, their mean age was 30.2 ± 5.63 years, and the mean BMI was 26.2 ± 4.79 Kg/m2. The mean AMH was 1.2 ± 0.6 ng/ml and the mean basal E2 was 44.6 ± 6.18 pg/mL. The mean antral follicle count was 10.02 ± 4.38. Regarding the type of infertility, 41 (73.21%) patients had primary infertility and 15 (26.79%) patients had secondary infertility. The mean duration of infertility was 7.5 ± 1.08 years. The mean time between previous attempt was 8.6 ± 4.3 months.

Table 1: Baseline characteristics of the overall population

		Patients (n=56)
Age (years)		30.2 ± 5.63
BMI (Kg/m^2)		26.2 ± 4.79
AMH (ng/ml)		1.2 ± 0.6
Basal E2 (pg/mL)		44.6 ± 6.18
Antral follicle count		10.02 ± 4.38
Type of infertility	Primary	41 (73.21%)
	Secondary	15 (26.79%)
Duration of infertility (years)		7.5 ± 1.08
Time between previous attempt (months)		8.6 ± 4.3

Data presented as mean ± SD, **BMI:** body mass index, **AMH:** anti-Müllerian hormone, **E2:** estrogen.

Table 2 shows the treatment data where the stimulation protocol was significantly different between both IVF and SAS protocols (*P<0.001*). In IVF protocol, antagonists were used in 42 (75%) cases, long agonist were used in 6 (10.71%) cases, short agonist were used in 4 (7.14%) cases and short agonist stop were used in 5 (8.93%) cases. IN SAS protocol, short agonist were used in 56 (100%) cases and DHEA supplementation was used in 2 (3.57%) cases. Gonadotropin, dose by day, AMH, AFC, cancellation rate and cause of cancellation were insignificantly different between both protocols.

Table 2: Controlled ovarian stimulation and IVF cycle

		IVF protocol (n=56)	SAS protocol (n=56)	*P value*
Stimulation protocol	Antagonist	42 (75%)	0 (0%)	*< 0.001**
	Long agonist	6 (10.71%)	0 (0%)	
	Short agonist	4 (7.14%)	0 (0%)	
	Short agonist stop	5 (8.93%)	56 (100%)	
	DHEA supplementation	0 (0%)	2 (3.57%)	
Gonadotropin	HMG	43 (76.79%)	42 (75%)	*0.825*
	R FSH	13 (23.21%)	14 (25%)	
Dose by day		329.5 ± 66.73	335.5 ± 61.22	*0.621*
AMH		1.2 ± 0.59	1.4 ± 0.52	*0.117*
AFC		7.7 ± 3.97	8.6 ± 4.36	*0.260*
Cancellation rate		8 (14.3%)	8 (14.3%)	*1.0*
Cause of cancellation	Insufficient ovarian response	5 (62.5%)	6 (75%)	*0.489*
	Inappropriate cycle	2 (25%)	1 (12.5%)	
	Premature ovulation	1 (12.5%)	0 (0%)	
	OI or IUI conversion	0 (0%)	1 (12.5%)	

Data presented as mean ± SD, **SAS:** short agonist stop, **IVF:** invitro fertilization, **DHEA:** dehydroepiandrosterone, **HMG:** human menopausal gonadotropins, **FSH:** follicle stimulating hormone, **AMH:** anti-Müllerian hormone, **AFC:** antral follicle count, **OI:** ovulation induction, **IUI:** intrauterine insemination

As shown in Table 3, cycles with oocyte retrieval was presented in all cases in both protocols. Freeze all rate, number of retrieved oocyte, number of metaphase II oocytes and number of transferred embryos were significantly higher in SAS protocol compared to IVF protocol (*P<0.05*). Cancellation before oocyte pick was insignificantly different between both protocols.

Table 3: Controlled ovarian stimulation and IVF cycle (continue)

	IVF protocol (n=48)	SAS protocol (n=48)	
Cycles with oocyte retrieval	48 (100%)	48 (100%)	---
Freeze all rate	8 (16.67%)	18 (37.5%)	0.039*
Cancellation before oocyte pick	7 (14.58%)	4 (8.33%)	0.523
Number of retrieved oocyte	8.6 ± 4.66	12.1 ± 5.86	0.002*
Number of metaphase II oocytes	5.7 ± 3.85	9.2 ± 6.27	0.001*
Number of transferred embryos	0.96 ± 0.85	1.38 ± 1.06	0.037*

Data presented as mean ± SD, **SAS:** short agonist stop, **IVF:** invitro fertilization, ***:** statistically significant as *P value <0.05*

Regarding the cumulative outcomes, number of cumulative ET was 1.3 ± 0.73 in IVF protocol and 1.5 ± 1.07 in SAS protocol, cancellation before oocyte pick was 7 (14.58%) in IVF protocol and 4 (8.33%) in SAS protocol, no usable embryo was 9 (18.75%) in IVF protocol and 5 (10.42%) in SAS protocol, biochemical pregnancy was 3 (6.25%) in IVF protocol and 2 (4.17%) in SAS protocol, miscarriage rate was 4 (8.33%) in IVF protocol and 0 (0%) in SAS protocol and ongoing pregnancy rate was 0 (0%) in IVF protocol and 6 (12.5%) in SAS protocol. Ongoing pregnancy rate was significantly higher in SAS protocol compared to IVF protocol (0% vs. 12.5%, *P=0.026*). Number of cumulative ET, cancellation before oocyte pick, no usable embryo, biochemical pregnancy, and miscarriage rate were insignificantly different between both protocols.

Table 4: Cumulative outcomes

	IVF protocol (n=56)	SAS protocol (n=56)	*P value*
Number of cumulative ET	1.3 ± 0.73	1.5 ± 1.07	*0.122*
Cancellation before oocyte pick	7 (14.58%)	4 (8.33%)	*0.523*
No usable embryo	9 (18.75%)	5 (10.42%)	*0.386*
Biochemical pregnancy	3 (6.25%)	2 (4.17%)	*1.0*
Miscarriage rate	4 (8.33%)	0 (0%)	*0.117*
Ongoing pregnancy rate	0 (0%)	6 (12.5%)	*0.026**

Data presented as mean ± SD, **SAS:** short agonist stop, **IVF:** invitro fertilization, **ET:** embryo transfer, ***:** statistically significant as *P value <0.05*

DISCUSSION

Ovarian hyper stimulation is cornerstone in ICSI procedure, as it induces multiple follicles growth, leading to a higher number of oocytes retrieved and higher number of embryos, so lead to more success to get pregnant[19]. Women with low ovarian reserve represent large section of women seeking for ICSI, they had a big problem due to reduced number of oocytes retrieved, increased cancellation rates, and decreased pregnancy rates. The most suitable protocol used in ovarian stimulation for poor responders is to tailoring dose to each patient, based on AFC and AMH[20, 21].

Ferraretti *et al*.[22] presented the Bologna criteria to determine a definition for poor responder. Among the various protocols, there was no evidence on the effectiveness of any one stimulation protocol over another[23].

GnRh agonist and antagonist have pregnancy and cancellation rate, but some studies clarified advantage of the flare-up over the letrozole/antagonist protocols[24, 25]. A recent comparison among GnRH-agonist protocols, clarified an advantage of long GnRH-agonist protocol over the short GnRH-agonist protocol in consideration to number of clinical pregnancies, number of oocytes retrieved, and cancellation rates[26].

Mauries *et al*.[16] study has documented that SAS stimulation is a short and original protocol strengthening the therapeutic arsenal of poor responders, which may offer promising results for those patients with low prognosis and a record of failed IVF. This protocol resulted in a significantly higher number of oocytes, mature oocytes, and embryos obtained and a non-significantly higher number of usable embryos, in comparison with their previous IVF cycle.

A previous study for poor responders, GnRH agonist flare up and long agonist protocols did not seem to be as advantageous as a reduction of GnRH-a doses, "stop" protocols, or micro-dose GnRH-a flare regimens. These regimens all appeared to improve outcomes, although the benefit of one approach over another has not been convincingly established, with no difference between their outcomes[27, 28]. The SAS protocol is a mix of flare and "stop" protocols. Yet, a most recent RCT found that the micro-dose flare-up seemed to be superior to the flare-up protocol, with significantly higher LBR (*p=0.036*), but with similar efficacy when compared to GnRH antagonist protocol[29]. The advantage of SAS over long protocol is the shorter duration of stimulation which could favour better compliance and tolerance[30].

Short use of GnRH-a (7 days) does not profoundly inhibit ovarian response through the ovarian

GnRH receptors while sufficiently inhibiting premature LH surges[1]. In the SAS group, no cancellation were observed due to premature LH surge or ovulation in the following 7 days after discontinuation of GnRH-a, as in Hazout's[12] RCT, showing the efficiency of latent agonist blockage, as shown in Pantos *et al*.'s[31] study, with up to 12 days without GnRH-a. After stopping GnRH-a (5-day course), endogenous GnRH activity appeared to be suppressed for at least 7 days afterwards[32], because the pituitary is in a refractory state of LH secretion, as found in Cedrin- Durnerin *et al*.'s[33] study, showing decreased LH concentrations after an early discontinuation of GnRH-a administration compared with a long agonist protocol. Indeed, hypophyseal desensitization is related to GnRH receptor reduction, leading to a progressive reduction in gonadotropin synthesis, that remains for some days[34].

We found that in the SAS group, significantly higher oocytes and mature oocytes were retrieved than in the previous attempt. The stimulation protocol was significantly different between both IVF and SAS protocols (*P<0.001*). Gonadotropin, dose by day, AMH, AFC, cancellation rate and cause of cancellation were insignificantly different between both protocols. Freeze all rate, number of retrieved oocyte, number of metaphase II oocytes and number of transferred embryos were significantly higher in SAS protocol compared to IVF protocol (*P<0.05*). Cancellation before oocyte pick was insignificantly different between both protocols.

In Sunkara's[35] study, the gap between having 1 vs 2 oocytes retrieved, or 2 vs 3, had a major impact on live birth rates: from 5 to 13% or 13 to 18% respectively in 35-37 years old patients. Consequently, maximizing the oocyte yield is pivotal for stimulation, so SAS protocol enabling more oocytes is paramount.

On the one hand, in a small cohort, poor responders undergoing ultrashort flare up GnRH-a versus GnRH-antagonist protocol also demonstrated a significantly higher number of oocytes

retrieved and embryos transferred as compared with the patients' previous IVF attempts[36]. When discontinued GnRH-a protocol is compared with long agonist protocol in POR patients, Garcia Velasco's RCT[37] found the retrieval of a significantly higher number of oocytes whereas Pantos *et al*.[31] found no difference in recovered oocytes.

Mauries *et al*.[16] found that the mean number of usable embryos were higher in the SAS group with no statistical significance. The number of cumulative ET in the SAS group was higher: 54 vs 42, but with no statistical difference (*p=0.124*). Twelve surplus embryos are waiting for ET (mainly because of an ongoing pregnancy), so the number of cumulative ET would probably be significant if all embryos were transferred, with potentially more pregnancies. Schachter *et al*.[13] also found significantly more cleaving embryos with improved morphology after discontinued GnRH-a protocol in comparison with long agonist protocol. The freeze all rate was significantly higher in the SAS group mostly due to prolonged stimulation, indication since prolonged stimulation is associated with decreased ART success because of impaired endometrium for implantation (except for PCOS)[38, 39]. However, a recent study showed that it is in fact the total dose of gonadotropin received that impacts LBR in fresh cycles[40].

Regarding the cumulative outcomes, ongoing pregnancy rate was significantly higher in SAS protocol compared to IVF protocol (0% vs. 12.5%, *P=0.026*). Number of cumulative ET, cancellation before oocyte pick, no usable embryo, biochemical pregnancy, and miscarriage rate were insignificantly different between both protocols.

Also, Mauries *et al*.[16] found that the miscarriage rate (MR) in the SAS group was particularly low, probably they explained that by the small size of our population and of the selection of our population with previous failed IVF cycle (no pregnancy, biochemical pregnancies, or miscarriages). There is no reason to believe that the SAS stimulation could reduce miscarriage by enhancing the ploidy rate, because recent studies show that ovarian stimulation does not impact the risk of aneuploidy[41, 42]. Other factors like individualized luteal support with adequate progesterone levels in FET might play a role, as it was most recently changed[43].

CONCLUSION

The SAS stimulation protocol may offer promising results (more mature oocytes, embryos and ongoing pregnancy rate) for poor responders with low prognosis and previous failed IVF. Those results must be confirmed with a large prospective study evaluating live birth rate after SAS protocol versus standard protocol. The SAS original protocol might strengthen the therapeutic arsenal of poor responders and enable a more tailored management.

CONFLICT OF INTEREST

There are no conflicts of interests.

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