Original Article

Ovarian Stimulation in Patient-oriented Strategies Encompassing Individualised Oocyte Number-4 Category; Antagonist versus Short-agonist Protocols

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Abstract

Background: Recently POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) classification was proposed to categorize patients with expected poor response to conventional stimulation. Searching for the ideal management of poor responders in IVF is still an active research area.

Aims: This study compares GnRH-antagonist and GnRH-agonist short protocols in ICSI cycles for the POSEIDON-4 group.

Settings and Design: This retrospective study was conducted in a tertiary infertility unit between January 2016 and December 2020.

Materials and Methods: Infertile women who met the criteria for POSEIDON 4 group and underwent fresh ICSI-ET in using GnRH-antagonist and GnRH-agonist short protocols was performed. POSEIDON-4 includes patients ≥ 35 years with poor ovarian reserve markers; AFC < 5 and AMH < 1.2 ng/ml.

Statistical Analysis Used: Numerical variables were compared between both groups by student's t test and Mann Whitney test when appropriate. Chi-square test used to compare categorical variables. Multivariate logistic regression models were utilized to adjust for the effect of the different study confounders on live birth rate.

Results: One hundred ninety fresh ICSI cycles were analyzed. Of the total cohort, 41.6 % (79) patients pursued antagonist protocol compared to 58.4% (111) underwent short agonist protocol. Fresh embryo transfer was accomplished in 55.7 % (44/79) vs. 61.3 % (68/111), P = 0.44 in antagonist vs. short protocol respectively. Cycle cancellation due to poor ovarian response was encountered in (32.9%vs. 27.9%, P = 0.50) in the antagonist and short groups, whereas no good-quality embryos were developed after ovum pickup in 11.4% vs. 10.8%, P>0.05. Comparable total gonadotropins dose, number of retrieved and mature oocytes, and good-quality embryos were found in both groups. Likewise, clinical pregnancy rate was not different for the antagonist and short groups [11/79 (13.9%) vs. 20/111 (18%), P = 0.45]. The live birth rate was comparable between both groups (8.9% vs. 10.8%, P = 0.659) for antagonist and short groups respectively. No significant impact for the protocol type on live birth rate was revealed after adjusting to cycle confounders in multivariate analysis (OR: 0.439, 95%CI 0.134-1.434, P = 0.173).

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Conclusion: This study shows comparable pregnancy outcomes for antagonist and short-agonist protocols in IVF/ICSI cycles for POSEIDON-4 category.

Keywords: *Antagonist protocol, patient-oriented strategies encompassing individualised oocyte number-4, short protocol*

Introduction

One of the important steps of *in vitro* fertilisation (IVF) and embryo transfer (ET) technique success is controlled ovarian stimulation (COS). COS involves stimulation of ovaries with gonadotropins drugs to recruit the number of mature follicles. Unfortunately, stimulation of poor ovarian responders (POR) does not succeed in yielding the adequate number of oocytes ready for fertilisation.[1]

POR are defined as women with reduced number of follicular responses, thus reduced number of oocytes retrieved. For the proper definition of POR, women must have two of the following criteria; advanced maternal age, previous poor response to conventional IVF stimulation, and/or abnormal ovarian reserve markers.[2] It was reported that 9-24% of women undergoing IVF cycles met these criteria of POR.[3]

Dealing with POR women is a real challenge to IVF specialists. Therefore, a new classification (patient-oriented strategies encompassing individualised oocyte number [POSEIDON] criteria) was elucidated to help fertility clinicians to obtain enough number of oocytes to achieve euploid embryos for transfer.[4] It included further subdivision of POR (POSEIDON Group 1 and 2 and POSEIDON 3 and 4) according to age, ovarian reserve markers (antral follicle count [AFC] and anti-Müllerian hormone [AMH]) and previous ovarian response to ovarian stimulation.[5,6] POSEIDON Group 4 encompasses women with maternal age >35 years, AFC <5 and serum AMH concentrations <1.2 ng/mL.

Several ovarian stimulation protocols are offered to achieve enough number of oocytes, including gonadotropin-releasing hormone (GnRH) antagonist, long agonist, letrozole priming and short agonist, but none of these protocols was confirmed to be the ideal stimulation strategy. Therefore, we conducted this study to compare GnRH antagonist versus short-agonist protocols in POSEIDON-4 women who underwent fresh IVF/intracytoplasmic sperm injection (ICSI) cycles.

Materials and Methods

After obtaining the local institutional review board approval (IRB number, 17300716), we conducted this retrospective analysis for ICSI cycles of cases that met the clinical and laboratory criteria of the POSEIDON-4 in our tertiary infertility unit.

Study participants

The study included ICSI cycles between January 2016 and December 2020. The study was performed with adherence to the principles of the Helsinki Declaration (2013). Informed consent was obtained from participants for the use of anonymized data for research purposes. The POSEIDON-4 involves patients ≥35 years with poor ovarian reserve markers; AFC <5 and AMH <1.2 ng/ml. We analysed ICSI cycles between January 2016 and December 2020 with the GnRH-antagonist and short-agonist protocols. The study sample was selected based on the number of patients who fulfilled the eligibility criteria during the study's period and not on a formerly estimated equation. The study did not include cases with surgically retrieved sperms, uterine factor infertility or pre-implantation genetic testing.

Controlled ovarian stimulation

Programming of the cycle was done with low-dose oral contraceptive pills. Ovarian stimulation was started on day 2 of the stimulation cycle. The dose of gonadotropins used in stimulation was determined based on age, ovarian reserve markers, body mass index (BMI) or ovarian response to previous conventional stimulations if present. The starting dose ranged from 300 to 450 IU. In the short-agonist protocol, gonadotropin-releasing hormone agonist (GnRHa); triptorelin (decapeptyl 0.1 mg, Ferring, Germany), was started on day 2 along with gonadotropins. Stimulation was conventionally started with follicle-stimulating hormone (FSH) for the first five days of the cycle, then adding human menopausal gonadotropin (HMG) from day 6 onwards. On the contrary, the antagonist protocol involved the start of gonadotropins on day 2, and GnRH-antagonist; cetrorelix (injection Cetrotide 0.25 mg SC daily, Merck-Serono, Germany) was given when the leading follicle reached 13 mm according to the flexible protocol. Ovulation was triggered with either 10,000 IU human chorionic gonadotropin (HCG) (Choriomon, IBSA, Switzerland) or two injections of 250 µg recombinant human chorionic gonadotropin (rHCG) (Ovidrel; EMD Serono, Canada) when ≥2 follicles achieved a mean diameter of 17 mm. Also, some cycles received dual trigger by adding two ampoules of GnRHa 0.1 mg to the HCG dose. Afterward, a transvaginal

ultrasound-guided egg collection was done 34–36 h after the trigger and fertilisation of mature oocytes by ICSI with the husband's sperm only. Luteal phase support with intramuscular progesterone (Prontogest, IBSA Pharmaceutical, Egypt) and vaginal progesterone was used after egg retrieval until checking the pregnancy test 14 days after ET. Transfer of best-quality embryos with a maximum of three according to the number of available embryos, embryo quality and patient's age was performed on either day 3 or day 4 after OPU. Good-quality embryos were defined according to Volpes *et al*.[7] as those achieving eight-cell stage on day 3 with <20 % fragmentation. Likewise, good quality day-4 embryos were either embryos with early blastulation or compacted morula.[8]

Study outcomes

The main study outcomes involved the live-birth and clinical pregnancy rates. Live birth was expressed as the number of patients with a living neonate delivered at ≥24 weeks of gestation per 100 initiated cycles, whereas clinical pregnancy rate was defined as the number of patients with detected foetal heartbeats by transvaginal ultrasound 4 weeks after ET divided by the number of initiated cycles per 100. The secondary outcomes included implantation and cycle cancellation rates. The implantation rate was estimated as the number of gestational sacs observed, divided by the total number of transferred embryos. The cycle cancellation rate was calculated as the percentage of cases that did not undergo ET. Numerical variables were presented as mean ± SD or median (interquartile range) according to the normality of data distribution. These continuous variables were compared between both groups by student's t test and Mann Whitney test when appropriate. Categorical variables were presented in numbers (percentages) and analyzed using Chi-square test. We performed multivariate logistic regression models to adjust for the effect of the different study confounders on live birth. The included sample was determined according to the available records during the study period in our infertility unit and not according to a previously calculated sample.

Results

One hundred and ninety fresh ICSI cycles were analysed. Of the total cohort, 41.6% (79) patients pursued antagonist protocol compared to 58.4% (111) who underwent short-agonist protocol. The baseline demographics and clinical data of both groups are presented in Table 1. Both groups were homogeneous in terms of infertility type and duration and number of previous failed ICSI trials. The number of patients who did not pursue any previous failed ICSI cycle was 48 (60.8%) versus 57 (51.4%), P = 0.123 for the antagonist and short groups, respectively. The antagonist

Table 1: Baseline clinical characteristics of study participants

	Antagonist protocol (*n*=79)	Short (*n*=111)	*P*
Infertility type			
Primary	38 (48.1)	57 (51.4)	0.659
Secondary	41 (51.9)	54 (48.6)	
Number of previous failed ICSI			
0	48 (60.8)	57 (51.4)	0.123
1	22 (27.8)	23 (20.7)	
2	7 (8.9)	18 (16.2)	
≥3	2 (2.5)	13 (11.7)	
Aetiology of infertility			
Male factor	23 (29.1)	24 (16.2)	<0.001
Ovulatory	11 (13.9)	5 (4.5)	
Tuboperitoneal	8 (10.1)	22 (19.8)	
Combined	18 (22.8)	51 (45.9)	
Unexplained	19 (24.1)	15 (13.5)	
Age	38 (3)	39 (4)	<0.001
BMI	29.9±4.5	28.5±2.6	0.006
Infertility duration	7.7±5.1	7.9±6.3	0.770
FSH	8.7±4.1	10.8±5.4	0.010
AMH	0.49 (0.56)	0.39 (0.29)	0.076
AFC	4 (2)	3 (2)	<0.001

Data are presented as number and %, mean±SD or median (IQR). BMI=Body mass index, AFC=Antral follicle count, FSH=Follicle-stimulating hormone, AMH=Anti-Müllerian hormone, SD=Standard deviation, IQR=Interquartile range, ICSI=Intracytoplasmic sperm injection

group had lower age (37.9 ± 3.2 vs. 39.3 ± 2.6, $P < 0.001$) and basal FSH level ($P = 0.010$). The antagonist group included a statistically significantly higher AFC (median [IQR] 4 [2] vs. 3 [2], $P < 0.001$). Similarly, the AMH was higher, yet statistically non-significant, in the antagonist group (0.49 [0.56] vs. 0.39 [0.29], $P = 0.076$) [Table 1]. The aetiology of infertility was different between both groups. However, the pregnancy outcomes for the different infertility aetiologies were homogeneous [Supplementary Table 1]. Therefore, this difference seems not to affect the comparison of both stimulation protocols.

Both groups achieved similar clinical and embryological outcomes, including total gonadotropins dose, good-quality embryos, implantation rate and number of retrieved and mature oocytes. Endometrial thickness was statistically, yet non-clinically, lower in the antagonist group (9.9 ± 3.2 vs. 11.2 ± 2.1, $P < 0.001$). Fresh ET was performed in 55.7% (44/79) versus 61.3% (68/111), $P = 0.44$ in antagonist versus short protocol, respectively. The number of transferred embryos and the day of transfer were comparable amongst both groups [Table 2].

Cycle cancellation due to poor ovarian response was encountered in (32.9% vs. 27.9%, $P = 0.50$) in the antagonist and short group, whereas no good-quality embryos were generated after OPU in 11.4% versus 10.8%, $P > 0.05$. The two groups had a comparable clinical pregnancy rate; 11/79 (13.9%) versus 20/111 (18%), $P = 0.45$ for the antagonist and short groups [Table 3]. The live birth rate was comparable between both groups (8.9% vs. 10.8%, $P = 0.659$) for antagonist and short groups respectively [Table 3]. The protocol type in the multivariate binary logistic regression model still does not statistically significantly affect live birth after adjusting to age, AFC, baseline FSH and BMI (OR: 0.439, 95%CI 0.134-1.434, $P = 0.173$) [Table 4].

Discussion

To the best of our knowledge, this is the first study to compare short-agonist and antagonist protocols in POSEIDON-4 women. We retrospectively analysed the IVF/ICSI cycles in our infertility unit. Our study showed comparable results between both protocols regarding live birth, pregnancy and implantation rates. Moreover, number of retrieved follicles, metaphase II, and fertilised oocytes did not differ significantly.

Although different ovarian stimulation protocols and adjuvant treatments were introduced to improve success rates in poor responders, no protocol was ideal.[9-14] To address this gap of knowledge, we conducted this

Table 2: Stimulation cycle parameters and embryological outcomes

	Antagonist protocol	Short-agonist protocol	*P*
Starting dose	428.0±48.6	443.2±27.8	0.007
Total gonadotropins dose	4350.0±1257.1	4117.2±1174.5	0.194
Endometrial thickness	9.9±2.3	11.2±2.1	<0.001
Peak estradiol	1277.6±1083.1	951.4±768.9	0.052
Ovulation trigger, *n* (%)			
Non-triggered (<2 follicles)	26 (32.9)	30 (27.0)	0.012
HCG trigger	46 (58.2)	80 (72.1)	
Dual trigger	7 (8.9)	1 (0.9)	
Expected oocytes	6.1±3.6	4.4±2.1	0.001
Retrieved oocytes	4.96±3.6	4.6±2.6	0.450
Mature oocytes	3.7±3.1	3.5±2.2	0.572
Fertilised oocytes	2.7±2.2	2.8±2.0	0.740
Good-quality embryos	1.9±1.7	1.78±1.4	0.592
Transferred embryos	2.4±0.97	2.5±0.87	0.521
ET day, *n* (%)			
Day 3	67 (89.3)	27 (60.0)	0.291
Day 4	8 (10.7)	18 (40)	

HCG=Human chorionic gonadotropin, ET=Embryo transfer

Table 3: Cycle outcomes of stimulation protocols

	Antagonist protocol, *n* (%)	Short-agonist protocol, *n* (%)	*P*
Fresh transfer			
No	35 (44.3)	43 (38.7)	0.442
Yes	44 (55.7)	68 (61.3)	
Cancellation aetiology			
No	44 (55.7)	68 (61.3)	0.508
Poor response	26 (32.9)	31 (27.9)	
Fertilisation failure	3 (3.8)	5 (4.5)	
Empty follicles	4 (5.1)	3 (2.7)	
Poor-quality embryos	2 (2.5)	4 (3.6)	
Implantation rate	14.02±28.29	12.99±22.42	0.832
Clinical pregnancy			
No	68 (68.1)	91 (82.0)	0.452
Yes	11 (13.9)	20 (18.0)	
Live birth	7 (8.9)	12 (10.8)	0.659

Table 4: Binary logistic regression analysis for the effect of cycle confounders and live birth

Covariates	AOR (95% CI)	*P*
Stimulation protocol (antagonist)	0.439 (0.134–1.434)	0.173
AFC	1.727 (1.067–2.796)	0.026
Age	0.835 (0.654–1.065)	0.147
FSH	0.928 (0.814–1.058)	0.264
BMI	1.053 (0.904–1.227)	0.504
Constant	9.861	0.674

AOR=Adjusted odds ratio, CI=Confidence interval, AFC=Antral follicle count, FSH=Follicle-stimulating hormone, BMI=Body mass index

study to compare IVF/ICSI outcomes between both protocols. Many investigators recommended the use of flare-up regimen in poor responder, whereas others considered the GnRHa protocol is the protocol of choice despite diminished ovarian sensitivity to gonadotropins stimulation.[15-17]

Therefore, the use of short protocol and antagonist protocols was proposed based on introducing GnRHa at the follicular phase to stimulate the release of endogenous gonadotropin flare, whereas antagonist protocols prevent pre-mature luteinising hormone (LH) surge without affecting follicular growth.[18-20] Akman *et al*. agreed with our results, they had comparable results between both protocols regarding pregnancy and implantation rates. They reported the GnRH antagonist protocol as a new hope for poor responders due to the decrease number of cycle cancellations. However, the antagonist protocol had less peak estradiol serum levels.[19] Mohamed *et al*. reported better ovarian response in both investigated protocols (n = 134) compared to long agonist GnRH-a protocol.[21] However, flare-up protocol took longer time of ovarian stimulation. They also showed decreased implantation rates. The possible explanation was that poor responder women had diminished ovarian reserve with lower quality oocytes.

Surprisingly, Lainas *et al*.[22] investigated the flexible antagonist protocol in women with previous failed IVF cycles; they showed better pregnancy rates over short protocol. Although they have the same numbers of oocytes retrieved, fertilised oocytes and implantation rates.[22] They explained their results that flexible antagonist protocol provides a hormonal serum level like that of the nature cycle, so this prevents high serum levels of LH in the early follicular phase like that of flare-up protocol. On the other hand, two cohort studies showed no difference in pregnancy rate between the three followed protocols (antagonist and short and long agonist) amongst poor responder women.[23,24] Moreover, another study compared four protocols in poor responders; they reported no difference in cancellation, implantation and pregnancy rates.[25]

The main limitation of this study is its retrospective design and the small number of women recruited. The cohorts differed in confounder frequency (age, baseline FSH, AFC and BMI) and that a type 2 error may have been introduced because of a selection bias. Even though an adjusted analysis has been done, a possibility of the short GnRH agonist protocol actually doing better than antagonist protocol in a well-powered study cannot be ruled out. Therefore, better-designed, well-powered studies are required to make a conclusion with certainty.

Conclusion

IVF clinicians can choose any of investigated protocols (short and antagonist) according to their experience and convenience because of their comparable results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

Raw data is available upon request.

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Supplementary Table 1: Aetiology of infertility and pregnancy outcomes in patient-oriented strategies encompassing individualised oocyte number-4

	Pregnant	Non-pregnant	*P*
Male factor (*n*=41)	6 (14.6)	35 (85.4)	0.524
Ovulatory (*n*=16)	2 (12.5)	14 (87.5)	
Tuboperitoneal (*n*=30)	6 (20)	24 (80)	
Combined (*n*=69)	10 (14.5)	59 (85.5)	
Unexplained (*n*=34)	7 (20.6)	27 (79.4)	