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Article

In poor ovarian responders, does the progestin used in progestin primed dual stimulation have a negative effect on the ovarian response? A randomized clinical trial

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Abstract. *Background***:** Poor ovarian responders involve 9–24% of patients undergoing IVF. the management of those patients is an everyday practice challenge. The dual stimulation protocol is an effective way to increase the number of oocytes and embryos obtained over a relative short period of time. Furthermore, there is increasing evidence that progestins can be a reliable method of preventing the premature LH surge during ovarian stimulation. *Objective***:** In this study we investigated the effect of the progestin used, Dydrogesterone, in the progestin primed dual stimulation protocol in poor ovarian responders on the ovarian response. *Methods***:** 90 infertile women indicated for ICSI with criteria of poor ovarian response defined by Bologna criteria were randomized in a prospective manner in Madina infertility center in Alexandria starting from 2020 till 2021.These were further subdivided based on computer randomization into 2 groups. Group I (Dual stimulation group) including 45 patients were given the progestin primed double stimulation protocol and Group II (Flexible antagonist group) including 45 patients were given the flexible GnRh antagonist protocol in 2 cycles. *Results***:** the M2 number and the fertilization rates showed no statistical significance between both groups in the age groups younger or older than 35 years.

Additionally, the resultant embryo number showed no statistically significant difference as well. *Conclusion***:** the progestin used in progestin primed dual stimulation had no negative impact on the ovarian response in poor ovarian responders.

Keywords: progestin primed; poor responders; dual stimulation; flexible; dydrogesterone; Egypt.

Introduction

Poor ovarian responders (PORs) involve 9–24% of patients undergoing invitro fertilization (IVF), meaning that up to one in four patients conceals a poor reproductive prognosis.(1, 2)
In contrast to the single recruitment episode during the menstrual cycle in women, multiple cohorts or 'waves' of antral follicle recruitment have been described(3, 4). Two or three waves Emergence of 4–14 follicles ≥4–5 mm was detected during the interovulatory interval (IOI) in a large population of healthy women. 68 % of women have two waves of follicle recruitment during the IOI, while the remaining 32 % of women have three waves. In women with two follicular waves, an anovulatory wave emerged at the time of ovulation (i.e., early-luteal phase) followed by emergence of the ovulatory wave during the early-follicular phase. In women with three waves, an anovulatory wave emerged at the time of ovulation, a second anovulatory wave emerged during the mid- to late-luteal phase and a third wave (the ovulatory wave) emerged in the early to mid-follicular phase(4).

From the start of the era of ART, controlled ovarian hyperstimulation was timed at the onset of the follicular phase for two primary reasons: First, to ensure that fresh embryo transfers took place during the receptive endometrial period; Second, the gonadotrophins had to act on antral follicles present in the early follicular phase for the fear that other hormonal environment—i.e., progesterone elevation— might negatively affect the quality of the harvested oocytes.

Two main factors have modified the terms of this concept that have controlled the stimulation protocols over the past years:

1. The introduction of embryo vitrification replacing cryopreservation by the slow freezing approach. This allowed the clinicians to have, and deferred embryo-transfers provide either improved or equal results as fresh transfer—based on the patient population—but never inferior results (5, 6)
2. The emergence of new trends in understanding of human ovulation as the multiple waves theory of ovulation (4)

Two consecutive ovarian stimulation protocols could be initiated in the follicular phase and the subsequent luteal phase. In the first report of this strategy—the Shanghai protocol—. more oocytes from the luteal phase OS were retrieved than the follicular phase. It was hypothesized follicular phase stimulation exerted a priming effect on the ovarian response(7).

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It has been noticed that that the follicular and luteal phase OS yielded a similar number of blastocysts.(8, 9)Moreover, Ubaldi et al have confirmed that follicular phase and luteal phase stimulations have yielded similar number of euploid blastocysts.(9)

The dual ovarian stimulation protocol is an effective way to increase the number of oocytes and embryo obtained over a relative short period of time. It has its place when the number of oocytes needs to be optimized over a short period of time, as in fertility preservation and in certain cases of poor responders.

Furthermore, there is increasing evidence that progestins can be a reliable method of preventing the premature LH surge during OS.(10, 11)

Recently, progestins as uterogestan and dydregesterone have been shown to be an effective oral alternative for preventing premature LH surges during ovarian stimulation in women undergoing IVF, with optimal reproductive outcomes in frozen-thawed embryo transfer (12-14).

Objective

The present study was conducted to investigate the effect of the progestin used, Dydrogesterone, in the progestin primed dual stimulation protocol in poor ovarian responders on the ovarian response.

Methods

Study design, setting and participants

The present study was a prospective study where randomization of patients was computer based in a serial manner. The sample size was calculated by the Department of Medical Statistics, Medical Research Institute, Alexandria University, Egypt. It was stated that A minimal total sample size of 60 infertile women indicated for ICSI with criteria of poor ovarian response defined by Bologna criteria [30 per group] is needed to detect an assumed significant proportional difference in the fertilization rate between group (1) and group (2); taking in consideration 80% power and 5% level of significance using Chi square test(15). (PASS program version 20) with numeric results

Power	n	k	N	Alpha	Beta	E(S)
0.80	30	2	60	0.05	0.20	24.38

The participants: 90 infertile women indicated for ICSI with criteria of poor ovarian response defined by Bologna criteria in a university fertility center and private IVF center in Alexandria starting from 2020 till 2021 were further subdivided into 2 groups.

Patient allocation: patients were allocated to the progestin primed dual stimulation and flexible antagonist groups (after being eligible by meeting both inclusion and exclusion criteria described later) in a serial randomization pattern using the computer. One patient is allocated to the intervention group and the next one to the non-intervention group in repeated sequence until completing sample size studied.

Inclusion criteria:

1. Indicated infertile women for ICSI of poor responders defined by Bologna criteria(16) either two or more of the following:
   (i) Advanced maternal age or any other risk factor for POR.
   (ii) A previous POR; less than 3-5 oocytes retrieved per cycle.
   (iii) An abnormal ovarian reserve test (ORT): AFC less than 5-7 or AMH was less than 1.1 ng/ml.

   Or two episodes of POR after maximal stimulation were sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

Exclusion criteria:

1. Male factor infertility due to azoospermia.
2. Patients with uncorrected uterine pathology.
3. Patients with the diagnosis of severe endometriosis.
4. Patients with BMI over 35.

Group 1: Controlled ovarian hyper-stimulation with 225-375 IU of gonadotropins was started day 2-3 of menses. Duphaston at 20 mg/day was started from the first day of the ovulation induction. Decapeptyl in a dose of 2 ampules of 0.2 mg was administered when leading follicle >18 mm in diameter for triggering. Then, Controlled ovarian hyper-stimulation the next day after the previous oocyte pickup simultaneously with Duphaston. Embryo transfer in a subsequent cycle was scheduled on Day 3, 4 or 5 with maximum number of 3 class A embryos whether of cleavage or blastocyst stage.

Group 2: This step was done twice in two different cycles. In each cycle. Controlled ovarian hyper-stimulation using antagonist protocol was used. Stimulation with 225-375 IU of gonadotropins was started day 2-3 of menses. Cetrotide ampule was given daily as the biggest oocyte reaches size 14 mm. ovulation triggering was administered when the leading follicle >18 mm in diameter. Embryo transfer was scheduled on Day 3, 4 or 5 with maximum number of 3 class A embryos.

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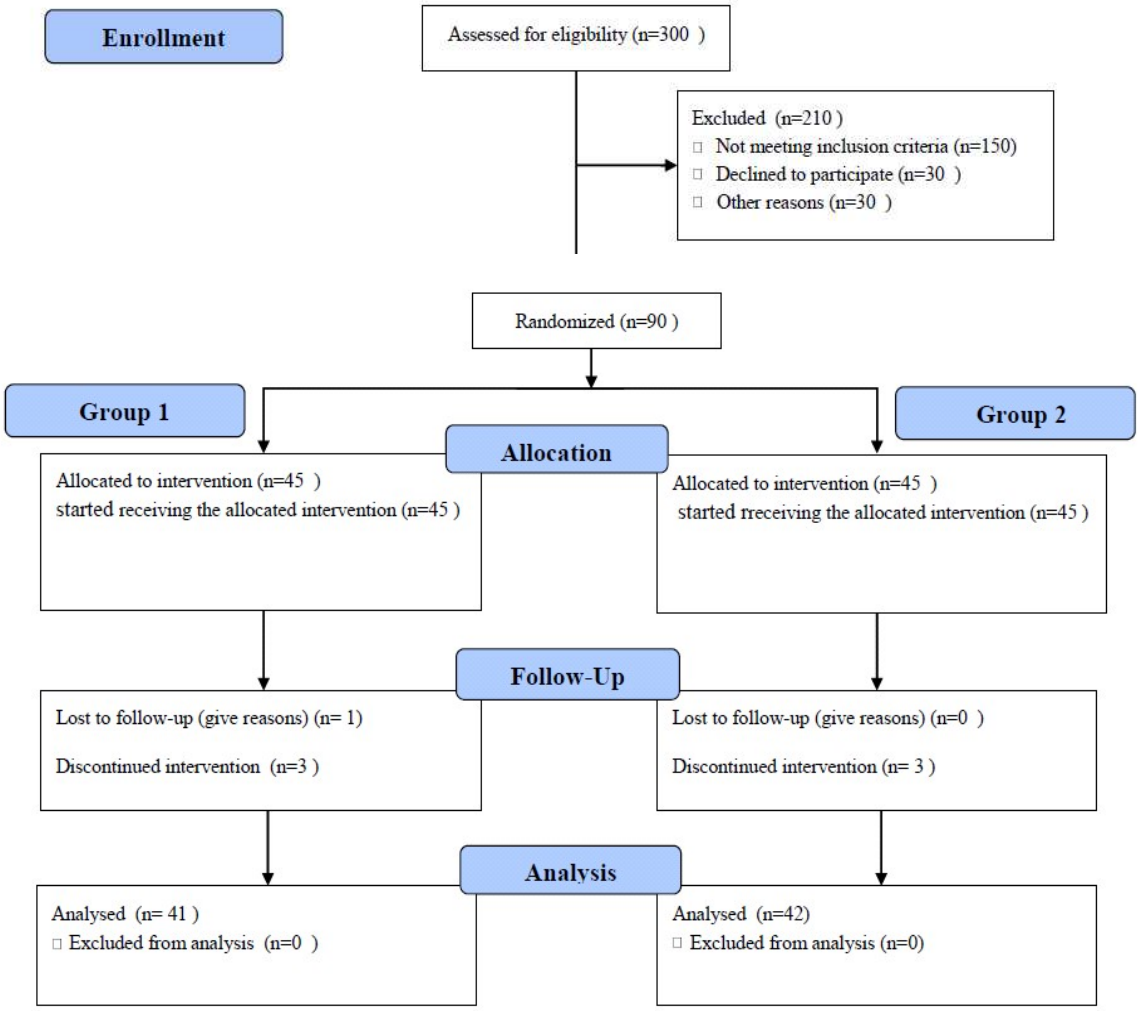
CONSORT diagram of the Design: Randomized Control trial (Figure 1)



Statistical analysis of the data

Data were fed to the computer and analyzed using The IBM SPSS software package version 20.0.(Armonk, NY: IBM Corp) is used to introduce the data to the computer and interpret it as well. Illustrating the qualitative data was performed by adopting number and percent. Establishment of

the normality of distribution was done by using the Kolmogorov-Smirnov test. The range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR) were applied to represent the quantitative data. Significance of the obtained results was judged at the 5% level. To compare between different groups, Chi-square test was applied. Student t-test was used to compare between two studied groups and for normally distributed quantitative variables. The F-test (ANOVA) was used to compare between more than two groups & for normally distributed quantitative variables. Receiver operator characteristic (ROC) curves were also constructed where appropriate.

Results

Table (1): Comparison between the two studied groups according to age and duration of infertility

	Dual (n =41)		**Antagonist (n =42)**		**p**
	No.	**%**	**No.**	**%**	
Age (years)					
<35	22	53.7	20	47.6	0.582
≥35	19	46.3	22	52.4	
Min. – Max.	24.0 – 44.0		22.0 – 46.0		0.287
Mean ± SD.	34.05 ± 5.0		35.48 ± 6.99		
Duration of infertility					
Min. – Max.	1.0 – 23.0		1.0 – 14.0		0.627
Median (IQR)	5.0(3.0 – 6.0)		5.0(2.0 – 8.0)		

SD: **Standard deviation** **IQR: Inter Quartile Range** χ^2: **Chi square test**

t: Student t-test **U: Mann Whitney test**

p: p value for comparing between the studied groups

The mean age of patients in the dual stimulation group was 34.05 ± 5.0 years vs 35.48 ± 6.99 years in the antagonist group with P value 0.582 which did not reach statistical significance.

The median duration of infertility in the dual stimulation group and the antagonist was the same 5 years with P value 0.627.

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Table (2): Comparison between the two studied groups according to lab data

Lab data	Dual (n =41)	Antagonist (n =42)	p
FSH			
Min. – Max.	5.0 – 25.90	5.0 – 19.0	0.335
Median (IQR)	8.0 (6.5 – 8.6)	8.25 (7.0 – 9.0)	
LH			
Min. – Max.	1.90 – 50.30	1.90 – 9.0	0.226
Median (IQR)	3.50 (2.9 – 5.3)	4.10 (2.9 – 5.8)	
TSH			
Min. – Max.	0.04 – 4.70	0.70 – 4.70	0.446
Mean ± SD.	2.15 ± 1.19	2.35 ± 1.23	
PRL			
Min. – Max.	3.80 – 47.0	3.80 – 47.0	0.859
Median (IQR)	21.0 (9.9 – 25.0)	13.15 (9.0 – 27.0)	
AMH			
Min. – Max.	0.15 – 1.05	0.10 – 1.01	0.010*
Median (IQR)	0.60 (0.3 – 0.8)	0.30 (0.2 – 0.6)	

SD: **Standard deviation** **IQR: Inter Quartile Range**

t: Student t-test **U: Mann Whitney test**

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

We have studied the hormonal lab investigation in both group and showed:

The median of FSH value in the dual stimulation group was 8 IU/ml vs 8.25 IU/ml in the antagonist group with P value 0.335 which did not reach statistical significance

The median of LH value in the dual stimulation group was 3.5 IU/ml vs 4.1 IU/ml in the antagonist group with P value 0.226 which did not reach statistical significance

The mean of TSH value in the dual stimulation group was 2.15 ± 1.19 miu/ml vs 2.35 ± 1.23 miu/ml in the antagonist group with P value 0.446 which did not reach statistical significance

The median of PRL value in the dual stimulation group was 21 miu/ml vs 13.15 miu/ml in the antagonist group with P value 0.859 which did not reach statistical significance

The median of AMH value in the dual stimulation group was 0.6 ng/ml which was statistically higher than the antagonist group of median 0.3 ng/ml with P value 0.01

Table (3): Comparison between the two studied groups according to different parameters in the ovarian stimulation phase at age <35 years

	Dual (n =22)	**Antagonist (n =20)**	**p**
Total days of stimulation			
Min. – Max.	17.0 – 31.0	17.0 – 30.0	0.549
Mean ± SD.	22.82 ± 4.38	23.55 ± 3.33	
Total dosage			
Min. – Max.	3300.0 – 11625.0	3900.0 – 8250.0	0.014*
Median	6300.0	6900.0	
Total No. follicles ≥ 14 mm at trigger			
Min. – Max.	4.0 – 26.0	4.0 – 19.0	0.116
Median	9.50	8.0	
Total No. oocytes retrieved			
Min. – Max.	2.0 – 21.0	2.0 – 14.0	0.141
Median	7.0	6.0	
M2 no.			
Min. – Max.	2.0 – 15.0	2.0 – 14.0	0.386
Median	5.50	3.0	
No. fertilized oocytes			
Min. – Max.	0.0 – 14.0	2.0 – 14.0	0.591
Median	4.0	3.0	
Embryos no			
Min. – Max.	0.0 – 9.0	2.0 – 8.0	0.529
Median	4.0	3.0	
Fertilization rate			
Min. – Max.	0.0 – 100.0	57.14 – 100.0	0.165
Median	71.43	80.0	

SD: Standard deviation

t: Student t-test

U: Mann Whitney test

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p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

We have subdivided the patients into POSEIDON group 3 and 4. In this table we have studied the different parameters of the ovarian stimulation phase in both groups, the dual and antagonist group, in patients being younger than 35 years

- we have found that the total days of controlled ovarian hyperstimulation did not statistically differ, in the Dual stimulation group the mean of total days of stimulation was 22.82 ± 4.38 days, while in the antagonist group was 23.55 ± 3.33 days with p value 0.549.
- However, the total dosage of the gonadotropins used was statistically higher in the antagonist group than the dual group with a median 6900 IU vs 6300 IU in the dual group with p value 0.014.
- The total number of follicles ≥14 mm at triggering did not statistically differ between both groups. the median in the dual group was9.5 oocytes vs a median of 8 oocytes in the antagonist group with p value 0.116.
- The total number of retrieved oocytes did not statistically differ. The median in the dual group was 7 oocytes vs a median of 6 oocytes in the antagonist group with p value 0.141.
- The M2 oocytes number showed no statistically significant difference. The median number of M2 oocytes in the dual stimulation group was 5.5 while the median number of M2 oocytes in the antagonist group was 3 with P value 0.386
- The total number of fertilized oocytes did not show statistically significant difference between both groups. the median of the fertilized oocytes in the dual group was 4 oocytes vs a median of 3 oocytes in the antagonist group with p value 0.591
- The resultant embryos number did not show statistically significant difference between both groups. The median of the resultant embryos number in the dual group was 4 embryos vs a median of 3 embryos in the antagonist group with p value 0.529
- The fertilization rate showed no statistically significant difference. The median of the fertilization rate was 71.43 % in the dual group while the median of the fertilization rate was 80 % in the antagonist group with P value 0.165.

Table (4): Comparison between the two studied groups according to different parameters in the ovarian stimulation phase at age ≥35 years

	Dual (n =19)	Antagonist (n =22)	p
Total days of stimulation			
Min. – Max.	18.0 – 31.0	18.0 – 28.0	0.146
Mean ± SD.	22.74 ± 3.30	21.36 ± 2.63	
Total dosage			
Min. – Max.	4275.0 – 7800.0	4050.0 – 9000.0	0.358
Median	6600.0	6000.0	
Total No. follicles ≥14 mm at trigger			
Min. – Max.	6.0 – 23.0	4.0 – 14.0	0.008*
Median	12.0	10.0	
Total No. oocytes retrieved			
Min. – Max.	4.0 – 15.0	2.0 – 11.0	0.011*
Median	9.0	6.50	
M2 no.			
Min. – Max.	2.0 – 12.0	2.0 – 11.0	0.322
Median	7.0	6.0	
No. fertilized oocytes			
Min. – Max.	2.0 – 11.0	1.0 – 10.0	0.389
Median	5.0	5.0	
Embryos no			
Min. – Max.	2.0 – 11.0	1.0 – 9.0	0.335
Median	4.0	3.50	
Fertilization rate			
Min. – Max.	57.14 – 100.0	37.50 – 100.0	0.873
Median	71.43	82.58	

SD: Standard deviation t: Student t-test U: Mann Whitney test

p: p value for comparing between the studied groups

*: Statistically significant at p ≤ 0.05

In this table we have studied the different parameters of the ovarian stimulation phase in both groups, the dual and antagonist group, in patients being ≥ 35 years.

- We have found that the total days of controlled ovarian hyperstimulation did not reach statistically significant difference, in the Dual stimulation group the mean of total days of stimulation was 22.74 ± 3.30, while in the antagonist group was 21.36 ± 2.63 with p value 0.146.
- The total dosage of the gonadotropins used was not statistically different between the two groups. The median of the gonadotropins used in the dual group was 6600 IU while

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the median of the gonadotropins used in the antagonist group was 6000IU with P value 0.358

- However, we have found the total number of follicles ≥ 14 mm at triggering was in the dual group was statistically significantly higher than the antagonist group with median of 12 oocytes vs a median of 10 oocytes in the antagonist group with p value 0.008.
- Additionally, the total number of retrieved oocytes in the dual group was statistically significantly higher than the antagonist group with a median of 9 oocytes vs a median of 6.5 oocytes in the antagonist group with p value 0.011
- The M2 oocytes number showed no statistically significant difference. The median number of M2 oocytes in the dual stimulation group was 7 oocytes while the median number of M2 oocytes in the antagonist group was 6 oocytes with P value 0.322
- The total number of fertilized oocytes did not show statistical significance between both groups. The median of the fertilized oocytes in both groups were the same 5 fertilized oocytes with P value 0.389
- The resultant embryos number did not show statistically significant difference between both groups. the median of the resultant embryos number in the dual group was 4 embryos vs a median of 3.5 embryos in the antagonist group with p value 0.335
- The fertilization rate showed no statistically significant difference. The median of the fertilization rate was 71.43 % while the median of the fertilization rate was 82.58 % with P value 0.873.

Discussion

The goal of the ART is the live birth of a healthy single baby, achieved with reduced time to pregnancy and costs, and increased patient`s safety. Unfortunately, the management of poor ovarian responders is an everyday practice challenge and is frustrating to the patient and the fertility expert.

The use of progestin has been suggested nowadays for pituitary suppression especially when no fresh embryo transfer was intended. In our research, we have explored the effect of the progestin used, Dydrogesterone, in the progestin primed dual stimulation in poor ovarian responders against conventional follicular antagonist.

Consequently, we have used dydrogesterone 20 mg/day in the dual stimulation group for pituitary suppression. As to study the effect of the progestin used on the ovarian response and the resultant embryos in poor ovarian responders, we have compared the progestin primed dual stimulation against the GnRh antagonist protocol.

A prospective controlled study carried by Iwami et al, poor ovarian responders were allocated to either a progestin primed stimulation using dydgesterone 20 mg/day starting on day 2 or 3 of the menses, as used in our study, or a GnRh antagonist protocol.(17) They have found that there was no significant difference in duration of stimulation, the M2 oocytes number, the fertilization rate and

the resultant embryos number coinciding with our findings. However, they have noticed that the dosage of gonadotropins was significantly higher in cases with the dydrogesterone usage. The mean of total gonadotropins used in the progestin primed stimulation was 1957.30 ± 682.86 IU against the mean of total gonadotropins used in conventional antagonist protocol of 1519.84 ± 541.86 IU with p value <0.001. while we have documented that in the age group<35 years the median of total gonadotropins used in the progestin primed stimulation was 6300 IU while the median in the antagonist group was 6900 IU with P value 0.014 which showed statistical significance while in the age group ≥35 years median of total gonadotropins used in the progestin primed stimulation was 6600 IU while the median in the antagonist group was 6000 IU with P value 0.358 which showed no statistical significance (17).

The recent systematic reviews and meta-analyses by Ata et al and Cui et al have found no statically significant differences in the total days of stimulation or the total dosage of the gonadotropins or the M2 oocytes number between the progestin primed stimulation and GnRh antagonist protocols.(18, 19) These findings coincided with our findings regarding the total days of stimulation and the M2 oocytes number. However, we have documented that, in the age group<35 years, the total gonadotropins used in the progestin primed stimulation was statistically lower than in the antagonist group while this was not the case in the age group ≥35 years, no statistical difference was found between the two groups. Nevertheless, Cui et al have found a statically increase in number of embryos in progestin primed protocol, However, no statistical difference in the number of embryos between the two groups in both age groups.(18, 19)

However, we have found, in the age group ≥35 years, the number of retrieved oocytes after the dual stimulation protocol was significantly higher than the antagonist protocol which was not the case in the age group<35 years. We have postulated that dual stimulation protocol might be advisable option in patients of the age group ≥35 years, yet it is in great need of multi center randomized controlled study to verify our postulation.

Conclusions

From our study, we may conclude that the use of progestin in progestin primed dual stimulation protocol in poor ovarian responders carries no negative impact on the ovarian response. Additionally, the progestin primed dual stimulation shows hope in the management of those patients. We shall recommend for Further multicentric randomized controlled studies are needed to verify the progestin primed dual stimulation as a first choice in management of poor ovarian responders.

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Conflict of interest

The authors declare no conflict of interest.

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