

*Research Article*

## Double stimulation (Duo Stim) versus conventional controlled ovarian hyperstimulation in improving pregnancy rate in poor responders undergoing ICSI



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### Abstract

**Objectives:** To compare conventional long protocol versus Duostim protocol to improve pregnancy rate in poor responders undergoing ICSI. **Patients & methods:** This prospective randomized study included fifty poor responders planned for ICSI in Minia infertility research unit (MIRU) between the period of January 2020 and Desember 2021. The participants were presented in two groups as follow: Group A: include 25 patients used the standard long protocol for controlled ovarian hyperstimulation & Group B: include 25 patients used the double stimulation protocol (Duo Stim) for controlled ovarian hyperstimulation. **Results:** Our results observed that both groups were comparable as regards to their baseline characteristics. The chemical pregnancy rate was insignificantly ( $P= 0.306$ ) higher in the Duostim group than the long protocol group. It was 28% in the Duostim group and 16% in the long protocol group. The clinical pregnancy rate was insignificantly ( $P= 0.44$ ) higher in the Duostim group than in the long protocol group. It was 20% in the Duostim group and 12% in the long protocol group. **Conclusion:** Duostim protocol is apromising protocol in poor responders

**Keywords:** luteal phase; Duosim; ICSI

### Introduction

The field of assisted reproductive technologies great steps forward have been made in recent years in terms of clinical knowledge and technological development especially in IVF laboratories. One of the fundamental steps to reach the success is still related to the number of eggs obtained after hormonal stimulation by gonadotropins in combination with GnRH analogues. In patients defined “poor responders,” the limited number of obtained eggs remains the main problem in optimizing the live birth rates. In fact, as a result of a lower number of oocytes retrieved, there are fewer embryos to select and transfer and subsequently these patients have lower pregnancy rates per

transfer and lower cumulative pregnancy rates per started cycle compared with normal responders. Although the concept of poor ovarian response was introduced over 30 years ago, we had not had a common definition of poor responder patients until 2011. In fact, Polyzos & Devroey<sup>(1)</sup> emphasized enormous variability of the definitions of poor responder patients proposals from the literature (in 47 randomized trials, 41 different definitions).

These results confirm the difficulty in obtaining an exact incidence of this condition (that has been estimated at 9–24% but it seems to be slightly increased in the last decade<sup>1</sup> the incapacity to compare the results of different trials and therefore

to identify the best treatment. Recently, the ESHRE working group on poor ovarian response has finally given a common definition of “poor responder,” where at least two of the following three features must be present: (a) advanced maternal age or any other risk factor for poor ovarian response (POR); (b) a previous POR; and (c) an abnormal ovarian reserve test<sup>(1)</sup>.

### Patients and methods

This prospective randomized study included fifty poor responders planned for ICSI in Minia infertility research unit (MIRU) between the period of January 2020 and Desember2021.

The participants were presented in two groups as follow:

- **Group A:** include 25 patients using the standard long protocol for controlled ovarian hyperstimulation.
- **Group B:** include 25 patients using the double stimulation protocol (Duo Stim) for controlled ovarian hyperstimulation consisting of 2 phases follicular and luteal stimulation.

**Inclusion Criteria:** all of the following criteria were to be fulfilled in women that were willing to do intracytoplasmic sperm injection with embryo transfer (ICSI-ET)

- Age 18 – 44 years old.
- Previous poor response, defined as a cycle previously cancelled because of absent ovarian response or if fewer than 5 oocytes were retrieved.
- AMH <1.2 (ng/ml)
- BMI >18,5 and <35 kg/m<sup>2</sup>
- normal hormonal profile (FSH, LH, PRL), normal ovarian ultrasound, normal pelvic ultrasound,

**Exclusion Criteria:**

- Age > 44 years or <18 years.
- Women with a known medical disease (e.g. severe hypertension or hepatic disease),
- history of altered karyotype in one or both partners
- Women with ovarian cyst, endometriosis stage III/IV, concurrent uterine pathology (e.g. adenomyosis, submucosal myomas, Asherman’s syndrome), sexually transmitted diseases, current or previous cancer diagnosis.

- History of untreated autoimmune, endocrine, or metabolic disorders
- Previous ovarian cystectomy or oophorectomy
- BMI <18,5 and > 35 kg/m<sup>2</sup>
- Polycystic Ovarian Syndrome and Premature Ovarian Insufficiency were further considered as exclusion factors.

### Results

Out of the 56 patients enrolled for this study, six were excluded because of no response to the stimulation. The non-responding patients in the FP stimulation did not undergo LP stimulation, Leaving 50 participants for randomization with 25 assigned to each group.

**As regards baseline characteristics: (table 1 & fig. 1)**

Both groups were comparable with regard to their baseline characteristics. There was no statistically significant difference (p-values > 0.05) between the two groups regarding the age, BMI, the duration of infertility, and the number of previous cycles with a poor response.

The average age of the 50 patients was  $35.31 \pm 7.27$  years for the long protocol and  $37.54 \pm 6.99$  years for the Duostim protocol.

As regards BMI (kg/m<sup>2</sup>), it was  $24.39 \pm 1.52$  for the long protocol and  $25.06 \pm 3.47$  for the Duostim protocol.

The average duration of their infertility period was  $6.62 \pm 2.13$  for the long protocol and  $6.35 \pm 2.01$  for the Duostim protocol.

As regards number of previous cycles with poor response it was  $2.5 \pm 0.18$  for the long protocol and  $2.56 \pm 0.28$  for the Duostim protocol

**Ovarian induction & ICSI parameters (table 2, fig. 2, 3)**

The number of ovarian stimulation days was significantly different between both groups (p-value < 0.0001), it was  $12.62 \pm 1.05$  days for the long protocol group &  $22.28 \pm 2.5$  days for the Duostim group, respectively.

The oocyte retrieved number was significantly (p-value = 0.0015) higher in the Duostim group  $3.9 \pm 2.3$  than in the long protocol group  $1.4 \pm 1.2$ . Furthermore, the mean number of MII oocytes was significantly (p-value = 0.0001) higher in the Duostim group  $3.3 \pm 1.36$  than in the long protocol group  $2.29 \pm 1.24$ .

The number of transferred blastocysts was significantly (p-value = 0.0001) higher in the Duostim group  $2.2 \pm 0.8$  than in the long protocol group  $1.1 \pm 0.9$ .

The mean number of the good embryo grade (G1) was  $0.7 \pm 1.0$  in the long

protocol group and  $1.2 \pm 1.5$  in the Duostim group (p-value = 0.172).

#### Fertilization and pregnancy rates:

##### (table 3, fig. 4)

The fertilization rate was comparable (p-value = 0.56) between groups. It was 60 % in the long protocol group versus 68% in the Duostim group.

The chemical pregnancy rate was insignificantly (p-value = 0.306) higher in the Duostim group than in the long protocol group. It was 28% in the Duostim group and 16% in the long protocol group.

**Table (1):** Baseline characteristics of both groups.

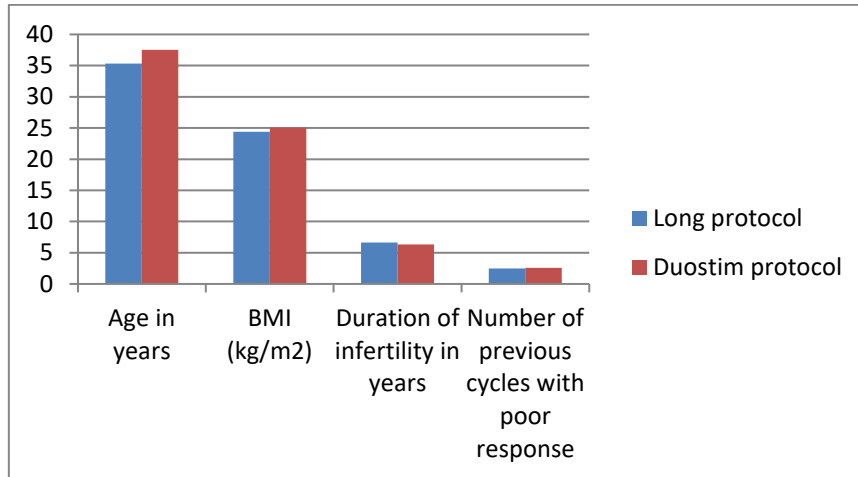
	Long protocol N=25	Duostim protocol N=25	p-value
Age in years mean $\pm$ SD	$35.31 \pm 7.27$	$37.54 \pm 6.99$	0.265
BMI (kg/m <sup>2</sup> ) mean $\pm$ SD	$24.39 \pm 1.52$	$25.06 \pm 3.47$	0.120
Duration of infertility in years mean $\pm$ SD	$6.62 \pm 2.13$	$6.35 \pm 2.01$	0.417
Number of previous cycles with poor response mean $\pm$ SD	$2.5 \pm 0.18$	$2.56 \pm 0.28$	0.113

**Table (2):** Ovarian induction, ICSI parameters.

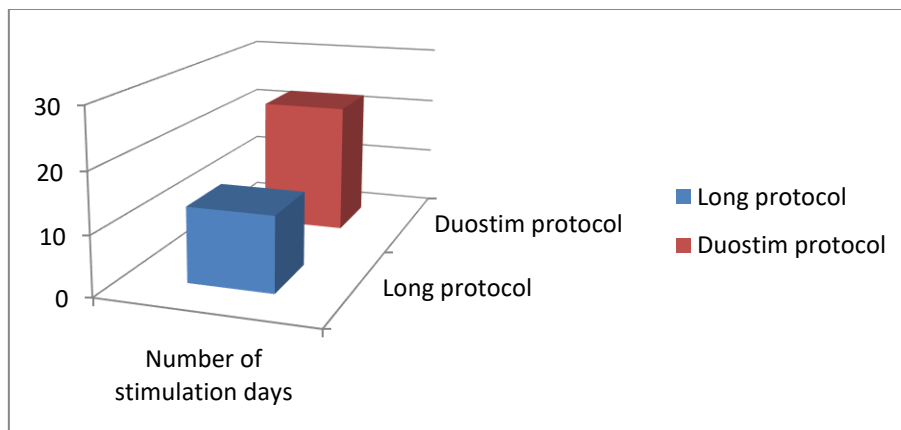
	Long protocol N=25	Duostim protocol N=25	p-value
Number of stimulation days mean $\pm$ SD	$12.62 \pm 1.05$	$22.28 \pm 2.5$	<0.0001
Oocyte retrieved number mean $\pm$ SD	$2.6 \pm 1.8$	$5.2 \pm 3.4$	0.0015
MIII oocytes mean $\pm$ SD	$1.4 \pm 1.2$	$3.9 \pm 2.3$	0.0001
Number of transferred blastocysts mean $\pm$ SD	$1.1 \pm 0.9$	$2.2 \pm 0.8$	0.0001
Number of good quality embryo mean $\pm$ SD	$0.7 \pm 1.0$	$1.2 \pm 1.5$	0.172

**Table (3):** Fertilization and pregnancy rates.

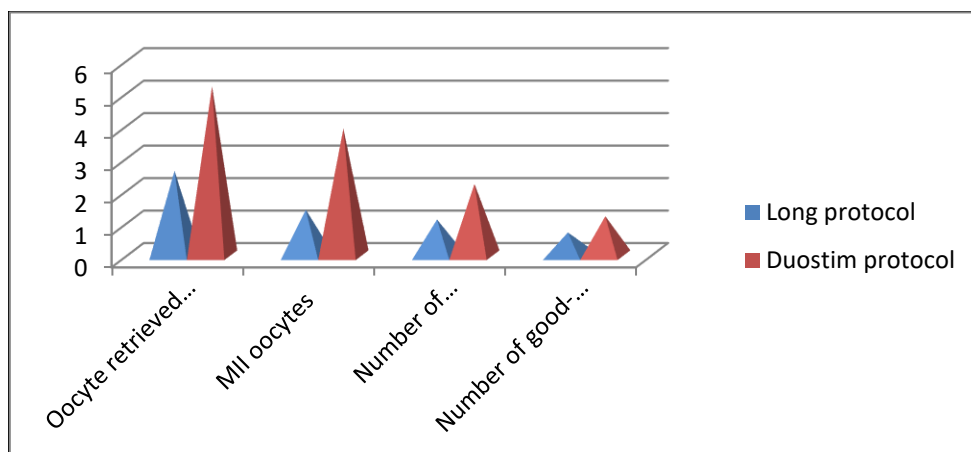
	Long protocol N=25	Duostim protocol N=25	p-value
Fertilization rate, n (%)	15 (60%)	17 (68%)	0.56
Chemical pregnancy rate, n (%)	16% (4)	28% (7)	0.306
Clinical pregnancy rate, n (%)	12% (3)	20% (5)	0.44



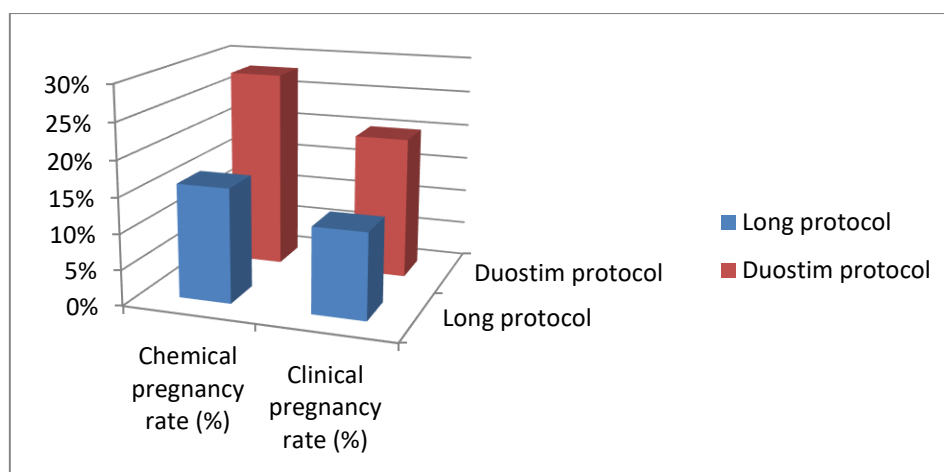
**Figure (1): Baseline characteristics of both groups.**



**Figure (2): stimulation days of both groups**



**Figure (3): ICSI parameters of both groups**



**Figure (4): pregnancy rates**

### Discussion

To date, the management of PORs still represents a clinical challenge. As was recently reviewed<sup>(2)</sup>, despite the fact that in the last two decades an enormous number of papers on the topic of poor ovarian response have been published, so far it has been impossible to identify any efficient treatment to improve the ovarian response and the clinical outcome of this group of patients. To the best of our knowledge, optimistic data have been published regarding the use of high doses of gonadotropins, flare-up GnRH analogue protocol (standard or microdose), stop protocols, luteal onset of GnRH analogue, and short protocol<sup>(3)</sup>.

In addition, the natural cycle or a modified natural cycle<sup>(4)</sup> was proposed as an appropriate strategy. Zargar et al.,<sup>(5)</sup>, compared conventional protocol versus Duostim group, found that Percentage of MII was higher in Duostim group (60.82%) than conventional protocol (45.24 %;  $P=0.02$ ), Assessment of in-vitro embryo quality showed that the percentage of good to highest quality embryos with grade 1 to 3 in women underwent Duostim protocol (93.44%) was significantly higher than their percentage in women underwent conventional IVF protocol (68,42%;  $P=0.009$ ). Also, the success rate of clinical pregnancy was higher in women underwent Duostim induction (42.50%) than those underwent conventional IVF (19.05%,  $P=$

0.03). but in our results clinical pregnancy rate was less, it was 20% in Duostim group and 12% in conventional group. Also, they disagreed with our results as they found that the number of retrieved oocytes were significantly higher in conventional group ( $2.43 \pm 1.33$ ) than Duostim group ( $1.76 \pm 0.93$ ,  $P=0.02$ ), in our study number of retrieved oocytes were significantly higher in Duostim group ( $P=0.0015$ ).

Also, our results resemble de Almeida Cardoso et al<sup>(6)</sup>, who studied 13 patients who underwent unsuccessful in vitro fertilization (IVF) cycles with a conventional antagonist ovarian stimulation protocol and repeat the attempt with a double stimulation protocol, they found that The mean number of oocytes collected was 6.7 in the antagonist cycle and 11.7 in the DuoStim group ( $P=0.007$ ). Of the oocytes collected, the mean number of mature oocytes in the conventional group was 5.3, while in the DuoStim it was 9.23 ( $P=0.01$ ). There was no statistical difference in the rates of fertilization (73.6% (51/69), 75.8% (91/120),  $P=0.78$ ) for conventional and Duostim group, respectively.

Liu et al.,<sup>(7)</sup> suggested that Duostim induction might be a promising alternative or a rescue approach for poor responders as their study demonstrated that the oocytes retrieved and available embryos in Duostim group were more than double those

originating from conventional stimulation. The number of ovarian stimulation days was significantly higher in Duostim group than conventional group ( $p < 0.001$ ), it was  $15.26 \pm 4.90$  days and  $8.26 \pm 3.52$  days for the Duostim group & the conventional group, respectively. Oocyte retrieved number was significantly higher in Duostim group than conventional stimulation ( $P = 0.001$ ), It was  $5.47 \pm 4.20$  and  $2.19 \pm 1.67$  for the Duostim & the conventional group, respectively. The number of MII oocytes was significantly higher in Duostim group  $4.22 \pm 4.05$  than conventional group  $1.84 \pm 1.78$ . Top quality embryo of Duostim group is higher than conventional group it was  $2.33 \pm 2.39$  &  $1.10 \pm 1.67$  respectively, On contrast: Massin et al.,<sup>(8)</sup> found that the ongoing pregnancy rate in conventional group was 29.3% (12/41) was higher than Duostim group 17.9% (7/39  $P = 0.23$ ). Also, some results showed clinical pregnancy rate higher than our results as<sup>(9)</sup> clinical pregnancy rate was 52.6% (30 /57), and <sup>(10)</sup> Clinical pregnancy was observed in 13 of 38 cases representing a clinical pregnancy rate per transfer of 34.2% (13/38).

Some results were different from our results as Anzawa et al.,<sup>(11)</sup> who conducted that, the average number of eggs acquired per cycle was 6.9 in the Conventional group and 3.5 in the Duostim group, and the egg maturation rate was 88% in the Conventional group and 95.7% in the DS group, which showed significant differences. The blastocyst arrival rate and Day 5 good blastocyst arrival rate in the obtained mature eggs were 66.5%, and 38.3% in the Conventional group and 70.5%, and 34.4% in the Duostim group and were not significantly different. Rates of clinical pregnancy and post-transplantation miscarriage were 41.1% and 17.8% in the Conventional group and 16.6% and 0% in the Duostim group, respectively, with no significant difference, although rates in the Conventional group tended to be better.

### Conclusion

Duostim protocol appears to be particularly feasible in the case of urgent fertility preservation such as in cancer patients,

when there is insufficient time for conventional follicular phase oocyte retrieval before chemotherapy must be initiated. Also luteal phase stimulation is comparable to follicular phase stimulation

### Conflict of interest:

The authors declare no conflict of interest.

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