

## The Minimal Stimulation Protocol for ICSI: An Alternative Protocol for Ovarian Stimulation

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**Abstract: Background:** The long agonist protocol has become the standard protocol in the IVF unit all over the world, because it associated with highest pregnancy outcome. In other hand the long agonist protocol is extremely complex and costly, creating considerable side effects, risk of complications notably ovarian hyper stimulation syndrome and twins pregnancy. So an alternative protocol for minimal stimulation IVF was developed to alleviate some of concerns associated with long agonist protocol. **Setting;** Azhar ART unit. **Patient and methods;** A retrospective study carried out at Azhar ART unit in the period from January 2012 to April 2013, in which 100 women with good prognosis were recruited for ICSI, they were classified into; 50 patients were received the minimal stimulation protocol and 50 patients were received long agonist protocol. The outcome measures were duration of stimulation, number of HMG ampules, total number of oocyte retrieved, total number of embryos available for transfer, number of transferred embryos and pregnancy outcome. **Results;** the duration of stimulation was significantly shorter in the minimal stimulation protocol, as well as number of HMG ampules was significantly lower in the minimal stimulation protocol. The incidence of ovarian hyper stimulation syndrome and twins pregnancy were significantly lower in the minimal stimulation protocol, but cancellation rate were significantly higher in the long agonist protocol (25 %). As regard clinical pregnancy outcome per embryo transfer, there were no significant differences between minimal stimulation protocol and long agonist protocol (35% vs 40%), but the pregnancy outcome per initiated cycle was significantly higher in the long agonist protocol. **Conclusions;** The minimal stimulation protocol is associated with minimal side effects, lower cost and comparable pregnancy outcome per embryo transfer, and can be used as alternative for long protocol in the selected patients. [Adel elsayed Ibrahim. **The Minimal Stimulation Protocol for ICSI: An Alternative Protocol for Ovarian Stimulation.** *N Y Sci J* 2014;7(4):19-23]. (ISSN: 1554-0200). <http://www.sciencepub.net/newyork>. 4

**Keywords:** ICSI, long protocol, short protocol, minimal stimulation protocol, OHSS, multiple pregnancies

### 1. Introduction

The IVF was introduced for clinical practice by Edward and Stepto in 1978 and since this time until now thousands of people has been delivered by this amazing technology (1). The ovarian stimulation is a basic step in assisted reproduction, which has been evolved since born of 1<sup>st</sup> IVF baby (louse Brown) in England in 1978 through fertilization of single preovulatory follicle achieved by natural cycle(1). Subsequent IVF pregnancy was reported from Australia to occur after ovarian stimulation by clomiphene citrate (2, 3). In the USA human menopausal gonadotropin was introduced for superovulation in the IVF practice either alone or in conjunction with clomiphene citrate which has produced a good number of follicles and more embryos for transfer which led to increases pregnancy outcome(4). The main drawback of the previous protocol is a premature LH surge which has reported in about 25 % of cases (5). In the later years, GnRh agonist has been introduced for clinical practice which has been led to complete prevention of premature LH surge, and associated with highest pregnancy outcome. With time the agonist long protocol has become the standard protocol in most of

IVF center around the world. Unfortunately the long agonist protocol become extremely complex and costly, creating considerable side effects, risk of complications (Ovarian hyper stimulation and multiple pregnancy and the need of intense monitoring of ovarian response. (6:8). Furthermore 50 % of retrieved oocytes with standard protocol were aneuploidy oocytes which explained the discrepancy between number of obtained oocytes and pregnancy outcome (9). With advent in the IVF practice, increases efficiency of embryological lab procedures, improving the culture media, and a trends towards single embryo transfer, and cost reduction of IVF. It has been a trend towards simple protocol with minimal cost, minimal side effects (multiple pregnancy as well as ovarian hyper stimulation syndrome) and associated with reasonable pregnancy outcome(10). With time the minimal stimulation protocol is becoming popular and several recent publications have described the success with this protocol (11:16).

The our aim to compare minimal stimulation protocols and standard long protocols

## 2. The patients and methods

This study is a retrospective study carried out at Azhar ART unit in the period from January 2012 until April 2013, in which 100 women scheduled for ICSI has recruited, the inclusion criteria was patient age less than 35 years, BMI was less than 30, male factor infertility rather than azospermia, female factors rather than uterine factors, FSH less than 10 IU/ml, the exclusion criteria were azospermia, severe male factor infertility, endometrial polyp, sub mucus myoma, endometrial septum, FSH more than 10, BMI more than 30, age more than 35 years. The patients were divided into; 50 patients received long agonist protocols, and 50 patients received minimal stimulation protocols;

In the minimal stimulation protocol, the patients received oral contraceptive pills for 21 days to induce endogenous suppression of FSH and LH. The clomiphene citrate 50 mg twice daily for 5 days was introduced in the third day of menses and HMG 2 amp/day started at day 8<sup>th</sup> and folliculometry started at day 11<sup>th</sup> daily until dominant follicles reaches 17 mm. The LH measured in the blood and urine, if LH surge documented, the cycle was cancelled, and another trial was done after 2 cycles, if LH was negative triggering of ovulation was done by HCG 10,000 IU and ovum pickup was arranged 34 hours later.

In the long agonist protocol, the down regulation was started in the day 21 by daily injection of triptorelin, when down regulation is completed, as evidenced by E2 level less than 50, thin endometrium and absence of functional cyst, the ovarian stimulation by HMG injection started daily (150- 225 according the age, BMI, pattern of ovarian response in the previous cycle, when 3 DF reached 18 mm in diameter triggering of ovulation was done by HCG 10,000 iu and ovum pickup arranged 36 hrs. later. The ICSI was carried out in the ordinary manner, and then 2-3 grades 1 embryo was transferred under U/S guide in the day 3 after ovum pickup.

Luteal phase support was achieved by using 100 mg/day IM progesterone or progesterone vaginal suppositories 200 mg /12 hours, which continued for 8 weeks if pregnancy test was positive.

Outcome measures; the primary outcome measures was pregnancy outcome, while secondary outcome measures were duration of stimulation, number of HMG ampules, incidence of OHSS,

number of oocyte retrieved, total number of embryos, number of transferred embryos and Cancellation rate.

Statistical methods; Statistical analysis of the present study was conducted using the mean, standard error, student t test, chi-square, linear correlation coefficient and analysis of variance (ANOVA) test by SPSS V19.

## 3. Results

**The table 1**, present the clinical characteristics of patients, there were no significant differences between the two groups regarding, age, BMI, duration of infertility FSH and LH level.

Table 2 which present the clinical outcome, The duration of stimulation was significantly longer in the long agonist protocol if compared with minimal stimulation protocol ( $15 \pm 2.5$  vs  $11.2$ ), also number of HMG ampoules needed for ovarian stimulation was significantly higher in the long agonist protocols if compared with minimal stimulation protocols ( $30 \pm 5.2$  vs  $5 \pm 2.1$ ). In the same manner the number of oocytes retrieved were significantly higher in the long agonist protocol if compared with minimal stimulation protocol ( $13.47 \pm 4.7$  vs  $5 \pm 1.8$ ). Also the number of obtained embryo were significantly higher in the long agonist protocol if compared with minimal stimulation protocol ( $7 \pm 2.7$  vs  $2 \pm 0.8$ ). As regard percent of fertilization, it was no significant differences between the two protocol (85 % vs 80%). In the same side the incidence of OHSS was significantly higher in the long agonist protocol if compared with minimal stimulation protocol (5% vs 0%). The cancellation rate was higher in the minimal stimulation protocol if compared with long agonist protocols (25 % vs 8 %, the difference was found to be highly significant. As regard cost, the minimal stimulation was significantly less expensive if compared with long agonist protocol ( $500 \pm 230E$  vs  $2700 \pm 820 E$ ), the difference was found to be highly significant.

As regard pregnancy outcome (pregnancy outcome per embryo transfer, there was no significant difference between the minimal stimulation protocol and long agonist protocol (35 % vs 40 %), but the pregnancy outcome per initiated cycle was significantly higher in the long agonist protocol if compared with minimal stimulation protocol.

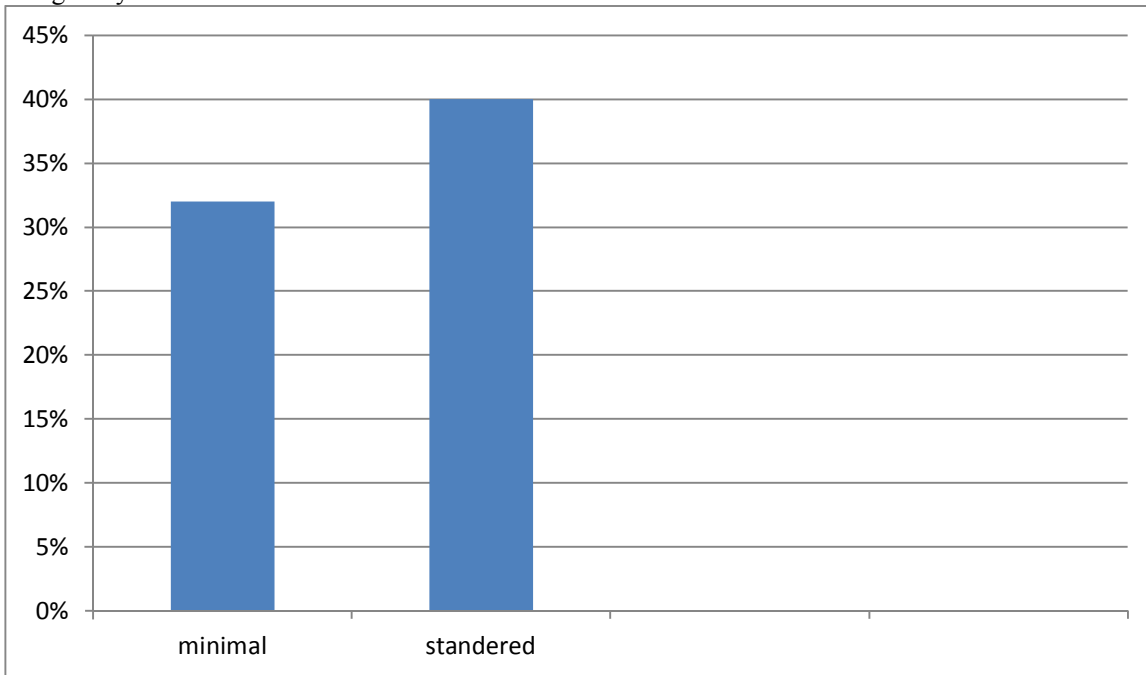
## Clinical characteristics of patients;

	Minimal stimulation	Long agonist protocol	Significance
Age	26 ±3,2	28±2.7	Not significant
BMI	27±3,8	26±2,2	Not significant
Duration of infertility	5±1.8	4,2±1,1	Not significant
FSH	6,2± 2,1	7,2±2,3	Not significant
LH	4,8±2.1	4.1±1,2	Not significant

## Clinical outcome

	Minimal stimulation protocol	Long agonist protocol	Significance
Duration of ovarian stimulation	11 ±2,1	15±2,5	Significant
Dose of HMG	5 ±2,1	30±5,2	Highly significant
Number of oocyte retrieved	5±1,8	13±4,7	Highly significant
Number of grade 1 embryos	2±0,8	7±2,7	Highly significant
Present of fertilization	80%	85%	significant
Incidence of OHSS	0%	5%	Highly significant
Cancellation rate	25%	8%	Highly significant
Coast	500 ±230	2700±820	Highly significant

## Pregnancy outcome



#### 4. Discussion

The minimal stimulation protocol for IVF is not anew topics. It has been used for certain period of time during an early IVF era. It was associated with high cancellation rate due to premature LH surge. This retrospective studies used 100 patients with good prognosis recruited for ICSI , 50 patients were received long agonist protocols and 50 patients were

received minimal stimulation protocol preceded by one pack of oral contraceptive pills for suppression of endogenous LH level.

We found that, the duration of stimulation as well as dose of HMG was significantly lower in the minimal stimulation protocol if compared with standard long agonist protocol (11±2.1 vs 15±2.5, 5±2.1 vs 30±5.2 respectively. Also no cases with

OHSS were reported with the minimal stimulation protocols if compared with standard protocols which associated with high incidence of OHSS (5 %). The most drawback of minimal stimulation protocol is a high cancellation rate due to premature LH surge which was reported in about 25 % of cases in the our work. Also we found that the standard protocol is more expensive if compared with minimal stimulation protocol, the minimal stimulation protocol represents about 20 % of cost of standard protocols. As regard ongoing pregnancy outcome, although the cancellation rate was higher with minimal stimulation protocol about 25 %, but the pregnancy rate per embryo transfer was comparable with standard protocol, there was no significance difference was obtained between two protocol per embryo transfer, but we found that, pregnancy outcome per initiated cycle was higher in the agonist protocol if compared with minimal stimulation protocol due to high incidence of premature LH surge. The our results were in agreement, with a study carried out in 2001(13), they recruited patients with good prognosis for ICSI, they obtained 37% pregnancy outcome with clomiphene citrate .A large Japanese study cohort(11), recruited 7244 patients had 20244 cycles with clomiphene citrate based minimal stimulation or natural cycle , they obtained reasonable pregnancy outcome based on single embryo transfer based on minimal stimulation protocol. Another retrospective study(17) concluded that minimal stimulation protocol based on clomiphene citrate stimulation, given comparable pregnancy outcome with long agonist protocols. Heignen *et al.* (16), compared in a randomized controlled study the success of four cycles of mild IVF with single embryo transfer to three cycles with conventional IVF with transfer with transfer of two embryos. Participant were good prognosis patients for IVF.They found that , pregnancy outcome was lower in the minimal stimulation protocol if compared with conventional protocol but cumulative pregnancy outcome over many cycles including fresh and cryo embryos were not significantly different. However the reported outcome is variable in the literature but in general pregnancy rates appear higher compared to natural cycle, but lower compared to conventional protocol. Again most of studies are uncontrolled but an extensive summary of 40,000 cycles reported in the literature suggested an overall pregnancy rate per embryo transfer of 20 %. The our study has the following limitation, its retrospective study and the number of patients were relatively small, So we need to carry out prospective study using a huge number of cases to confirm efficacy of such protocol.

In conclusion; the minimal stimulation protocol based on clomiphene citrate and HMG stimulation can be a possible alternative for good prognosis patients, but their efficiency need to be confirmed in the larger trial.

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