

GnRH agonist long protocol versus short protocol in women 40 years or more undergoing ICSI: a multicenter study

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ABSTRACT

Objective: to compare results of GnRH agonist long protocol vs. short protocol in women forty years or older undergoing ICS cycles

Setting: multicenter comparative trial

Materials and methods: Participants & Interventions: a total of 531 women ranging between 40-47ys were included in this study. Two hundred eighty five women received long protocol while two hundred forty six women received short protocol. All women had FSH less than 20 before start of treatment. Standard ICSI program was done and follow up for all cases. Women with previous poor response were excluded from the study.

Results: In total, among 531 participants, clinical pregnancy was achieved in one hundred and one women (19%) and miscarriage rate was (32%) mainly in the first eight weeks. There was a wide variation in regarding both protocols (long protocol achieved pregnancy rate of 26.6 % while short protocol achieved only 10.2% pregnancy rate ($P < 0.001$). No cases of severe OHSS were reported. Cost of drugs were significantly reduced with the short protocol ($P = 0.031$)

Conclusion: this multicenter study shows that long protocol of GnRH agonist was better than short protocol in women with age of forty or above.

Numerous demographic studies suggest a consistent decline in fecundity with increasing age (1). About 15% of IVF cycles are in women over 40 and For women $< \text{or} = 35$ years of age the cumulative live birth rate in IVF was 64.6%, for women 36-39 years of age it was 48.7%, and for women 40-42 years of age 31.0% (2). There is a higher chance of the IVF cycle being cancelled before egg collection in women over 40 (22% vs. 12%) (2).

Gonadotropin releasing hormone agonists (GnRHa) are used in assisted reproduction cycles to reversibly block pituitary function and prevent a

luteinizing hormone surge. In the short and ultrashort protocols of GnRHa administration, injection of gonadotropins is commenced a few days after the start of GnRHa. In the long protocols (with GnRHa started either in the midluteal phase or in the early follicular phase) gonadotropin administration is delayed until pituitary desensitization has been achieved, usually 2-3 weeks. (3).

Short protocol for IVF is the traditionally used one in women over forty; however, there is lack of evidence to support the use of short protocol in advanced female age. In fact, on the basis of clinical pregnancy rate per cycle started, long protocol was demonstrated to be better over the short protocol in IVF (4). The aim of the present

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study is to compare results of short vs. long protocols for IVF/ICSI in women over forty

MATERIALS AND METHODS

The present study was a retrospective analysis of women forty years old and above undergoing ICSI cycles in different centers in Egypt (Mansoura Infertility center and Fertility integrated centers) in the period from December 2005 till December, 2006. The inclusion criteria were female age > 40 years old with normal hormonal profile and no pelvic pathology. We included women undergoing first trial of ICSI (or previous trial with good response). We excluded cases with male partner having functional azoospermia. No ethical approval was needed as it is a retrospective analysis of already available data.

Women in Group I (short protocol) received Decapeptyl 0.1mg/day starting on day 1 of the cycle till the day of hCG injection while women received the GnRHa long protocol (Group II), Decapeptyl 0.1mg/day starting on day 20 of the cycle till the day of hCG injection. In this group of patients (group II), after down regulation was confirmed, 300-450 I.U of hMG/day was started for 7 days, then the dose was adjusted according to the response. HCG was given using the same criteria in both groups.

Oocyte retrieval was performed under ultrasound control by the transvaginal route on day 0, 36 hours after the injection of hCG. All patients underwent intracytoplasmic sperm injection (ICSI), according to published procedures (5). Embryo transfer was done on day 2 or 3 after OPU using the Wallace catheter (H.G.Wallace Ltd, West Sussex, UK) or a Cook catheter (Cook, Australia) if the Wallace catheter could not be inserted. Luteal phase support was given routinely in the form of a daily progesterone injection (100 mg, progesterone; Steris, Phoenix, AZ, USA). A serum B-hCG test was done to confirm pregnancy two weeks after embryo transfer. Clinical pregnancy was diagnosed 3 weeks after a positive test by the presence of a gestational sac with fetal echoes and pulsations on ultrasound.

The results of two stimulation protocols were compared with respect to number of follicles greater than 17 mm, peak serum estradiol level,

number of oocytes retrieved and fertilized, fertilization rate per oocyte, number of embryos transferred, and pregnancy rate per initiated cycle.

Statistical evaluation

Data are presented as mean \pm SD. Different outcome measures were compared using Student's t-test or Fisher's exact test where appropriate. P values < 0.05 were considered to be significant. Statistics were done using Arcus Quickstat version I.

RESULTS

A total of 531 women ranging between 40-47ys were included in this study divided into two groups:

Group I (Long protocol) included 285 subjects while group II (short protocol) included 246 subjects. There was no statistically significant difference between the two groups regarding their age, infertility duration and FSH level.

Regarding all women, clinical pregnancy was achieved in 101 women (19%) and miscarriage rate was (32%) mainly in the first eight weeks. No pregnancies were achieved above 43 years. Cancellation rate was higher for Long protocol 19.5% vs. 11% for Short protocol ($P < 0.05$). No single case of severe OHSS was developed and only one twin case was in the long protocol group.

Cost of drugs were significantly reduced with the short protocol ($P = 0.031$) as hMG units were significantly less in short protocol group. However,

Table 1. Outcome measures in both groups

Variable	Short	Long	P value
Age (years)	43 \pm 0.4	42 \pm 1.6	N.S.
Duration (years)	10.2 \pm 3.1	11.3 \pm 4.5	N.S.
FSH	11.8 \pm 1.9	12.4 \pm 2.6	N.S.
hMG units	4260 \pm 585	5730 \pm 1930	0.03
E2	1400 \pm 680	2100 \pm 1230	0.023
Oocytes	5.1 \pm 2.4	9.4 \pm 3.2	0.04
Fertilization rate	43%	62%	0.03
Embryos	3 \pm 1.3	6 \pm 2.4	0.01
ET	2.2 \pm 1.5	4.3 \pm 1.8	0.03
Pregnancy rate	10.2%	26.6%	<0.001
Miscarriage rate	29%	32%	N.S.
OHSS	0	0	

the number of oocytes obtained, fertilization rate, embryos transferred were significantly higher in the long protocol. Clinical pregnancy rate were more than double in the long protocol than in short protocol (Table 1) but miscarriage rate was the same.

DISCUSSION

Fertility declines gradually from the age of 30 years, but decline dramatically after 40 years. Decline may be due to decrease in ovarian reserve with advancing age, or decrease in the quality of oocytes as indicated by the increased incidence of oocyte aneuploidy, or a decrease in endometrial receptivity (6).

The long protocol is the most widely used protocol because it is the best for suppression of endogenous LH levels in normogonadotropic patients (7). Traditionally, the short protocol is used for older women because of well-known 'flare-up phenomenon'. The objective of controlled ovarian hyperstimulation (COH) is to ensure the adequate development of early antral follicles to increase the number of viable oocytes (8).

One of the key points of such a procedure is the achievement of adequate synchronization of follicular growth so that ovulation can be triggered when most follicles have reached concomitant maturation. However, to obtain a good follicular coordination during COH, the nature selection of follicles observed during the early follicular phase should be overcome (9). Our participants were normogonadotropic and GnRH agonist long protocol resulted in better follicular synchronization and more or less symmetrical oocyte development ending into higher number of oocytes that allowed better selection of embryos to be transferred.

Very few studies compared long vs. short protocols in advanced women age and our results are interesting and needs to be confirmed by other investigators. It has been shown that older women (>39 years old) have a shorter follicular phase, probably due to an earlier start of follicular growth during the previous luteal phase, defined as "advanced growth," than in younger patients. Therefore, in older patients it has been shown that the available cohort of antral follicles starting

growth in each cycle is significantly smaller than in younger women (10).

It has been shown that higher doses of GnRH analogue used for desensitization in the long protocol gave better results in terms of number of oocytes and embryos in a normal responder (11). This might be due to the extended time when FSH is above threshold: a longer time of FSH stimulation might allow more follicles to enter the FSH-dependent growth stage and be recruited. This might be the case in our study for older patients treated with the long protocol (12).

Pituitary suppression with long GnRH-a protocol before and/or during ovarian stimulation with hMG resulted in improved clinical pregnancy rates. Follicular recruitment was enhanced, and premature LH surges and follicular luteinization were avoided. Finally, it would be important to note that the numbers of embryos transferred in the two groups were significantly different and that this could be the reason for the increased pregnancy rates in the long agonist group.

In conclusion, this multicenter study shows that long protocol of GnRH agonist was better than short protocol in women with age of forty or above because long protocol produce a cohort of follicles that grow simultaneously and this allows retrieval of more oocytes, production of more embryos with ultimate better pregnancy rate.

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