

Research Article

Modified Fixed Two Step Short Protocol versus Classic Short Protocol in ICSI

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Abstract

Objectives: The objective is to compare the new short protocol with traditional short protocol in ICSI programs.

Study design: Controlled trial.

Materials and methods: 40 cases scheduled for ICSI after a variable period of infertility classified into two groups according to stimulation protocol. group1(20 case) with fixed 2 dose regimen (given merional ampoules) 4 ampoules first four days of stimulation the 3 ampoules thereafter while the other 20 patients given the traditional short protocol starting with 3 ampoules then dose adjusted according to patient response.

Results: Days of stimulation, Number of merional ampoules, were significantly less in the new modified short protocol than in the classic short protocol; while number of M2 oocytes, number of good embryos, pregnancy rate were significantly high in the group 1. Pregnancy rate was 75% in the new modified protocol and 50% with the classic short protocol.

Conclusion: The new short fixed 2 dose short protocol regimen offers a benefit in all the ways in ICSI success and pregnancy rate with less time of gonadotropin stimulation and less cost.

Keywords: Infertility; ICSI; Short protocol; HMG

Introduction

During IVF treatment the primary aim of Controlled Ovarian Hyper-Stimulation (COH) using gonadotrophin injections is to stimulate the development of several mature oocytes, rather than a solitary oocyte that would develop in an unstimulated "natural" cycle.

Because of the considerable natural attrition that occurs during IVF treatment (failed fertilization, poor embryo development), this COH approach maximizes the chances of producing good quality embryos available for transfer or cryopreservation, thereby ultimately boosting pregnancy rates.

The production of less than five oocytes has been shown to significantly reduce a woman's chances of a live birth [1,2] while the development of more than 15 oocytes places her at considerable risk of potentially dangerous Ovarian Hyper-Stimulation Syndrome (OHSS).

Three decades after the birth of the first IVF baby, poor response to ovarian hyperstimulation still remains a frustrating limiting factor for IVF programs throughout the developed world.

The "standard" approach to predicting a patient's response to COH has been based on age and early follicular phase FSH levels. Good prognosis patients (age <36 years, normal FSH level) are generally started on 150 IU/day of FSH, while women with probable diminished ovarian reserve (age >36 years, elevated FSH, one ovary) are started on 200 - 300 IU/day of FSH [3].

The starting dose of FSH used in any subsequent cycle is then adjusted according to the individual patient's response in their first cycle. Unfortunately this approach is less than ideal since it results in an inadequate response in about 50% of patients and an excessive response in 2-5% of cycles [4,5].

Tests that are sensitive enough to accurately quantify ovarian reserve have the potential to help clinicians individualize the starting dose of rFSH used in a first cycle of IVF, thereby potentially improving the efficacy and safety of treatment.

Previous studies have shown that maternal age, antral follicle count, ovarian volume, ovarian doppler score and smoking status can help to predict a patient's response to COH [3].

A prospective randomized control trial that compared a standard starting dose of gonadotrophins in the first cycle of IVF (150 IU/day FSH) with an individualized starting dose (100 - 250 IU/day) based on such a predictive normogram (age, antral follicle count, ovary volume, Doppler score and smoking status) confirmed that an individualized starting dose was more effective at achieving an "ideal response" (5-14 oocytes) than a standard starting dose (77.1% vs. 65.6% ideal response, $p < 0.05$).

The optimized ovarian stimulation for ICSI is the target for IVF doctors and many stimulation protocols set to reach this target with the fixed new two step protocol the number of gonadotropin is less and the outcome is good regarding pregnancy rate for all patients in the reproductive period.

Materials and Methods

Title: Modified short protocol regimen in ICSI in comparison with traditional short protocol.

Study site: Elshorouk hospital IVF division Benha city -qalubia-egypt.

Study duration: From Mayo 2012 to mayo 2013.

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Study design: Controlled trial.

Sample size: Total number 40 case 20 for the new short protocol and 20 for the traditional short protocol.

Outcome measures:

- Days of stimulation
- Number of merional ampoules
- M2 oocytes
- Embryos
- Pregnancy rate

Ethical approval: A written consent signed by both the husband and the case.

Patient Evaluation

All the cases in both groups will be subjected to the following.

History

Examination

Investigations: In the form of Standard semen analysis, Basal day3 FSH, LH, Hysteroslapigeography, Hysteroscopy.

Exclusion criteria

Female age more than 39, FSH>15 miu/ml, Azospermic males.

The cases subdivided in two groups according to the stimulation protocol

Group 1 (Modified short): 20 given decapeptyl ampoules 0.1(half the ampoule subcutaneously in the abdominal wall from first day of menses till HCG injection. merional 75 units ampoule started in the second day of the cycle four ampoules from day 2 for four days then 3 ampoules after that till the leading follicles (at least 4) reached 20 mm.

Group 2 (Classic short): Decapeptyl (0.1 mg) half the ampoule given subcutaneously from the first day of menses until HCG injection then merional ampoules given intramuscular from (day 2 to day 5) 3 ampoules; then dose adjusted according to the size of follicles seen by vaginal ultrasound every other day.

HCG injection 5000 units (2 ampoules) given intramuscularly when the leading follicles reached 20 mm then ICSI done 36 h after the HCG injection.

Luteal support with

- Prontogest 400 mg vaginal suppositories.
- Folic acid 5 mg tablets.
- Vitastress tablets (vit E, A, B1, B2, B6, copper, zinc and vitamin C).

Pregnancy test: (Quantitative HCG) Done 15 days from the day of embryo transfer.

Statistical analysis: Done by SSP program.

Results

There is a significant difference in means regarding the number of HMG ampoules, the days of gonadotropin stimulation, number of embryos and the pregnancy rate so the short fixed 2 step high start regimen can be applied to all patients with better results (Tables 1-3).

ampoules	M2 oocytes	embryos	Days of stimulation
Mean 34.4	7.2	5.8	10.1
St d 2.96	1.8	1.3	0.9

Table 1: Group 1 modified short.

	Ampoules	M2 oocytes	embryos	Days of stimulation
mean	38.75	5.3	4.1	12.2
St d	2.8	1.08	1.49	1.4

Table 2: Group 2 classic short.

	Group 1	Group 2	p value
ampoules	M = 34.4	M = 38	0.0002
M2 oocytes	M = 7.2	M = 5.2	0.0002
emryos	M = 5.8	M = 4.1	0.0001
Days of stimulation	M = 10.1	M = 12.2	0.000002
Pregnancy rate	75%	50%	<0.005

Table 3: Comparison of means between 2 groups.

Discussion

At present, different gonadotropin preparations are used in pituitary-suppressed women who are undergoing controlled ovarian stimulation for IVF procedures. Several randomized, prospective trials, comparing the effect of FSH alone and hMG preparations in IVF by using a long GnRH-a protocol, have shown that severe suppression of serum LH levels (1 IU/L) may occur in about half of the FSH-treated subjects [6,7].

Although follicular growth can be induced by FSH in the total absence of LH, the resulting follicles have developmental deficiencies such as abnormally low production of E2 and an inability to luteinize and rupture in response to hCG stimulus [7-12].

Optimal follicular development is therefore also dependent on a minimal exposure to LH or the LH threshold.

In meta-analyses of the effectiveness of hMG and r-FSH in IVF-ICSI cycles, it became evident that hMG treatment resulted in a higher clinical pregnancy rate and in higher ongoing pregnancy and live birth rates than did r-FSH, but the latter difference was of borderline significance [6].

However, the heterogeneous pituitary suppression regimens and the flexible gonadotropin dosages used in those studies limited the potential for discriminating the features of these 2 gonadotropin preparations. A prospective comparative study by Chi-Hong (2008) investigating cost and effectiveness of IVF/intracytoplasmic sperm injection (ICSI) treatments after stimulation with recombinant gonadotrophins following either the short or long Gonadotrophin-Releasing Hormone (GnRH) agonist protocol.

Patients in the short protocol (n = 120) were administered buserelin nasal sprays from day 2 of the menstrual cycle and recombinant FSH from day 5. Patients in the long protocol (n = 120) were administered buserelin from the previous mid-luteal phase and recombinant FSH after achieving down-regulation.

The average age and basal FSH concentrations of both groups were similar.

The serum LH concentrations during ovarian stimulation were significantly higher with the short protocol.

The total cost of recombinant gonadotrophins (US\$527 184 versus US\$795 244, p < 0.001) was significantly lower in the short protocol, but

there was no significant difference in delivery rates (47.5 versus 36.7%) between the short and long protocols.

LH flare-up during the short protocol does not seem to impair the treatment outcome using recombinant gonadotrophins. The short GnRH agonist protocol is an effective and cheaper choice for IVF/ICSI treatments [12].

The current work compared the classic short protocol with the new short fixed dose two step protocol and concluded that the fixed short protocol have good results with less cost and fewer days of gonadotropin stimulation.

This protocol also solved the problem of poor responders and old age patients so can be used in developing countries like Egypt to reduce the cost of treatment with good results.

Conclusion

The desire of anyone who works in infertility is to maximize and optimize success rate in ICSI. Protocols of ovulation induction affect significantly the success rate in ICSI. The short protocol has the advantage of greater number of follicles and embryos. The current study suggests a new way of starting high dose 4 ampoules of HMG for 4 days then reducing the dose to 3 thereafter.

The short protocol is highly efficient in old age and poor responders, especially the new one had significant high results with fewer days of stimulation and more number of mature oocytes.

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