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Minimal ovarian stimulation and IVF

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OBJECTIVE(S) : To evaluate the efficacy of a minimal stimulation protocol in IVF.

METHOD(S) : The study included 31 couples who attended our hospital from 1st January 2003 to 31st December 2003. They were unable to afford full-fledged IVF programme. Basal scan was performed on day 2 to exclude any cyst. Clomiphene citrate 100 mg from day 2 to day 6 was given. Follicular monitoring was done from the 7th day. Inj. HMG 75-150 IU was given daily intramuscularly. Subsequent visits were determined according to each patient's response. Cetrorelix 0.25 mg was started when the lead follicle was >13 mm and continued until ovulation induction. For comparison, a group of women (n=49) undergoing 1st IVF cycle with standard long protocol was used as control.

RESULTS : There was no cancellation of any cycle due to premature luteinisation. Fertilization rate and pregnancy rate / transfer in the study and the control group were 71.2% vs 70.1% and 28.6% vs 30.6% respectively.

CONCLUSION(S) : Minimal ovarian stimulation protocol is a good alternative approach.

Key words : minimal stimulation, clomiphene citrate, GnRH antagonist, invitro fertilization

Introduction

Clomiphene has been used for decades for ovulation induction. It has also been used in stimulation protocols of IVF in early years. But with introduction of GnRH agonists in early 1980s, GnRH agonist and gonadotropin protocols have been proven to be much more effective in terms of quality and number of oocytes retrieved, and clinical pregnancy rates [1].

The main advantage of clomiphene is its low price and negligible risk of OHSS. But the problems are its antiestrogenic effect on the endometrium, premature LH surge and a possible risk of ovarian cancer on prolonged use.

The antiestrogenic effect on the endometrium might be overcome by adjunctive use of gonadotropins. This however, will also increase the risk of premature LH surge. With the introduction of GnRH antagonists, this early untimed LH surge after combined use of clomiphene and gonadotropins can now be prevented [2,3].

We evaluated the efficacy of a protocol with minimal ovarian stimulation in IVF-ET for low income group of patients.

Methods

Our study included 31 couples who attended our hospital from 1st January 2003 to 31st December 2003. They could not afford full-fledged IVF program. The benefits and disadvantages of using a minimal stimulation protocol were carefully discussed with them. Financial considerations were the primary reason for accepting this protocol.

Day 2 basal scan was performed. Patients were excluded from the study if endometrial thickness was > 4 mm and if there was presence of any cyst. Day 2 serum FSH was done in all cases. Patients were excluded from study if FSH was > 10 IU/L. Only patients having normal ovaries or at the most ones with mild endometriosis were included in the study. There may be a selection bias as only potential good respondents got included in the study. Stimulation was started with clomiphene citrate (CC) 100 mg daily from 2nd day to 6th day. Patients returned on day 7 for follicular monitoring. Depending on the follicular size inj. hMG 75 or 150 IU daily was given intramuscularly. Subsequent visits were determined

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according to patient's response. Subcutaneous inj. of 0.25 mg cetrorelix (Cetrotide 0.25 mg) was given daily when the lead follicle was > 13 mm and continued until induction of ovulation. Ovulation was induced by inj. hCG 10000 IU given intramuscularly when at least two follicles were > 16 mm size. We considered an elevation of LH > 15 mIU/mL on day of hCG as premature LH surge. Oocyte retrieval was performed 34-35 hours after hCG. Day 3 embroyos were transferred in each case. For comparison, a group of women (n=49), who underwent first IVF cycle with standard long protocol were used as control. In the control group, down regulation was started on 21st day of previous cycle with inj. Buserelin (Inj Suprefact). Stimulation was started on day 2 with inj. FSH/hMG. The dose was adjusted according to patient's response.

Both the study and the control groups were matched for age and diagnosis. Statistical analysis was done using either test of significance between two proportions of large samples or large sample test for the significance between two sample means. P value < 0.05 was considered significant.

Results

The results are summarized in Table 1.

Table 1. Comparison of the two groups.

Variables	Study Group	Control Group	P-value
No. of Cycles	31	49	
Age (years)	33.1 ± 3.2	32.9 ± 3.5	0.79
Mature oocytes	3.6 ± 2.1	10.2 ± 5.4	< 0.01
Fertilization rate	71.2%	70.1%	0.8
Embryos transferred	2.8 ± 1.1	3.4 ± 0.7	0.007
Pregnancies per transfer	8/28 (28.6%)	15/49 (30.6%)	0.09

The age in both the groups varied from 24 to 37 years. The duration of infertility was 1-7 years. In the study group, two cycles had to be cancelled because less than 2 follicles of 14 mm size formed on the 10th day. We did not find a single case of premature luteinization in the study group.

No oocytes were recovered in one case in the study group. Fertilization rate was 70.2% in the study group, where as it was 70.1% in the control group.

We had eight pregnancies in the study group (pregnancy rate / transfer was 28.6%) and 15 pregnancies in the control group (Pregnancy rate / transfer was 30.6%).

Discussion

There were significantly fewer oocytes per ovum pick up in the study group compared to the control group. The number of available embryos was satisfactory and sufficient because of the present trend of transferring lower number of embryos. Several studies have shown this to be very effective in terms of clinical pregnancy rates and reduction of high order multiple births [4].

We achieved acceptable pregnancy rates with significant reduction in the number of gonadotropin ampoules used resulting in significant cost reduction. At the same time we avoided premature LH surge. Some other studies [5,6] have also shown similar results.

CC continues to be valuable during assisted reproduction as a part of minimal stimulation protocol like CC + gonadotropin + GnRH antagonist as well as part of other protocols [7].

However there may be a possible bias with regard to selection of preferentially good responders. The minimal stimulation regimen produces expected results with fewer oocytes recovered and fewer embryos available for transfer. But the pregnancy rate is comparable with that obtained by long GnRH agonist protocol [5,6].

The main drawback of minimal stimulation regimen is the lower total reproductive potential as judged by pregnancies resulting from fresh and frozen-thawed embryos resulting from a single stimulation cycle. But again frozen thawed cycles are not without significant costs.

Thus the couples accepting this protocol must realize that for a lower cost, they are not likely to have embryos available for selection or cryopreservation.

Minimal ovarian stimulation with CC with the use of GnRH antagonist is a good alternative approach to long protocols particularly for patients with limited financial means.

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