Intrauterine Insemination After Ovarian Stimulation As A Treatment For Subfertility Because Of Subnormal Semen

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Citation

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Abstract

Objective: To determine whether intrauterine insemination (IUI) after ovarian stimulation with clomiphen citrate (CC) gives a better pregnancy rate (PR) than natural intercourse in couples with subfertility because of subnormal semen.

Design: prospective randomized controlled trial.

Patients: Couples with subnormal semen as only identifiable cause of subfertility.
Interventions: In control cycles, the couples had natural intercourse. In IUI cycles, IUI was performed after ovarian stimulation with CC and human chorionic gonadotropin.

Main Outcome Measure: The clinical PRs and complications of IUI cycles and control cycles were compared.

Results: There were four clinical pregnancies in the 32 IUI cycles, whereas there was no clinical pregnancy in the 32 control cycles. The clinical Pr in IUI cycles (12.5%per cycle) was significantly higher than that in control cycles (0%). None patients developed ovarian hyperstimulation syndrome in IUI cycles.

Conclusion: Intrauterine insemination after ovarian stimulation with CC is useful in treatment of subfertil couples with subnormal semen.

INTRODUCTION

Although intrauterine insemination (IUI) has been performed for a long time treatment of various forms of sub fertility, only few control trials confirm its therapeutic efficacy ([1]). In the past few years, there was increased interest in the use of IUI after ovarian stimulation with human menopausal gonadotropin and pregnancy rate was significantly better than the natural cycle ([2,3]). Cruz et al. ([4]) showed that in couples with sub fertility due to oligoasthenospermia receiving hMG with or without clomiphen citrate (CC) for ovarian stimulation, the pregnancy rate (PR) of IUI was significantly better than intracervical insemination. However, a control group having natural intercourse without ovarian stimulation was not included in their study. Kemmann et al.([5]) reported that ovarian stimulation with CC and / or hMG improved the PRs of patients treated with IUI, but their study group included couples with either subnormal semen or poor postcoital test (PCT). Moreover the study was not a prospective randomized study, and only historical controls were used. Recently, Chaffkin et al. ([6]) reported that the PRs of IUI combined with hMG was significantly higher than hMG or IUI alone, but the study was only a retrospective analysis. In a prospective randomized comparative trial, Martinez et al. ([7]) found that after ovarian stimulation with hMG the PRs of timed intercourse and IUI were similar. Because of the designs of these studies, it is difficult to concluded whether IUI after ovarian stimulation with hMG gives a better PR than natural intercourse alone. In this study we have been a prospective randomized controlled trial, to determine whether intrauterine insemination (IUI) after ovarian stimulation with clomiphen citrate (CC) gives a better pregnancy rate (PR) than natural intercourse in couples with sub fertility because of subnormal semen.

METHOD AND MATERIAL

Couples with sub fertility because of subnormal semen were recruited for the study and were assessed at our infertility clinic. The husband was examined by an endocrinologist and surgeon to exclude medical and surgical problems and was asked to submit at least three samples of semen for routine analysis ([8,9]). Semen would be sent for culture if there were an increase in leukocytes in the semen. The PCT was performed as described by Glass ([10]). The selection criteria were as follows:

1. the duration of infertility was>2 years;
2. at least three semen analyses of the male partner were subnormal: sperm count was <2000000 / ml, progressive motility at 2 hours was < 50% or normal morphology was < 50% (8);
3. there was no other identifiable factor responsible for the sub fertility. The female partner was ovulating regularly (with cycle length usually between 25 and 35 days).

With midluteal progesterone > 32 nmol/ L there should be no coital problem. HSG was performed in all patients and they were recruited into the study if there was no abnormality and both tubes were patent.

The trial was designed as a sequential trial of natural intercourse cycles and IUI cycles. The first cycle was randomized into either natural or IUI cycles. Subsequent cycle were then alternated so that each patient was treated for a maximum of 6 cycles with three natural cycles and three IUI cycles.

During the natural cycle, the couple was advised to have intercourse once every 2 days, starting 2 days before the expected day of ovulation until there was a sustained rise in basal body temperature (BBT). The expected day of ovulation was estimated from previous BBT charts. They were asked to mark down the days when they had intercourse on the BBT charts. During the IUI cycle , the patient was asked to attend the clinic on day 2 of the cycle. A transabdominal pelvic ultrasound (US) scan was performed to ensure that there was no abnormality. The patient was given 100 mg clomiphen citrate in days 5-9 then followed by 10000 IU of human chorionic gonadotropin (hCG) IM on days 14 of cycle. The IUI was performed 34 to 36 hours after the administration of hCG.

Two hours before the IUI , the husband was asked to submit a sample of semen for preparation. The semen was prepared with the discontinuous percoll gradient method ([11]).The IUI was performed by a Tomcat catheter ([1]). In the luteal phase, the patient was given 1500 IU of hCG every 5 days for two doses. A clinical pregnancy was diagnosed when the patient had a delayed period > 16 days after the ovulating dose of hCG with a positive pregnancy test and there was ultrasonographic evidence of intrauterine pregnancy. Differences in proportions were analyzed with X2 and Fisher's exact test. Differences in means were analyzed with students t-test.

RESULT

Although, 14 couples were enrolled for the trial. The mean age of the women was 25 years (SD, 2.3) and that of the husbands was 29 years (SD, 5.4). The mean duration of infertility was 3.8 years (SD, 3.3). Twelve of these couples (85.7%) had primary infertility, and 2 had secondary infertility. The semen parameters showed a single defect in 7 patient (50%), double defect in 4 patients (28.5%), and triple defect in 3 patients (21.5%). The sperm count was subnormal in 9 patients (64.2%), the motility was < 50% in 9 patients (64.2%), and percentage of normal forms was < 50% in 6 (42.8%) patients. The semen characteristics of the patients are shown in Table 1.None of the patients or their male partners had detectable antisperm antibodies. None of them had increase in leukocytes in the semen. The PCTs of these couples showed normal cervical mucus. They were treated with 32 IUI cycles and 32 cycles natural cycles. In all the natural cycles, the couples had recorded on the BBT charts that they had at least one act of intercourse 12 to 16 days before the onset of the next menstruation. There were four clinical pregnancies in the 32 IUI cycles, whereas there was no clinical pregnancy in the 32 natural cycles. The clinical Pr in IUI cycles (12.5% per cycle) was significantly higher than that in natural cycles (0%) ($P< 0.05$ by fisher's exact test). The postwash sperm count and total number of motile sperms inseminated in the pregnant cycle was significantly higher than those in the nonpregnant cycles ($P< 0.05$), but there was no significant difference in the other parameters. The percentage of patients with more than one defect in the three prewash semen parameters (counts, motility, percentage of normal forms) in pregnant cycle (75%) was also similar to the nonpregnant cycle (80%) and there wasn't significantly by Fisher's exact test ($P >0.05$). None patients developed ovarian hyper stimulation syndrome in IUI cycles. One of the patients with abnormalities in all three parameter conceived.

DISCUSSION

Although there were a number of studies reporting on the success of IUI after ovarian stimulation ([4,6,12,13]), none of them was a prospective randomized, controlled trial comparing the PR of natural intercourse with IUI after ovarian stimulation. In some of these studies, infertile patients because of a variety of causes were treated ([5,12,13]). Many of these studies are retrospective.

Our study was a prospective randomized, controlled trial comparing the PR of IUI after ovarian stimulation with natural intercourse. In the natural intercourse cycles, we asked the couples to time the intercourse according to previous BBT charts. We have not employed any tests for LH surge because there is no evidence that they can improve the PRs in natural intercourse or artificial insemination programs ([14, 15]) We have shown that in this specific group of patients, IUI after ovarian stimulation gave a better PR than natural cycle intercourse. Therefore, these patients should be offered this form of treatment before assisted reproduction, which is more complicated and expensive. Our results differ from the other studies, who did not find any improvement in PRs with superovulation and IUI in a prospective controlled trial ([7]). However, they used ampules of hMG for ovarian stimulation in their study but we used clomiphen citrate for ovarian stimulation that is not expensive (compared with the HMG). Our treatment group differs from the control group in two aspects: ovarian stimulation and timed IUI. Ovarian stimulation produced a large number of oocytes available for fertilization. The ovarian stimulation may also correct subtle defects in ovulation that may not be detected with the usual midluteal serum P assays. The insemination at 34-36 hours after hCG may give a better timing for the sperms to meet the oocyte(s). Finally, the injection of highly motile sperms into the uterine cavity may also be a contributory factor. The anticipated result was the patients with multiple sperm defects are not less likely to conceive with this form of treatment, but one of patients with triple sperm defects conceived in our series. It is also interesting to note that although the prewash sperm parameters in the pregnant and nonpregnant cycle are similar, the post wash sperm count and number of motile sperms inseminated were significantly higher in the pregnant cycles. We are uncertain of the reason for the increased recovery of motile sperms, but this increased recovery may account for the improved fecundity. In this study we had not any theoretical complications with IUI after ovarian stimulation include pelvic infection, ovarian hyperstimulation syndrome, and multiple pregnancy.

The number of couples studied in our trial is small and the semen profiles are also heterogeneous. Therefore, this may be considered a pilot study, and confirmation in a large series will be necessary. In particular, further studies are necessary to assess whether men with more sever defects would benefit from IUI after ovarian stimulation and whether ovarian stimulation without IUI will also be effective.

Figure 1

Table 1: semen characteristics of male partrners

Patient no	Semen Volume(cc)	Sperm Count x10^6/ml	Sperm Motility (%)	Normal Morphology (%)
1	1.0	6.5	52	65
2 *	2.5	18.2	20	20
3	2.0	25	40	7
4	2.5	30	40	55
5	4.0	18.6	60	70
6	3.3	19	20	56
7	3.0	25	40	70
8 *	3.5	19	55	60
9 *	3.0	25	35	30
10	4.0	15	40	40
11 *	2.5	19	50	40
12	3.0	35	30	60
13	4.0	10	20	33
14	3.5	1.5	50	60

◙ Value are means

*Wives of these patients pregnant during IUI treatment cycles.

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