A randomised prospective trial of intrauterine insemination versus timed intercourse in superovulated cycles with clomiphene

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Background & objectives: Despite its wide use, the benefits of intrauterine insemination (IUI), its over timed intercourse (TI) in couples with unexplained infertility is a matter of debate. Studies in Indian couples with unexplained infertility showing benefit of IUI over TI are not available. The present study was done with the objective of comparing TI and IUI with husband’s sperm in couples with unexplained infertility undergoing superovulation with clomiphene.

Methods: A total of 140 couples with unexplained infertility were subjected to controlled ovarian hyperstimulation (COH) with clomiphene and prospectively randomized to receive either TI (group A) or IUI (group B). Complete follow up was available for 113 couples only.

Results: The pregnancy rate and cycle fecundity rate after COH/TI was 41 and 8.8 per cent and after COH/IUI 18 and 3.4 per cent respectively. The difference was statistically not significant.

Interpretation & conclusion: The findings of the present study showed that in women with unexplained infertility addition of IUI to ovulation induction does not improve conception rates. COH/TI can help to achieve good results and save the expense and discomfort due to a invasive procedure.

Key words Controlled ovarian hyperstimulation - intrauterine insemination - timed intercourse - unexplained infertility

Unexplained infertility is a common problem, with prevalence between 5-28 per cent of the infertile population, depending on the criteria used for definition1,2. Patients with unexplained infertility comprise a heterogeneous group from an ill defined population whose basic infertility investigations yielded normal results. Treatment of such couples is empirical, and pregnancy rates after treatment is no better than the spontaneous conception rate of untreated couples3. The use of superovulation and artificial insemination as an empirical treatment for unexplained infertility became popular based on the hypothesis that such couples do not have an identified reproductive insufficiency leading to infertility that can be overcome by increasing the number and proximity of gametes in the reproductive tract. In addition, this modality of treatment probably overcomes the problems caused by subtle defects in the sperm, oocytes, fertilization or the implantation process. Intrauterine insemination (IUI) offers couples with male subfertility benefit over timed intercourse (TI), both in natural cycles and in cycles with
controlled ovarian hyperstimulation (COH). Meta-analysis has shown that couples treated for unexplained infertility can benefit from the addition of IUI to superovulation. However, only 2 of the 7 individual studies included in the meta-analysis reported significantly increased benefit from the addition of IUI to superovulation versus that with timed intercourse.

The benefit of IUI over TI remains a matter of debate. There is paucity of information available from India. The present study was therefore undertaken to evaluate the role of IUI compared with TI in couples with unexplained infertility undergoing COH in the Indian set up.

Material & Methods

Couples with unexplained infertility attending the Gynecological Outpatients of All India Institute of Medical Sciences (AIIMS), New Delhi over the period of three years (March 2000-2003) were followed up. In all, 140 women were enrolled in the study. The duration of infertility ranged from 1-18 yr with a median of 5 yr. All women had the following test results: biphasic basal body temperature charts, in-phase late luteal endometrial biopsy, normal serum levels of thyroid, prolactin, luteinising hormone and follicle stimulating hormone, hysterosalpingogram indicating normal uterine contour and laparoscopy indicating bilateral tubal patency, absence of pelvic adhesions and endometriosis.

All men had normal values on at least two standard semen analyses (sperm concentration above 20 million/ml, more than 50 per cent motile and more than 50 per cent morphologically normal spermatozoa), a positive post-coital test. Tests for immunological causes of infertility of both partners revealed negative results (antisperm antibodies).

The 140 couples were divided into two groups using random number table, 70 in each group and followed over three years. Twenty six women in group B and one in group A did not have complete follow up and were thus excluded from the analysis. Complete follow up was available for 113 couples, group A (69 couples) and group B (44 couples). The drop out rate in group B was high due to financial constraints for the treatment. Each group began with one of the two treatment modalities: COH/TI (protocol A) or COH/IUI (protocol B) for 6 consecutive cycles or till the time of conception whichever was earlier.

Ovarian stimulation: All women were treated with clomiphene citrate 50-150 mg orally from day 3 to 7 of menstrual cycle depending on response. Follicular monitoring was done by serial vaginal ultrasonography beginning from day 10 till demonstration of ovulation. Human chorionic gonadotropin (HCG) 10,000 IU intramuscular was administered when not more than four leading follicles >16 mm were seen. Couples in group A were advised to have intercourse 36-40 h after administration of HCG. For group B couples IUI was performed 36-40 h later.

Sperm preparation: This was carried out by Percoll gradient and centrifuged at 500 x g for 15 min. Sperm cells present in 90 per cent fraction were used after two washes to remove the Percoll. Culture media used were Ham’s F10 (SIGMA, USA) enriched with either 7.5 per cent patient’s serum or 1 per cent human serum albumin. A volume of 0.3-0.4 ml of the preparation was taken for IUI using an IUI cannula for the procedure. The woman was instructed to lie in supine/ lateral position for 30 min after the procedure. The study protocol was approved by the ethics board of the institute.

Statistical analysis: Results were analysed statistically to calculate the conception rates and cycle fecundity rates. Comparison of conception with non-conception cycles was done by evaluation of mean number of follicles, endometrial thickness and mean follicular size. Semen parameters were studied in terms of sperm concentration and motility in couples undergoing IUI in conception and non-conception cycles. Students t-test was used for comparison of quantitative data. Percentages were compared by means of the X^2 test and Fisher’s exact test. P<0.05 was considered significant.

Results

The 113 couples - 69 in COH/TI group and 44 in COH/IUI group had complete follow up. The mean age of the women was 28.83±4.76 and 29.52±3.65 yr
in TI and IUI groups respectively and duration of infertility varied from 1-18 yr in both the groups with mean duration of 4.93±3.27 and 4.91±2.72 yr respectively in TI and IUI groups. Primary infertility was seen in 81 (72%) and secondary in 32 (28%) couples. Comparison of the treatment outcome between IUI and TI groups in superovulated cycles of patients with unexplained infertility is shown in the Table. The pregnancy rate after COH/TI was 41 per cent and after COH/IUI 18 per cent. The difference was statistically not significant.

A comparison of conception and non conception cycles showed no significant difference in follicle number with diameter of ≥16 mm (conception cycle 3.6 ±0.1; non conception cycle 3.3 ± 0.1), mean follicular size (conception cycle 20.2 ± 1.0 ; non conception cycle 19.6 ± 3.3) and endometrial thickness (9.8± 1.4 ; 9.0 ± 1.8mm). Similarly no significant difference in sperm concentration and sperm motility were found between conception and non conception cycles in women undergoing IUI.

Four women undergoing COH/IUI reported signs and symptoms of pelvic infection and uterine cramps. Of the 36 pregnancies delivered, 28 had full term live babies, 2 pairs of twins and 2 premature birth (34-35 wk gestation). Missed abortion occurred in 3 and spontaneous abortion in 1, all requiring vacuum aspiration. There were 2 pregnancies with twin gestation.

**Discussion**

Considerable controversy surrounds IUI and the conditions that respond best to this simple form of infertility treatment. Despite numerous reports, so far there has been no consensus regarding the usefulness of adding IUI to COH in unexplained infertility. Martinez et al reported the first randomized study on comparison of TI and IUI in gonadotropin stimulated normal ovulatory cycles without any significant differences. Kirby et al compared IUI with LH- timed intercourse during spontaneous cycles and found no significant improvement in pregnancy rates except in couples with severe semen defect. However, based on a meta-analyses of 980 cycles in randomized prospective studies, addition of IUI to superovulation with gonadotropins in couples with unexplained infertility produced better results than superovulation alone. Though 5 of the 7 studies included in this meta-analysis failed to show significant benefit of IUI, the overall evaluation of all 7 studies revealed a significant increase in the pregnancy rate with addition of IUI. Two individual studies reported a significantly increased benefit of IUI over TI.

Our study did not show any benefit of IUI over TI in COH cycles in women with unexplained infertility. Pregnancy rates were 41 per cent and cycle fecundity 8.8 per cent after COH/TI. Most studies have indicated that IUI is only useful if the cause is oligospermia and mild asthenozoospermia. IUI may increase the likelihood of infection and discomfort. It is also more invasive and a time consuming procedure involving expense as a result of involvement of medical staff and facility for sperm preparation. The determination of the cost-benefit ratio of addition of IUI to superovulation depends on the local cost of these interventions. Despite these disadvantages of IUI, certain studies do provide evidence of increased success of adding IUI in treatment protocols for women with unexplained infertility.

Large multicentric randomized controlled trials including normal ovulatory and superovulated cycles on such couples can answer questions regarding the benefit, cost-effectiveness and potential adverse effects of IUI over TI for unexplained infertility. Also it can help to evaluate subtle endocrine/ovulatory defects which may influence beneficial outcome. The mechanism by which IUI, either combined or not with ovarian stimulation may enhance cycle fecundity in
couples with unexplained infertility remains to be elucidated. In conclusion, our study showed that addition of IUI to ovulation induction does not improve conception rates in women with unexplained infertility.

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