

Intrauterine Insemination vs Timed Intercourse in Letrozole and FSH-stimulated Cycles in Dysovulatory Infertility

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ABSTRACT

Background: Dysovulatory infertility is a major cause of infertility. It is treated with ovulation induction complemented with an assisted reproductive technique such as intrauterine insemination (IUI) and timed intercourse (TI). The data to compare the efficacy of IUI vs TI in super-ovulated cycles is limited.

Aim: Comparison of pregnancy rates following IUI vs TI in letrozole and follicle-stimulating hormone (FSH) cycles in dysovulatory infertility.

Method: Following the history and examination of subjects enrolled, baseline hormonal levels were done on day 2, transvaginal ultrasonography (TVS) for number and size of follicles and endometrial thickness was done on days 8, 10, and 12, and ultrasonography (USG) to confirm ovulation was done on day 14, if confirmed, it was followed by IUI or TI. Urine pregnancy test (UPT) at 2 weeks established successful conception. Those not conceiving received another cycle, to a maximum of 3 cycles.

Result: A total of 120 subjects received 320 cycles. Intrauterine insemination shows better conception rates than TI (p -value < 0.05). The clinical pregnancy rate for the IUI group is 18.5% (28 in 154 cycles) and 10% (16 in 166) in the TI group. The success rate is positively correlated with younger age of patients, better educational status, and higher socioeconomic status.

Conclusion: Intrauterine insemination combined with letrozole and FSH-stimulated dysovulatory infertility is an effective method to improve pregnancy outcomes.

Keywords: Extended letrozole protocol, Human menopausal gonadotropin, Infertility, Intrauterine insemination, Ovulation induction letrozole, Timed intercourse.

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INTRODUCTION

The World Health Organization (WHO) estimates that 48 million couples and 186 million individuals worldwide currently suffer from infertility.¹ Infertility rate varies across the world and is estimated to affect 8–12% of couples worldwide.² According to WHO estimate the overall prevalence of primary infertility in India is between 3.9 and 16.8%.³

One of the major contributors to ovarian causes of infertility are anovulation and dysovulatory cycles (30–40%). Dysovulatory infertility is generally easily diagnosed and is the most treatable.⁴

Oligoovulation is usually treated with ovulation induction; these women achieve fecundability nearly equivalent to that of normal couples.⁵

Ovulation induction can be done using clomiphene citrate (CC), gonadotropins, pulsatile gonadotropin-releasing hormone (GnRH) therapy, aromatase inhibitors such as letrozole, and dopamine agonists.

Assisted reproductive techniques such as intrauterine insemination (IUI) are used in addition to ovulation induction. Timed vaginal intercourse involves interfering with natural coital habits by asking couples to refrain from intercourse until some marker shows that ovulation is imminent. It is the usual control treatment in trials of IUI.⁶

This study was done to compare the effectiveness of IUI vs timed intercourse (TI) in letrozole and FSH-stimulated cycles in dysovulatory infertility.

AIM

To compare pregnancy rates following IUI vs TI in letrozole and FSH stimulated cycles in dysovulatory infertility.

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Objectives

To study pregnancy rates following IUI and TI in letrozole and FSH stimulated cycles in dysovulatory infertility.

Methodology

Prospective randomized hospital-based comparative study.

Sample Size

A total of 134 women were enrolled at the beginning of the study, and 120 subjects completed the study.

Inclusion Criteria

- Age 20–35 years.
- Infertility duration >2 years.
- Cases with dysovulatory infertility (History of oligomenorrhea, anovulatory cycles) or history of any ovulation induction failure.
- Cases with a normal hysterosalpingogram.
- Cases with husband semen analysis within normal limits.
- Cases willing to come for follow-up.

Exclusion Criteria

- Seropositivity for human immunodeficiency virus (HIV) for any couple member.
- Significant medical or surgical comorbidity-renal failure, liver cirrhosis, etc.
- Not giving informed consent.

After thorough history taking, a physical examination of the patients was conducted to rule out any significant medical or surgical comorbidity. Sonography of whole abdomen and pelvis, hysterosalpingography, and the husband’s semen analysis were analyzed. Prolactin and serum TSH levels were assessed, followed by ovulation induction with tablet letrozole 2.5 mg twice a day from day 2 to day 10.⁷ Gonadotropin was given in the form of injection of FSH 150 IU intramuscular was given on days 8, 9 and 10th day of the menstrual cycle.⁸

This was followed by folliculometry with transvaginal ultrasonography (TVS) to assess the number, and size of follicles and endometrial thickness on every alternate day starting from the 8th day till the appearance of a mature dominant follicle. A repeat dose of Injection FSH is given to patients whose follicular size was less than 15 mm on folliculometry. The follicular growth and endometrial development were monitored with the aid of serial TVS starting on days 8, 10 and 12. When the leading follicle measures 18–20 mm, ovulation was triggered by administration of HCG injection (10,000 IU IM).⁹

A day 14 scan was done to see the signs of ovulation. Patients were divided randomly in two groups to undergo interventions of interest for this study. This is described as:

Group I (Intrauterine insemination group/IUI) – Intrauterine insemination was done after 36–40 hours of ovulation trigger.

Group II (Timed intercourse group/TI) – Cases were counseled for TI within 36–40 hours of ovulation trigger.

Intrauterine insemination was done with semen collection after an abstinence period of 2–3 days. Sperm washing was followed by the swim up method. The patient was asked to lie in a lithotomy position, cervix was exposed using Cusco’s bivalve speculum or Sims’s speculum with an anterior vaginal wall retractor. The IUI cannula was flushed with 1–2 mL of flushing media to wash away any toxic factors present. The sperm suspension was then drawn in the cannula. Normally an insemination volume of 0.4–0.6 mL was used. Inseminate was deposited very slowly into the uterine cavity over 3-minutes period. After the deposit, the cannula was withdrawn very slowly. The patient was allowed to resume her normal activities after insemination. Luteal phase support was given in the form of natural micronized progesterone 200 mg per vaginally twice a day, up to two weeks.

Follow-up

The cases were called after 2 weeks and a urine pregnancy test (UPT) was done. Urine pregnancy test positive cases were followed up to 8 weeks or till the appearance of fetal cardiac activity whichever

was earlier. Urine pregnancy test negative cases were subjected to another cycle of treatment. It was repeated for 3 cycles of treatment. Subjects not conceiving after 3 cycles were labeled no response to treatment.

Statistical Analysis

All the data collected in the specified time frame was analyzed using SPSS ver. 1.0.0.1406 software package for Windows and appropriate statistical tests were applied to get the result of this thesis research.

RESULTS

Table 1: Sociodemographic characteristics

Sociodemographic characteristics	Group I (IUI)	Group II (TI)
Age (in years)	27.80 ± 3.54	27.83 ± 3.44
Years of education (in years)	9.9 ± 4.4	10.0 ± 4.7
Area of residence (urban)	60%	56.7%
Per capita income (Rs/month)	4,437	4,757
Duration of infertility (in years)	5.37 ± 2.44	4.67 ± 1.70
Age of husband (in years)	31.50 ± 3.06	32.60 ± 3.19
BMI (Kg/m ²)	26.24 ± 1.81	25.75 ± 1.72
Menstrual pattern (Normal/frequent/infrequent)	12/7/11	11/8/11
History of any prior ovulation induction (Present)	15	14

Table 2: Correlation between demographic characteristics and success rate in both the groups

		Group I (IUI) success rate	Group II (TI) success rate
Age of patient (in years)	Correlation coefficient	-0.41142	-0.42562
	Sig. (2-tailed)	0.0239	0.01903
Age of husband (in years)	Correlation coefficient	-0.16466	0.14484
	Sig. (2-tailed)	0.3845 (Not significant)	0.4451 (Not significant)
Duration of infertility (in years)	Correlation coefficient	-0.15705	-0.21523
	Sig. (2-tailed)	0.40722 (Not significant)	0.2533 (Not significant)

Significant between the two variables when p-value < 0.05 at 95% confidence interval

DISCUSSION

Out of the 144 enrolled, 120 patients completed the study. About 24 patients were lost to follow-up during the study. About 60 patients were assigned to IUI treatment and 60 patients were assigned to TI and were labeled as group I (IUI) and group II (TI), respectively.

The age of cases, years of education, area of residence, socio-economic status, duration of infertility, age of husband, BMI of the study, menstrual pattern, and history of any prior ovulation induction were compared for the two groups (Tables 1 and 2). It is seen that the difference is not significant at p-value > 0.05.

Baseline hormonal investigations (LH, FSH, Prolactin and TSH) are done on day 2 of the first cycle for each patient. Statistical analysis



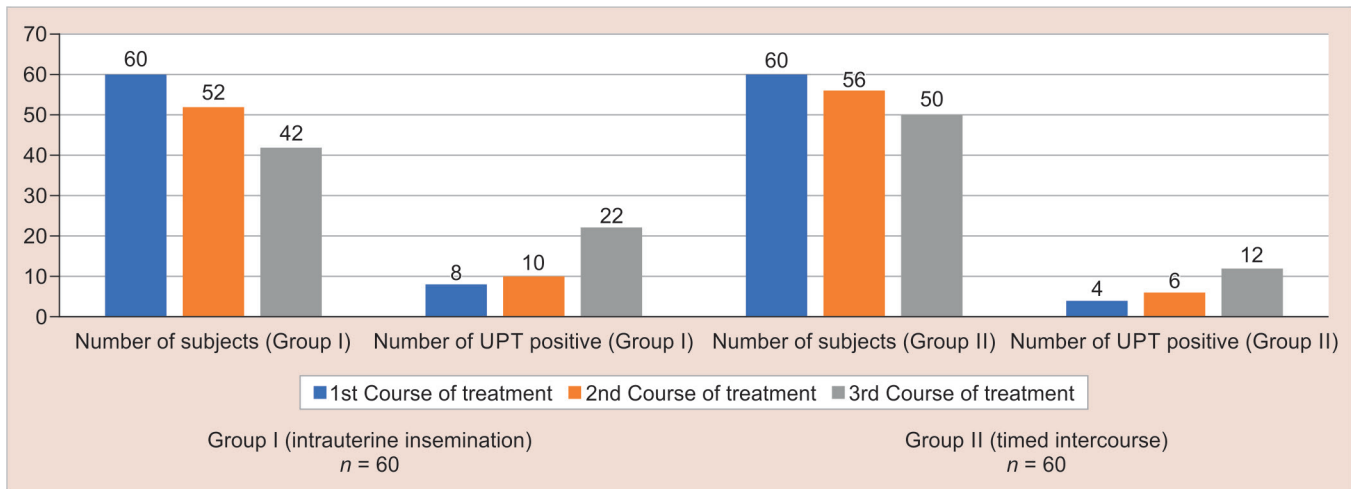


Fig. 1: Pregnancy outcomes in both groups in 3 cycles

reveals no significant difference in the two groups (p -value > 0.05). The ratio of LH to FSH was 1.04 ± 0.10 in group I and 1.07 ± 0.18 in TI group statistical analysis reveals no significant difference (p -value > 0.05). The findings are similar to a study by Hembram et al.¹⁰ and Oğlak SC et al.¹¹ Above findings establish that there is no difference in the two groups based on demographic characteristics and baseline investigations.

Transvaginal USG findings of days 8, 10, and 12 are analyzed. In group I, of the 154 cycles, 33 had follicle size ≤ 15 mm on day 10, and 4 had follicle size ≤ 15 mm on day 12. In group II, of the 166 cycles, 35 had follicle size ≤ 15 mm on day 10, and 5 had follicle size ≤ 15 mm on day 12. Number of follicles, size of follicles in mm, and endometrial thickness on days 8, 10, and 14 reveal no statistical difference between the two study groups (p > 0.05). The findings are similar to a study by Hembram et al.¹⁰

Of the 154 cycles of ovulation induction, in IUI Group, 120 were documented to have ovulated. In TI group, 124 out of 166 were documented to have ovulated. It translates to ovulation rates of 78% and 75%, respectively. No statistically significant difference is noted in the groups (p > 0.05). The ovulation rates are similar to study by Jain S et al.¹² (82%) and Legro et al.¹³ (88%).

In the IUI Group, 60 patients received 1st cycle of treatment. 44 were documented to have ovulated (73% ovulation). Of this, 8 (13%) got UPT positive. The remaining 52 patients received the second cycle of treatment of these 40 were documented to ovulate (77% ovulation) and 10 (19%) got UPT positive. The remaining 42 subjects received 3rd cycle of treatment of these 36 were documented to have ovulated (86% ovulation) and, 22 (52%) were UPT positive. In the IUI group, 20 patients did not conceive after 3 cycles.

In the TI group, 60 patients received the first course of treatment. 44 were documented to have ovulated (73% ovulation). Of this, 4 got UPT positive (6%). The remaining 56 patients received a second course of treatment of this 42 were documented to ovulate (75%) ovulation and 6 got UPT positive (11%). The remaining 50 subjects received 3rd cycle of treatment of this 38 were documented to have ovulated (76%) ovulation and 12 were UPT positive (24%). The results are comparable to a study by Jain S et al.¹²

Primary Outcome

In the IUI group 40 of the 154 women conceived. In group II, UPT turns out to be positive in 22 of the 166 cycles. Intrauterine insemination shows better conception rates than TI (p -value < 0.05).

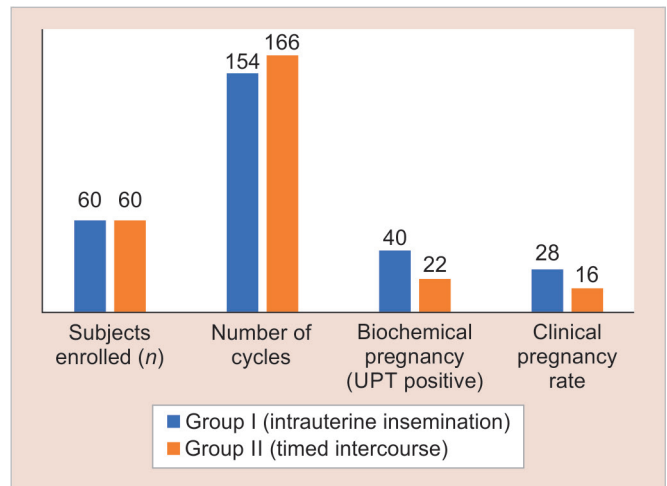


Fig. 2: Comparison of pregnancy outcome in both groups

Findings are consistent with a metaanalysis by Zeyneloglu HB et al.¹⁴ that concluded that a patient's chances of becoming pregnant are greater with IUI than with TI (Figs 1 and 2).

Secondary Outcome

The clinical pregnancy rate for the IUI group is 18.5% (28 in 154 cycles) and 10% (16 in 166) in the TI group. Clinical pregnancy rates of our study were comparable with Oğlak SC et al.,¹¹ where Letrozole + FSH and IUI were used, the clinical pregnancy rate was 17%.

Similarly missed abortion occurred in 12 cases of IUI Group and 6 cases of TI Group. No statistically significant difference is noted in the IUI and TI groups (p > 0.05). No ectopic pregnancy was reported in any of the groups.

CONCLUSION

Intrauterine insemination combined with letrozole and FSH-stimulated dysovulatory infertility is an effective method to improve pregnancy outcomes in comparison to TI. The age of the patients had a significant correlation with the pregnancy rates. There was no significant correlation found between the age of husband and duration of infertility with pregnancy rates.

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