



Obstetrics & Gynaecology

COMPARATIVE STUDY BETWEEN TIMED INTERCOURSE AND INTRAUTERINE INSEMINATION IN OVULATION STIMULATED CYCLES IN UNEXPLAINED INFERTILE COUPLES

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ABSTRACT

Background and Objective: Every couple hopes to have children at least once in their lifetime. A painful reality is not being able to have one, even in today's generation, especially in developing countries, talking about infertility is frowned upon & therefore is a taboo, therefore it has become a significant life stressor. The present study was done with an aim to study the efficacy & compare the result of TI & IUI in unexplained infertile couples with clomiphene citrate resulting in clinical pregnancy. **Methodology:** In this crossover observational study, total 60 patients were investigated with unexplained infertility were given COH, with clomiphene citrate followed by TI (group A) & IUI (group B), on not achieving pregnancy in either of the groups with three cycles each, these groups interchanged & received respective interventions. A positive UPT test was the comparing factor for assessing the effectiveness of the two interventions, i.e., TI & IUI. **Results:** Clinical pregnancy rates were seen both in COH/TI & COH/IUI 7.4% & 31% respectively (4 in TI & 13 in IUI), out of which 76.45% were viable pregnancy & 23.5% were non viable (1 from TI & 3 from IUI). **Interpretation & Conclusion:** Being a diagnosis of exclusion, treatment of unexplained infertility, has been shown by both TI & IUI in this study, however addition of IUI to ovulation induction gave better conception rates.

KEYWORDS : Unexplained infertility, controlled ovarian hyperstimulation, clomiphene citrate, timed intercourse, intrauterine insemination.

INTRODUCTION

Infertility is a disorder of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse¹. Infertility with an unknown cause or standard infertility is made by diagnosis of exclusions. When clinical investigations and tests for ovulation in the female partner with normal uterine cavity fails to identify any obvious barriers to conception, the couple can be put in the category of unexplained infertility. Unexplained infertility is a common problem, with prevalence between 5%-28% of the infertile population.² About 90% of couple should conceive within 12 months of unprotected intercourse. Now days some prefer to use the term subfertility, to describe the couple who delay longer than average in conceiving.

"Fecundability refers to the likelihood of becoming pregnant throughout each menstrual cycle then average which is thought to be 20% among fertile couples.³ Whereas fecundity is the probability that a cycle will result in a live birth.

From "reproductive health education" to Assisted Reproductive Technologies, there are several ways to manage infertility (ART).⁴

Over the past decades, there has been marked increased in the use of Controlled Ovarian Hyperstimulation (COH), followed by IUI, more common and widely accepted, replacing other insemination techniques, for unexplained infertility, increasing the cycle fecundability as combination of superovulation & deposition of the maximum active motile sperms as close to the oocyte, around the time of ovulation has strongly improved the chance of conception.

A breakthrough in the treatment of female infertility, particularly in cases where anovulatory causes of infertility existed, was the induction of ovulation by a variety of medications. A weak synthetic non-steroidal estrogenic agonist/antagonist known as clomiphene citrate (CC) was first created in 1956. It continues to be the most widely used medication for ovulation induction in the treatment of subfertility. Greenblatt et al. reported that it was effective at inducing ovulation in 1961.⁵

In advent of same, the present study was planned to compare the effectiveness of Timed Intercourse (TI) and Intra Uterine Insemination (IUI) in super ovulated couples taking Clomiphene Citrate for unexplained infertility that results in pregnancy, this study is proposed. Since ours is a tertiary care centre, the couples who came with unexplained infertility received superovulation by clomiphene citrate & IUI, after latest sperm preparation methods & TI by husbands' semen were compared.

Material & Methods

After approval and clearance from the institutional ethical committee this cross over study was done in Department of Obstetrics & Gynaecology at Index Medical College Hospital & Research Center, Indore on a total 60 couples attending infertility OPD who were eager to conceive and qualified the inclusion criteria.

The diagnosis of unexplained infertility was based on the investigations like modified criteria 2010 according to WHO for semen analysis for male partners & baseline USG TVS for regular uterine cavity with endometrial thickness, follicular study for size of follicles, hystrosalpingography for tubal patency & tests for ovarian reserve for female partners, hormonal assays & blood investigations for both the partners including LH, FSH, TSH, PRL, Testosterone, SHBG, & CBC, serology etc. Informed written valid consent was taken from each couple at the time of enrollment into the study.

The couples were randomly divided into 2 groups; Group A & Group B after being diagnosed with unexplained infertility

- Group A – TI Group (30 couples)
- Group B – IUI Group (30 couples)

All the couples were included in the study based on the following inclusion and exclusion criteria.

Inclusion criteria:

Infertile couples (primary or secondary infertility) with no previous history of treatment with ovulation induction drugs with no history of IUI.

1. Female partner with normal parameters
2. Male partner having normal semen parameters

Exclusion criteria:

1. Female partner with abnormal tubal function or any other uterine or ovarian factor suggesting cause of infertility.
2. Male partner having abnormal semen parameters.

Both the groups (female partner) were given Tab clomiphene citrate 50mg once a day for 5 days from day 2 to day 6 of the menstrual cycle followed by daily Follicular and endometrial thickness monitoring by TVS starting from Day 10, 12, 14 till the day of ovulation. Transvaginal sonography was done for the follicular monitoring which determined the day of ovulation. The female partner in both groups received Inj. Human Chorionic Gonadotrophin (HCG 5,000 IU IM when the Graffian follicular size was around 18-20mm size. Both TI &

IUI were timed 32-36 hours after HCG injection & all couples were strictly advised to maintain abstinence for four days before the expected time of ovulation until TI or IUI.

Group A: The couples were advised to have TI for 2 days (once in 24hrs) 36 hours after the trigger with injection HCG. The couples underwent 3 cycles of TI in group A till conception. Couples with failure of conception after 3 cycles of TI, underwent 3 cycles of IUI in group B.

Group B: The couples were subjected to IUI 36 hrs after stimulating with injection HCG. IUI was done using husband semen after preparing the semen sample by the 'Swim-Up' technique. Each couple received 3 cycles of IUI till conception. Failure of conception after 3 cycles had to undergo 3 cycles of TI in group A.

This was cross over observational study as both interventions were applied to both the groups. Female partner in both groups were asked to follow up on day 10 of missed periods. Urine pregnancy test (UPT) and TVS was performed for the visualization of the intrauterine gestational sac at 6 weeks of gestation. A positive UPT test was the determining factor for assessing the effectiveness of the two interventions i.e., IUI and TI. All pregnant women were followed up for pregnancy outcome and were analysed as viable or unviable pregnancy or pregnancy wastage. P wastage includes the abortions and perinatal mortality & later on for live birth/still birth & fetal demises.

For IUI, semen specimen was collected by masturbation after 2-3 days of abstinence. The ejaculate was allowed to liquefy for 20-30 minutes & was placed in double volume of pre-warmed (37 degree) HAM's F-10 media and centrifuged at 1000 rpm for 5 mins. (The ratio of semen media is 1:2). The supernatant is discarded & pellet at bottom is resuspended in 1ml of media & re-centrifuged. The pellet is added with 1 ml of media & is kept in incubator for 30-45 mins at an angle of 45 degree to allow the motile sperms to "swim up" to the top most layer of the cloud. After incubation, 0.5 – 1ml of active motile sperms are aspirated from the top layer which are used for insemination. The IUI procedure was completed within 10-15 minutes after preparation in which single IUI was performed using a flexible intrauterine cannula (Gynetics).

The cervix was exposed with Cusco's speculum, external os is cleaned gently with normal saline with a cotton swab, & the tip of processed semen of IUI cannula, preloaded with 0.5-1ml of processed semen sample, catheter is gently introduced into the uterine through external OS into the internal OS not touching the fundus & is injected very slowly over 3 minutes, to avoid regurgitation. The subject is allowed to rest for 20-30 minutes and was discharged with Tab Folic acid 5 mg once a day and tab Dydrogestrone 10 mg twice a day, both for 14 days.

Statistical Analysis

Especially designed pre-structured proforma was used for collecting the data. The data was also entered to master chart in Microsoft Excel 2016. It was imported to IBM SPSS ver-25 for analysis. Quantitative data was expressed in terms of mean and standard deviation and difference in means was tested by Student's t-test (for parametric) or Mann Whitney-U Test (for non-parametric). Qualitative data was expressed in terms of percentages and difference was tested by Chi-square test or Fisher's Exact test. P value of < 0.05 was considered as statistically significant.

Results

A total of 60 patients were enrolled and categorized into Group A of 30 patient who initially underwent three cycles of TI till conception, followed by the three cycles of IUI until conception and Group B of 30 patients who initially underwent three cycles of IUI until conception followed by three cycles of TI until conception.

In Group A, 9 (30%) cases reported positive UPT compared to 7 (23.3%) cases in Group B. The P value was 0.5593 which was statistically not significant (p<0.05).

Table 1: Comparison of Urine pregnancy test (UPT) in study groups

UPT	Group A		Group B		Total		p-value*
	No.	%	No.	%	No.	%	
Positive	9	30	7	23.3	16	26.66	0.5593
Negative	21	70	23	76.67	44	73.33	

Total	30	100	30	100	60	100	
*Calculated using the chi-square test. P<0.05 considered statistically significant							

In Group A, 30 patients underwent timed intercourse first, out of which 2 got pregnant (6.67%). The remaining 28 went for IUI after cross-over out of which 7 got pregnant (25%). Therefore, out of 58 patients after crossing over; there were 9 (15.51%) pregnancies in Group A.

Table 2: Outcome of Timed Intercourse and IUI cycles in Group A

Group A	No. of patients	No. of pregnancies	% of pregnancies
Timed intercourse	30	2	6.67
IUI	28	7	25
Total	58	9	15.51

In Group B, 30 patients underwent IUI, out of which 6 got pregnant (20%). The remaining 24 were subjected to timed intercourse, after cross-over out of which 2 got pregnant (8.33%). Therefore, out of 54 patients after crossing over, there were 8 (14.81%) pregnancies in Group B.

Table 3: Outcome of Timed Intercourse and IUI cycles in Group B

Group B	No. of patients	No. of pregnancies	% of pregnancies
IUI	30	6	20
Timed intercourse	24	2	8.33
Total	54	8	14.81

The pregnancy outcome in both the study groups who underwent timed intercourse and IUI. There were 17 pregnancies out of which 13 were viable pregnancies (76.45%) and 4 Non-Viable Pregnancy (23.5%).

Table 4: Pregnancy outcome in both study groups

Pregnancy outcome Status	Timed intercourse		IUI		Total	
	No. of pregnancy	% of pregnancy	No. of pregnancy	% of pregnancy	No. of pregnancy	% of pregnancy
Viable Pregnancy	3	75	10	76.92	13	76.45
Pregnancy wastage	1	25	3	23.1	4	23.5
Total	4	100	13	100	17	100

Table 5 shows the outcome of Timed Intercourse and IUI cycles with respect to Infertility. Out of 49 couples with primary infertility, there were 3 pregnancies (6.12%) in patients who underwent 42 cycles of timed intercourse. These primary infertile couples underwent 26 cycles of IUI and 11 (22.44%) conceived with that, while 1 couple out of 11 with secondary infertility conceived with timed intercourse and 2 conceived with IUI after undergoing 9 and 3 cycles of Timed intercourse and IUI respectively.

Table 5: Outcome of Timed Intercourse and IUI Cycles with Respect to Infertility Category

Category	No. of couples	Timed intercourse			IUI			Total no. of pregnancy
		No. of cycles	No. of pregnancy	%	No. of cycles	No. of pregnancy	%	
Primary infertility	49	42	3	6.12	26	11	22.44	14
Secondary infertility	11	9	1	9.1	3	2	18.18	3
Total	60	51	4	6.66	29	13	21.66	17

Table 6: Effect of number of cycles of treatment on pregnancy for Timed Intercourse and IUI in all patient categories combined

Cycle	Timed intercourse			IUI		
	No. of cycles	No. of pregnancies	% of pregnancies	No. of cycles	No. of pregnancies	% of pregnancies
1	1	0	0	1	7	53.8
2	2	0	0	2	4	30.7

3	3	4	100	3	2	6.67
Total	12	4		21	13	

Table 6: Effect of number of cycles of treatment on pregnancy for Timed Intercourse and IUI in all patient categories combined

Cycle no.	Timed intercourse			IUI		
	No. of cycles	No. of pregnancies	% of pregnancies	No. of cycles	No. of pregnancies	% of pregnancies
1	1	0	0	1	7	53.8
2	2	0	0	2	4	30.7
3	3	4	100	3	2	6.67
Total	12	4		21	13	

Table 6 shows the effect of number of cycles of treatment of Timed Intercourse and IUI on pregnancy in all patient categories.

Timed Intercourse: Of those pts who had 3 cycles of TI there were 4 pregnancies while those who had 2 or 1 cycle had no pregnancies.

Intrauterine Insemination: Of those pts who had 1 cycle of IUI there were 7 pregnancies while those who underwent 2 cycles had 4 pregnancies and with 3 cycles of IUI there were 2 pregnancies.

DISCUSSION

As many couples choose not to seek medical attention, statistics based on hospital data are difficult to analyses when it comes to infertility, whether it be primary or secondary. Our study had certain limitations to it as it was a small sample size over a short duration with just a fixed ovulation induction protocol and using a particular method of sperm preparation for the intervention of Intrauterine insemination. Our study however intended to make a humble effort to study the comparison of result of the two methods of IUI vs timed Intercourse in unexplained infertility after ovulation stimulation. It also aimed to study the efficacy of IUI and Timed intercourse with regard to pregnancy outcome.

Various factors like age of the wife and husband, years since marriage, type of infertility were analyzed quantitatively. The total pregnancy outcome in IUI and timed intercourse in the study groups was studied in this cross-over study design. The criteria used to evaluate the efficacy of the two therapies, IUI and TI, was a positive UPT Test. The outcome of the pregnancy i.e., viable or non-viable pregnancy, Pregnancy wastage, was studied. This study was done over a span of one and half years among 60 participants. The findings from our study are presented here, along with a comparison to earlier research published in the medical literature.

With regarding to the groups (including cross-over) the conception outcome i.e., positive UPT was seen in 9 cases from group A (30%) and 8 cases got pregnant from Group B. (23.3%) (Table No.1). According to the study groups, After and before cross over, there were in total 9 pregnancies, 7 and 2 with both IUI and Timed Intercourse respectively in Group A (Table No.2). While in Group B there were 8 pregnancies, 6 after IUI and 2 after timed intercourse. (Table No.3)

Defining the pregnancy outcome, there were 10 viable pregnancies and 3 P wastage with IUI while 3 viable pregnancies and 1 P wastage with Timed Intercourse. (Table No.4)

Timed Intercourse: The patient who underwent timed intercourse, out of the 4 patients, 1 delivered term live baby, while 3 are on follow up. **Intrauterine Insemination:** The patients who underwent IUI, out of 13 pregnancies, 4 underwent LSCS with one twin gestation and three singleton term live births. There were 4 pregnancy wastage, 2 being missed and incomplete abortion in the first trimester, 1 ectopic pregnancy, 1 biochemical pregnancy, while 5 are on follow up.

Discussing the effect of number of cycles on the pregnancy outcome, our study had a fixed number of cycles for each intervention. Of those patients who had 3 cycles of TI there was 4 pregnancy while those who had 1 or 2 cycles had 0 pregnancies. Of those patients who had 1 cycle of IUI there was 7 pregnancies while those who underwent 1 or 2 cycles had 2 and 4 pregnancies. (Table no.5,6)

In our study, CC has given better results and good prognosis for conception where ET on USG scan gives >8mm at ovulation which has given better conception rates in stimulated cycles.

Considerable controversy surrounds this simple form of infertility treatment called IUI and the conditions that respond to it.⁶ There is still scope for research for understanding the advantage of the addition of COH to IUI despite numerous reports done in couples with unexplained infertility.

Martinez et al.,⁷ reported the first randomized study on gonadotropin stimulated normal ovulatory cycles and compared the two modalities of TI and IUI and found no any significant differences. Our cross-over study did show some benefit of IUI over TI in ovulation stimulated cycles with CC in women with unexplained infertility. Pregnancy rates were 30% in Group A and 23.3% in group B in CC stimulated cycles. The majority of research have shown that IUI is only helpful when oligospermia and mild asthenozoospermia are the underlying causes.^{8,9}

Deaton et al.,¹⁰ conducted a cross-over experiment in 1990 comparing CC/IUI and timed intercourse with 67 couples and 298 treatment cycles. While the pregnancy outcome was not statistically different Between the two groups, the difference in fecundities was statistically significant.

Sonika et al.,¹¹ randomised prospective trial of intrauterine insemination versus timed intercourse in superovulated cycles with clomiphene revealed that adding IUI to ovulation induction did not increase conception rates in women with unexplained infertility.

However, Costello MF et al.,¹² (2004) reviewed effectiveness of CC with TI and IUI and concluded that CC combined with IUI is more effective than timed intercourse in the natural cycle at achieving pregnancy in couples with ovulatory infertility. However, treatment with gonadotrophins and IUI is superior to CC and IUI.

Sayanti Paul et al.,¹³ (2018) in her prospective RCT stated that there was no statistical significance of IUI over TI and raised the probability that the outcome of the procedure may not be well accepted.

Annabelle Sabu et al.,¹⁴ (2020) in her cross over study stated addition of IUI to ovulation induction has increased the cycle fecundability, but it does not improve the fecundity.

In our study cross over design, sample size: 60 couples, both interventions TI and IUI were applied to both the groups which concluded the pregnancy outcome, there were 10 viable pregnancies and 3 P wastage with IUI while 3 viable pregnancies and 1 P wastage with Timed Intercourse.

Controlled ovarian hyperstimulation with timed intercourse can however, help to achieve good results and cut the cost and discomfort of an invasive procedure like IUI. IUI is considered a comparatively invasive and time-consuming procedure involving expense due to the semen preparation technique and the skill of the doctor. It may cause some amount of discomfort to the patient and may increase the likelihood of infection. The determination of the cost-benefit ratio of addition of IUI to ovulation induction depends on the local cost of these interventions as well as the cost and availability of the drugs needed.

In spite of these shortcomings of IUI, there are also certain studies which offer substantiation of augmented success of the addition of IUI in treatment regimens for women with unexplained infertility. There is much scope and extent for further studies and various controlled trials which included both normal ovulatory and ovulation stimulated cycles in cases of unexplained infertility. Further in-depth analysis is crucial to settle on the advantages, cost-effectiveness and adverse side effects of IUI for infertility and understanding the mechanism by which IUI may improve pregnancy rate in couples with unexplained infertility is the need of the hour.

CONCLUSION

Both TI & IUI with ovulation stimulated cycles has shown positive pregnancy outcome in couples with unexplained infertility. Although many studies failed to show significant differences but overall ovulation induction revealed a higher PR in ovulation induced cycles with addition of IUI.

In our cross-over study, it suggests that ovulation induction with CC followed by IUI was much effective than CC in TI for achieving pregnancy in couples with unexplained infertility. Though TI is noninvasive & inexpensive to IUI, but IUI has proved to be initial

treatment option which is less invasive, less expensive and has enhanced success rates. IUI may help some couples to avoid the cost & inconveniences of more invasive technique such as GIFT & IVF.

REFERENCES

1. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. *Fertil Steril*. 2009; Vol. 92, pg. 1520-1524.
2. Healy DL, and Trounson AO. Female infertility (causes and treatment). *Lancet*. 1994;343:1539-1544
3. Jonathan S. Berek. Infertility. 15th edition. Berek & Novak's Gynaecology. New Delhi; Wolters Kluwer Health, India; 2012. p 1134.
4. Laffont, I. and Edelmann, R.J. (1994) Perceived support and counselling needs in relation to in vitro fertilization. *J. Psychosom. Obstet. Gynecol.*, 15, 183-188.
5. Sandro Gerli, M.D., Hossein Gholami, M.D., Antonio Manna, M.D., Antonio Scotto Di Frega, M.D., Costantino Vitiello, M.D., and Vittorio Unfer, M.D. Use of ethinyl estradiol to reverse the antiestrogenic effects of clomiphene citrate in patients undergoing intrauterine insemination: a comparative, randomized study. *Fertil Steril* Jan 2000;73(1):88
6. Allen NC, Herbert CM III, Maxson WS, Rogers BJ, Diamond MP, Wentz AC. Intrauterine insemination: a critical review. *Fertil Steril* 1985; 44: 569-75.
7. Martinez AR, Bernardus RE, Voorhorst FJ, Vermeiden JPW, Schoemaker J. Pregnancy rates after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles: a controlled study. *Fertil Steril* 1991; 55: 258-65.
8. Crosignani PG, Walters DE, Soliani A. 1991. The ESHRE multicentre trial on the treatment of unexplained infertility: a preliminary report. *Hum Reprod*. 6:953-958
9. Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JDF. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. *Cochrane Database Syst Rev* 2000; 2: CD000360.
10. Deaton JL, Gibson M, Blackmer KM, et al. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. *Fertil Steril* 1990;54:1083-8.
11. Sonika Agarwal and Sunneta Mittal. A randomised prospective trial of intrauterine insemination versus timed intercourse in superovulated cycles with clomiphene. *Indian J Med Res* 120, December 2004, p.519-522
12. Costello MF. Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. *Aust N Z J Obstet Gynaecol*. 2004 Apr; 44(2):93-102
13. Sayanti Paul, Saumen Mandal, Arghya Pal. *international journal of reproduction, contraception, obstetrics and gynaecology*. March 2019; Volume 8, issue 3, pg 1035-1040. Dept. of obs and gynae HIMs, dehradun, uttrakhand, INDIA
14. Vaddukut Annabelle Sabu, Sabrina Mhapankar, Sushil Kumar. *International journal of Scientific Study*; June 2020; Volume 8; Issue 3; 20-23; Dept. of Obs and Gynae MGM, Navi Mumbai, Maharashtra, INDIA