

## FACTORS AFFECTING THE SUCCESS OF INTRAUTERINE INSEMINATION- A CASE COMPARATIVE STUDY IN A TERTIARY HOSPITAL

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### ABSTRACT

#### BACKGROUND

IUI is one of the simple techniques of assisted reproductive technique for treating infertility by artificial insemination. It has the advantage of positioning good quality sperm with increased count prepared by special semen washing technique into the uterine cavity, so that factors like decreased sperm count, poor sperm motility, impenetrable or absent cervical mucus or antisperm antibodies can be overcome. Sperm preparation method includes wash and swim-up technique using Percoll gradient. IUI is done by simple method and does not require the elaborate setup, investment and personnel like the other procedures of ART.

The aims and objectives-

1. Factors associated with effectiveness of IUI among couples with primary infertility.
2. Factors studied include- Age of female partner, duration of infertility, menstrual regularity, menstrual flow, ovarian stimulation protocol, timing of IUI, endometrial thickness, number of cycles of IUI, luteal support, semen analysis findings.

#### MATERIALS AND METHODS

This is a case comparative study conducted in a tertiary hospital during three year period in which the forty women who conceived were considered as "study group" and another forty non-conceived women selected at random were taken as "control group."

#### RESULTS

Factors like age of female showed statistical significance- when the age of female increased from 20-24 years to 30 years and above, the rate of conception reduced from 50% to 9%. Other factors like menstrual regularity, menstrual flow timing of IUI and number of cycles of IUI yielded no significant association with conception rates. Regarding the mode of ovarian induction, 90% of conceived group was given controlled superovulation using clomiphene citrate and gonadotrophins and 39% had ovulation triggered by HCG, which were statistically significant. In the conceived group, the mean endometrial thickness was 9.3 mm contrary to 7.8 mm in the non-conceived group. Minimum duration of infertility has got an increased conception rate- 3.8 years in conceived group against 5.1 years in non-conceived group. Regarding semen parameters, active motile sperms showed a positive correlation with the success rate.

#### CONCLUSION

IUI entails superovulation, timed administration of HCG, sperm preparation and sperm insemination into the uterine cavity. It is an effective, invasive, relatively simple and economical method of treatment of infertility. IUI is proved most beneficial to young women with patent fallopian tubes, no ovulatory disorders, mild-to-moderate degree of endometriosis and no severe degree of male factor infertility.

#### KEYWORDS

Intrauterine Insemination, Semen Preparation, Ovarian Stimulation, Swim-Up Method.

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#### BACKGROUND

IUI (intrauterine insemination) is one of the simple techniques of assisted reproductive techniques for treating infertility by artificial insemination. Intrauterine insemination has the great advantage that an increased number of good quality sperms are being positioned above the cervix inside the uterine cavity close to the oocyte in the fallopian tube. The sperm contacts the ova between the distal end fallopian tube and the uterus, when decreased sperm count, poor sperm motility, impenetrable or absent cervical mucus or antisperm antibodies are present.

The rationale for the use of IUI is to reduce the effect of factors such as vaginal acidity and cervical mucus hostility and to benefit from the deposition of a bolus of concentrated motile morphologically normal sperm as close as possible to oocytes. Sperm preparation methods include wash and swim-up technique and the use of Percoll gradients and this has resulted in a significant reduction in side effects associated with use of neat semen for IUI such as painful uterine cramps, collapse and infection with relatively no complications.

IUI is done by simple methods and does not require the elaborate setup investment and personnel like the other procedures of reproductive medicine. In ART centres, IUI represents the first step of the therapy concept in the treatment of infertility.

### Counseling

Before starting IUI, couples are informed of the expected course, the procedure, the risks and the complication, expected outcome and the cost. Counseling must be adequate and realistic expectation for pregnancy rates should be explained.

### Indication for IUI

- Unexplained infertility.
- Cervical factor- cervical mucus hostility and poor cervical mucus.
- Endometriosis- mild-to-moderate.
- Ovulatory dysfunction.
- Male factor- diagnosed if sperm concentration <15 million/mL, total motility (a+b) <32%, normal morphology <4%.
- Immunological factor.
- Combined male and female factors.
- Coital dysfunction.

### Contraindications for IUI

- Tubal pathology.
- Genital tract infections.
- Genetic abnormality in male partner.
- Unexplained genital tract bleeding.
- Multiple failures at IUI (more than six).

### Semen Analysis and Sperm Preparation

A detailed semen analysis is required as part of the initial diagnostic work up of infertile couple before the decision for IUI is made. The semen sample should be properly labeled to avoid mix-up.

Normal values of standard semen analysis (by WHO 2010)

1. Semen volume  $\geq$ 1.5 mL.
2. Sperm concentration >15 million/mL.
3. Total sperm number >39 million/ejaculate.
4. Progressive motility >32%.
5. Total motility (PR+NP) >40%.
6. Vitality >58%.
7. Normal morphology >4%.
8. White blood cell <2 million/mL.

### Ideal Sperm Preparation

According to Pardo and Banalls 1989, any method used for sperm preparation should be able to achieve from the semen sample, largest number of sperms of good motility and normal morphology. These sperms should be free from seminal plasma leucocytes, dead and abnormal sperm, cellular debris and bacteria. To achieve a better IUI conception rate, the sperm concentration of at least one million spermatozoa per mL is advised. The preparation method mimics the action of cervix and cervical mucus yielding high concentration of capacitated motile sperms.

Some sperm preparation methods include;

- Wash and swim-up method.
- Density gradient method.
- Direct layers.
- Self-migration sedimentation.
- Swim-down method.

Choice of sperm preparation method depends on the characteristics of semen sample. When sperm parameters such as concentration and motility are within the normal range. The direct swim-up method is preferred. For significantly oligozoospermic, teratozoospermic and asthenozoospermic samples, density gradient centrifugation is preferred as it leads to a higher recovery of motile sperms Cooper TG and et al (2010).<sup>1</sup>

### MATERIALS AND METHODS

The study was designed as a case comparative study in which the infertile couples who conceived during the study period has been designed as 'study group' and the non-conceived as 'control group.' The setting of the study was the Fertility Centre of the Department of Obstetrics and Gynaecology, SAT Hospital Medical College, Trivandrum. The population for the study was all the infertile couples posted for Intrauterine Insemination (IUI) during the study period. The population size was estimated as 400 cases out of which 10% were selected as sample for the study in each group. The sampling procedure was systematic random sampling for the selection of control group. For selection of study group, a consensus type was followed and 40 consecutive conceived cases of IUI were taken into the study.

### Selection Criteria

1. Female partner age under 40 yrs.
2. Minimum of one year of infertility.
3. Normal tubal factor.
4. Presumptive proof of ovulation.

All those cases where both male and female were having secondary infertility and those who had disease, both systemic as well as local pathology were excluded from the study and others included.

### **Sperm Preparation Method Used in the Study- Wash and Swim-Up Method**

1. Pipette 4 mL of culture medium (Quinn's solution) into a centrifuge tube.
2. Pipette 1 mL of liquefied semen and mix.
3. Centrifuge the diluted sperm at 500 g for 10 minutes, remove the supernatant.
4. Re-suspend the pellet in 2 mL culture medium and centrifuge at 250 g for 5 minutes, remove the supernatant.
5. 1 mL of medium is layered onto the pellet.
6. Transfer the tube carefully to 37 deg. C incubate and store with 5% CO<sub>2</sub> for 60 minutes at a slanting position of 45 deg.
7. Carefully remove 0.4 mL of the supernatant motile upper fraction from the pellet and used for IUI.

### **Following are the Basic Needs for IUI**

1. Hand gloves, which are powder free.
2. Sterilised paper towel, cotton wool balls, gauze pieces and drapes.
3. IUI tray consisting of a speculum, tenaculum, sponge and artery forceps.
4. 1 mL syringe for insemination.
5. IUI catheter.
6. A good light source to expose cervix and vagina.
7. A table in a well-equipped IUI room.

Natural cycle is offered to patients with no thyroid derangement, hyperprolactinaemia, hyperandrogenemia and excellent cycle quality.

### **Stimulated Cycle**

The following drugs were used for stimulation.

1. Clomiphene citrate- 50 mg daily from D<sub>2</sub>-D<sub>6</sub>, gradually increase up to a maximum daily dose of 150 mg in subsequent cycles.
2. Gonadotrophins - Both FSH and HMG were used.

Whenever required ovulation was triggered with 5000 IU of HCG.

The rationale for use of super ovulation with IUI is to increase the number of oocytes available for insemination and thus the chance of implantation occurring. Stimulation also increases steroid production, which may in turn decrease the cervical hostility and improve the chance of fertilisation and embryo implantation. Even though, there is increased success rate with superovulation the cost is high and chance of side effects like ovarian hyperstimulation syndrome and increased maternal and neonatal complication associated with multiple pregnancies.

### **Ovulation Monitoring and Timing of IUI**

Ovulation was monitored by transvaginal ultrasound. The best time of IUI procedure to achieve the best conception rate should be at the time of ovulation and the procedure of IUI was done 24 hrs. and 36-48 hrs. (on the day of ovulation) after HCG injection. The expectation is that viable

spermatozoa will be present in the female genital tract at the time of ovulation. Cycle monitoring, administration of HCG and insemination should allow satisfactory overlap of the period of viability of the inseminated spermatozoa and ovulated oocytes. Oocyte release after HCG injection occurs in waves and not all at once. Therefore, the second insemination is carried out 48 hrs. after HCG injection. In patients with natural or spontaneous cycles, the standard regimen is of two IUI procedures.

### **Number of IUI**

To achieve the optimum conception rate, two IUI are advised, since these two procedures will provide enough time period to cover the survival duration of oocyte, which may be released at any time. If one procedure is done, the chance of sperm survival for longer period is doubtful.

### **Techniques of IUI**

All aseptic precautions are carried out. Cervix and uterine cavity are handled gently avoiding any trivial trauma to these structures. Patient is put in dorsal supine position with semiflexed legs or lithotomy position. Vulva is well exposed with a good light. Vulva and vagina are cleaned with normal saline. Speculum is inserted in vagina and cervix is properly visualised. The exposed cervix is gently wiped with cotton wool ball soaked in normal saline. Now, insert the IUI catheter, which is loaded with sperm volume of 0.4 mL into the uterine cavity. This catheter should be passed beyond the internal os.

In conventional method of IUI, the catheter is attached to 1 mL syringe and sperm sample (0.4 mL) is drawn up the catheter. By doing so, the dead space is estimated from the IUI catheter. Now, this loaded catheter is passed through the cervical canal into the uterine cavity. Meanwhile, one should monitor the pulse of patient and she should be asked whether she felt any severe pain while passing the catheter. If severe pain is felt, then IUI should be done a little later. Once the catheter is inside the uterine cavity, the plunger of the 1 mL syringe is pushed slowly to expel the spermatozoa-containing fluid into the uterine cavity. Care should be taken to push it very slowly to avoid any back flow of the sperm fluid. After this, the catheter is withdrawn gently and slowly from the uterine cavity and cervical canal. Speculum is also removed. After the IUI procedure, she is kept in Trendelenburg's position for 15-30 minutes to ensure that no sperm fluid comes out. Alternatively, keeping a pillow under the hips elevates the patient's hips. Later, patient is allowed to go home.

In case difficulty is met with while negotiating the catheter through internal os, slight traction on cervix will help to straighten the cervicouterine angle. Also, a stiff or firm IUI catheter could be useful for these women. For conventional IUI, one can use various types of catheter like Makler's cannula, Jelco sheath, Gynetics catheter. In our study, we used Sun catheters.

Drugs given for luteal support

- Micronized progesterone.
- Dydrogesterone.

In some cases, luteal support was not given.

The data were collected on a prestructured pretested proforma after pilot study. The collection procedure was done by the investigator herself. The important outcome variables include duration of infertility, menstrual history, age, endometrial thickness, timing of IUI, luteal support etc. Regarding male characteristics, the semen analysis findings were also gathered.

The data collected were entered into a master chart and statistical constant such as mean, standard deviation, percentage, etc. were computed. Also to test the hypothesis, the Student's 't' test was applied in the case of quantitative data and chi-square test was applied in case of qualitative data.

All the computations were made with the help of computer packages. Diagnosis and charts were also drawn wherever necessary to substantiate the most important findings.

**RESULTS**

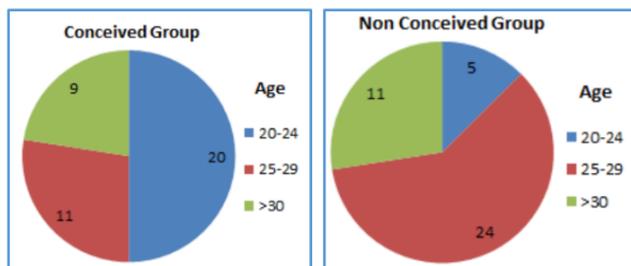
The study was conducted at SAT Hospital, Thiruvananthapuram. During the study period, 40 cases who conceived by IUI were considered as 'study group' and every next non-conceived case as 'control group'.

**Age of Female Partner**

Age (In Years)	Conceived Group		Non-Conceived Group	
	No.	%	No.	%
20-24	20	50	5	12
25-29	11	28	24	60
>30	9	22	11	28
<b>Total</b>	<b>40</b>	<b>100</b>	<b>40</b>	<b>100</b>

**Table 1. Distribution of Conceived/Non-Conceived Cases According to Age of Female**

$\chi^2 = 9.9, d.f. = 1; p < 0.01$



From table 1, it is observed that 50% of the conceived women were in the age group 20-24 years in place of only 12% in the non-conceived group. Similarly, the percentage of women in the non-conceived group increased to 60% in the age group 25-29 yrs. in place of 27% in the conceived group. In fact, 88% of the women who did not conceive happen to be in 25 and above age group, whereas it was

only 50% in the conceived group. The association between the age of female partner and success IUI has been established statistically. This has been reported by various other studies.

**Duration of Infertility**

Group	Duration of Infertility (Year)		t-value	p-value
	Mean	S.D.		
Conceived	3.8	1.5	2.5	<0.05 (significant)
Non-Conceived	5.1	2.7		

**Table 2. Mean and S.D. of Duration of Infertility and Level of Significance**

It is seen that the mean duration of infertility in the conceived group was 3.8 yrs. when compared to 5.1 yrs. of the non-conceived group. Thus, it is evident that the duration of infertility had more chances of statistically by Student's 't' test and was found to be significant ( $p < 0.05$ ).

**Ovarian Stimulation**

Method of Stimulation	Conceived Group		Non-Conceived	
	Number	%	Number	%
Natural cycle	4	10	7	18
Clomiphene citrate/Gn	36	90	33	82

**Table 3. Distribution According to Ovarian Stimulation**

$\chi^2 = 4.2, df = 1, p < 0.05 (S)$

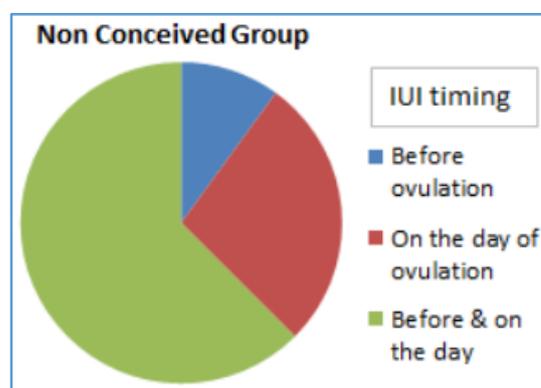
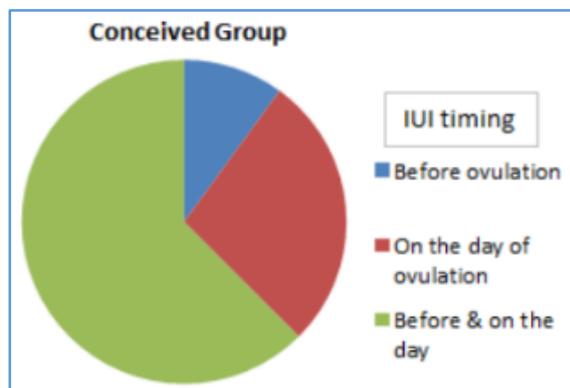
In the present study, the success rate was high among women who were given stimulation like clomiphene citrate and gonadotrophins. The percentage of conceived women in the natural cycle was only 10%, whereas the corresponding percentage in the non-conceived group was 18%. At the same time, those who conceived in the stimulated in 36 cases and increased effectiveness of ovarian stimulation was established statistically with  $p$ -value  $< 0.05$ .

**Timing of IUI**

Timing of IUI	Conceived Group		Non-Conceived	
	Number	%	Number	%
Before ovulation	6	15	4	10
On the day of ovulation	8	20	11	27.5
Before and on the day of ovulation	26	65	25	62.5

**Table 4. Distribution According to Timing of IUI**

$\chi^2 = 0.95, df=2, p > 0.05 (NS)$ .

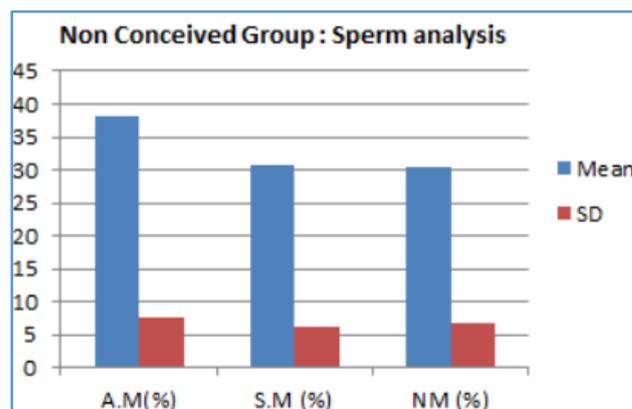
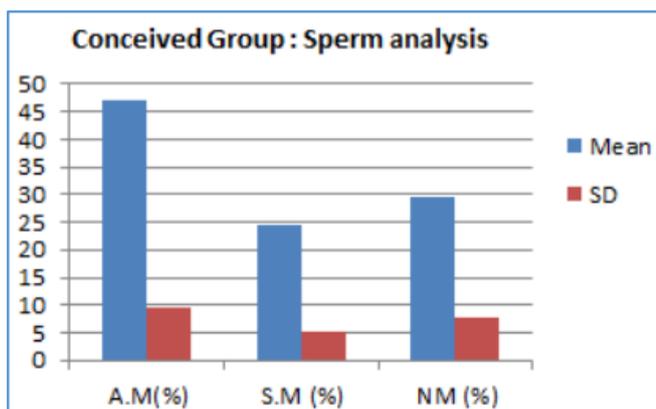


It is observed that in 65% of the conceived group IUI was done before as well as on the day of ovulation whereas the corresponding percentage in the non-conceived group was 62.5%. Out of the remaining cases of conceived group, 15% were inseminated before ovulation and 20% on the day of ovulation. Even in the case of non-conceived group, more or less similar pattern was observed. The 'p' value also showed no significant association between the timings of IUI and success rate.

**Semen Analysis Finding**

Sperm Analysis Finding	Conceived		Non-Conceived		't' value	'p' value
	Mean	S.D.	Mean	S.D.		
A.M. (%)	47.1	9.7	38.1	7.7	4.4	<0.01
S.M. (%)	24.5	5.2	30.7	6.1	4.7	<0.01
N.M. (%)	29.5	7.7	30.5	6.6	0.60	>0.05 (NS)
<b>Total Count (Million/mL)</b>	<b>59.3</b>	<b>22.7</b>	<b>58.4</b>	<b>24.0</b>	<b>0.16</b>	<b>&gt;0.05 (NS)</b>

*Table 5. Mean and S.D. of Semen Analysis Findings and Level of Significance*



From the above table, it is observed that the mean percentage of active motile spermatozoa was 47.1% in conceived group whereas it was only 38.1% in the non-conceived group. Thus there was a mean reduction in the mean active motile spermatozoa level in the non-conceived group compared to conceived group. The statistical test showed the difference as highly significant (t=4.4, p<0.01). At the same time, the difference noted in the percentage of sluggishly motile spermatozoa turned out to be significant with a 'p' value <0.01. The nonmotile spermatozoa in the conceived group was 29.5 and non-conceived group 30.5, which was statistically insignificant.

In the case of total count, the conceived group had a mean of 59.3 million compared to 58.4 million in the non-conceived group. Numerically, it appears that the mean total

count was rather high in the conceived group, but was not significant statistically.

**DISCUSSION**

The demographic factor like age of female showed statistical significance- a strong positive correlation of effectiveness of IUI with age of the women. When the age of female partner increased from 20-24 years to 30 yrs. and above, the rate of conceptions reduced from 50% to 9%. Goverde et al (2000)<sup>2</sup> has statistically proven the importance of woman's age as a determinant of the chance of conception with IUI in a randomised trial on IUI or IVF in subfertility and male subfertility.

Other factors like menstrual regularity, menstrual flow, timing of IUI, number of cycles of IUI yielded, no significant

association with conception rate. Regarding the number of insemination per cycle, Osuna C et al 2001,<sup>3</sup> and Ragni G et al 1999<sup>4</sup> on a randomised prospective trial comparing two inseminations versus one insemination concluded that pregnancy rate per cycle was somewhat higher in the two inseminations per cycle group (14.9% vs. 11.4%) even though these were not statistically significant. An article by Guzick DS<sup>5</sup> in *Fertility Sterility* 2004 July states that one well-timed insemination within several hours of ovulation represents a reasonable balance between efficacy and cost. Ransom et al 1994,<sup>6</sup> observed no difference in the results when comparing the number of insemination per cycle.

Regarding the mode of ovarian induction, it was definitely advantageous for increasing the conception rate because, 90% of conceived group was given controlled superovulation using drugs like clomiphene citrate and gonadotrophins and 39% had their ovulation triggered by HCG, which were statistically significant. Hughes E.G. (1997)<sup>7</sup> evaluated the effectiveness of IUI with or without ovarian stimulation using gonadotrophin. It was concluded that there was a significant improvement with IUI following ovulation induction.

The role of endometrial thickness is proven beyond doubt in the present study. In the conceived group, the mean endometrial thickness was 9.3 mm contrary to 7.8 mm in the non-conceived group ( $p < 0.01$ ). Endometrial thickness, which measures between 10 and 14 mm at the time of ovulation. Blumenfeld 1990<sup>8</sup> is of prognostic importance in the success of IUI.

Regarding duration of infertility, it is seen that women with minimum duration of infertility has got an increased conception rate. Here, the mean duration of infertility in the conceived group is 3.8 yrs. when compared to 5.1 yrs. of the non-conceived group with a 'p' value, 0.05, which is significant.

With regard to semen analysis findings, active motile spermatozoa showed a positive correlation with the success rate. Also, the percentage of nonmotile spermatozoa showed a negative correlation. Van Voorhis BJ et al (2001)<sup>9</sup> in a retrospective cohort study on the effect of total motile sperm count on the efficacy and cost effectiveness of IUI has shown that the average total motile sperm count in the ejaculate was an important factor with a threshold value of 10 million/mL.

## CONCLUSION

Intrauterine insemination entails super ovulation, timed administration of human chorionic gonadotrophin, sperm preparation and sperm insemination into the uterine cavity.

IUI is an effective, invasive, relatively simple and economical method of treatment of infertility. IUI is proved to be most beneficial to young women with patent fallopian tubes, with no ovulatory disorders, mild-to-moderate degree of endometriosis and no severe degree of male factor infertility. All couples require elaborate advise and counseling about the method, the effectiveness and the complication of the treatment.

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