Original Article

Determinants of Success in Intra-uterine Insemination

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Abstract

Background : Little progress has been made over the years to improve the success rate of Intra-uterine Insemination (IUI). We evaluated the independent factors that contribute to the success of an IUI cycle.

Material and Methods : We performed a prospective study including 666 IUI cycles from February, 2018 to April, 2019. All the couples undergoing IUI/Controlled Ovarian Stimulation with IUI for treatment of unexplained infertility, male factor (mild oligozoospermia, ejaculatory disorders), anovulation, mild endometriosis, tubal factor with at least one tube patent and sero-discordant couples were included in the study conducted at a level II ART clinic in a Tertiary Care Hospital. Factors affecting success rate of IUI were analysed.

Results : There was a decline in the Clinical Pregnancy Rate (CPR) with the declining age of the women (>29 years). The CPR of the first, second, third IUI cycles were 11.84%, 11.49% and 9.9%, respectively. The highest CPR was observed in women with Polycystic Ovary Syndrome (PCOS) (16.16%, p=0.04) followed by couples with different male factor infertility(14.3%, p=0.349). Endometrial thickness on the day of trigger <8.9mm significantly decreased the chance of pregnancy (p= 0.0315). The Lowest Total Motile Sperm Count (TMSC) pre-wash at which pregnancy was achieved after an IUI was 8 million. The success rate of an IUI cycle was highest with human menopausal gonadotropin used alone (33.33%) followed by letrozole with human Menopausal Gonadotropin (14.29%) and clomiphene with human Menopausal Gonadotropin (9.63%).

Conclusion : PCOS, ovulation induction with human menopausal gonadotropin with or without clomiphene or letrozole and endometrial thickness >8.9 mm are associated with better clinical pregnancy rates.

Key words : Clinical Pregnancy Rate, Controlled Ovarian Stimulation, Endometrial Thickness, Infertility, Intra-uterine Insemination, Male Factor Infertility, Total Motile Sperm Count.

Infertility is estimated to affect nearly 68 million people worldwide[1,2]. The problem is prevalent in both developing and developed nations. The treatment options for this vary from first line simple measures like Medically Assisted Reproduction (MAR) ie, Ovulation induction with Intra-uterine Insemination (IUI) to elaborate and expensive Assisted Reproductive Techniques (ART) like In-Vitro Fertilization (IVF) and Intra-cytoplasmic Sperm Injection (ICSI) etc.

Intra-uterine Insemination (IUI) is an assisted reproductive technique that involves the deposition of a processed semen sample in the upper uterine cavity, overcoming natural barriers to sperm ascent in the female reproductive tract[3]. Since the introduction of IUI by Cohen in 1962[4], it has been widely used as a first line treatment in anovulatory infertility, mild male factor Infertility, patients with minimal to mild endometriosis and unexplained Infertility. It has the advantage of being a simple, non-invasive, inexpensive and effective option compared to other Assisted Reproductive Techniques. It enhances the likelihood of a maximum number of healthy sperms reaching the site of fertilization[5]. Barring a few cases like bilateral tubal block, most

Editor's Comment :

- This research, encompassing 666 IUI cycles, highlights the critical importance of a comprehensive and precise diagnostic workup for couples seeking fertility treatment.
- Findings illustrate how such a thorough evaluation can expand the applicability of IUI as a first-line intervention, thereby offering a less invasive and more economical alternative to IVF for many patients. Moreover, a robust understanding of key determinants of IUI success empowers clinicians to offer highly personalized and evidence-based counseling, managing expectations and improving patient satisfaction.

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cases of severe endometriosis and severe male factor infertility, IUI must be attempted in all cases of infertility as a first line of treatment. However, the success rate of this procedure continues to remain low and is reported to vary from 10 to 20%[6]. Little progress has been made over the years to improve the success rate of IUI. The principle and technique of the procedure has essentially remained the same over the years. However, a number of advances have come up in the types of stimulation protocols, gonadotropins, sperm preparation techniques and ultrasound monitoring which have resulted in promising pregnancy rates with IUI[3].

In a retrospective study, Ahmed B, *et al* did not find any significant difference between various stimulation protocols in ovulatory women undergoing ovulation induction and IUI. Age, duration of infertility, number of mature ovarian follicles and endometrial thickness were found to be important predictors of outcomes of IUI. They showed that IUI in general, even in a young age group, had an overall pregnancy rate of 21.58% and the results were equal to those achieved with IVF[1].

Kastury, *et al*[7] concluded from a retrospective study, showed that motile sperm count in the unprocessed semen and total motile sperm inseminated were significant factors associated with the occurrence of pregnancy. The age of female, type of ovarian stimulation, gonadotropins were statistically significant in predicting a positive outcome. Gonadotropin stimulation improved the outcome by 30%.

If IUI results are optimized by a careful selection of patients and treatment regimes, several million couples worldwide will benefit from this simple procedure and will not need to undergo the elaborate and expensive ART procedures[5].

In this study we attempt to ascertain the independent variables which affect the success rate of an IUI cycle and factors which optimize the clinical pregnancy rates in IUI cycles.

Aims and Objectives

To ascertain the independent factors that contribute to the success in an IUI cycle.

Primary Objective :

(1) To determine the Clinical pregnancy rate after IUI

Secondary Objective :

(1) To determine the optimum endometrial thickness at the time of ovulation trigger.

(2) To determine the desirable pre-wash and post-wash Total Motile Sperm Concentration recommended for pregnancy.

Materials and Methods

A prospective study was conducted in a level II ART Clinic, at a Tertiary Care Hospital from February, 2018 till April, 2019. The study was started after obtaining ethical clearance from Institute Ethics Committee. Informed consent was taken from all participants before inclusion into the study.

Inclusion criteria :

All the couples undergoing IUI/ Controlled Ovarian Stimulation with IUI for the treatment of unexplained infertility, male factor (mild oligozoospermia : 10-20 million sperms/ml, ejaculatory disorders), anovulation, minimal and mild endometriosis, tubal factor with at least one tube patent and sero-discordant couples were included in the study.

Exclusion Criteria :

The following patients were excluded from the study:

(1) Moderate to severe endometriosis.

(2) Severe male factor infertility (pre-wash Total Motile Sperm count <10 million/ml) (however, if a patient with previous normal count was found to have a low count on the day of IUI the cycle was not cancelled).

(3) Bilateral tubal block.

The following data was registered for the couples who met the eligibility criteria in a prestructured proforma: patient and partners age primary/secondary Infertility, duration of infertility, diagnosis, type of ovarian stimulation protocol used, endometrial thickness on the day of trigger, pre-wash & postwash total motile sperm count.

Definitions :

Male factor Infertility was defined as per WHO Guidelines 2010 ie, total sperm concentration <15 million/ml, normal morphology <4% and progressive motility <32% in the pre-wash sample[8].

Unexplained Infertility was assigned in the couples in whom the standard investigations for Infertility

evaluation were normal (ovulatory cycles, normal semen analysis and both tubes patent by hysterosalpingogram or laparoscopy)[9].

Minimal (score: 1 to 5) and mild (score 6-15) endometriosis were defined according to revised AFS Criteria[9]. Polycystic Ovarian Syndrome (PCOS) was diagnosed using the Rotterdam's criteria: any 2 of the following 3 criteria :

(1) Oligo-ovulation/ anovulation.

(2) Clinical or bio-chemical evidence of hyperandrogenism.

(3) Polycystic ovarian morphology (PCOM)- defined as in either ovary ovarian volume ≥10ml (ensuring no corporus luteum, cyst or dominant follicle) or/and follicle number per ovary ≥20 follicles[10].

Ovulation Induction :

The couples recruited for the study were asked to report on day 2 - day 5 of the menstrual cycle. A baseline transvaginal scan was done using 8 megahertz transducer. A note was made of the follicle count per ovary and endometrial thickness. Ovulation induction with clomiphene citrate (100mg once a day for 5 days) or letrozole (2.5 mg once a day for 5 days) was initiated. They were called for a follow up 5-6 days later. If the follicles were not recruited, urinary gonadotropins (HmG) were added in dose varying from 37.5mg, 75mg to 150mg per day depending upon the patient profile. The aim of the stimulation was to achieve a response of 1 to 3 follicles. The cycle was cancelled if >3 follicles reached the size of 16mm or more. A trigger for ovulation was given with inj. Human chorionic gonadotropin 10,000 units when the leading follicle reached the size of 18-22mm. An IUI was planned 36 hours later or a double IUI 12hours and 24 hours post trigger in patients with male factor infertility and in cases where there was rupture of follicles over two days in succession.

Semen preparation : On the day of planned IUI, the husband was instructed to collect the semen in the IUI laboratory. The semen was analyzed for volume, count, motility and was then prepared by swim up or double-density gradient method. The post-wash sample was analyzed and IUI performed using a soft catheter with an insemination volume of 0.5ml. The patients were advised a rest of 15 min after the procedure.

Micronised progesterone 200mg vaginal insert or 200mg twice a day were added post-ovulation to provide luteal phase support. In patients non-compliant to micronized progesterone, dydrogesterone 10 mg twice a day was prescribed instead. The women were called 14 days later for a urine HCG/ serum HCG test. A clinical pregnancy was demonstrated by a positive HCG test (urine/serum) and an ultrasound showing intrauterine Gestation sac/ fetal node with cardiac activity.

Statistical method : Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows :

(1) Quantitative variables were compared using Mann-Whitney Test (as the data sets were not normally distributed) between the two groups.

(2) Qualitative variables were correlated using Chi-Square test/Fisher's Exact test.

(3) Receiver operating characteristic curve was used to find out cut off point of parameters for predicting success.

A p-value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Analysis of 666 IUI cycles was performed over a period of 15 months. Detailed patient characteristics are given in the Table 1. Mean female age and husband age was 28.23 ± 3.86 years and 31.6 ± 4.49 years, respectively. The oldest woman to conceive was 36 years old. There was a decline in Clinical Pregnancy Rate (CPR), with increasing age of the women (age >29 years). However, the difference did not reach statistical significance (p value - 0.54)(Table 3).

Out of the 666 IUI cycles studied, 283, 154, 91, 69 women underwent first, second, third, fourth or more IUI cycle, respectively. The CPR of the first, second, third IUI cycles were 11.84%, 11.49% and 9.9%, respectively and it dropped significantly after the fourth IUI (2.13%)(Table 4).

The mean duration of Infertility was 6 years. No correlation was observed between duration of

Table 1 — *Correlation of Patients' Characteristics with the Success of IUI*

	Success		P value
	No (N=597)	Yes (N=69)	
Age (W), in years			
Mean±SD	28.26 ± 3.87	27.96 ± 3.78	0.541
Age (H), in years			
Mean±SD	31.62 ± 4.49	31.44 ± 4.47	0.692
Duration of Infertility			
Median (IQR)	6 (1.5-21)	5 (3.4-9)	0.358
ET on the day of trigger, in mm			
Mean ± SD	8.47 ± 1.91	9.09 ± 2.02	0.034
Pre wash total sperm motility	(N=563)	(N=60)	
Mean ± SD	38.06 ± 13.5	39.4 ± 12.42	0.541
Median (IQR)	38.5 (30-48.7)	39 (32.5-49)	
Post wash total sperm motility	(N=594)	(N=69)	
Mean ± SD	49.1 ± 17.2	50.3 ± 14.4	0.774
Median (IQR)	52.3(38.3-61.7)	52.3(40-58.2)	

SD = Standard Deviation, IQR = Inter Quartile Range

infertility and success in an IUI cycle (p value-0.36)(Table 3).

A total of 403 (60.5)% of women presented with primary infertility. The common causes of infertility identified were PCOS (14.86%), Unexplained (57.21%), tubal factor (20.87%), male factor (7.36%), uterine (2.10%), Poor Ovarian reserve (4.05%) and endometriosis (3.75%)(Table 2).

The total Clinical Pregnancy Rate (CPR) per cycle was 10.4%. The highest clinical pregnancy rate was observed in women with PCOS (16.16%, p value-0.04) followed by couples with different male factor infertility (14.3%, p value - 0.349). However, the success rate of different groups did not show statistical significance as compared to former (Table 5). The success rate was lower in women with Endometriosis (4.00%) and h/o Tuberculosis (6.25%). However, it did not reach statistical significance.

Table 2 — *Distribution of causes of Infertility among the Study Population*

	N = 666 (Percentage)
Infertility : Primary	403(60.5%)
Secondary	263 (39.5%)
PCOS	99 (14.9%)
Unexplained	352 (52.8%)
Endometriosis	25 (3.7%)
Tubal	109 (16.4%)
H/o of tuberculosis	32 (4.8%)
Poor ovarian reserve	27 (4.1%)
Hypothyroid	49 (7.4%)
Ectopic pregnancy	23 (3.5%)
Asherman's syndrome	2 (0.3%)
Fibroid uterus	2 (0.3%)
Male factor	49 (7.4%)
Hyperprolactenemia	7 (1.1%)
Mulerian Anomalies	10 (1.5%)

Table 3 — *Determinants of achieving Clinical Pregnancy after IUI*

	Area under curve	Standard error	Sensitivity	Specificity	P value
Age (W)	0.52	0.04	71	36.3	0.53
Age (H)	0.51	0.04	73.9	32.3	0.69
Duration of infertility	0.53	0.04	40.6	66.3	0.37
ET on the day of trigger	0.57	0.04	54.4	59.9	0.03
Pre wash total motile sperm count	0.52	0.04	86.7	21.3	0.57
Post wash total motile sperm count	0.51	0.03	65.2	43.3	0.75

Endometrial thickness on the day of trigger <8.9mm significantly decreased the chance of pregnancy (p value- 0.0315) (Table 3).

The Lowest Total Motile Sperm Count (TMSC) pre-wash at which pregnancy was achieved after an IUI was 8 million.

Protocol used for ovarian stimulation affected the success rate of the cycle (Table 6). It was highest with human menopausal gonadotropin used alone (33.33%) followed by letrozole with human menopausal gonadotropin (14.29%) and clomiphene with human menopausal gonadotropin (9.63%).

A few women (47) underwent double IUI once at 12 hours followed by 24 hours post trigger instead of a single IUI at 36 hrs, due to non-availability of the couple for single IUI at 36 hrs. The CPR was 14.89%

Table 4 — *Success Rate Achieved after Each Cycle of IUI*

Cycle number	Success (N) (Percentage)	P value
1	38 (11.84%)	
2	20 (11.49%)	
3	10 (9.9%)	0.13
4	1 (2.13%)	
>4	0 (0%)	
Total	69 (10.36%)	

Table 5 — *Clinical Profile of Patients in Successful IUI Cycles*

N=666	Success 69 (Percentage)	P value
PCOS	16 (2.5%)	0.04*
Unexplained	36 (5.5%)	0.9
Endometriosis	1 (0.2%)	0.5
Tubal	10 (1.5%)	0.66
H/o of Tuberculosis	2 (0.4%)	0.76
Poor ovarian reserve	3 (0.6%)	0.75
Male Factor	7 (0.9%)	0.35

Table 6 — *Success of Stimulation Protocol Used for Ovulation Induction*

Stimulation protocol	Success percentage
HMG alone	33.33%
Letrozole + HMG	14.29%
Clomifene + HMG	9.63%

in the former group against a CPR of 10.02% in the latter. However, the difference was not statistically significant (p value-0.29).

Discussion

The study attempted to determine the parameters that predicted a successful outcome in an IUI cycle which may benefit the clinician in optimizing the IUI results.

As per recent global recommendations, atleast three consecutive IUI cycles should be performed in couples with an indication for IUI[11]. It is important to understand that the choice of ovulation induction agent can affect the success rate of an IUI cycle and hence, improve the cumulative pregnancy rates. It also helps to improve the cost-effectiveness of the IUI to the patient. As the cost of the treatment to the patient not only depends on the cost of drugs but also on the other running costs like the scans, consultation, repeat procedures, loss of working hours etc.

Gonadotropins (33.3%) used alone had highest CPR, followed by their use with letrozole (14.29%) or clomiphene (9.63%). These two regimes were more effective than either of the oral agents for ovulation induction, as also reported by several other studies[5,12]. Mark Adams, *et al*[13] studied the effect of obesity on oral ovulation induction agents on 33,867 patients and 67,662 treatment cycles. At higher BMI, the odds ratio of having clinical pregnancy was significantly dependent on the protocol used, and was more with gonadotropins than either of the oral agents combined with gonadotropins (OR=1.16, P<0.05). However, as the BMI decreased, this effect diminished. Their result is similar to this study except that the present study, did not evaluate the correlation of BMI and ovulation induction drugs.

No benefit of oral ovulation induction agents IUI over natural cycle IUI was demonstrated by Wild, *et al* similar to the present study[14]. A retrospective study done by Jinyong Liu, *et al*[15] on 8893 treatment cycles, also could not demonstrate any benefit of oral ovulation induction, over natural cycle IUI in ovulating women. However, there was significantly increased pregnancy rate when letrozole along with gonadotropins was used. A systematic review comparing clomiphene IUI and gonadotropin IUI with natural cycle IUI also failed to demonstrate any statistically significant difference in the clinical pregnancy rate achieved[16].

An endometrial thickness of more than 8.9mm (p value-0.0315) on the day of trigger was reported to have resulted in significantly higher pregnancy rates. No pregnancy was reported below the endometrial thickness of 5.8mm. A recently conducted systematic review and metaanalysis of studies of an overall low to moderate quality, found no evidence of an association between endometrial thickness prior to ovulation and chances of pregnancy in patients undergoing IUI with ovulation induction[19].

A cut-off of 9mm, similar to our study was reported by Wolff, *et al*[17] and Jayakrishnan, *et al*[9]. Drugs like Aspirin, ethinyl estradiol, sidenafil have been used to improve the endometrial thickness[5,16,18].

Amongst the various indications of IUI, the success rates were significantly higher for women with PCOS. Though the clinical pregnancy rates were higher also in couples with male factor infertility, it did not reach statistical significance. Jayakrishnan, *et al*[9] also reported higher pregnancy rates in women with PCOS (20.2%) and male factor Infertility (17.5%). Pregnancy rates of 12.8% have been reported by Allahbadia for male factor infertility[3]. The CPR was lower in women with endometriosis and h/o tuberculosis, although it was not statistically significant. Lower pregnancy rates (8%) in women with endometriosis have been reported in other studies as well[9].

In this study, while there was a decline in success rate with increasing age (>29 years, p value-0.5375, sensitivity 71.01, specificity 36.35), the difference however, was not statistically significant. While many studies conclude that a woman's age is known to affect the success rate of an IUI cycle[20] a German study on 4246 IUI cycles has shown that overall pregnancy rates were stable in women up-to the age of 40 and comparable to women in their thirties, even after several insemination cycles[21]. All the women in the present study were <40 years (mean age around 28 years) and this may explain why age did not influence the IUI outcome.

No correlation was found with Total Motile Sperm Count (TMSC), probably due to the fact that most men were normozoospermic, as men with moderate to severe male factor infertility were excluded from the study. The minimum Total Motile Sperm Concentration (TMSC) pre-wash at which a pregnancy was achieved was 8 million. This is corresponding to a minimum range of 5-10 million, necessary to achieve pregnancy with IUI, as reported

in a systematic review by Ombelet, *et al*[22]. As per a recent systematic review, it is not possible to define clear lower cut-off levels for pre- or post wash sperm parameters below which IUI should be withheld and it is not recommended either for or against IUI in couples with only poor sperm quality in the male partner[11].

Ovulation Induction and IUI is the first line treatment for anovulatory infertility/PCOS, mild male factor infertility, minimal to mild endometriosis and unexplained infertility. The overall pregnancy rate in this study was 10.36%. PCOS etiology, mild male factor infertility, endometrial thickness >8.9 mm on the day of hCG trigger, ovulation induction with gonadotropins with/without oral ovulation induction agents lead to improved clinical pregnancy rates. IUI can be offered as a first line option to women <40 years, with no other contra-indication to IUI. Hence, optimizing the IUI cycles and careful selection of patients can help clinicians offer the benefit of IUI to some and timely refer the others for ART procedures without wasting their time and resources.

We inferred from this study that PCOS, ovulation induction with human menopausal gonadotropin with or without clomiphene or letrozole and endometrial thickness >8.9 mm are associated with better clinical pregnancy rates.

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