

An Intrauterine Insemination Audit at Tertiary Care Hospital: A 4½ Years' Retrospective Analysis of 800 Intrauterine Insemination Cycles

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ABSTRACT

Background: There are many variables that may influence the success rates of intrauterine insemination (IUI) treatment. Therefore, a regular audit program is needed for planning effective infertility treatment and improving pregnancy outcomes. **Aims and Objectives:** The main objective of this study was to identify the crucial predicting factors that can influence the IUI success. **Materials and Methods:** A retrospective analysis of 800 IUI cycles done from January, 2013 to August, 2017 in 651 couples with various etiologies of infertility. The common etiologies included female factor of ovulatory dysfunction, tubal, endocrinal, male factor, male and female factors combined, and unexplained factors. Ovulation induction was done either by clomiphene citrate (CC) alone or in combination of CC with gonadotropins or pure gonadotropins only. Human chorionic gonadotropin trigger was given when at least one dominant follicle measuring ≥ 18 mm with an endometrial thickness of >7 mm was obtained. IUI was done post 36 h of trigger. The double-density gradient method was the preferred method of sperm preparation. **Results:** In 800 cycles in corresponding 651 couples, the total outcome was 113 pregnancies (14.1%) per cycle with overall pregnancy rate (PR) per couple of 17.3%. The highest PR was observed in the patient with ovulatory dysfunction (21.2%), followed by patients with combined factor (15.1%) and male factor (14.7%). In the study, a higher PR was achieved in the female ≤ 25 years (18.9%) $P < 0.04$ with significant findings with duration of infertility ≤ 5 years (15.1%) having primary infertility (14.5%) with low body mass index < 25 (14.1%). IUI success rate was highest in the first cycle (14.6%) followed by second cycle (14.0%) and third cycle (3.5%). **Conclusion:** IUI audit enables the characterization of prognostic factors to achieve improved PR. This study identifies the factors that can predict improved pregnancy outcome in women age ≤ 25 years and endometrium thickness between 9 and 11 mm. We also recommend IUI as a first line of infertility treatment for couples in low-income setting provided the women age and duration of infertility are acceptably low.

KEYWORDS: Audit, clinical pregnancy rate, controlled ovarian stimulation, intrauterine insemination, pregnancy rate

INTRODUCTION

Infertility is defined as failure to achieve the clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.^[1] It has been reported that infertility or subfertility affects around 8%–12% of couples worldwide and that includes 40%–50% due to male factor either solely (20%) or in combination with the female factor (30%–40%), and another 30%–40%

are idiopathic or unexplained.^[2-4] An exhaustive workup is required for both the partners to arrive at a decision to

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choose the best assisted reproductive technology (ART), whether the couple should go for intrauterine insemination (IUI) or *in vitro* fertilization-embryo transfer (IVF-ET). IUI is one of the simplest techniques of ART for treating infertility by artificial insemination.

The rationale behind IUI is to increase the gamete density of both oocyte and sperms at the site of fertilization. Nevertheless, artificial insemination with husband's semen remains a widely used treatment option for many couples. There are various clinical indications for IUI that includes couples with cervical factor subfertility, unilateral tubal defect, ovulatory dysfunction, unexplained infertility, physiologic or psychological sexual dysfunction, immunological infertility, and suboptimal semen parameters as per the WHO 2010 standards.^[5] This therapy is relatively minimally invasive and an uncomplicated procedure. IUI involves the processing of semen sample in the laboratory to yield active sperms devoid of seminal plasma, which are then directly placed into the uterus. There are various semen preparation techniques such as density gradient, swim-up, and simple wash techniques that are utilized for separation of human spermatozoa from seminal plasma. The final processed semen sample contains high percentage of progressively motile and morphologically normal sperms free from debris, nongerm cells, and dead spermatozoa.

It is essential to do regular monitoring of each IUI cycles for all the variables including female, male, and techniques-related factors influencing the success rate. Then, there could be certain interventions that can be preferred before planning for new cycles to get the maximum benefits for the patients. There are many variables that could influence the success rates of IUI treatment. Hence, it is very important to monitor each cycle and document all the factors by doing audit on monthly basis for improving the pregnancy outcomes. The statistics obtained after analyzing all the IUI cycles on monthly/quarterly basis can be further presented to the entire infertility unit for planning an effective treatment protocol with necessary clinical and laboratory interventions. The present study is a retrospective analysis done as part of an audit of 4 ½ years of IUI practice of 800 cycles at a tertiary care hospital. The main objective of this study was to identify the predictive factors that can influence the IUI success with improved pregnancy outcome.

MATERIALS AND METHODS

This is a retrospective analysis of 800 IUI cycles done in between January 2013 and August 2017 on 651 couples. A basic infertility workup was performed before starting controlled ovarian stimulation (COS) that

included detailed medical history, physical examination, transvaginal ultrasonography, hormone study, hysterosalpingogram, and semen analysis. The hormonal study, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2), prolactin, and thyroid-stimulating hormone (TSH) on the second day of menstrual cycle was done. Male factor was categorized based on the semen analysis reported as per the WHO manual 5th edition standards. Based on the semen analysis, the sample was characterized as normozoospermia (≥ 15 million/ml), oligozoospermia (≤ 15 million/ml) or azoospermia (no sperms), and oligoasthenoteratozoospermia (OAT) were classified as follows: mild OAT (total motility of sperm [TMS] > 10 –15 million); moderate OAT (TMS 5–10 million); and severe OAT (1–5 million sperm).

All the women planned for IUI cycles underwent COS protocol between the 2nd and 5th day of the cycle. OS was done with clomiphene citrate (CC) alone or combination of CC with human menopausal gonadotropins (HMG) or pure gonadotropin cycle using recombinant FSH dosages 75–150 IU. The most frequent starting dose of CC was 50–150 mg/day. The dose of the drug was adjusted according to each patient's characteristics, especially age, body mass index (BMI), previous ovarian response, and ovarian reserve. Ovarian functions were evaluated on day 2 by serum concentration level of FSH (IU/L), LH (IU/L), and E2 (pg/ml). A baseline ultrasound scan on day 2 of the menstrual cycle was done to assess the antral follicle count (AFC), size of follicles and endometrial thickness (ET). In female, endocrinological factors were also considered such as hypothyroid with elevated level of TSH ≥ 3 IU/L and serum prolactin ≥ 25 ng/ml causing hyperprolactinemia. Regular follicular monitoring was done through ultrasound after start of COS cycle to evaluate ovarian response. Ovulation was triggered by intramuscular injection of human chorionic gonadotropin (hCG) 10,000 IU when at least one dominant follicle ≥ 18 mm and an ET > 7 mm was obtained. IUI was done after 36 h of trigger injection.

The sample preparation was done within 1 h of collection of semen sample after 2 days of abstinence. Frozen donor semen samples were procured from ART bank for all donor cycles for the treatment of male factor. The semen sample was washed to free from seminal fluid through double-density gradient (45% and 90%) protocol, and total sperm concentration (TSC) and TMS of the processed sample was determined before insemination. A 15-cm soft catheter was used for IUI insemination. The proximal end of the catheter was introduced in the uterine cavity, and 0.5 ml of prepared semen sample was slowly injected over about 15 s. Post-IUI luteal phase

support was provided by prescribing natural micronized progesterone 200 mg twice a day administered vaginally starting on the night of insemination and continued until the pregnancy test. If pregnancy occurred, administration continued until the 12th week of gestation.

All the patient-related information and variable factors were captured daily in Microsoft Excel spreadsheet, and analysis was done using the statistical package for social sciences IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.00, IBM, Armonk, NY, United States of America. Categorical variables were presented in number and percentage (%). Qualitative variables were correlated using the Chi-square test/Fishers exact test. Multivariate logistic regression was used to find significant factors of positive pregnancy after adjusting for confounding factors. $P < 0.05$ was considered statistically significant.

RESULTS

In the analyzed 800 cycles corresponding to 651 couples between 2013 and August, 2017, the outcome was 113 pregnancies with pregnancy rate (PR) per cycle (14.1%) and the PR per couple of 17.3%. There were various etiologies for doing IUI with husband and donor semen sample. The female factors and male factors were detected in 213 (33%) and 91 (14%) of the cases, respectively. There were 86 (13%) women that showed both female and male factors, i.e., combined factor, and the remaining 261 (40%) of patients were categorized into unexplained factor of etiology with no other reason observed for infertility [Figure 1]. The highest PR was observed in the patient with ovulatory dysfunction (21.2%) followed by patients with combined factor (15.1%) than in male factor (14.7%) and unexplained infertility (11.8%). In total, there were 149 donor cycles with positive pregnancy in 22 (PR - 14.7%) [Table 1].

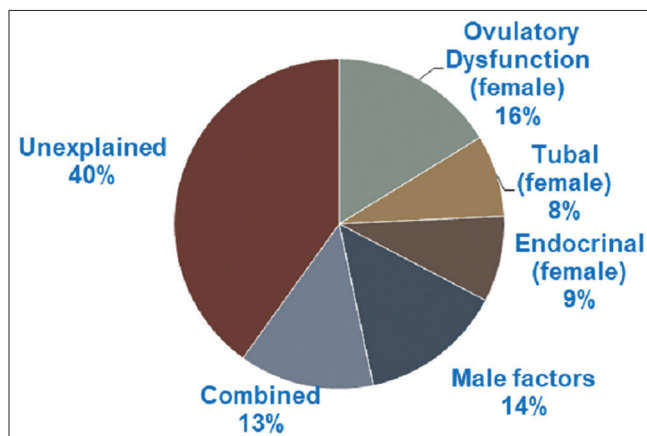


Figure 1: Different etiologies for infertility

The mean age of the participants was 27 years (range, 19–39 years), and the mean BMI was 23 (range 18–26). The PR per cycle for the female age of ≤ 25 years was 18.9% ($P < 0.04$) compared to higher age groups with gradual decline in PR with increased age groups [Table 2]. In the majority of cycles (97.8%), the women had a BMI between 18.5 and < 24.9 with PR of 14.1% the remaining cycles (2.2%) with BMI 25–35 achieved a PR of 11.7% with nonsignificant results ($P > 0.05$). Infertility was primary and secondary in 72.3% and 27.6% of the cases, respectively. The mean duration of infertility was 5.03 ± 3.27 years (range 1–17 years). The PR achieved decreased in line with years of infertility [Table 2].

The female infertility factors were contributed in 213 (33%) patients which were further classified into ovulatory dysfunction 106 (16%), tubal 52 (8%), endocrinological 55 (9%), and unexplained in 261 (40%) of women. Among the female factor, the highest PR was obtained in the patient with ovulatory dysfunction (21.2%), followed by endocrinal (13.4%) and lowest in tubal factor (11.5%). Ovarian reserves were evaluated on day 2, and the mean value of serum concentration of FSH was 6.94 ± 2.59 IU/L; LH 6.76 ± 2.95 IU/L; and E2 49.36 ± 30.78 pg/ml with AFC of 10.47 ± 1.53 . The higher PR of 12.6% (101) was observed in women with good ovarian reserve (FSH ≤ 10 IU/L) as compared to poor responders with elevated FSH concentration with PR of 1.5% (12) with nonsignificant results ($P > 0.05$). Similarly, higher PR of 12.8% (103) was achieved in women LH ≤ 10 IU/L as compared to poor responders with elevated LH concentration with PR of 1.25% (10) with nonsignificant findings. The estradiol value on the 2nd day of the cycle within the range of ≤ 80 pg/ml was observed with PR of 13.3% (107) cycles and PR of 0.75% (6) with elevated concentration with nonsignificant results ($P > 0.05$).

Table 1: Distribution of etiologies of infertility with corresponding pregnancy rate

Etiologies	Cycles (patient)	Pregnancy	PR (%)
Female factor			
Ovulatory dysfunction	94 (106)	20	21.2
Tubal	69 (52)	8	11.5
Endocrinological	186 (55)	25	13.4
Unexplained	236 (261)	28	11.8
Male factor	149 (91)	22	14.7
Combined (both male and female)	66 (86)	10	15.1
Total	800 (651)	113	14.1

PR=Pregnancy rate

Table 2: Demographic factors affecting the pregnancy outcome in intrauterine insemination cycles including age, body mass index, type, and duration of infertility

	Age (years)				Type of infertility		Duration of infertility (years)			BMI	
	≤25	26-30	31-35	>35	Primary	Secondary	≤5	5-10	>10	18.5-24.9	25-35
Cycles (n)	274	360	133	33	579	221	534	208	58	783	17
Positive	52	42	16	3	84	29	81	26	6	111	2
PR (%)	18.9	11.6	12.0	9.0	14.5	13.1	15.1	12.5	10.3	14.1	11.7
<i>P</i>	0.04				0.615		0.446			1	

BMI=Body mass index, PR=Pregnancy rate

The PR/cycle was maintained between 14.0% and 14.6% and was observed until the second cycle, after which the rate decreased noticeably from the third cycle onward (3.5%) [Table 3]. In the majority of the cycles, 533 (66.6%) CC was administered for ovulation induction with PR of 81/533 (15.1%). This was followed by another 219 (27.3%) cycles with both CC and HMG achieved a PR of 12.7% lower than pure CC cycle with nonsignificant results ($P > 0.05$). There were very few cycles of letrozole and tamoxifen along with gonadotropins with no positive pregnancies [Table 4]. There were two or more dominant follicles of more than 18 mm in 300 (37.5%) cycles and achieved a higher PR (15%) as compared to single dominant follicle PR (13.6%) with nonsignificant results. The mean ET of 8.42 ± 1.69 mm was observed on day of hCG trigger. The highest PR of 17% was achieved within ET of ≥ 9.1 –11 mm followed by ET of 7–9 mm and ET ≤ 7 mm with significant findings ($P < 0.04$) [Table 4].

IUI was performed with average of 35.62 ± 17.28 million/ml total motile spermatozoa count and with total motility (%) of 56.81 ± 10.73 . In 723 cycles, the postwash total motile spermatozoa count of ≥ 15 million/ml was observed with positive and biochemical PR in 102 (14.1%) cycles and PR subsequently decreased with fall in total spermatozoa count [Table 5]. The multivariate analysis was used to determine whether there was an association between pregnancy and the predictors that were found to be significant. Women with age ≤ 25 years have 0.44 times (odds ratio [OR] 0.56; 95% confidence interval [CI]: 1.1–5.0 times) more chance of getting pregnant than the women at higher age group. It was also observed from data that increase in ET on day of hCG trigger after adjusting for age has significantly higher chances of positive pregnancy in women with ET ≥ 9.1 –11 mm and were 2.4 times more likely to become pregnant than the women with ET ≤ 7 mm (OR 2.4; 95% CI: 1.1–5.0 times) [Table 6].

DISCUSSION

In this present analysis, the woman's age significantly affected the PR ($P < 0.05$). The PR of 18.9% per

Table 3: Details of positive pregnancies (pregnancy rate percentage) per intrauterine insemination cycle

Number of cycles	Cycles	Positives	PR (%) per cycle	<i>P</i>
1	648	95	14.6	0.380
2	107	15	14.0	
3	28	1	3.5	
4	14	1		
5	3	1		
Total	800			

PR=Pregnancy rate

cycle was observed for women age ≤ 25 years and was 9.0% for the women ≥ 35 years of age. Whereas there are some studies that have reported that with controlled ovarian hyperstimulation age did not affect the PR provided the woman age was < 40 years achieving PR of 13.7% per cycle and a rate of 4.1% thereafter.^[6,7] However, other researchers consider age to be an important factor in achieving pregnancy as observed in this present study.^[8,9] In our analysis, it was observed that BMI nonsignificantly affected the PR in women, although BMI between 18.5 and 24.9 could achieve a higher PR (14.1%) than women with a BMI ≥ 25 (11.7%). In a systematic review, PR of 13.0% was reported for BMI ≥ 35 and 7.84% for BMI between < 18.5 and 24.9 with no significant difference among groups.^[10] Studies have pointed out the impact of weight loss and lifestyle-related changes before becoming pregnant as key factors in the treatment of infertility.^[11-13] There are also contradictory studies that have found no differences for weight, although they did observe that higher gonadotropin doses were necessary for OS in obese women.^[14]

One of the important factors to assess as a predictor of pregnancy in response to IUI is the duration of infertility. There are number of studies that have reported higher PRs corresponding to shorter duration of infertility.^[15,16] In this retrospectively analysis, a nonsignificant difference was observed ($P = 0.446$) with a higher PR of 15.1% in infertility ≤ 5 years group compared to the duration of infertility with 5–10 years. Other studies have reported significant differences with infertility period with more and < 6 years (6.1%

Table 4: Effect of different stimulation protocols, number of dominant follicles, and endometrium thickness on day of human chorionic gonadotropin trigger as technique related factor contributing in pregnancy success

	Pure CC cycle	CC + gonadotropins	Pure gonadotropin cycle	Natural cycle	Letrozol + gonadotropin	Tamoxifene + gonadotropins	Number of dominant follicle		ET (mm)		
							1	≥2	<7	7-9	9.1-11
Cycles, n (%)	533 (66.6)	219 (27.3)	10 (1.2)	24 (3)	7 (0.87)	7 (0.87)	500 (62.5)	300 (37.5)	131 (16.3)	433 (54.1)	236 (29)
Positive	81	28	2	2	0	0	68	45	10	63	40
PR (%)	15.1	12.7	20	8.3	0	0	13.6	15	7.6	14.5	16.9
P				0.538				0.656		0.046	

PR=Pregnancy rate, ET=Endometrium thickness

Table 5: Effect of postprocessed semen parameters inseminated during intrauterine insemination on the pregnancy rates

Semen parameters	Number of cycles	Number of pregnancies	PR (%) per cycle	P
Sperm density (×10 ⁶ /ml)				0.974
<5	6	1	16.6	
5-10	31	5	16.1	
10-15	40	5	12.5	
≥15	723	102	14.1	
Sperm motility (%)				0.267
<20	3	0	0	
20-40	52	4	7.7	
40-60	465	75	16.1	
60-80	276	34	12.3	
>80	4	0	0	
IUI donor cycles	149	22	14.7	

IUI=Intrauterine insemination, PR=Pregnancy rate

Table 6: Multivariate analysis done to determine possible association between significant predictors including age of the patient and endometrium thickness on day of trigger

	P	OR	95% CI for OR	
			Lower	Upper
Age (years)				
≤25		1		
26-30	0.010	0.560	0.36	0.87
31-35	0.088	0.590	0.32	1.08
>35	0.203	0.450	0.13	1.54
ET on day of HCG trigger (mm)				
<7		1		
7-9	0.043	2.064	1.02	4.16
9.1-11	0.0164	2.451	1.18	5.10

HCG=Human chorionic gonadotropin, OR=Odds ratio, CI=Confidence interval, ET=Endometrium thickness

vs. 14.2%).^[6,8] It was observed that PR falls as the duration of infertility increases suggesting that other ART such as IVF/ICSI should be used for the longer duration of infertility.

The hormone analysis on day 2 of the cycle is the main method for evaluating ovarian reserve. Cycle day 3 FSH and E2 levels are popular screening tools for predicting success in IVF. In our study, we found a higher PR of 12.6% with FSH levels ≤10 IU/L as compared to higher levels of ≥10 IU/L ($P = 0.588$). In general, higher FSH and E2 (>15 IU/L and >80 pg/ml, respectively) levels are considered strong predictors of poor IVF outcomes. Various studies by different authors had supported that higher levels of FSH reduces the number of follicles and ultimately affects the oocyte quality and thus predicting an unfavorable prognosis for infertility treatment.^[17-19] In a retrospective analysis of 806 patients undergoing 1875 IUI cycles reported by Mullin *et al.*^[20] observed that day 3 FSH and E2 levels cannot be used as markers to predict PR. In the present study, the PR per cycle was highest for the patients of ovulatory dysfunction achieved highest PR (18.8%) followed by combined factor PR (15.1%). It is evident that COS corrects ovulatory dysfunction, therefore, results in a higher PR. The PR was higher (14.2%) in euthyroid patients with TSH ≤3.0 mIU/L with nonsignificant difference with other group with TSH >3. Studies have also reported that euthyroid patients, with preconception TSH values in the high-normal range (between 2.5 and 4.9 mIU/L) are not associated with adverse IUI outcomes.^[21]

In the present analysis in all IUI cycles, double-density gradient method was the only preferred method for semen sample processing with overall observed PR of 14.1%. In a Cochrane review on sperm preparation techniques, it was concluded that there were insufficient randomized studies to choose the best method. However, density gradient centrifugation method showed to be superior to the swim-up and simple wash technique with a clear improvement of morphological normal spermatozoa with Grade A motility and normal DNA integrity.^[22] In the present study, using donor sperm in cases of azoospermia resulted in PR of 14.7%. One pregnancy was obtained out of six IUI cycles with TSC of 1–5 millions/ml. Studies have shown that in patients

with OAT the PR decreased in line with the severity of semen parameters including TSC and motility.^[23] Sakhel *et al.* reported a direct relationship between sperm count and poor sperm motility with the PR.^[24] It has been reported that PRs are lower if prewash count is <10 million/ml.^[25] In a Cochrane review, it was clearly shown that there is insufficient evidence to conclude whether IUI is effective or not in moderate and mild male factor infertility.^[26] In the present study, there was no identifiable cause of infertility in 40% of the couples labeled as unexplained infertility. In these cases, the PR per cycle was 11.8% in CC cycle alone or in combination with HMG. Similar to this study meta-analysis showed that the combination of OS with gonadotropins and IUI significantly improves live-birth rates in couples with unexplained infertility.^[27] Few studies have achieved a PR of 15% in unexplained infertility after stimulation by gonadotropins.^[28]

In this study, the mean number of IUIs per couple was 1.2. Over 97.3% of pregnancies occurred in the initial two cycles (14.6%), with the PR dropping noticeably from the third cycle (3.5%). In a study with 811 cycles observed that the highest PR occurred in the first cycle and that 97% of all pregnancies occurred within four cycles.^[6] In our study, the number of preovulatory dominant follicles recruited was not a significant predictor of pregnancy though the PR was slightly higher (15% vs. 13.6%) as compared to single recruited follicle. There are studies that found the recruitment of at least two follicles increased success rates in COS in combination with IUI by 2% for one follicle, and by 15% for two or more follicles significantly.^[29,30] Another study in 9963 cycles showed PRs of 7.6% for one follicle, 10.1% for two follicles, 8.6% for three follicles, and 14% for four follicles.^[6,31]

In the majority, 66.6% of the cycle's CC was administered for ovulation induction with PR of 15.1%. In 27.3% cycles, both CC and HMG were used for superovulation giving lower PR as compared to pure CC cycle, i.e., 12.7%. It was further observed that IUI has low dropout rate, low risk for OHSS (ovarian hyperstimulation syndrome), and a low multiple PR in natural cycles and CC or low-dose HMG OS protocols.^[32] There were total ten cycles with pure gonadotropin cycle and yielded two positive pregnancies. It seems that higher PRs result when gonadotropins are primarily used.^[33,34] However, studies have reported higher PRs for the HMG rather than the recombinant FSH products.^[35] In this study, no significant difference in PRs was found using different stimulation protocols used. In this study, OS protocol was mild by giving CC (CC, 50–100 mg/day for 5 days) and it remained

the first-choice drug. Contrary to gonadotrophins, CC is easily available, easy to use, and less costly.

CONCLUSION

This study is aimed at identifying factors that predict pregnancy following IUI, and it was found that the probability of clinical PR was greatest for women with age ≤ 25 years with a duration of infertility <5 years having a ET between 9 and 11 mm at the time of trigger. The PR was higher in women with FSH value on day 3 of cycle below 10 IU/L and also in women anovulation as a factor of infertility. According to our results, the “ideal” stimulation protocol is with CC to induce ovarian response. We recommend IUI as a first-line treatment for couples in low-income setting provided the woman's age, and the duration of infertility are low. It is further proposed to perform at least three IUI cycles and proceed to *in vitro* fertilization along with complex-ART, if pregnancy did not occur.

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Conflicts of interest

There are no conflicts of interest.

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