Original Research

Predictive factors for pregnancy in intrauterine insemination

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Abstract

Aims and Objectives: Intrauterine insemination(IUI) is one of the common treatment option given to couples with infertility. The success of an IUI cycle can depend on various factors. Several studies in the past have reported numerous factors affecting the result of IUI. We aimed to study various factors which can positively affect the success of IUI cycle. **Materials and Methods:** This is retrospective study conducted at Department of Reproductive Medicine from January 2016 to December 2019 where data from1027 IUI cycles was analysed. **Results:** The clinical pregnancy rate and live birth rate in our study was 7.4 % and 6.3 % respectively. Factors which favoured a positive outcome in IUI were the number of preovulatory follicles, endometrial thickness on the day of trigger, total motile sperm count. Also the use of low dose gonadotropins had a better outcome when compared to letrozole alone. Factors which did not affect the IUI outcomes were the cause of infertility or the number of IUI cycle. **Conclusion:** The chances of conception in an IUI cycle correlate positively with the number of preovulatory follicles, the endometrial thickness and total motile sperm count. Based on these parametrers couples can be counselled about their outcome and steps can be taken to improve their outcome in an IUI cycle.

Keywords: IUI (intrauterine insemination), CC (clomiphene citrate), GN (gonadotropins), TPMSC (total progressively motile sperm count), NMSI (number of motile spermatozoa inseminated), TMF (total motile fraction), LE (letrozole), CPR (clinical pregnancy rate), LBR (live birth rates), EMT (endometrial thickness), hMG (human menopausal gonadotropin), rFSH (recombinant follicle stimulating hormone)

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INTRODUCTION

Intrauterine insemination (IUI) is one of the first-line treatment for infertile couples. Common indications for IUI are unexplained, mild male factor, and anovulatory infertility.

But the pregnancy rate per IUI cycle is quite variable in literature. Several prognostic factors have been proposed to positively affect the IUI outcome, most common of which are the causes of infertility for which IUI is performed, that is, female age, number of preovulatory follicles, semen parameters, sperm preparation technique, and endometrial thickness.

In this study, we have tried to identify the factors associated with positive outcome after an IUI. A prognostic model based on these predictive factors can be developed to guide couples regarding the success probability and whether to go with IUI or proceed to advanced treatment/IVF.

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Significance on reproductive health: Chances of a successful conception after IUI can depend on several parameters that can help in counselling the couple about the outcome. Various studies have shown the successful outcome to be dependent on factors like stimulation protocol used, age of the female partner, endometrial thickness (EMT), semen parameters. However some studies have shown no relevant association of these parameters with outcome of IUI. This study aims at identifying factors that have favored the chances of a successful pregnancy after IUI and thus can be used in couple counselling and both the clinician and the intending couple can have realistic expectation with their treatment.

MATERIALS AND METHODS

Retrospective cohort study in the Department of Reproductive Medicine at a private hospital, Bhopal from January 2016 to December 2019.

Inclusion criteria were couples who underwent IUI for various indications like anovulatory, mild male factor, unexplained infertility, or mild endometriosis. Male factor infertility was defined as erectile/ejaculatory dysfunction or an abnormal semen analysis (WHO 2010 criteria). Semen Parameters (sperm counts <15 million per mL, motility <32%, normal morphology <4%) less than 5th centile were considered as male factor infertility.

Exclusion criteria were patients with bilateral tubal block and total motile sperm fraction (TMF) <1 million/mL.

Ovulation induction was done with either clomiphene citrate (CC) 100 mg or letroz 5 mg from second day of periods for 5 days. Transvaginal scan was done from day 7. In cases where stimulation was done by both clomiphene/letroz and gonadotropins (GNs), a low-dose 75 IU of hMG was added from day 7. When GNs alone were used for ovulation induction, either GNs (hMG/rFSH) were started from day two of menses in low doses (50 to75 IU). Follicular monitoring was done from day 7/8 by transvaginal ultrasound and continued till HCG 5000 IU was given as trigger when follicular size was 18 to 20 mm. Also, EMT at the time of trigger was noted. IUI was done 36 hours after the trigger under ultrasound guidance. In cases where dual IUI was planned, IUI was done at 18 hours and 48 hours. On the day of IUI, fresh semen sample was prepared using either density gradient/swim up technique. Postwash TMF was assessed. TMF was calculated according to the standard formula to calculate total motile sperm count, that is postwash volume × postwash sperm concentration × postwash progressive motility divided by 100.

IUI was done under ultrasonography (USG) guidance using soft catheter with insemination volume 0.5 mL. Patients were given luteal support with vaginal progesterone gel daily for 14 days and pregnancy test was done after 14 days of IUI. If the urine pregnancy test was positive, transvaginal scan was done at 6 weeks and pregnancy was followed till delivery. If the pregnancy test was negative, patient was advised to discontinue the progesterone gel and wait for periods. Next cycle of stimulation was started from day 2 of periods. Clinical pregnancy was defined as the presence of an intrauterine gestational sac confirmed by ultrasound.

Ethical Clearance: Appropriate approval was taken from institutional ethical committee.

RESULTS

A total of 1027 stimulated IUI cycles between 2016 and December 2019 were evaluated.

Of the total COH/IUI cycles analyzed, 573 were the first-treatment cycle, 300 were the second-treatment cycle, 141 were third-treatment cycle, and 11 were fourth-treatment cycle during the study period. One cycle was fifth-treatment cycle and one was sixth-treatment cycle. The mean female age was 29.4 years (range, 20–43 years). Mean duration of infertility was 5.02 years [Table 1]. Cause of infertility was anovulatory in 17, male factor in 444, and unexplained in 563 of the patients. The continuous variables were compared using the independent *t* test.

The overall pregnancy rate per cycle was 7.4% (76).

The clinical pregnancy rate per cycle was 7.1% (73). Of these, 65 pregnancies resulted in live birth (6.3%). Eight pregnancies resulted in miscarriage. Two pregnancies were biochemical and one pregnancy was ectopic [Table 2].

The clinical pregnancy rate per cycle with COH/IUI in our study was 7.4% and live birth rate (LBR) per cycle was 6.3%.

Table 1: Factors Affecting Pregnancy Rate in IUI

	Pregnancy (Yes)	Pregnancy (No)
1. Mean age (female)	29.4	30.5
2. Mean duration of infertility (years)	5.02 (74)	6.41 (913)

Factors positively affecting IUI outcomes: number of preovulatory follicles, EMT, TMF, and use of GNs for ovulation induction were significantly associated with better IUI outcomes.

Significantly higher pregnancy rates were observed when the duration of infertility was <3 years, and the TMF was between 9 and 15 million and EMT was >1.1 cm. Pregnancy rates were higher when the number of preovulatory follicles was ≥3 (14.7% when preovulatory follicles were three or more than three when compared with 7.2%, with two follicles) [Table 3 and Table 4].

Cycles in which GNs were used for ovulation induction and higher pregnancy rates (12.1%) when compared to those cycles where only clomiphene or letrozole (LE) was used (2.5%). This difference was statistically significant [Table 5].

Factors that did not affect the outcome significantly: cause of infertility, as well as the number of IUI cycle not related to successful IUI outcomes. Although pregnancy rates were higher in the younger age group 19–24 years (13.4%) and decreased in older age group (3.1%) where female age was more than 37 years, but this difference did not reach statistical significance. Pregnancy rates were similar (8%) in both the first and the second IUI cycles but were decreased in third IUI cycle and none of the women conceived in their fourth IUI cycle [Table 6].

Table 2: Pregnancy Outcomes of IUI

Parameters	Outcome (%)
1. Multiple pregnancy	13 (1.2%)
2. Ectopic pregnancy	1 (0.09%)
3. Miscarriage	8 (9.8%)
4. Clinical pregnancy	73 (7.1%)
5. Live births	65 (6.3%)

Table 3: Demographic Factors Affecting Pregnancy Rate in IUI

Factors	Pregnancies/Cycles	Percentage	Chi-square
INFERTILITY ETIOLOGY			
Male factor	31/444	6.9	Chi-square 0.527 *P* value 0.768
Unexplained	43/563	7.6	
Anovulation	2/17	1.1	
Endometriosis	0/3	0	
DURATION OF INFERTILITY (years)			
<3	30/242	12.3	0.03
≥3 to ≤7	30/417	7.1	
>7 to ≤14	13/244	5.3	
>14 to ≤21	2/82	2.4	
>21	½		
FEMALE AGE			
19–24	11/79	13.9	Chi-square 6.308 *P* value 0.09
25–30	36/473	7.6	
31–36	26/378	6.8	
37–42	3/94	3.1	

Table 4: Patient Factors Affecting Pregnancy Rate in IUI

No. of Preovulatory Follicles	Pregnancies/Cycles	Percentage	
1	35/509	6.8	Chi-square 7.0259 *P* value 0.029
2	23/318	7.2	
≥3	18/122	14.7	
Total	76/949		
Endometrial Thickness	Pregnancies/Cycles	Percentage	
<0.5	0/24	0	Chi-square 12 *P* value 0.000
0.5 to <0.7	18/285	6.3	
≥0.7 to <0.9	30/402	7.4	
≥0.9 to <1.1	11/178	6.1	
>1.1	17/69	24.6	
TMF	Pregnancies/Cycles	Percentage	
<3	19/246	7.7	Chi-square 12.43 *P* value 0.014
≥3 to ≤6	36/440	8.1	
>6 to ≤9	7/240	2.9	
>9 to ≤12	10/80	12.5	
>12 to ≤15	4/21	19	

Table 5: Stimulation Protocol Affecting Pregnancy Rate in IUI

Stimulation Protocol	Pregnancies	Cycles	Percentage	
Clomiphene citrate/letrozole	6	233	2.5	
Clomiphene/letrozole + gonadotropins	66	761	8.6	
Gonadotropins	4	33	12.1	Chi-square 9.565 *P* value 0.008
Total	76	1027		

Table 6: Pregnancy Rates in Number of IUI Cycles

No. of Cycles	Pregnancies	Cycles	Percentage	
First	46	572	8	
Second	24	297	8	Chi-square 2.274 *P* value 0.32
Third	06	142	4.2	
Fourth	0	12	0	
Total	76	1027		

Table 7: Pregnancy Rates in Single and Dual IUI per Cycle

	Pregnancies	Cycles	Percentage	
Single IUI	40	718	5.57	Chi-square 9.81*P* value 0.0017
Dual IUI	36	309	11.65	

Also in our study, pregnancy rates were significantly higher when dual IUI was done as compared to single IUI (11.65% vs. 5.57%) [Table 7]. The cause of infertility did not affect the pregnancy outcome after IUI. Pregnancy rates were higher (7.7%) in unexplained infertility, but this difference did not reach statistical significance.

Table 8 showing various subgroups where dual IUI was performed.

Table 8: Dual IUI Indications

Indications	Number	Percentage
Male factor	80	25.9
Unexplained	222	71.8
Female factor	7	2.3
Total	309	

DISCUSSION

The present retrospective study was done in the Department of Reproductive Medicine at a private hospital, Bhopal from January 2016 to December 2019.

The clinical pregnancy rate per cycle with COH/IUI in our study was 7.4% and LBR per cycle was 6.3%. Tominaga *et al.* in their study observed a positive pregnancy rate of 11%, CPR 8.2% per IUI cycle, and 13.6% per treated couple.[1] Another study by Sicchieri *et al.* found clinical pregnancy rate of 7.59% in IUI cycles.[2] Another retrospective study by Wang *et al.* reported the clinical pregnancy rate was 16.3%, biochemical pregnancy rate was 19.3%, the clinical pregnancy abortion rate was 15.4%, and the ectopic pregnancy rate was 1.8%.[3] In a retrospective study by Guan *et al.*, clinical pregnancy rate (CPR) was 13.7% per cycle and 28.9% per couple; 6 (9.8%) had abortion, whereas 1 (1.6%) was ectopic pregnancy; 59 (96.7%) were singleton pregnancies; and 2 (3.3%) were twins.[4]

In our study, female age and number of IUI cycles were not related to successful IUI outcomes. Although pregnancy rates were higher in the younger age group of 19 to 24 years (13.4%) and decreased in older age group (3.1%) where female age was more than 37 years, but this difference did not reach statistical significance. Wang *et al.* in their retrospective study found that the average female subject age was significantly lower in the clinical pregnant group (28.97 ± 4.06 years) than in the nonpregnant group (30.47 ± 4.84 years) ($p < 0.05$). Based on age, the female study subjects were divided into three groups: group A: aged <25 years; group B: aged 25–35 years; and group C: aged >35 years. A significant decrease in CPR with age was found (23.8%, 16.3%, and 8.8%, respectively; $p = 0.000$).[3] Sicchieri *et al.* in their retrospective observational study found patient age was inversely and significantly correlated with pregnancy rates ($p = 0.001$) (pregnant women $= 32.56 \pm 5.64$ years, nonpregnant women $= 36.64 \pm 5.03$ years).[2] Cause of infertility, ovulation induction method, number of mature

follicles, and sperm with progressive motility were not associated with pregnancy rates in their study.

The clinical pregnancy rate and live birth rate declined as the age of the female partner increased showing an inverse relation between female and success rates, which were <30, 30–34 years, and >35 years. The CPR and LBR declined along with the age of the female. As women reached >35 years old, the CPR declined from 15.34% and 14.52% to 2.22%.[4]

In our study, the number of preovulatory follicles, EMT, TMF, and use of GNs for ovulation induction were significantly associated with better IUI outcomes. Pregnancy rates were similar (8%) in both first and second IUI cycles but decreased in third IUI cycle and none of the women conceived in their fourth IUI cycle. In our study, cycles in which GNs were used for ovulation induction had higher pregnancy rates (12.1%) as compared to those cycles where only CC or LE was used (2.5%). This difference was statistically significant.

In another randomized controlled study by Peeraer comparing GNs with CC in IUI cycles, ovarian stimulation with low-dose GNs was superior to clomiphene with respect to clinical pregnancy (14.4% and 9%, respectively) and LBRs (13.8% and 8.7%), without increased incidence of multiple LBR (6.5% and 3.6%, respectively, $P<0.99$).[5]

In an individual patient data meta-analysis, moderate-quality evidence showed that GNs increased the chance of a live birth compared to both CC and LE, whereas low-quality evidence due suggested it may also increase the chance of a multiple pregnancy.[6]

This finding was observed in other studies also. In a retrospective study by Manish Banker *et al.*, the CPR was significantly higher in patients who received GN alone or in combination with CC, in comparison with patients who received CC alone, that is, 14.55% and 7.82% ($p = 0.05$). CPR was comparable between the groups receiving GN with CC and GN alone (14.44% vs. 14.97%; $p = 0.86$).[7] Wang *et al.* in their study reported higher pregnancy rate when GNs were used along with LE for ovarian stimulation as compared to either CC or LE or hMG alone.[3]

However, in an open-label, multicentric, randomized, superiority trial by Danhof *et al.*, there was no statistically significant difference between FSH and CC in IUI in terms of cumulative ongoing pregnancy rates ([Absolute Risk Difference] = 0.04, 95% CI: −0.02 to 0.11), with both strategies leading to very low multiple pregnancy rates when adhering to strict cancellation criteria. Ongoing pregnancies were 31% in the FSH treatment arm and 26% in the CC treatment arm (RR = 1.16, 95% CI: 0.93–1.47).[8]

Similarly, Guan *et al.* reported in their retrospective study that the CPR in LE combined with hMG group was higher than the natural, CC, LE, and hMG group, although the results had no statistical significance.[4]

In a meta-analysis by Weiss *et al.*, no difference was found between EMT and pregnancy rate in IUI cycles.[9] Their pooled data showed that women treated with CC had a marginally thinner EMT than women treated with GNs. There was no evidence for a difference in EMT between CC and LE. The combination of CC plus GNs resulted in a slightly thinner endometrium than LE, and LE alone resulted in a slightly thinner EMT than GNs alone.

We reported a higher CPR when EMT was more than 10 mm. Other studies also showed similar trends. Wang *et al.* reported that the EMT was significantly thicker in the clinical pregnant group than in the control group (10.46 ± 2.02 mm and 10.25 ± 2.10 mm, respectively; $p < 0.05$). Based on EMT, the cases were divided into three groups: group A: <8 mm; group B: 8–12 mm; and group C: >12 mm. The pairwise comparison results for the three groups showed that the CPR was significantly higher in group B than in group A ($p = 0.018$).[3]

Gaun *et al.* in their study found no significant differences in CPR and LBR when patients were studied according to the type of endometrium, which includes A group (<7 mm), B group (7–14 mm), and C group (>14 mm).[4]

Most studies have demonstrated cut-offs for total motile count of 5 to 10 million sperm. There are no data suggesting a difference in pregnancy or miscarriage rates across swim-up, wash and centrifugation, and density gradient preparation techniques. Postwash sperm count > 1 million is recommended, with increasing pregnancy rates as count increases but with a plateau in pregnancy rates after postwash sperm count reaches 4 million. Double IUI, in which patients under went insemination twice per cycle, didnot see to increase in pregnancy rates. In our study, the CPR was higher when the postwash TMF was more than 9 million. In a recent retrospective study by Gubert *et al.*, increasing female age,

average NMSI (number of motile spermatozoa inseminated < 1.0 (× 106), and duration of infertility ≥36 months were associated with decreased odds of clinical pregnancy.[10]

However, in a retrospective cohort study by Findeklee *et al.*, there was no correlation between spermiogram parameters (concentration, motility, density) analyzed and the probability of pregnancy in women who underwent an infertility treatment. Pregnancy rate was 14.3% whose partners had a below-average spermiogram, 23.1% in average spermiogram, and 14.5% in women with partners with an above-average spermiogram.[11]

Liu *et al.* in their retrospective study compared prewash and postwash total progressively motile sperm count (TPMSC) on clinical pregnancy after IUI. TPMSC was defined as the product of total sperm count and percent progressive motility. No pregnancies were seen when there was prewash TPMSC of <9 million or postwash TPMSC of <2 million. In the prewash TPMSC groups, the group of 10 to 100 million showed no statistically significant difference in the pregnancy rate (PR) compared with >100 million group. In the postwash TPMSC groups, no statistically significant difference in the PRs was observed between 3 and 10 million group and >10 million group. When the postwash TPMSC was <3 million, the pregnancy rates decreased with TPMSC declining.[12]

Based on the above study, we can predict to a certain extent the chances of a couple to have a successful IUI. Couples who do not have a fair chance of a successful IUI (advanced age, severe male factor with postwash TMF <1 million) can be offered alternative treatment like IVF. Whereas, couple with a younger female partner, normal semen parameters, IUI can be offered with the use of GNs for ovarian stimulation to improve the outcomes. Bensdrop *et al.* based on their randomized trial concluded that IUI rather than IVF should remain the preferred first-line treatment for couples with unexplained or mild male subfertility and a female age between 18 and 38 years.[13]

Limitations of the study included its retrospective nature, no strict criteria as to which patients received dual IUI. As TMF did not take into account the morphology of sperms, this subgroup was not studied separately. Also, tubal factor with only one blocked tube was not studied separately.

CONCLUSION

In our study, the overall pregnancy rate was 7.4% and LBR was 6.3%. Several factors were significantly associated with positive pregnancy rates like multifollicular development, TMF, EMT, and the use of GNs for stimulation and dual IUI, whereas female age, cause of infertility, and the number of IUI cycles were not significantly associated with positive pregnancy rates after IUI. On multivariate regression, use of GNs for stimulation and dual IUI were found to positively correlated with IUI outcomes, whereas other factors lost their significance on multivariate regression.

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Conflicts of interest
There are no conflicts of interest.

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