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Original Research Article

Comparative analysis of single versus double intrauterine insemination

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ABSTRACT

Background: IUI is simple, less costly compared to other reproductive techniques but there is discrepancy even in recent studies about the timing of IUI. Compared with single IUI, a second consecutive IUI adds significantly to cost and psychological burden, making it important to confirm its beneficial effects before recommending this procedure on large scale.

Methods: It is hospital based retrospective study, carried out in a private tertiary care hospital of Mumbai over a period of one year. All cases who had already undergone IUI during the given time frame were consecutively selected as per inclusion & exclusion criteria for the study. We considered different factors in the study group and their effect on the fertility of the couples.

Results: Out of 150 couples, 119 (79.3%) underwent single IUI during the study and 31 (20.7%) underwent double IUI. 72.67% couple had infertility for 1-3 years, 90.67% primary and 9.33% secondary infertility, 51.3% women with normal BMI and 77.8% with PCOS, 29.4% of single IUI and 32.3% of double IUI group had positive pregnancies. As only the couples with normal semen analysis were selected, male factors like age and co-morbidities in the male did not show any significant effect on the fertility in the study groups.

Conclusions: Women with younger age, normal BMI and with PCOS have better chances of pregnancy in first 3 attempts of IUI with controlled ovarian stimulation and there is no difference in the pregnancy rates by using either double IUI or single IUI in the treatment of sub fertile couple.

Keywords: HCG, Infertility, Intrauterine insemination

INTRODUCTION

Infertility is a global issue and it has become a major healthcare concern.

Infertility is generally defined as the inability to conceive despite regular and unprotected intercourse for 1 year. The term Subfertility is used to describe women or couples who are not sterile but exhibit decreased reproductive efficiency.

One in every four couples in developing countries is affected by infertility. As per WHO (World Health

Organization) 2004, 60- 80 million couples are suffering from infertility globally every year, out of which 15- 20 million are in India alone.

Fertility rate in India has been declining; it was 2.7 as per 2009 survey.

The probability of achieving a live birth without treatment decreases with increasing age and duration of subfertility. The probability of pregnancy without treatment decreases by about 5% for each added year of female partner age and by 15-25% for each added year of subfertility.¹ Most of the spontaneous pregnancies occur

within first 3 years; thereafter, the prognosis for success without treatment is relatively poor.

Taking into account that the possibility of spontaneous pregnancy is 2% without any therapy, assisted reproduction is the next logical step to increase the possibility of pregnancy.²

Intrauterine insemination (IUI) is an assisted reproductive technique which involves the deposition of a processed semen sample in the uterine cavity. IUI is based on the natural ability of the sperm to fertilize an egg in female reproductive tract.

However many aspects that could optimize the rate of success of IUI remain to be defined. Among the debated issues is the correct timing of insemination, the impact of follicle rupture at the time of IUI and the number of insemination per cycle.

No difference has been detected among the timing of IUI, as shown by recent Cochrane review.³ The timing of IUI in the majority of published studies is 32 to 36 hours following HCG administration. As regards the impact of the number of inseminations per cycle pregnancy rate (CPR), the majority of available studies have reported no significant difference between single and double IUI, while few studies have suggested better cycle outcome with double IUI.

Although few studies showed that superovulation with double IUI had better pregnancy rates than with a single application, recent studies found that ovarian stimulation with double insemination has not increased pregnancy rates.

Thus some authors have suggested that increasing the number of inseminations per cycle from one to two may increase the probability of conception. There is discrepancy even in recent studies. Compared with single IUI, a second consecutive IUI adds significantly to cost and psychological burden, making it important to confirm its beneficial effects before recommending this procedure on large scale.

METHODS

The present study is hospital based retrospective study, carried out in a private tertiary care hospital of Mumbai over a period of one year.

All cases that had already undergone IUI during the given time frame were consecutively selected as per inclusion & exclusion criteria for the study.

The study was carried out after the approval of the Hospital Ethics Committee.

All the records of couples with primary or secondary infertility who came to the hospital for treatment and who

underwent IUI and fitting into inclusion criteria were reviewed.

Inclusion criteria

1. Age group: ≤ 35 years
2. Infertility equal to or more than one year (primary or secondary)
3. At least one patent fallopian tube on hysterosalpingography (HSG)
4. Normal semen analysis

Exclusion criteria

1. Age > 35 years
2. Tubal factor infertility
3. Abnormal endometrial cavity (as seen on HSG)
4. Male factor infertility

The intention was to postulate the better modality between the two procedures and modify the treatment plan for better management of sub fertile couples depending upon the results of the study.

Total number of couples who passed inclusion criteria was 150.

As the study was retrospective, allocation of patient to single or double IUI were carried out by the physician as per medical expertise and no special criteria were applied for choosing a particular type of IUI (single or double) in a particular patient.

The example of the standard hospital protocol usually followed in each couple for the procedure of IUI is as mentioned below:

1. History of the couple as per proforma.
2. General, physical and gynaecological examination.
3. Baseline ultrasonography to assess ovaries (antral follicles/cysts) on day 1 or day 2 of menses.
4. Tablet clomiphene citrate 100mg at bedtime from day 2 to day 6 of cycle for 5 days.⁴
5. Injection recombinant FSH 100 units on day 7, 8, 9th of cycle.⁵
6. Injection HCG 10,000 IU IM when dominant follicle is more than 18-20 mm size.
7. (Dose of tablet clomiphene citrate, Inj. FSH and Inj. HCG modified according to patient's BMI, PCOS status and follicular response as shown on ultrasonography).
8. Informed and written consent for intrauterine insemination.
9. Sperm preparation (partner's) by standardized sperm preparation techniques. Swim up technique preferred for all patients.
10. Single (after 36 hours of inj. HCG) or double (after 12 hours and 36 hours of inj. HCG) intrauterine insemination under all aseptic precautions.
11. Pregnancy test on day 14 by serum beta HCG levels.

RESULTS

Table 1: Factors affecting clinical pregnancy rate.

	Groups	Number (n)	Positive pregnancy	Percentage (%)	P value	Difference of significance
Age of female (years)	<25	51	19	42.2	0.013	S
	26-30	68	22	48.8		
	31-35	31	4	8.8		
Type of infertility	Primary	136	40	88.9	0.624	NS
	secondary	14	5	11.1		
BMI (kg/m ²)	Upto 24.99	77	29	64.4	0.045	S
	25-30	43	12	26.7		
	>30	30	4	8.9		
PCOS	Yes	55	35	77.8	0.000	S
	No	95	10	22.2		
Type of IUI	Single	119	35	29.4	0.758	NS
	Double	31	10	32.3		
Number of IUI	Upto 3	126	44	97.8	0.002	S
	≥4	24	1	2.2		
Tubal patency	Unilateral	19	4	8.9	0.069	NS
	Bilateral	131	41	91.1		

(S- significant, NS- not significant)

Table 2: Duration of infertility and clinical pregnancy rate.

Duration of infertility (yrs)	N	Mean	Std. Deviation	Median	IQR	Mann-Whitney Test	P Value
Positive	45	2.76	0.688	2.50	1.000	-0.341	0.733
Negative	105	3.07	1.342	3.00	1.750	Difference not significant	

We included male patients with normal semen analysis only as per WHO guidelines 2010. We used swim up technique for sperm washing for all the patients.

Amongst females, 51(34%) were in ≤25 years of age group, 68 (45.33%) were in 26 to 30 years of age group and 31 (20.67%) were 31 to 35 years of age. We included patients equal to or less than 35 years of age.

109 (72.67%) couples had infertility for 1-3 years, 39 (26%) of couples had infertility for >3-6 years and 2 (1.33%) couples had more than 6 years of infertility.

Out of 150 patients of our study 136 (90.67%) had primary infertility and remaining i.e. 14 (9.33%) patients had secondary infertility.

Out of 150 women, majority i.e. 77 (51.3%) women had BMI (body mass index) in the normal range i.e. ≤24.99 kg/m², 43 (28.7%) women were overweight with BMI in the range of 25 to 30 kg/m² and 30 (20%) were obese with BMI more than 30 kg/m².

In our study 3 (2%) women were diabetic, 5 (3.33%) had endometriosis as diagnosed by laparoscopy and 55 (36.67%) women had PCOS, whereas 87 (58%) women

had no associated co-morbid conditions; most probably unexplained infertility.

Among the study population 10 males were diabetic and 2 were hypertensive.

Before the procedure of IUI, all female patients were subjected to hysterosalpingography (HSG) to determine the state of tubal patency. Out of 150 patients, 19 (12.7%) had unilateral tubal block and remaining i.e. 131 (87.3%) patients had normal bilaterally patent tubes.

Out of 150 patients, 126 patients had history of previous 1 to 3 IUI cycles done in the past and 24 patients had more than or equal to 4 IUI cycles in the past.

Out of 150 couples, 119 (79.3%) underwent single IUI during the study and 31 (20.7%) underwent double IUI.

In our study the overall pregnancy rate per couple was 30% i.e. 45 out of 150 patients conceived.

DISCUSSION

In 2014 Laka Dinelli in a retrospective study suggested that women with secondary infertility have significantly

better pregnancy rates after IUI than women with primary infertility i.e. 16.7% versus 13.5% ($p=0.04$).⁶

In our study, out of 150 couples, 136 had primary infertility and 14 couples had secondary infertility. Out of total 45 patients with positive pregnancy results, 40 (88.9%) belonged to primary infertility group and 5 (11.1%) were from secondary infertility group. But the association was not statistically significant ($p>0.05$).

In a study, in 2012, by Hao Huang et al, 169 women were in 20-29 years of age group, 306 were in 30-34 years and 189 were 35-40 years of age and the pregnancy rates per couple were 21.9%, 19%, 20.6%, respectively ($p=0.734$).⁷ Thus there was no significant difference in pregnancy rates in different age group of women in this study.

In our study, females belonged to different age groups, 51 (34%) were in ≤ 25 years of age group, 68 (45.33%) were in 26 to 30 years of age group and 31 (20.67%) were 31 to 35 years of age. Pregnancy rates were 42.2% ($n=19$), 48.8% ($n=22$), 8.8% ($n=4$) respectively. Mean age in women with positive pregnancy results was 26.2 years. Significantly better positive pregnancy results were found in women with younger age group ($p=0.009$).

In the study by Hao Huang, 149 couples had infertility for 12 to 23 months, 166 couples for 24 to 35 months and 349 couples were infertile for more than 36 months.⁷ Pregnancy rates were 26.2%, 19.9% and 17.8%, respectively ($p=0.1$). Thus they concluded that duration of infertility does not affect pregnancy rates.

In our study, median duration of infertility was 2.5 years in the group with positive pregnancy results ($n=45$) and that in the couples with negative pregnancy results ($n=105$) was 3 years. The association was not statistically significant ($p=0.733$). Suggesting that duration of infertility did not affect the pregnancy rates in our study.

A retrospective chart review by Randi H. Goldman included 1438 women, divided into BMI groups of <25 , 25-30, 30-35 and >35 kg/m², they found that positive pregnancies were found in the group with mean BMI of 24.9 ± 5 kg/m² ($p<0.01$) which was statistically significant.⁸

In our study, out of 150 women, 77(51.3%) had BMI ≤ 24.99 kg/m², 43 (28.7%) had BMI of 25 to 30 kg/m² and 30 (20%) women had BMI of >30 kg/m², pregnancy were 29 (64.4%), 12 (26.7%) and 4 (8.9%) respectively ($p=0.045$). This shows that woman with lower BMI had significantly better pregnancy rates as compared to overweight or obese women.

A retrospective observational study in 2005 by Sulit et al, there were 44 patients with PCOS and 242 were non PCOS.⁹ Clinical pregnancy rates were 40.9% and 22.73%, respectively ($p=0.01$). Thus PCOS patients have

significantly higher pregnancy rates than non PCOS patients.

In our study, out of 150 women, 55 (36.67%) women had PCOS. Out of 45 women with positive pregnancy results, 35 (77.8%) were PCOS and 10 (22.2%) were non-PCOS ($p=0$). Thus our study showed that women with PCOS had significantly better pregnancy rates compared to non-PCOS patients.

In a study conducted by Hill MJ et al, in 2013, the clinical pregnancy rates were similar between the two groups (single IUI: 16.4%, double IUI: 13.6%, $P=0.07$).¹⁰

A meta-analysis by Apostolos Zavos, et al included five trials involving 1125 IUI cycles.¹¹ There was a two-fold increase in pregnancies in double IUI group compared with single IUI group ($P<0.03$). Sensitivity analysis, excluding a large trial, revealed higher pregnancy rates among double IUI cycles but without statistical significance ($P=0.20$).

Cochrane database involved six studies with 1785 women.¹² They found that double IUI gives rise to higher pregnancy rates. (peto odds ratio 1.8, 95% confidence interval, 1.4 to 2.4).

In our study, out of 150 patients, 119 patients underwent single IUI and 31 patients underwent double IUI during the study. Amongst the 119 of single IUI group positive pregnancies were 35 (29.4%) and out of 31 of double IUI group 10 (32.3%) were positive. The association was found to be non-significant ($p>0.05$).

The retrospective study by Patel D et al, the pregnancy rate in cycle 1-3 (36.1%) was significantly higher than in cycles 4-6 (21.6%) ($P<0.0001$).¹³ Thus they concluded that pregnancy rates significantly decreases with increasing numbers of IUI cycles.

In our study, 126 (84%) patients underwent ≤ 3 IUI cycles in the past and 24 (16%) had history of ≥ 4 IUI cycles done in the past. Out of total 45 conceived patients, 44 (97.8%) belonged to the first group and 1 (2.2%) was from the second group ($p=0.002$). Hence it was found out in our study that pregnancy rate reduces beyond 3rd IUI cycle.

In our study, out of 150 women, 19 (12.7%) had unilateral tubal block and 131 (87.3%) had bilaterally patent tubes. Out of 45 patients who conceived with IUI, 4 (8.9%) were from unilateral tubal block group and 41 (91.9%) were from bilaterally patent tubes group ($p=0.069$). Thus patients with bilaterally patent tubes had better pregnancy rates but the association was not statistically significant.

In our study, out of 150 women only 5 had endometriosis and 3 had diabetes, hence effect of these conditions on fertility could not be studied in the population group. As

only the couples with normal semen analysis were included in the study, age of male and co-morbidities in male had no significant effect on clinical the pregnancy rate.

CONCLUSION

From our retrospective study carried out at a private tertiary care hospital, it can be concluded that:

There is no difference in the pregnancy rates by using either double IUI or single IUI in the treatment of sub fertile couple.

Our study also concludes that women with younger age, normal BMI and with PCOS have better chances of pregnancy in first 3 attempts of IUI with controlled ovarian stimulation.

Pregnancy rates in women with bilaterally patent fallopian tubes are higher than women with unilaterally blocked tubes but the association in our study was not statistically proven.

We found that IUI remains the first line of treatment in patients with younger age group, at least one patent fallopian tube and normal semen analysis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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