A Study Of Predictive Factors Affecting Outcome Of Intrauterine Insemination In Male Factor Infertility

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Abstract:

Purpose : This study is aimed to determining the predictive factors influencing successful pregnancy following intrauterine insemination(IUI).

Method : A comparative prospective study of 222 couples of infertility performed .All women in this study after applying both inclusion and exclusion criteria underwent ovarian stimulation using letrozole analysed for endometrial thickness followed by injection human chorionic gonadotropin for triggering ovulation. Then insemination was performed with washed husbands semen after 36-40 hours. Clinical pregnancies were diagnosed by TVS were included in final analysis. predictive factors evaluated were female age, husband's age, BMI, duration of infertility, endometrial thickness, preovulatory follicle number, type of IUI (single/double) and semen parameters.

Results : The overall pregnancy rates were 15.77%. Factors like patient'age, husband'age, BMI, duration of infertility, prewash sperm count and motility, preovulatory follicle number, endometrial thickness not affected the outcome of IUI. Among the predictive factors evaluated, only type of IUI (single/double) significantly affects outcome of IUI. **Conclusion :** Our study indicate no significant association between predictive factors and outcome of IUI. We found significant improvement in pregnancy rate with double IUI as compared to single IUI.

Keywords: Intrauterine Insemination, controlled ovarian hyperstimulation, predictive factors

Introduction:

Infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse".1 It is a global health problem and affects about 80 million people (8-10% of couple) worldwide. Primary infertility is failure to conceive at all, whereas secondary infertility is failure to conceive after having borne a child or abortion. The last two decades have seen many advances in the management of infertility. Intra Uterine Insemination (IUI) is a therapeutic process of placing washed spermatozoa transcervically into the uterine cavity for the treatment of infertility.2

Male factor infertility affects almost 30-50% of infertile couples worldwide with most infertile men experiencing low sperm density or other semen abnormalities without the presence of any specific underlying cause.3 It may be one or a combination of oligospermia, asthenospermia, or teratospermia.

Double IUI is a method with increased frequency and change in timing versus single IUI. To further increase the total concentration of sperm delivered and the window of sperm exposure to the oocyte,

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performing IUI,S on two consecutive days (double IUI) has been proposed to increase pregnancy rates.4 We carried out a comparative study to find out the pregnancy rates in single versus double IUI in couples having male factor infertility.

Method:

This comparative study was carried out in Zenana Hospital, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur during the year April 2020 - April 2021, after approval by Research Review Board of our Institute. Written informed consent by each subject was sought before the study. The study population included all infertile couples meeting the inclusion and exclusion criteria. The study couple undergone a basic infertility evaluation consisting of detailed anamnesis (age, duration of infertility, type of infertility, lifestyle, body mass index and semen analysis. It included women with 23 to 35 year age group and normal ovarian reserve whose endometrial biopsy for TB PCR was negative and had no obvious pathology and atleast one patent tube was present, and any other factor which affect female fertility also excluded. In the couples having Male Infertility, the volume of semen was >2cc, sperm count was 5-15 million/cc, motility was around 30-50% and sperm having normal shape was about 5 to 30%. The exclusion criteria was applied in cases where in the husband semen analysis showed semen count as <20 million,

its concentration < 10 million/ml and morphology <5% normal [severe teratospermia]. Women whose Diagnostic Laparoscopy revealed moderate to severe Endometriosis, abnormal ovarian cycle, PCOS , cervical stenosis, acute pelvic infection and any other causes of infertility were excluded. Tubal patency was confirmed by hysterosalpingography or laproscopy. Eligible and Consenting Couples having male factor infertility were categorised into single (A) and double(B) IUI groups. In SINGLE IUI GROUP (A) - IUI was done 34-40 hrs after hCG injection. In DOUBLE IUI GROUP (B) - IUI was done twice. First in 34 hrs and second in 48 hrs after hCG injection Controlled Ovarian Stimulation was done by giving orally tab letrozole 5 mg from day 2 – day 6 of the cycle. TVS was used to monitor follicle size and detect ovulation. It was performed from day 8 onwards on alternate days. The hCG 5000 IU was administered when the mean follicular diameter was

>18-20 mm. Semen was prepared by swim up procedure. To 1 volume of semen, 1.5 volumes of wash medium was added and was mixed with a sterile pipette which was then centrifuged at 1200 rpm for 10 minute and supernatant was discarded. Pellet was resuspended with 0.6 ml of wash medium in single IUI. In double IUI 0.6 ml wash medium was used in 1st and 0.4 ml wash medium in second insemination. Once the semen specimen was ready, IUI cannula was introduced into the uterus without applying any force and the semen specimen was slowly ejected from the syringe. The patient was advised to remain on the table for 15 minutes. The patient was prescribed vaginal micronized progesterone 200 mg BD and Tab folic acid 5 mg 1 OD for 14 days. If patient missed a menstrual period 16–18 days after final insemination, a quantitative beta hCG was done. If it was positive, TVS was performed. Clinical pregnancies diagnosed by TVS were considered in the analysis.

Statistical Analysis:

It was carried out by entering all the qualitative and quantitative data in Excel Sheet and analysed statistically. Quantitative data was summarised in the form of Mean ± SD and difference in mean of both groups were analyzed using student't' test. Qualitative data was summarized in the form of proportion and difference in proportions were analysed using Chi-Square test. The level of significance and alpha error was kept 95% and 5% respectively.

Results:

In our study we recruited 222 patients of male factor infertility. Out of these 222 cases, 35 cases had a positive outcome. The mean value of various variables affecting the treatment outcome according to distribution of cases has been depicted in Table-1. Majority of pregnancies (39.19%) occurred in the age group of 30-34 years. The average age of patients in the positive outcome group was 28.40 ± 3.77 years while in the negative outcome group it was 29.25

± 3.76 years. The difference was statistically not significant (p-value = 0.2198). The average age of husband in our study was 31.29 ± 3.93 years. The average duration of infertility in positive outcome group was 6.11 ± 2.50 years while in negative outcome group it was 6.76 ± 2.38 years. However the

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difference was not statistically significant (p- value = 0.1558). The average age of the husband in the positive outcome group was lesser than in the negative outcome group (31.17 ± 3.85 versus 31.89 ± 4.35 years). However the difference was not statistically significant (p-value = 0.3620). In our study 177 patients had a BMI < 25 while 45 patients had a BMI > 25. We found that although the pregnancy rates in patients with BMI <25 (15.25%) was lesser than in those with BMI >25 (17.78%), however the results were not significant statistically (p = 0.6783). In our study 200 patients had both tubes patent (90.10%) while 22 patients had single tube patent (9.90%). While the pregnancy rate in patients with single tube patent (18.18%) was higher than in those with both tubes patent (15.50%), the difference was not statistically significant (p-value = 0.7432). In 157 cycles there was monofollicular development on the day of hCG injection, in 65 cycles there was development of 2 follicles. Although the pregnancy rate with 2 follicles (20%) was higher than with single follicle (14.01%) however the difference was not statistically significantly (p-value = 0.2653). The average endometrial thickness in the positive outcome group was 7.95 ± 0.77 mm while in the negative outcome group it was 7.93 ± 0.73 mm. We found no association between endometrial thickness and IUI results (p-value = 0.8928).The average prewash sperm count in male factor infertility was 15.64 ± 2.65 million/ml. The average prewash sperm motility in our study in patients with male factor infertility was 55.09 ± 14.00%. In patients with male factor infertility, the prewash sperm count in the positive outcome group was 15.58 ± 2.56 million/ml while in the negative outcome group it was 15.65 ± 2.67 million/ml. The difference was not statistically significant (p-value = 0.8956). The prewash sperm motility in patients with male factor infertility in the positive outcome group was 57.64 ± 14.66% while in the negative outcome group it was 54.60 ± 13.85%. The difference was not statistically significant (p-value = 0.2560). The overall pregnancy rate with IUI in our study was 15.77%. The pregnancy rate with Double IUI (20.72%) was higher than Single IUI (10.81%). However the difference was statistically significant (Chi-square, p = 0.0428).

Table 1

Mean values of various variables according to their distribution in the study

Parameters	Mean
Patient's age (in years)	28.54
Husband' age (in years)	31.29
Patient' BMI	23.11
Duration of infertility (in years)	6.66
Prewash sperm count (in million/ml)	15.64
Prewash sperm motility (in %)	55.09
Preovulatory follicle no. (on the day of hCG injection)	1.29
Endometrial thickness in mm (on the day of hCG injection)	7.94
Day of menstrual cycle when inj hCG given	12.92

Table 2

Mean values of various variables according to outcome in the study

Variables	IUI				p-value
	Positive (35)		Negative (187)		
	Mean	SD	Mean	SD	
Patient's age (in years)	28.40	3.77	29.25	3.76	0.2198

Husband' age (in years)	31.17	4.35	31.89	3.85	0.3620
Patient' BMI	23.31	1.74	23.08	1.53	0.4622
Duration of infertility (in years)	6.11	2.50	6.76	2.38	0.1558
Prewash sperm count (in million/ml)	15.58	2.56	15.65	2.67	0.8956
Prewash sperm motility (in %)	57.64	14.66	54.60	13.85	0.2560
Preovulatory follicle no. (on the day of hCG injection)	1.39	0.49	1.28	0.45	0.2083
Endometrial thickness in mm (on the day of of hCG injection)	7.95	0.77	7.93	0.73	0.8928
Day of menstrual cycle when inj hCG given	12.58	1.32	12.99	1.33	0.0974

Discussion:

In our study the mean age of patients who had a positive outcome with IUI was 28.40 yrs while in the patients who had a negative IUI outcome it was 29.25 yrs.

Though the p-value was not statistically significant (p = 0.2198). The positive outcome was higher in younger age group.

Several studies have shown an association between increasing maternal age and poor pregnancy rates following IUI.

Demir B et al (2011)5 showed that pregnancy rate was the highest in IUI cycles when woman was <25 years old. With decreasing costs and increase in safety IVF has become a favoured option in women with age >35 years.

Govindrajan M et al (2017)6 analysis showed that the pregnancy rates in younger aged female were significantly higher than that in older aged females.

Starosta A et al (2020)7 found that advancing maternal and paternal age negatively impact pregnancy rates. Patil D et al (2021)8 also found that with aging there is physiological decrease in fertility.

Immediata V (2021)9 also found that clinical pregnancy rate and live birth rates after COS-IUI's were significantly influenced by female age and FSH level.

Although the outcome of IUI was better in couples with younger age of the husband (Mean age of the husband in the positive outcome group was 31.17 years compared to 31.89 years in the negative

outcome group, yet the difference in pregnancy rates was not significant (p = 0.3620).

Increased paternal age due to a probable impact on sperm DNA structure has been thought to have a negative impact on IUI outcome independent of other semen parameters. There are several studies that support the above finding.

Recently Demir B et al (2011)5 showed that partner's age significantly affected the pregnancy rate per cycle in women aged <30 years and TMS >10 x 106.

Govindrajan M et al (2017)6 showed that younger aged males had a significantly higher success rates in IUI as compared to older aged males.

Starosta A et al (2020)7 advancing paternal age negatively impact pregnancy rates, although the effect of paternal age are inconsistent in literature.

Sharma R et al (2015)10 published a study showing that with an increase in male age, the fertility rate was reduced.

Souter I et al (2011)11 found that clinical pregnancy rates following IUI did not differ significantly among different BMI categories.

Huyghe S et al (2017)12 found obesity affecting fecundity adversely.

Whynott RM et al (2021)13 concluded that a BMI between 25 and 29.99 mg/m2 or □30 kg/m2 does not have a negative effect on live birth after IUI.

In our study the mean duration infertility in the positive outcome group was 6.11 years while in the negative outcome group it 6.76 years. The above table shows that increased duration of infertility negatively influences pregnancy rates following IUI.

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However the results were not significant statistically (p = 0.1558).

Our findings are supported by several other studies.

Zadehmodarres S et al (2009)14 stated that duration of infertility was one of the three predictive variables as regards pregnancy following IUI cycles.

Kamath MS et al (2010)15 found that duration of infertility significantly influenced the clinical pregnancy rate in IUI cycles.

Yavuz A et al (2013)16 found that pregnancy rate in couple with a period of infertility of less than 6 years was 2.33 times higher than those with infertility problems for over 6 years.

Yildirim G et al (2017)17 also found that duration of infertility significantly influences pregnancy rate with IUI.

In our study there was no significant association between the prewash sperm count, sperm motility and the IUI results in male factor infertility.

Most of the studies in literature support the view that there is no significant association between prewash semen parameters and IUI results.

Haim D et al (2009)18 stated that the concentration and overall motility of sperms determined before or after selection did not have any significant influence on the outcome of IUI.

Zadehmodarres S et al (2009)14 – Pregnancy rate did not have any independent relation to sperm count.

The pregnancy rate with double IUI was 20.72% and with single IUI it was 10.81%. We found statistically significant improvement in pregnancy rates with double IUI as compared to single IUI.

Our result are similar to those of Liu W et al (2006)19, Randall GW et al (2008)20

Patil D (2021)8 conclude that double IUI is an essential, economic and more patient friendly treatment option for selected subset of infertile patients. Before resorting to advanced, invasive and costly option and it may be more prudent to invest in double IUI.

Rakic L et al (2021)21 concluded that clinical pregnancy rate may increase in double IUI group.

Conclusion:

To conclude, COH-IUI is an effective first line method of treatment in patients with mild male factor infertility. We found no statistically significant association between patients age, husband's age, patient's BMI, duration of infertility, number of preovulatory follicles on the day of hCG, endometrial thickness on the day of hCG, patency of tubes (single v/s double), type of infertility, etiology of infertility or prewash semen parameters and IUI outcome. The disadvantage with double IUI is the increase in cost and burden to both healthcare provider and the couple. These factors should be taken into consideration before going for double IUI in clinical practice. Further, large multicentric trials are needed to determine whether double IUI increases pregnancy rates in any subgroup of patients.

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