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Research Article

INTRA UTERINE INSEMINATION AN EXPERIENCE IN RURAL POPULATION

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ABSTRACT

Objective:1) To find out efficacy of various ovulation induction protocols in IUI 2) To find out the efficacy of IUI in treatment of infertility **Method**: All infertility patients of our OPD underwent a standard investigation protocol The infertility work-up included patients' history, physical examination, conformation of ovulation by follicular monitoring, tubal patency test by diagnostic laparoscopy, and semen analysis of male partner & PCT. All women underwent a standard treatment protocol that included either natural cycle or ovulation induction to achieve superovulation by clomiphene citrate alone, or combined with gonadotrophins. Follicula monitoring using transvaginal sonography was done from D6-8 onwards and all women were given injection Human chorionic gonadotrophin 5000 U for LH surge when the dominant follicle was ≥18 mm. IUI was Performed at 18 hours and 40 hours from the time of HCG injection. Semen for IUI was prepared by the standard Swim Up technique, or by the Density Gradient method. Progesterone (Transvaginal micronized progesterone 200mg/day) for luteal phase support for 14 days following IUI was given to patients who were affording. **Results**: Majority of couples were having primary infertility (60.97%) Patients of secondary infertility were of 39.03% only. In our study only 11.82% patients were having multiple factors contributing to infertility. Male factor was in 42.59% of couples as against 30.34% of couples were having only anovulation as causative factor for infertility. Unexplained infertility was present in 13.82% patients only. The outcome variable for success of IUI was occurrence of pregnancy. This was defined by delay in menses associated with presence of positive pregnancy test or a detectable rise in serum beta HCG levels. In our study overall pregnancy rate per cycle was 8.01% & per couple it was 21.65%. Per cycle fecundity according to the factor responsible for infertility, the highest success rate was observed in cervical factor (33.33%). For male factor it was 7.74% and for combined factors overall it was 5.92%. Out of 152 pregnancies that occurred during study 108 had Full Term live birth of the baby (71.05% Miscarriage was there in 9.87% patients only. Only three patients had multiple pregnancies (1.97%) and one patient had ectopic pregnancy. Per cycle fecundity was little better in patients with only anovulation(10.51%). When we compared various regimen used for ovulation induction for IUI we found that though percentage of pregnancies achieved by Low dose HMG either with (13.89%) or without Clomiohene (15.58%), pregnancy rate achieved with clomiphene alone was 7.43% . This was promising at low affordable cost.

In our study, we achieved 40.13% pregnancy with second attempt and collectively with first two attempts pregnancy rate achieved was 71.71%.

Keywords: Intra uterine insemination, Assisted reproduction, Ovarian stimulation in intra uterine insemination. Swim up technique, Density gradient method

INTRODUCTION

Despite revolutionary advances in the field of assisted reproduction such as in vitro fertilization (IVF) intracytoplasmic sperm injection (ICSI) and subzonal insemination (SUZI), intrauterine insemination (IUI) remains an inexpensive, non-invasive and effective first line therapy for selected patients with cervical factor, moderate male factor, unexplained infertility, immunological infertility and infertility due to ejaculatory defects. It is also proposed as therapy for endometriosis, ovarian dysfunction, and even for tubal factor. [1] Though the technique of IUI has remained same, several advances in type of stimulation protocol, gonadotrophins, sperm preparation techniques and ultrasound monitoring have led to promising success rate with IUI. IUI is preferred conception- enhancing technique for women <35 years, with functional tubes, short period of infertility and moderate male factor, particularly in a rural set up due to monitory limitations. It is a method of choice vs. timed intercourse or natural cycle IUI.

MATERIAL AND METHOD

It is Prospective study done at Mohini Hospital Shrirampur. Written informed consent was taken from each patient.

Sample size: 702 Patients

Study period: Between May 2001 to December 2012

Inclusion criteria: 1) Patients ready to give informed consent 2) Patients willing to come for regular follow up 3) Patients <35 years, with antral follicular count > 5 **4)** Patients with at least one functional tube 5) Patients with mild to moderate male factor sub fertility. 6) Patients with anovulation and unexplained infertility

Exclusion criteria: 1) Uncooperative patients. 2) Patients not willing to follow the protocol. 3) Patients with azoospermia 4) Patients with bilateral fallopian tube block. 5) Patients with advanced stage endometriosis (stage III & IV) 6) Patients with documented failure with endometriosis stage I & II

All infertility patients of our OPD underwent a standard investigation protocol.

The infertility workup included patients' history, physical examination, and conformation of ovulation by follicular monitoring; tubal patency test by diagnostic laparoscopy, and semen analysis of male partner & PCT All women underwent a standard treatment protocol that included. either natural cycle or ovulation induction to achieve super ovulation by clomiphene citrate alone, or combined with gonadotrophins. Follicular monitoring using transvaginal sonography was done from D6-8 onwards and all women were given injection Human chorionic gonadotrophin (HCG) 5ooo IU for LH surge when the dominant follicle was ≥18 mm.

IUI was performed at 18 hours and 40 hours from the time of HCG injection. Semen for IUI was prepared by the standard Swim Up technique, or by Density Gradient method. Progesterone (Transvaginal micronized progesterone 200mg/day) for luteal phase support for 14 days following IUI was given to patients who were affording.

RESULTS

Seven hundred and two sub fertile couples enrolled in our study acc/to the inclusion and exclusion criteria were observed for 1897 treatment cycles.

Table. 1: Baseline Characteristics of Couples Undergoing IUI

Variable	No. Of Couples	Percentage Of Couples
Age Of Female		
< 30 years	442	62.96%
≥ 30 years	260	37.04%
Age Of Male Partner		
< 30 years	372	52.99%
≥ 30 years	330	47.01%
Duration Of Infertility		
< 5 years	485	69.09%
5-10 years	147	20.94%
> 10 years	70	9.97%
Tpe Of Infertility		
Primary	428	60.97%
Secondary	274	39.03%

It is evident from table no1, in most of the couples both the partners were < 30 years of age. Female partners of < 30 years were 62.96% & male partner were 52.99%. Majority of couples were having primary infertility (60.97%) Patients of secondary infertility were of 39.03% only.

Table. 2: Cycle fecundity by factor causing infertility

diagnosis	No Of Patients	No Of cycles	No Of Pregnancy	Fecundity
Male Factor	299	749	58	0.08%
Anovulation	213	495	52	0.11%
Tubo-Peritoneal				
a)Endometriosis	2	8	1	0.13%
b)Peritubal adhesions	2	6	1	0.17%
c)one side tubal block	1	6	0	0%
Cervical factor	5	12	4	0.33%
Combined factors				
a)Male Factor + Anovulation	82	249	14	0.06%
b)Endometriosis + Anovulation	1	4	1	0.25%
Unexplained	97	368	21	0.57%

In our study only 11.82% patients were having multiple factors contributing to infertility. Male factor was in 42.59% of couples as against 30.34% of couples were having only anovulation as a causative factor for infertility. Unexplained infertility was present in 13.82% patients only. The outcome variable for success of IUI was occurrence of pregnancy. This was defined by delay in menses associated with presence of positive pregnancy test or a detectable rise in serum beta HCG levels. In our study overall pregnancy rate per cycle was 8.01% & per couple it was 21.65%.

Per cycle fecundity according to the factor responsible for infertility, the highest success rate was observed in cervical factor (33.33%) . For male factor it was 7.74% and for combined factors overall it was 5.92%. . Per cycle fecundity was little better in patients with only anovulation (10.51%).

Table. 3: Pregnancy Outcome In Patients Conceived By IUI

outcome variable	No. Of Females	Percentage of Females
Live Births		
Term	108	71.05%
Preterm	3	1.97%
Still Births	1	0.66%
Miscarriage	15	9.87%
Ectopic Pregnancy	1	0.66%
Multiple Pregnancy	3	1.97%
Ongoing Pregnancy	8	5.26%
Lost To Follow Up	13	8.55%

Out of 152 pregnancies that occurred during study 108 had Full Term live birth of the baby (71.05%).

Miscarriage was there in 9.87% patients only. Only three patients had multiple pregnancies (1.97%) and one patient had ectopic pregnancy.

Table.4: The regimens and clinical evidence of their benefits

Type of regimen used for superovulation	No Of Cycles	No Of Conceptions	% of prenancy per Cycle
Natural cycle	16	1	6.25%
CC+HCG	1548	115	7.43%
HMG+HCG			
a)Low Dose	154	24	15.58%
b)High dose	19	1	5.26%
CC+HMG + HCG			
a)Low Dose	72	10	13.89%
b)High Dose	15	1	6.67%

When we compared various regimens used for ovulation induction for IUI we found that though the percentage of pregnancies achieved by Low dose HMG either with (13.89%) or without Clomiohene (15.58%), pregnancy rate achieved with clomiphene alone was 7.43% . This was promising at low affordable cost.

Table. 5: Cycle Fecundity By Attempt Of IUI

No. Of Attempts For IUI	No Of Patients	Pregnancy/cycles	Fecundity
1	702	48	0.068
2	648	61	0.094
3	392	36	0.092
4	82	4	0.049
5	45	2	0.044
≥ 6	28	1	0.036

In our study, we achieved 40.13% pregnancy with second attempt and collectively with first two attempts pregnancy rate achieved was 71.71%.

Table.6: Effect of sperm parameter on IUI

Sperm Parameters	No Of Cycles	No Of Patients	No Of Conceptions	% of Conception	Conception/Cycle
Sperm Count					
a) < 5	66	10	1	10%	0.015
b) 5 ≥ - ≤ 10	573	143	30	20.98%	0.052
c) > 10-≤ 20	340	141	25	17.73%	0.074
d) > 20	918	403	96	23.82%	0.105
Sperm Motility					
WHO Motility grade					
a) a+b≥ 50 with grade a ≥ 25	807	409	101	24.69%	0.125
b) a+b< 50	1090	293	51	17.41%	0.047

Table.7: Complications in IUI

Complictions in IUI	No of Females	Percentage of Females
Cervical contact bleeding	68	9.69%
Abdominal Cramping	104	14.82%
Spontaneous abortions	10	1.43%
Blighted ovum	5	0.71%
Ectopic Pregnancy	1	0.14%
Infections	nil	0%
OHSS	nil	0%
Multiple pregnancy	3	0.43%

DISCUSSION

Super ovulation coupled with intrauterine insemination is considered to be a popular treatment option for women <35 years, functional tubes, short period of infertility and moderate male factor, particularly in rural population. The universal preference for this method is based on the hypothesis that both these methods increase the proximity of gametes in the reproductive tract. Therefore this treatment modality is often advised before attempting more invasive therapies such as IVF, gamete intrafallopian transfer[2] The National Institute of Clinical Excellence (NICE), UK has revised the evidence for assessment and treatment of infertile couples and recommended that the IUI should be offered to couples with infertility because it is as effective as IVF, less invasive and requires fewer resources[3] The rational put forth in support of super ovulation & IUI is that ovarian stimulation corrects subtle, unpredictable ovulatory dysfunction and there is increased probability of conception if increased density of motile spermatozoa is placed closer to multiple fertilizable oocytes. Hence it is considered to be a viable treatment option for male factor, cervical factor and unexplained infertility.[4]

\In this study we have analysed couples with male and female subfertility undergoing superovulation with IUI. In our study the overall pregnancy rate per cycle was 8.01% as against 8.2% and 9.2 percent reported by Steures et al[5] & Iberico et al[6] respectively are comparative. The pregnancy rate per couple was 21.65% in our study as compared to 28.1% reported by Shibahara et al.[7]

IUI may be performed with or without superovulation depending on the patient's characteristics.

Better IUI outcome is seen in terms of number of preovulatory follicles, clinical and ongoing pregnancy rates (OPRs), and live birth rates following ovulation induction(OI) compared with the natural cycle[8,9] However, Chen and Liu concluded though stimulated cycles of IUI is superior to natural cycle of IUI in patients <35 years, natural cycle is preferable for

Patient's ≥ 35 years[8] In our study conception rate of natural cycle was 6.25% as against with Superovulation by various methods was 8.037%

Ovarian stimulation by clomiphene citrate (CC) and IUI remains the first choice treatment for ovulatory dysfunction, unexplained infertility, endometriosis, male subfertility. [9] with pregnancy rate averaging 7% per cycle [10] Owing to the negative influence of CC on endometrial thickness, the medication should be reduced to three days in patients with retarded endometrial growth confirmed on USG. [11] In our study pregnancy rate was 7.43%.

Gonadotrophin such as FSH and HMG, alone or in conjunction with the GnRH agonist / antagonist, are often used for ovulation induction. In our study we used HMG in a daily low dose of 75IU of HMG + HCG and in 19 patients higher doses of HMG were required with HCG. Low dose protocols are advised since pregnancy rates do not differ from those obtained with high dose regimens. Prospective randomized trials are needed to determine whether daily or alternate day FSH is to be given for better results. [12]

Clomifene citrate may be used in conjunction with gonadotrophins/dexamethasone for stimulation. Combination protocols are less costly and equally effective, with potentially less multiple births than with gonadotrophin alone. In our study we used CC+HMG+HCG in low doses of 75 IU HMG in 72 patients, while 15 required higher doses of HMG,.the conception rate was 13.89% & 6.67% respectively.

There are several sperm separation techniques, and these are based on different principles like migration, filtration or density gradient centrifugation (DGC). Swim up yields a high no. of progressively motile sperm count and effectively separates sperm from bacteria and cell debris; it is of limited use in case of low sperm count and asthenozoospermia, where DGC is useful. A single sperm defect may be rescued by DGC. The time of centrifugation is more important than g-force for inducing ROS formation in semen, and shorter centrifugation period in preparation for ART may be beneficial. [13] In our study centrifugation time was 10 minutes for Swim up method & 20 minutes for DGC..

Luteal phase support with vaginal progesterone gel (Cione 8%) yields significantly higher CPR/cycle and per patient compared to patients who received no luteal phase support [14]

In our study Progesterone (Transvaginal micronized progesterone 200mg/day) for luteal phase support for 14 days following IUI was given to patients who were affording.

Studies have reported significantly better pregnancy rates following double insemination (18 and 42 hour after HCG) versus single insemination (34 hours after HCG) [15] Despite the 36 hour being preferred timing for IUI, no statistical differences regarding pregnancy rates has been reported between 24 hour and double insemination (12h & 36h)[16]

In our study the cycle fecundity by no of attempts was6.84 % after first IUI & increased subsequently to 9.41 % after second IUI. Thereafter fecundity declined sharply from fourth IUI. Khalil et al., a reported highest pregnancy rate in first treatment cycle [17] Four to Six IUI cycles may be performed before considering alternate therapy such as IVF [18]

Patient's age ≤ 35years is a favourable predictor of outcome of IUI, irrespective of the method of

sperm preparation used [19] According to aetiology, Pregnancy rates/cycle may vary among women with different aetiologies. The cumulative pregnancy rates varied greatly by diagnosis from 16% for patients with male factor infertility to 60% for patients with ovulation disorder [20]

Cervical factor yields a favourable outcome [5] In our study pregnancy rate per cycle for cervical factor was 33.33% , for male factor alone it was 7.74% but with anovulation it was 5.62%. For anovulation alone pregnancy rate per cycle was better (10.51%).

Patients with original sperm motility ≥ 30% had a higher cumulative pregnancy rate (74%) than patients with motility < 30% with a four times increase in PR with an increase in motility of ≥ 30% [21] Significantly higher PR have been reported with samples with normal sperm morphology of > 4% (according to Kruger's criteria) compared to ≤ 4% [22] In our study conception rate per cycle in the group between sperm count 5 ≥ - ≤ 10 was marginally better (20.98%) as compared to count between > 10 - ≤ 20 (17.73%). According to WHO criteria for sperm motility, patients having motility grade a+b ≥50% before sperm wash with grade a ≥ 25% had a better conception rate 24.69% as compared to other group of sperm motility grade a+b < 50% (17.41%).

Though complications after IUI are rare w**e** observed mild abdominal discomfort and or cramps **(**14.82%) and cervical contact bleeding in 9.69% of patients. **S**tudies have reported slight cervical contact bleeding and mild abdominal discomfort and or cramps. [24]

Vaginal administration of misoprostol at the time of IUI is associated with a significant increase in vaginal bleeding and abdominal cramping rates does not seem to enhance the outcome [25]

Spontaneous abortions, blighted ovum, and ectopic pregnancies have been reported in COH-IUI cycles **[26]** In our study spontaneous abortion was to the tune of 1.43% and blighted ovum was in 1.43% of patients.

Infectious complications associated with IUI are frequently cited. According to Sacks and Simon, Most reported cases of infection fail to show evidence for the actual presence of infection, and the prevalence is unaltered by the administration of prophylactic antibiotic or washing the semen sample with antibiotic. [27] In our study we did not have an infection or OHSS.

The adverse effect of COH, such as OHSS and Multiple pregnancies are a concern [28] Miscarriage rate ranging from 11.8% [29] to 34% [30]

CONCLUSION

In rural areas where masses cannot afford expensive health care, IUI is a simple, cost effective, non-invasive first line therapy for cervical factor, anovulatory infertility, moderate male factor, unexplained infertility, and immunological infertility. Strict patient selection criteria with individualizing stimulation protocols tailored according to age and aetiological factor with a strict cycle canccelation policy will help to reduce the associated complications, such as multiple pregnancies and OHSS, while maximising the overall pregnancy outcome. Three to six IUI cycles should be offered to patients before considering alternative therapy with IVF/ICSI.

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