Original Research Article

Factors determining successful intrauterine insemination

Parul Sinha[1]*, Kiran Pandey[2], Anand Srivastava[3]

[1]Department of Obstetrics and Gynecology, Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India
[2]Department of Obstetrics and Gynecology, GSVM Medical College, Kanpur, Uttar Pradesh, India
[3]Department of Respiratory Medicine, KGMU, Uttar Pradesh, India

*Correspondence:
Dr. Parul Sinha,
E-mail: drparulanand@gmail.com

ABSTRACT

Background: Infertility is defined as failure to conceive even after one year of regular, frequent and unprotected intercourse. Infertility can be attributed to male causes in approximately 25-40% cases, female causes in 40-50% cases, both in 10-20% and unexplained causes in 10-15% cases. Artificial insemination (Intrauterine Insemination) involves placement of processed sperms from husband (AIH – artificial insemination homologous) or from donor (AID – artificial insemination donor) into the female genital tract.
Methods: Objectives of the study were to do sperm preparation to obtain normal good quality motile sperms, to perform intrauterine insemination using husband semen around the time of ovulation, to study factors responsible for successful pregnancy rates by this method. Out of 100 infertile females recruited for the study 34 underwent artificial insemination by IUI with controlled ovarian hyper stimulation. Sperms were washed by density gradient centrifugation or by a direct swim-up technique that does not involve centrifugation.
Results: Overall pregnancy rate per patient for male factor infertility was 23.52%. None of the patients consented for more than three cycles of IUI. Maximum pregnancy was achieved in third cycle of IUI. Sperm motility >40% was related with pregnancy in 8 cases. Duration of infertility didn't influence pregnancy rate. The majority of pregnancies were achieved in the age group of 25-29 years (50%). No pregnancy occurred with >15 years of infertility.
Conclusions: This study concluded that intrauterine insemination after ovarian stimulation or controlled ovarian hyperstimulation is a successful and efficacious therapy for infertility.

Keywords: Infertility, Intrauterine insemination, Semen analysis

INTRODUCTION

Infertility is defined as failure to conceive even after one year of regular, frequent and unprotected intercourse. It is not merely a somatic illness, but a human problem implicating social and psychological aspects that require search for solution unlikely to be relegated to a sole medical option.

Infertility is a major problem affecting approximately 2-10% of all married couples. Infertility is of two types:

- Primary infertility-when no previous pregnancies have occurred.
- Secondary infertility-when patient has achieved at least one previous pregnancy (not necessarily a live birth).

Infertility can be attributed to male causes in approximately 25-40% cases, female causes in 40-50% cases, both in 10-20% and unexplained causes in 10-15% cases. Ovarian dysfunction accounts for approximately 30-40% of cases of female infertility.

Male factors may be due to defective spermatogenesis, bilateral obstruction of the epididymis, the vas or the ejaculatory ducts or failure to deposit spermatozoa in the vagina. Unexplained infertility refers to infertility with normal results on standard investigations (normal semen analysis, objective evidence of ovulation, a normal uterine cavity and bilateral tubal patency).

Artificial insemination (Intrauterine Insemination) involves placement of processed sperms from husband (AIH – artificial insemination homologous) or from donor (AID – artificial insemination donor) into the female genital tract in cases with male factor infertility, few cases of female factor infertility (cervical and vaginal factors) and unexplained infertility. It is done usually with ovulation induction therapy or controlled ovarian hyperstimulation (COH). Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. COH together with IUI is commonly offered to couples with subfertility and factors not involving the fallopian tubes. IUI gained its popularity because it is simple, non-invasive, and a cost-effective technique.[1] This method is indicated in cases of cervical infertility, relative male factor infertility, anovulation, endometriosis with a healthy fallopian tube, and unexplained infertility. Pregnancy rates after IUI differ between studies according to patient selection criteria, the presence of various infertility factors, ovarian stimulation methods, number of cycles performed, different sperm parameters and preparation technique.[2] Objectives of present study were

- to evaluate the infertile the couple and determine the causative factor/ factors.
- Sperm preparation to obtain normal good quality motile sperms
- to perform intrauterine insemination using husband semen around the time of ovulation
- to study successful pregnancy rates by this method.

METHODS

The study was carried out on 100 infertile couples. Both partners were completely evaluated by taking proper history, examination and investigations to assess the cause of infertility. Total of 48 couples were included for IUI. Out of them 34 underwent artificial insemination by IUI with controlled ovarian hyperstimulation. Out of remaining 14 patients, 3 patients of azoospermia did not opt for Donor IUI and 11 patients underwent ovarian hyperstimulation without IUI.

Semen analysis

Complete semen analysis was done by manual method (in haemocytometer – Neubauer Chamber or Makler Chamber) or auto analyser in laboratory.

Specimen was collected after 3 to 5 days abstinence by masturbation in clean, sterilized jar.

The standard value of semen analysis as laid down by WHO (2010)[3]

- Volume – 1.5 ml (1.4-1.7)
- PH – ≥7.2
- Viscosity < 3 (scale 0-4)
- Sperm concentration 20 million/ml or more (15 million/ml)
- Total sperm number (million per ejaculate): 39
- % total motility (progressive and non-progressive):40
- % progressive motility: 32
- Sperm morphology (normal forms %):4
- Vitality (live sperm %): 58

Ovulation induction protocols

- Clomiphene citrate only
- Clomiphene citrate+ HCG
- CC+HMG+HCG
- Gonadotrophin+Gnrh agonist+HCG
- Clomiphene + Metformin

Ultra sound examiantion

The patients undergoing ovulation were then subjected to Folliculography from 8th day of cycle to assess

- Number of follicles present
- The maximum size of dominant follicle
- The endometrial thickness
- Approximate time for giving HCG injection
- Whether follicle ruptures or not and day of rupture

When the diameter of the dominant follicle was >18mm and the endometrial thickness were >8 mm, injection β HCG was given to induce ovulation.

Ovulation was assessed by Folliculography and Hormonal assay.

Folliculography showing

- Collapse of the follicle with Cremated margins
- Presence of fluid in the cul-de-sac

Hormonal assay

- Plasma LH > 0.65 IU / ml
- Plasma progesterone > 1 ng / ml
- Urinary pregnanediol > 5μmol / 24 hours

Intra uterine semination

Sperm preparation

Sperms were washed by density gradient centrifugation or by a "direct swim-up" technique that does not involve centrifugation. In normal semen samples, centrifugation

causes no more DNA damage to spermatozoa than a direct swim-up technique4

Washed sperm is concentrated in Hams F10 media without L-glutamine, warmed to 37 °C (99 °F). The direct swim up is used for semen with normal parameters that is a count of more than 20 million / ml with more than 50 % motility. It is not used for viscous samples.

The Density Gradient Method is used for marginally abnormal sperm and viscous samples.

Timing of insemination

In unstimulated cycle, insemination was done when the size of dominant follicle was ≥18 mm and endothelial thickness was ≥ 8 mm. In stimulated cycle IUI was done within 12-48 hours after HCG injection.

IUI procedure

- Proper washing and stabilization of equipment.
- Treatment of infections and discharge in previous cycle.
- Time interval between sample collection and IUI should not be more than 1 hr 15 min.
- Cervix to be exposed properly by Cusco's bivalve speculum or Sims speculum.
- Preparation of vagina by normal saline. No antiseptic should be used, as it will kill the sperm.
- Cannula should be loaded properly to eliminate the dead space. Cannula should be attached properly to a disposable 1 ml syringe and then loaded with the sample by aspirating it from the test tube with the tip of cannula dipped into the prepared sample.
- The cannula is then introduced into the uterine cavity above the level of internal os, close to the cornual opening.
- Insemination volume of not more than0.5 ml is used. The inseminate is deposited very slowly over 3 minutes.
- Cannula is then withdrawn very slowly and patient is kept on the table for 15 mins.
- Luteal support is given for 14 days in form of Duphaston tab 10 mg x BD, antibiotic cover for 4 days after IUI.
- Urinary Beta HCG on day 14 of insemination will detect pregnancy

RESULTS

21 patients of male factor infertility opted for IUI of which 3 conceived (14.28 %).04 patients of cervical factors opted for IUI and 2 conceived. 09 patients of unexplained infertility opted for IUI and 3 conceived. Overall pregnancy rate per patient was 23.52%.

None of the patients consented for more than three cycles of IUI. Maximum pregnancy was achieved in third cycle of IUI.

Table 1: Results of controlled ovarian hyperstimulation.

Factors causing infertility	Cases (n=34)	Conceived	%
Male factor	21	3	14.28
Cervical	4	2	50
Unexplained	9	3	33.33

Table 2: Pregnancy rate per IUI cycle in stimulated cycle.

No. of cycles	No. of patients (n=34)	No. of pregnancy	%
1	20	1	12.5
2	6	2	25
3	8	5	62.5
4	-	-	-
5	-	-	-
6	-	-	-

Table 3: Comparison of pregnancy rate with total motile sperm count.

Total mobile sperm count x 106	No. of cases	No. of cases conceived	%
≤1	2	-	-
2-3	4	1	33.3
4-6	13	2	66.67
≥7	2	-	-
Total	21	3	14.28

Out of 3 patients who conceived with COH and IUI 2 (66.67%) patients had total motile. Sperm count in the range of 4-6 million while 1 (33.33%) patient had total motile sperm count 2-3 million.

Table 4: Comparison of pregnancy rate with sperm motility.

Motility % after sperm wash	No. of patients	No. of pregnancy
< 40%	11	0
>40%	23	8

These results demonstrated that the percentage of post washed sperm motility >40% was related with pregnancy in 8 cases and pregnancy wasn't observed with sperm motility <40% in post washed sperm analysis ($p<0.001$).

The mean age of female was (range 20-40 years). The majority of pregnancies were achieved in the age group of 25-29 years (50%).

Table 5: Outcome of IUI procedure for different female age groups.

Age (years)	No. of patients	No. of pregnancy (%)
20-24	7	1 (14.29%)
25-29	10	5 (50%)
30-34	9	2 (22.22%)
35-39	5	0 (0%)
40-42	3	0 (0%)

Table 6: Outcome of IUI procedure for different male age groups.

Age groups (years)	No. of patients	No. of pregnancy (%)
24-29	5	2 (40%)
30-34	10	3 (30%)
35-39	12	3 (25%)
40-44	4	0 (0%)
>45	3	0 (0%)

There was not a significant relationship between husband's age and pregnancy rate.

Table 7: Outcome of IUI procedure for different durations of infertility.

Durations of infertility (Years)	No. of patients	No. of pregnancy (%)
<5	13	5 (38.46)
5-10	9	2 (22.22)
10-15	7	1 (14.29)
>15	5	0 (0)

Duration of infertility didn't influence pregnancy rate, but the pregnancy rate according to infertility durations <5 years, 5-10 years, 10-15 years observed in patients were 5(38.46%), 2(22.22%), 1(14.29%) respectively. No pregnancy occurred with >15 years of infertility.

DISCUSSION

Infertility is a multifactorial problem affecting 2-10% couples and has far reaching social and psychological implications. Our study lays special emphasis on the active management of infertility with ovulation induction (ovarian stimulation and controlled ovarian hyperstimulation) and intrauterine insemination with the help of ultrasonographic follicular monitoring and endometrial dating. The study shows that the majority of the patients 46 (73%) have primary infertility and 54 (27%) has secondary infertility. Present findings are comparable to the results of Templeton et al[5] (primary infertility in 75% and secondary infertility in 25% cases). Present study involves 34 couples who underwent intrauterine insemination involving 21 cases of male factor infertililty, 4 cases of cervical factor infertility and 9 cases of unexplained infertility. All these patients underwent controlled ovarian hyperstimulation by various protocols followed by time synchronized IUI. Pregnancy rate with male factor infertility was 14.28% and with cervical factor infertility was 50%. Allen et al showed pregnancy rate with male factor infertility 25% and cervical factor 60%.[6]

Out of 34 patients, 20 underwent only one cycle if IUI and only 1(12.5%) patients conceived. 6 patients underwent 2 cycles of IUI and from these 2 (25%) conception occurred and 8 patients had three cycles of IUI and out of which 5 (62.5%) patients conceived. None of the patients consented for more than the three cycles of IUI. Therefore, maximum pregnancy was achieved in three cycles of IUI. In study of Chafkin LM, Nulsen JC, Luciano AA et al recommended a maximum three trial of COH/IUI, based on cycle fecundity cumulative pregnancy rates observed in historical controls involving 594 patients of unexplained infertility.[7] Thus benefit of continuing COH/IUI treatment beyond three cycles appears to be minimal.

Out of three patients of male factor infertility who conceived with COH and IUI, 2 (66.67%) patients had total motile sperm count in the range of 4-6x10^{6} while 1 (33.33%) patient had total motile sperm count in the range of 2-2x10.[6] Patient with total motile sperm count less than 1 million did not achieve pregnancy. According to Dickey RP et al, Matorras R et al and Huang H Y et al with sperm count more than 5 million/ml, motility >30% and normal morphology more than 14% in the given semen sample, pregnancies were achieved in IUI program with variable pregnancy rate.[8-10] Compana A et al showed that it is highly impossible that pregnancy can be achieved after homologous insemination of less than 1 million spermatozoa.[11] According to Kerrin J et al when more than 15 million motile sperms are inseminated, there is no increase in the pregnancy rate; however, there is an increase in multiple pregnancy when inseminate exceeds 20 million motile sperms.[12] Yavuz A showed that progressive motile sperm percentage was found to be an independent factor for pregnancy after IUI in multivariate analyses.[13] Present results demonstrated that the percentage of normal form post washed sperms >40% was related with pregnancy in 8 cases; and pregnancy wasn't observed with sperm motility less than 40% in post washed sperm analysis (p<0.001).

The mean age of female was in range of 20-40 years. The majority of pregnancies were achieved in the age group of 25-29 years (50%). This was comparable to the work of Westerkalen LA et al.[14] In a study by Dinelli L et al, the authors conclude that in women aged ≤38 years, IUI-H should be considered as an option, particularly in cases of female infertility from ovulation disorders, in cases of a normal ovarian reserve, in cases of secondary infertility, or when ≥1 million progressive sperm are inseminated.[15] Bifollicular stimulation is required. In other cases, in vitro fertilization should be discussed as the first-line treatment. In present study, there was not a significant

relationship between husband's age and pregnancy rate. This agrees with Compana's study.[11] However, no pregnancy was achieved in males > 40 years old. This can also be compared with the study of Brezechffa PR et al.[16] Duration of infertility didn't influence pregnancy rate, but the pregnancy rate according to infertility durations <5 years, 5-10 years, 10-15 years observed in patients were 5 (38.46%), 2 (22.22%), 1 (14.29), respectively. No pregnancy occurred with >15 years of infertility. IUI has now evolved and has become standard adjunct to any superovulation treatment in unexplained infertility. In present study, successful pregnancy outcome after COH with IUI came out to be 23.53%. This was comparable to meta-analysis of prospective randomized trial by Zeyneloglu HB et al comparing IUI and timed intercourse in women with unexplained infertility in which the pregnancy rate was higher with IUI (20% versus 11.4%).[17]

CONCLUSION

This study concluded that intrauterine insemination after ovarian stimulation or controlled ovarian hyperstimulation is a successful and efficacious therapy for infertility.

REFERENCES

1. Cantineau AE, Cohlen BJ, Al-Inany H, Heineman MJ. Intrauterine insemination versus fallopian tube sperm perfusion for non tubal infertility. Cochrane Database Syst Rev. 2004:CD001502.
2. Dorjpurev U, Kuwahara A, Yano Y, Taniguchi T, Yamamoto Y, Suto A et al. Effect of semen characteristics on pregnancy rate following intrauterine insemination. J Med Invest. 2011;58:127-133.
3. World Health Organization, Department of Reproductive Health and Research. WHO laboratory manual for the Examination and processing of human semen. 5th Ed. 2010.
4. Younglai EV, Holt D, Brown P, Jurisicova A, Casper RF. Sperm swim-up techniques and DNA fragmentation. Hum Reprod. 2001;16(9):1950-3.
5. Templeton AA, Penney GC. The incidence, characteristics, and prognosis of patients whose infertility is unexplained. Fertil Steril. 1982;37(2):175-82.
6. Allen NC, Herbert CM, Maxson WS, Rogers BJ, Diamond MP, Wentz AC. Intrauterine insemination: a critical review. Fertil Steril. 1985;44(5):569-580.
7. Chaffkin LM, Nulsen JC, Luciano AA, Metzger DA. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. Fertil Steril. 1991;55(2):252-7.
8. Dickey RP, Pyrzak R, Lu PY, Taylor SN, Rye PH. Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal sperm. Fertility and Sterility. 1991;71:687-9.
9. Matorras R, Corcóstegui B, Perez C, Mandiola M, Mendoza R, Rodríguez-Escudero FJ. Sperm morphology analysis (strict criteria) in male infertility is not a prognostic factor in intrauterine insemination with husband's sperm. Fertil Steril. 1995;63(3):608-11.
10. Huang HY, Lee CL, Lai YM, Chang MY, Wang HS, Chang SY et al: The impact of the total motile sperm count on the success of intrauterine insemination with husband's spermatozoa. J Assist Reprod Genet. 1996;13:56-63.
11. Campana A, Sakkas D, Stalberg A, Bianchi PG, Comte I, Pache T et al. Intrauterine insemination: evaluation of the results according to the woman's age, sperm quality, total sperm count per insemination and life table analysis. Hum Reprod. 1996;11:732-6.
12. Byrd KJ. Supracervical replacement of spermatozoa. Ir. Soules MR (Ed.): Controversies in reproductive endocrinology and infertility. Elsevier, Amsterdam;1989.
13. Yavuz A, Demirci O, Sözen H, Uludoğan M. Predictive factors influencing pregnancy rates after intrauterine insemination. Iran J Reprod Med. 2013;11(3):227-34.
14. WesterkalenLA, Naaktgeboren N, Helmerhorst FM. Evaluation of pregnancy rates after intrauterine insemination according to indication, age and sperm parameters. Assist Repro Genet J. 1998;15:359-64.
15. Dinelli L, Courbière B, Achard V, Jouve E, Deveze C, Gnisci A, Grillo JM, Paulmyer-Lacroix O. Prognosis factors of pregnancy after intrauterine insemination with the husband's sperm: conclusions of an analysis of 2,019 cycle. Fertil Steril. 2014;101(4):994-1000.
16. Brezechffa PR, Daneshmand S, Buyalos RP. Sequential clomiphene citrate and human menopausal gonadotrophin with intrauterine insemination: the effect of patient age on clinical outcome. Hum Reprod. 1998;13:2110-4.
17. Zeyneloglu HB, Arici A, Olive DL et al Comparison of Intrauterine Insemination with Timed Intercourse in Superovulated Cycles with Gonadotropins: A Meta-analysis. Fertil Steril. 1998; 69: 486-91.