CLINICAL SUCCESS OF INTRAUTERINE INSEMINATION IN A PRIVATE FERTILITY CENTRE

Mafruha Khanam[1*] Yasmin Akhter[2] Md Mahfuzul Haque Sarkar[3] Mohamed Mazih Fazyl[4]

Abstract

Background : IUI is one of the most frequently and widely used therapeutic modalities to treat various forms of infertility. Achieving pregnancy after IUI is presumably due to increase in the number of highly motile spermatozoa with a high proportion of morphologically normal spermatozoa near the site of fertilization. The objectives were to compare the success rates of IUI with that of timed intercourse, compare the success rate of IUI according to the protocols, review methods used to time the IUI with ovulation, identify the factors to determine IUI outcome.

Materials and methods : This is a cross sectional prospective study conducted in Surgiscope Fertility Centre, Chattogram, Bangladesh over a period of 21 months from 596 patients who underwent IUI. Multiple variables were selected such patient parameters like age of woman and cause of infertility, parameters related to ovulation induction such as drugs used for COH, number of mature follicles and endometrial thickness and laboratory parameters such as post wash sperm count and type of IUI (Single or double IUI) which were recorded and statistically analysed.

Results : The minimum age for females and males were 18 and 19 respectively and the maximum age for females and males were 40 and 66 respectively. The mean age for females was 27.3 +/- 0.4 years and the mean age for males was 35.9 +/- 0.5 years. Another variable was endometrial thickness where the mean was 8.9 mm ± 0.2 mm and median was 8.5 mm. Furthermore, successful pregnancies also depend on total motile sperm count taken post-wash. The total motile sperm count was 29.8 million ± 1.5 million and median was 30 million. Pregnancy rate for total motile sperm count less than 10 million was 8.6%. For women over 28 and total motile sperm count <10 million, the success rate was only 2.7%.Most of the patients who underwent IUI were between the ages of 28-31, which was 175 (29.3%). The successful conception rate for females over the age 28 was 9.6% compared to the whole group at 12%. Among 596 patients, 71 patients (11.91%) had successful conceptions while 525 patients (88.09%) did not. There is a statistically significant relationship between number of IUI cycles completed and the rate of successful pregnancy. There is also a relationship between the number of inseminations and the success rate.

Conclusion : IUI is a successful contemporary treatment especially as a good first line invasive treatment for couples with unexplained infertility, male factor infertility, anovulation, female less than 30 years of age. Percentage of actual number of motile sperms appear to have an important impact on outcome. Success rate of conception was also found to be statistically significant in patients with appropriate endometrial thickness. Careful and criteria-based selection of patients along with ovarian stimulation seem to be the ideal model for achieving clinical success in IUI.

Key words

Intrauterine Insemination (IUI); Controlled Ovarian Hyper stimulation (COH); Semen; Infertility.

Introduction

Intrauterine Insemination (IUI) is the therapeutic process of placing washed spermatozoa transcervically into the uterine cavity for the treatment of infertility. IUI theoretically allows a relatively higher number of motile spermatozoa to reach the oocyte and it has been used for a variety of indications such as non-severe male factor infertility, unexplained infertility, cervical mucus hostility, ovulatory disturbances, mild endometriosis, PCOS,

1. Associate Professor of Obstetrics &Gynaecology Institute of Applied Health Sciences (IAHS) Chattogram.
2. Assistant Professor of Obstetrics & Gynaecology Institute of Applied Health Sciences (IAHS) Chattogram.
3. Assistant Professor of Forensic Medicine and Toxicology Army Medical College, Jashore.
4. Intern Doctor of Obstetrics & Gynaecology Bangabandhu Memorial Hospital (BBMH) Chattogram.

***Correspondence:** **Dr. Mafruha Khanam**
E-mail: drporag@yahoo.com
Cell : 01819 32 03 86

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male sexual dysfunctions like impotency, hypospadias, and retrograde ejaculation, and husband abroad. The rationale behind IUI is increasing the gamete density at the time and site of potential fertilization i.e increasing the chances of spermatozoa meeting the oocyte in the fallopian tube after ovulation has occurred[1-4]. In majority of the cases, IUI is frequently the realistic management before stirring on to IVF and ICSI as its success rate with Controlled Ovarian Stimulation (COS) varies between 8 to 22%, also is a less invasive and a less costly process[5,6].

The overall success rates of IUI remains controversial and depends on several factors, with published pregnancy rates varying from as low as 5% to as high as 70% per patient, however a 10%-20% clinical pregnancies per cycle is an acceptable range for all aetiologies. The pregnancy rates per IUI cycle are quite variable in the literature due to differences in cause and duration of infertility, type of ovarian stimulation, sperm preparation techniques, treatment cycles and number of times IUI is performed during a cycle (Single or double)[2].

Several prognostic factors with regards to IUI treatmentoutcome have been identified, and include factors such aspatient profile, duration of infertility, type of infertility, stimulation protocol, follicular response, endometrial thickness, timing and number of IUI, percentage of sperm with normal morphology, type and percentage of sperm motility and total number of motile sperms inseminated.The aim of this study is to analyse the variables that contribute to the success of stimulated intrauterine cycles. A prospective study was done to identify the most important parameters regarding IUI success that would provide important data for predicting the success of IUI and further help in planning sub fertility treatment for the couples[3,5]. We postulate that IUI success is dependent on a combination of optimum endometrial thickness, successful ovulation with precise timing of insemination.

Material and methods

This is a cross sectional prospective study which was performed on 596 couple & conducted in Surgiscope Fertility Centre, Chattogram, Bangladesh for 21 months from December 2017 to September 2019. Inclusion criteriafor this is unexplained cause, PCOS, mild endometriosis, male factor like oligospermia, asthenoteratozoospermia, impotence, husband abroad.Furthermore, the exclusion criteria issevere endometriosis, hypospadias, retrograde ejaculation, bilateral tubal block. Ethical clearance was obtained from the proper authority.

Ovarian Stimulation

Couples with unexplained infertility, mild oligospermia, minimal to mild endometriosis and polycystic ovaries who failed to conceive after trying ovulation induction with timed intercourse for 6 cycles were counselled for IUI. The protocol for ovulation induction started with the first line drug, Clomiphene citrate (50-100mg 1HS x 5 days, Day 3 to Day 7). If the patient had already underwent ovulation induction with Clomiphene citrate for a maximum of 6 cycles or if the patient failed to achieve ovulation with Clomiphene citrate, then ovulation induction was performed with gonadotrophins, either HMG in non-PCO patients or FSH in PCO patients. A maximum of 4 cycles of IUI were performed and if the patient failed to conceive, the couple were counselled to the next line of management either laparoscopy or ART. For couples who were unable to progress to the next line of management after 4 cycles due to financial constraints or personal reasons, a maximum of 6 cycles of IUI were done.

In cycles stimulated with gonadotrophins, Inj. Gonal F 75 IU or Inj. FSH 50 IU or 75 IU was administered on a daily basis from day 3 to day 7. On day 8 of stimulation, assessment of follicular development was performed using transvaginal ultrasound. Further stimulation with gonadotrophin was determined according to follicular response. The aim of stimulation was to achieve a multifollicular (2 or 3 follicles) response. Once a follicle of >17 mm size was identified, inj. human Chorionic Gonadotrophin 5000 IU (hCG) was given as an ovulation trigger and a single IUI 36 h later or a double ovulation trigger and a single IUI 36 h later or a double IUI, 10-12 hours prior to ovulation and 8-10 hours after ovulation was planned. Single IUI was done for selected group of patients with moderate oligoasthenospermia (5-10 million sperms/ml) who had financial constraints and insisted on underwent IUI for a few cycles.

If four or more mature follicles (>17mm) developed, the cycle was cancelled.

Semen Preparation

On the day of IUI, the husband was instructed to

give semen that was prepared by the swim up technique or double-density gradient method with Nutrient Mixture F10 Ham. The post wash sample parameters were assessed. Under aseptic precautions, IUI was carried out with a soft IUI catheter with an insemination volume of 0.5ml. After the procedure, the patient was advised 20 to 30 minutes of bed rest. All women were provided luteal phase support with dydrorgesterone for 12 weeks. If menstrual cycle was delayed, urine pregnancy test was carried out. When positive, a transvaginal ultrasound was performed 2 weeks later to confirm a clinical pregnancy. The primary end point of this study was a positive urine pregnancy test.

Statistical Analysis

The variables selected were: patient parameters like age of woman and cause of infertility; parameters related to ovulation induction such as drugs used for COH, number of mature follicles and endometrial thickness and laboratory parameters such as post wash sperm count and type of IUI (Single or double IUI). Of these parameters, age of the women and men were recorded as continuous variable, in addition to the motile sperm count and follicle size. Other parameters were taken as categorical variables. An Ordinary Least Squared (OLS) regression model was used in the statistical analysis. A p-value of <0.05 was considered to be significant. Data were entered in SPSS version 17.

Results

Data was analysed using appropriate statistical techniques and the results were presented with tables and graph where applicable.

The age of couples both male and female were recorded. The minimum age for females and males were 18 and 19 respectively and the maximum age for females and males were 40 and 66 respectively. The mean age for females was 27.3 +/- 0.4 years and the mean age for males was 35.9 +/- 0.5 years. One of the most important variable observed during this study was endometrial thickness where the mean was 8.9 mm ± 0.2 mm and median was 8.5 mm. Furthermore, successful pregnancies also depend on total motile sperm count taken post-wash. The total motile sperm count was 29.8 million ± 1.5 million and median was 30 million. Pregnancy rate for total motile sperm count less than 10 million was 8.6%. For women over 28 and total motile sperm count <10 million, the success rate was only 2.7%.

Table I shows that the majority of the patients who underwent IUI were between the ages of 28-31, which was 175 (29.3%).

Table I : Age distribution of all patients.

Age Group	Number of Patients	Percent
18-23	156	26.2%
24-27	152	25.5%
28-31	175	29.3%
32-35	78	13.1%
35-40	35	5.9%
Total	596	100%

Maximum success rate of IUI was observed 25 years age group (Table II). The successful conception rate for females over the age 28 was 9.6% compared to the whole group at 12%.

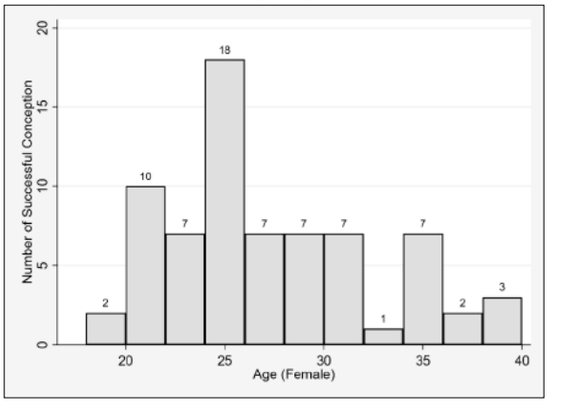

Fig 1 : Age distribution of successful patients.

Among 596 patients, 71 patients (11.91%) had successful conceptions while 525 patients (88.09%) did not. In table II, the success rate between the two ovulation inducing drugs were compared. It was observed that 62 patients (12.42%) successfully conceived with FSH while 9 patients (9.28%) conceived with Gonal_F.

Table II : Cross tabulation of the success rate of ovulation induction drugs used.

Ovulation Inducing Drugs	Conception Success NO	YES	Total
GONAL_F	88	9	97
	90.72%	9.28%	100%
FSH	437	62	499
	87.58%	12.42%	100%
Total	525	71	596
	88.09%	11.91%	100%

Table II shows that there is a statistically significant relationship between number of IUI cycles completed and the rate of successful pregnancy. There is also a relationship between the number of inseminations and the success rate.

Table III: Regression between success and no. of IUI applied, number of insemination and ovulation inducing drugs.

	A	B
Constant	-.1467674	-.1871823
No. of IUI Cycles	. .0989171***	.1016626***
No. of Insemination	.0557491**	.0529281**
Ovulation Agent		.0471749
R Squared	0.0567	0.0595
No. of Obs	595	

*, **, *** indicates significance at the 90%, 95% and 99% respectively.

Discussion

The study attempted to identify the important IUI variables with regard to successful outcome and to form a model for success from which the outcomes of subsequent cycles could be more accurately predicted. The variables studied include factors such as patient profile, medical history, ovulation inducing agent, follicular response, endometrial thickness, trigger, semen preparation method, semen parameters like prewash and post wash sperm count, timing and number of insemination and number of IUI. Our analysis found four significant variables: age of the patient, endometrial thickness, post wash sperm count and number of IUI.

Among the patient parameters, age of the couple, especially the female, was found to be a significant variable. Majority of the successful conceptions after IUI were patients below the age of 30 whereas the patients above 30 years had a significantly low (2.7%) success ratelike Montanaro-Gauci., et al. in 2001 and AMIGOS trial in 2016 who proposed that advancing age related to decrease pregnancy rate may be due to less number and bad quality of oocytes[7,8]. Even more effective treatment options like ART-IVF cannot completely overcome the negative impact of age[9,10]. In a study by Wasteraken V et al a trend toward reduction in success rate with IUI was noted in women with age >35 years, although the difference was not statistically significant, which correlates with our study[11]. Age >40years had a negative impact on the success of IUI. This decline in success in probably due to a combination of progressive follicular depletion, decline in granulose function, poor oocyte quality, reduced endometrial receptivity, higher rate of chromosomal abnormalities and increase in frequency of an ovulatory cycles after age 40, ageing of the reproductive tract and diseases of the reproductive tract.

Many studies have documented a significant drop in the success rate beyond the age of 40 years, with reported live births being as low as 1.4%. Put together, for women over 35, COH/IUI as a treatment option needs careful consideration, and for women over 40, IUI is a poor treatment option[12-14]. On the other hand, in women of younger age group with no risk factors, IUI can be offered as a treatment option as it has increased chances of pregnancy compared to natural methods of conception.

The use of ovulation inducing drugs such as FSH and Gonal F shows an increase in conception success of 12.42 % and 9.28% respectively. FSH was shown to have higher birthrates than Clomephine Citrate and Letrazole, according to a multicenter, randomized trial by Diamond et al which showed that live birth rates after FSH was 32%, 23% after CC and 19% after Letrozole[15].

The success rate of IUI was significantly increased at endometrial thickness of 8.9 mm ± 0.2 mm. Endometrial thickness on the day of hCG administration was significantly greater in cycles where pregnancy was achieved.Correlation between endometrial thickness with pregnancy rate and predisposing factors for growth of endometrium are unclear. In our study, we evaluated endometrial thickness ranges between 6 to 17mm. We found that pregnancy rates were maximum when the endometrial thickness was between 9-10mm ($p<0.001$) though there is an increasing trend to positive pregnancy with endometrial thickness between 7mm -14 mm. The aim should be to keep the endometrial thickness between 7-14 mm prior to IUI. Similar results were obtained by Victoria et el who did not find a correlation between age, number of follicles and gonadotropin ampoules with endometrial thickness but in all age ranges, chance of pregnancy was higher with endometrial thickness of 6-10 mm[16].

Post wash sperm count of >10 million during IUI was found to be significantly increasing the success rates. In our study, the majority of patients had a post wash count between 10-30 million and this could be one of the reasons why we obtained a statistical significance. It is also supported by a retrospective review by Abdallah M.E et al that a total motile sperm count less than 5 million seem to have a negative impact on pregnancy rate but each extra million motile sperm in the washed insemination sample seem to increase the chance of pregnancy by 2%[17]. The total motile sperm count independently predicts success of IUI and that cycles with less than 10 million total motile sperm are significantly less likely to result in a pregnancy.

The timing of insemination relative to ovulation is critical for an optimal success rate. There was significant difference regarding pregnancy rates between single and double inseminations. The success rate was significantly better with double IUI. Double IUIs have higher pregnancy rates in subfertile couples compared to single IUI. A meta-analysis by Osuna et al including a Cochrane review also shows that the PR was significantly increased with two inseminations in cases in which stimulation was performed with CC with or without gonadotropins and ovulation triggering with 5000 IU of hCG[18]. Increasing the number of inseminations improve the chance of conception because of the unsynchronized ovulation pattern in COH with multiple ovulations sequentially over more than 24 hours. Although first insemination would provide sufficient spermatozoa before the first released oocyte, the second insemination provide additional spermatozoa to fertilise oocytes likely to be released subsequently.

Limitation

The study was based on one centre instead of multiple centres, as a result the sample population was restricted. We also excluded patients with severe male infertility, severe endometriosis, hypospadias, retrograde ejaculation, bilateral tubal block.

Conclusion

IUI is a successful contemporary treatment for appropriate indications. It maybe considered as a good first line invasive treatment for couples with unexplained infertility, male factor infertility, anovulation, female less than 30 years of age. Percentage of actual number of motile sperms appear to have an important impact on outcome. Success rate of conception was also found to be statistically significant in patients with appropriate endometrial thickness. Careful patient selection criteria coupled with ovarian stimulation appear to be the model for IUI success. Additional information on the predictors of IUI to provide a more exact basis for counselling patients on expectations and treatment options is needed.

Recommendation

Further studies should be carried out involving large number of participants in multiple centres to improve success of IUI for treatment of infertility.

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Contribution of authors

MK -Conception, design, acquisition of data, drafting & final approval.

YA-Acquisiton of data, interpretation of data, critical revision & final approval.

MMHS-Data analysis, drafting & final approval.

MMF-Acquisition of data, data analysis, interpretation of data, critical revision & final approval.

Disclosure

All the authors declared no competing interest.

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