

Effectiveness of Intrauterine Insemination in Unexplained Infertility and Male Subfertility with Mild Form of Oligo Asthenoteratozoospermia

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Abstract: *Introduction:* Male infertility is typically determined through routine sperm analysis, but recent publications have called into question its diagnostic and prognostic accuracy, as well as the effectiveness of IUI itself. The aim of the study was to evaluate the pregnancy rate following IUI in unexplained infertility and male infertility (a mild form of oligo astheno teratozoospermia). *Methods:* This interventional study was carried out in the outpatient department (OPD) of the infertility Unit of Gynaecology and Obstetrics Department of Bangabandhu Sheikh Mujib Medical University, Dhaka, from July 2014 to June 2015. A total of 148 couples were enrolled, out of which 74 couples where only a male partner had oligospermia or asthenozoospermia or teratozoospermia were considered group I (case) and 74 couples had unexplained infertility was considered group II (control). All-female patients took Tab clomiphene citrate 100mg from D2-D5 and inj Menogon (75IU) I/M was received on D3 and D8. TVS for folliculometry was done from D9 onwards every alternate day. Statistical analysis of the results was obtained by using windows computer software with Statistical Packages for Social Sciences (SPSS-version 22). *Result:* Follicle was developed (≥ 17 mm) in 71 (96.0%) in group I and 68 (91.9%) in group II up to D₁₃. Pre-wash motility < 50 percent was found in all cases in group II and group II respectively. Post motility ≥ 50 percent was found in 10 (15.6%) in group I. The difference was statistically significant ($p < 0.05$) between the two groups. Biochemical pregnancy occurs 3 (4.7%) in group I and 5 (8.5%) in group II. Clinical pregnancy 2 (3.1%) and 3 (5.1%) in group I and group II respectively. Biochemical and Clinical pregnancy differences were not statistically significant ($p > 0.05$) between the two groups. *Conclusion:* Stimulated IUI should be the first choice treatment for mild male factor infertility, and unexplained infertility, which is a less costly and easy procedure. it can be done before going through more invasive and costly treatments like IVF or ICSI.

Keywords: Intrauterine Insemination, Infertility, Subfertility, Oligo Asthenoteratozoospermia

1. Introduction

1.1. Background

Infertility is defined as the inability to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. It has been reported that infertility or subfertility affects around 8%–12% of couples worldwide and that includes 40%–50% due to male factor either solely (20%) or in combination with the female factor (30%–40%), and another 30%–40% are idiopathic or unexplained [2, 3]. The spouses must have a thorough examination before deciding on the best assisted reproductive technology (ART), such as intrauterine insemination (IUI) or in vitro fertilization-embryo transfer (IVF-ET) (IVF-ET). IUI is one of the most basic forms of assisted reproductive technology (ART) for treating infertility by artificial insemination. The goal of IUI is to boost the gamete density of both the egg and the sperm at the fertilization site [3]. Clinical indications for IUI, according to WHO 2010 criteria, include couples with cervical factor subfertility, unilateral tubal defect, ovulatory dysfunction, unexplained infertility, physiologic or psychological sexual dysfunction, immunological infertility, and inadequate semen parameters [4]. In roughly half of the infertile couples, abnormal sperm quality or sexual dysfunction are contributing reasons [5]. Because natural pregnancy is significantly reduced in these instances, the male should be evaluated by a reproductive medicine clinic's adequately educated gynecologist or a clinical andrologist. Because they see subfertility as a threat to their masculinity, many subfertile men put off consultations. After three years, Scholten *et al.* discovered that the ceased treatment group had 18 pregnancies (25%) compared to 41 pregnancies in the IUI group (28 percent) [6]. Both groups had a cumulative pregnancy rate of 40% after three years, indicating that there was no difference in time to continuous pregnancy. IMSI resulted in considerably higher embryo quality, implantation, and pregnancy rates than earlier ICSI cycles, according to Goswami *et al.* [7]. They found that the IMSI treatment enhanced embryo growth and clinical results in infertile couples with male infertility and poor embryo development when compared to earlier ICSI attempts and that it can be used as a replacement for ICSI [8]. In 30–45% of cases, the cause of abnormal semen parameters is idiopathic; however, a standardized approach for the treatment of idiopathic male infertility remains elusive. Rahman *et al.* discovered that IUI is possible in a relatively new center with limited technology in a study conducted in Bangladesh [9]. It may be considered a good treatment option for couples with unexplained infertility, male factor infertility, and anovulation-related infertility. It is worth noting that there is a need for a good number of randomized clinical trials comparing IUI with expectant management in these couples. Therefore, the present study is aimed to evaluate the effectiveness of intrauterine insemination in unexplained infertility and male subfertility with a mild form of oligo Asthenoteratozoospermia.

1.2. Objective

To evaluate the pregnancy rate following IUI in unexplained infertility.

To evaluate the pregnancy rate following IUI in male infertility.

2. Methods

This interventional study was conducted at the Infertility Unit of the Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The study duration was 1 year, from July 2014 to June 2015. A total of 148 couples were enrolled for a single cycle of IUI at the study hospital. Among them, 74 couples who had unexplained infertility were considered group I (control), and 74 couples where only male partners had oligospermia or asthenozoospermia or teratozoospermia was considered group II (case). The objectives of the study along with its procedure, risk, and benefits to be derived from the study were explained to the patients in an easily understandable local language and then informed consent was sought from them. Ethical approval was also obtained from the ethical review committee of the study hospital. All-female patients were given Tab clomiphene citrate 100 mg from D2–D5 and inj Menogon (75 IU) I/M was given on D3 and D8. TVS for folliculometry was done from D9 onwards every alternate day. When the mature follicle becomes 17mm, inj HCG 1 ample I/M was given, and IUI was done around 36–40 hours of inj HCG. On the day of IUI pre-wash and post-wash semen analysis was done. Semen was processed through the “Swim-up” method. Female patients were asked to tie down in a lithotomy position. Cusco's speculum was introduced and the cervix was washed with normal saline. Semen was introduced into the uterine cavity through a soft rubber catheter. Two weeks after IUI beta HCG is done when menstruation did not occur. As empiric ovarian stimulation with clomiphene citrate or exogenous gonadotrophin is commonly combined with IUI in the treatment of couples with male factors infertility based on the observation that cycle fecundability is higher after combined treatment than after IUI or ovarian stimulation alone in couples with unexplained infertility. For this reason, in this study, empiric ovarian stimulation was done. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated by frequencies and percentages. The quantitative observations were indicated by frequencies and percentages.

2.1. Inclusion Criteria

Patients who had given consent to participate in the study.
Female Criteria:

- 1) Age between 18–35 years.
- 2) Regular menstrual cycle & ovulation confirmed by TVS for folliculometry.
- 3) Both tubes are patent.

4) Normal uterine cavity.

Male Criteria:

- 1) Age between 20-50 years.
- 2) normal seminal parameter according to WHO.
- 3) had mild oligospermia (semen count 10-20 million/ml).
- 4) Had a mild form of asthenozoospermia (total motility 30%-50%).
- 5) Had a mild form of teratozoospermia (morphology 30-50%).

2.2. Exclusion Criteria

- 1) Mentally ill.
- 2) Unable to answer the criteria question.
- 3) Exclude those affected with other chronic diseases etc.

Female Criteria:

Women with PID, endometriosis, fibroid uterus, and other pelvic pathology.

Male Criteria:

Semen count <10 million/ml.

3. Results

The mean age of the wife was 29.1±4.8 years in group I and 29.2±4.1 years in group II. The mean age of the husband was 36.3±4.5 years in group I and 36.6±4.1 years in group II. Primary infertility was found in 55 (74.3%) and 53 (71.6%) in group I and group II respectively. Duration of infertility was found <10 years 63 (85.1%) in group I and 59 (79.7%) in group II. IUI could not be done in 10 and 15 cases in group I and group II respectively. Semen analysis showed that the total semen count was ≥20 million/ml in 100.0% of group I and <20 million/ml in 100.0% of group II. Total motility and total morphology were ≥50 percent found in 100.0% of group I and ≤50 percent in 100.0% of group II. The duration of infertility, total semen count, total motility, and total morphology were significant.

Table 1. Ovulatory response of the patients (n=148).

Ovulatory response	Group-I (n=74)		Group-II (n=74)		P value
	n	%	n	%	
Endometrial thickness on D ₁₂					
≤8 mm	38	51.4	44	59.5	^a 0.321 ^{ns}
>8 mm	36	48.6	30	40.5	
Size of the mature follicle D ₁₂					
<16 mm	14	18.9	20	27.0	^a 0.241 ^{ns}
16-22 mm	60	81.1	54	73.0	
Endometrial thickness on D ₁₃					
≤9 mm	3	4.0	6	8.1	^b 0.440 ^{ns}
>9 mm	11	14.9	14	18.9	
Size of the mature follicle D ₁₃					
<17 mm	3	4.0	6	8.1	^b 0.440 ^{ns}
17-24 mm	11	14.9	14	18.9	

s= significant, ns= not significant, P-value reached from ^aChi square test and ^bFisher exact test.

Table 2. Distribution of the study patients by semen analysis (n=123).

Semen analysis (on the day of IUI)	Group-I (n=64)		Group-II (n=59)		P-value
	n	%	n	%	
Pre-wash concentration of semen (million/ml)					
≤20	64	100.0	0	0.0	^a 0.001 ^s
>20	0	0.0	59	100.0	
Pre-wash motility (%)					
<50	64	100.0	0	0.0	^a 0.001 ^s
≥50	0	0.0	59	100.0	
Post-wash motility (%)					
<50	10	15.6	0	0.0	^b 0.001 ^s
50-100	54	84.4	59	100.0	

s= significant, ns= not significant, P-value reached from ^aChi square test and ^bFisher exact test.

Table 3. Serum β HCG two weeks after IUI (n=123).

Serum β HCG two weeks after IUI (mIU)	Group-I (n=64)		Group-II (n=59)		P-value
	n	%	n	%	
<5	61	95.3	54	91.5	0.314 ^{ns}
≥5 (biochemical pregnancy)	3	4.7	5	8.5	

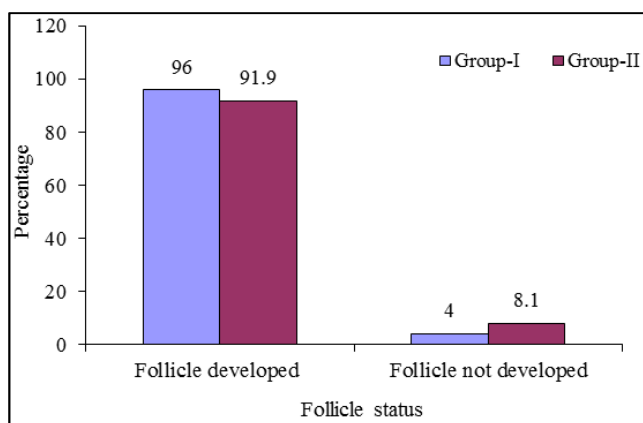
ns= not significant, P-value reached from Fisher exact test.

Table 4. Sonographic evidence of pregnancy (n=123).

Sonographic evidence of pregnancy	Group-I (n=64)		Group-II (n=59)		P-value
	n	%	n	%	
Gestational sac present	2	3.1	3	5.1	0.714 ^{ns}
Gestational sac absent	1	1.6	2	3.4	

ns= not significant, P-value reached from Fisher exact test.

Note: In group, I (control) total of 15 cases of IUI could not be done (due to inadequate follicular development in 6 cases, 4 cases could not be given semen, 4 cases could not present due to illness and 1 case could not be present due to accident). In group II (case) a total of 10 cases of IUI could not be done (3 cases had inadequate follicular development, 6 cases could not give semen, 1 case could not ejaculate).

**Figure 1.** Distribution of the patients by the ovulatory response (n=148).

4. Discussion

Intrauterine insemination (IUI) with ovulation induction is a popular assisted reproduction therapy option for couples who have at least one patent uterine tube. Mild-moderate male infertility, infertility owing to ovulation abnormalities, unexplained infertility, and endometriosis are the most common reasons for IUI. Tang et al. discovered that the Mean \pm (SD) age of the female subjects in their study was 31.0 \pm 4.8 years [10]. Soria et al. showed the female mean age of the participants was 32.2 years varying from 23 to 41 years in the unexplained group [11]. Similarly, Peeraer et al. study also found similar men's age in their study, which was comparable with the present study [12]. In this present study, it was found that the mean age of wife and husband were almost alike between the two groups, and no statistically significant ($p>0.05$) difference was observed between the two groups. Tang et al found that the mean age of males in the unexplained group was 33.2 \pm 5.4 years, which is similar to the current study [10]. In their study, Benbella et al. discovered that primary and secondary infertility affected 77.2 percent and 22.8 percent of couples, respectively [13]. The frequency of primary infertility was reported by Parsanezhad et al. in Iran where primary infertility was documented in 78.4% of couples [14]. Soria et al. mentioned in their study that infertility was primary and secondary in 87.8% and 12.2% of the cases, respectively [11]. Infertility

variables were found in 21.9 percent of female cases and 26.3 percent of male cases, respectively. In 35.3 percent of instances, infertility was caused by a combination of variables, whereas 16.5 percent of cases were unexplained. The mean duration of infertility was significantly ($p<0.05$) higher in unexplained infertility in this study. Soria et al. study observed the mean duration of infertility was 3.04 years varied from 1 to 10 years, which was comparable with the current study [11]. The almost similar mean duration of infertility was also observed by Tang et al. [10]. Male infertility has been reported that semen counts have declined over the past 50 years [15]. According to Agarwal et al.'s findings, at least 30 million males globally are infertile, with Africa and Eastern Europe having the highest rates [16]. Soria et al. mentioned in their study that based on semen analysis, male infertility factors were classified as follows, in order of frequency: asthenospermia 29.4%; mild oligo/astheno/teratospermia (OAT) 24.0%; moderate OAT 18.9%; severe OAT 6.0%; oligospermia 0.7%; teratospermia 4.1%; azoospermia 12.5%; and causes unrelated to semen quality, such as erectile dysfunction, positive serology results, etc in 4.4% [11]. Dorjpurev et al. investigated the impact of sperm characteristics on IUI pregnancy rates [17]. Because it represents both sperm concentration and motility, as well as the consequences of sperm processing, the number of motile spermatozoa inseminated may have special significance as a predictive tool [18]. During the initial infertility workup, the total motile sperm count and morphology will lead to pregnancy rate counseling [19]. Only sperm with motility of +4 was shown to boost clinical conception rates, which could be explained by the fact that this study only included an unexplained and moderate male subfertile patient group. Cao et al. concluded that IUI can be performed when the NMSI (number of motile sperm inseminated) exceeds 2x10⁶ [20]. The conception success rates increased only if the number of sperms with +4 motility increased. Because sperm motility has such a high predictive value for a higher chance of conception, it is often considered the most important factor in IUI success [21-24]. In Soria et al.'s study, using donor sperm for patients with azoospermia resulted in a pregnancy rate of 16.7% each cycle [11]. Soria et al.'s study found no significant differences when just mobility and altered morphology were evaluated; however, when OAT was included, the pregnancy rate fell in accordance with severity (9.4 percent, 8.5 percent, and 6.4 percent for mild, moderate, and severe OAT, respectively) [11]. In this series, it was observed that follicle was developed (≥ 17 mm) in 96.0% in group I and 91.9% in group II up to D13. Follicle was not developed in 4.0% in

group I and 8.1% in group II up to D13. The difference was statistically significant ($p > 0.05$) between the two groups. In their study, Orvieto et al. and Abbara et al. discovered that triggering is done once two to three ovarian follicles are at least 17–18 mm in diameter in most centers [25, 26]. As a result, ultrasound folliculogram used to estimate follicle size on the morning of the trigger were routinely performed two days before those used to determine follicle size on the day of oocyte retrieval. Because follicles grow at a rate of 1.7 mm per day, the follicle sizes in the Abbara et al. study should be 3–4 mm smaller than comparable studies examining follicular diameters on the day of oocyte retrieval [26–28]. Sometimes, few follicles reach the required size while others are still small or medium size, and it is common to “sacrifice” the larger on behalf of allowing the development of the smaller cohort of follicles. Orvieto et al.’s study demonstrated that by letting follicles develop to a larger diameter (≥ 24 mm), not only are they not sacrificed, but they also have a good probability to yield mature oocyte (MII) oocytes, and once recovered, to develop to a top-quality embryo [25]. According to the findings of Abbara et al., follicles measuring 12–19 mm on the day of trigger injection contributed the most to the number of oocytes retrieved [26]. This is in line with the findings of the current study, which found that follicles with a diameter of 16–22 mm on the day of oocyte retrieval (measured two days later) contribute the most to the number of oocytes retrieved [27]. In their study, Panda et al. found that as the size of follicles increased from 15 to 16 or 17 mm, the live birth rate increased as well (LBR) [29]. This connection was also visible in terms of the ovulatory state. In 71.87 percent of cycles, a monofollicular response was detected. Indeed, when the number of preovulatory follicles increased, so did the number of preovulatory follicles. Dankert et al. showed that the number of follicles > 14 mm did not significantly influence the outcome [31]. In the 174 cycles with monofollicular development, 13 (7.5%) ongoing pregnancies were seen. This ongoing pregnancy rate was 9.2 percent when two or three follicles > 14 mm developed. In this series, it was discovered that 15 cases of IUI could not be performed in Group I (control) (due to inadequate follicular development in 6 cases, 4 cases could not be given semen, 4 cases could not present due to illness and 1 case could not be present due to accident). In group II (case) a total of 10 cases of IUI could not be done (3 cases had inadequate follicular development, 6 cases could not give semen, and 1 case could not ejaculate). The inability of a man to conceive a child from a fertile female is known as male infertility. Infertility caused by the “male-factor” is defined as a change in sperm quantity, motility, or morphology in at least one sample of two sperm analyses obtained 1 and 4 weeks apart. It causes 40–50 percent of human infertility and affects approximately 7% of all males [33]. Semen quality is utilized as a surrogate measure of male fecundity since male infertility is frequently caused by defects in the sperm [4]. Spermatozoa with a forward movement of at least 25 m/s are more likely to pass through the cervical mucus efficiently [33]. At least 50.0

percent grade A and B, increasingly motile spermatozoa must be present in a normal sperm assay. Poor motility that persists is a predictor of fertilization failure [34]. Idiopathic male infertility is the name given to this illness, and nonspecific treatments based on theoretical notions are commonly used. Empiric therapy can also be utilized for males who have a recognized but otherwise untreatable cause of infertility, or for patients who have been diagnosed with a potentially curable cause of infertility but have failed to respond to earlier treatments. To treat these people, a range of empiric medical interventions have been suggested. With a few exceptions, none of these treatments have been demonstrated to be beneficial in multiple randomized controlled trials. Since effective therapies are available, such trials are difficult to conduct, and few infertile couples are ready to wait [35]. Wash only Vs density gradient centrifugation: The pregnancy rate for wash only was 11.6% & the rate for density gradient centrifugation (DGC) was 14.3% [36]. However, in samples with less than 22 million motile sperm in the inseminate, pregnancy rates were 4% for wash & 18% for DGC. So, samples with an acceptable number of motile sperm can be processed efficiently by wash only, while poor-quality semen samples should be processed using DGC [37]. In another study, Zadehmodarres et al. obtained that the overall pregnancy rate was 22.0% [38]. The reported pregnancy rates attained with IUI have typically ranged from 8% to 22%, however, rates as low as 2.7 percent and as high as 66.0 percent have also been recorded [39]. They had an 88.3 percent rate of evolutive pregnancy (pregnancies that did not miscarry). It's difficult to pinpoint a cause for such a large incidence of losses due to variances in semen preparation and ovarian stimulation procedures. Sperm morphology, rather than motility is a more sensitive guide to an outcome and found no correlation between the number of spermatozoa inseminated and pregnancy [34]. In this present study, it was observed that biochemical pregnancy was not statistically significant ($p > 0.05$) between the two groups. Clinical pregnancy was 3.1% in group I (mild male factors infertility) and 5.1% in group II (unexplained infertility). The difference was not statistically significant ($p > 0.05$) between the two groups. Similarly, in another study by Cocuzza and Agarwal, it was obtained that after approximately 3 months of hCG therapy, intramuscular injections of FSH at a dose of 37.5 to 75 IU are added three times per week [35]. FSH is available in a recombinant form as well as in a highly purified urinary form. Serum testosterone levels and seminal analysis are followed during treatment. On average, it takes 6 to 9 months for spermatozoa to appear in the ejaculate [40]. This period, however, can be much longer [41]. Once sperm concentrations are satisfactory, FSH can be stopped and spermatogenesis can be maintained solely with hCG [42]. The mean clinical pregnancy rate per IUI, according to Evans et al., varied from 13.0 percent with one mature follicle to 19.6 percent with five mature follicles [43]. Each extra mature follicle raised the pregnancy rate somewhat (adjusted odds ratio: two follicles vs. one: 1.3, 95 percent CI 1.2–1.4; three follicles vs. one: 1.4, 95 percent CI

1.3–1.5; four follicles vs. one: 1.5, 95 percent CI 1.4–1.7; and five follicles vs. one: 1.6, 95 percent CI. Regardless of the number of mature follicles, there was only a 1.9 percent increase in singleton pregnancies per IUI (from 12.4 percent with one follicle to 14.3 percent with five follicles). In developed countries, a study done by WHO in the U.S showed trial pregnancy rate per couple was 18.0% for treatment with insemination alone and 19.0% for gonadotropins and IUI [44]. Similarly, The European Society for Human Reproduction and Embryology (ESHRE) WHO found pregnancy rate per cycle were 15.2% in gonadotropin only cycles 27.4% in gonadotropin and IUI cycle and 25.7% in IVF cycles [45]. The above study findings are higher than the current study, which may be due to the use of a fixed drug protocol for ovarian stimulation in this study. That's why there was no scope to increase the doses of gonadotropins when necessary. They had done their study with a long duration of follow-up, whereas the current study was conducted in a short period. Besides unexplained infertility, there may be an abnormality in the sperm, oocyte function, fertilization, implantation, and embryo development than can not be detected by the standard method of evaluation. On the other hand WHO (1992) mentioned in their study that cycle fecundity varied from 3.0% to 10.0% when IUI is performed using infertile partner sperm, which is comparable with the current study [45].

5. Limitations of the Study

This study had some limitations including a small sample size, only one center study, a short duration of the study period as well as IUI could not be done in 10 cases of group I and in 15 cases of group II.

6. Conclusion

Most of the female and male partners were in the 3rd and 4th decade respectively. Endometrial thickness on D12, Endometrial thickness on D13, Size of the mature follicle D12, and size of the mature follicle D13 were significant between the two groups. Total semen count, total motility, total morphology, the pre-wash concentration of semen, pre-wash motility, post-wash concentration of semen, and post-wash motility were significant factors between the two groups. Two weeks after IUI, no statistical significance was observed in terms of S. β HCG between the groups. Sonographic evidence of pregnancy as well had no significant difference between the two groups. IUI has a place as a first-line treatment for couples experiencing unexplained or male factor infertility. Even in patients with moderate sperm quality impairment, pregnancy rates of up to 20% per couple are possible.

7. Recommendation

Since this technique is much easier to perform and less expensive than other methods of assisted reproduction and

seems to be reasonably effective, it should be considered in mild to moderate forms of male factor infertility when no specific treatment can be offered. Better results are expected in patients with initial motility above 40–50% or when the total motile sperm count after processing is above 1–5 million/ml. COH using hMG improves the results in couples undergoing IUI for male factor. The efficacy of IUI in male factor infertility has not been consistently documented in the literature. Much work is needed in order to standardize the technique and to improve the outcome in various forms of male infertility among different clinics offering this treatment modality.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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