Original Article

Impact of Intrauterine Insemination as first line treatment of subfertility

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Abstract

Objective: To determine the success rate of intrauterine insemination (IUI) in couples presenting with subfertility following controlled ovarian hyperstimulation (COH) by the use of cost effective intrauterine catheter (insertion tube).

Methods: An experimental study was conducted at the Obstetric and Gynaecology Departments of Combined Military Hospital Kharian and PNS SHIFA Karachi in collaboration with the Department of Pathology from June 2002 to March 2005. A total of 89 couples were studied, out of which 28 couples presented with abnormal finding in the seminal fluid of husband whereas in 61 couples no identifiable cause could be detected. The mean age of women was 29 years and the duration of infertility was variable. All women had tubal patency confirmed before undergoing COH. IUI was performed at follicular maturity of 18-22 mm. Main outcome measures analyzed were pregnancy rate per cycle of IUI, miscarriage rate and ongoing pregnancy rate. Prognostic factors associated with successful outcome in IUI, such as maternal age and motile sperm count was also observed. For cost effective measures, we used the sterilized disposable insertion tube of the 'Copper-T 380 A' device for insemination of reated sperms into the uterine cavity. Chi-square test was applied to assess the effectiveness of IUI in relation with these variables.

Results: A total of 205 insemination cycles were performed resulting in achievement of pregnancy in 31 patients. Miscarriage occurred in 3 patients. Out of these 31 women who conceived, 21 (67.7%, p=0.003) were aged < 35 years with higher pregnancy rate per cycle (21 / 90 = 23.3%).

Conclusion: Intrauterine insemination may be regarded as valuable procedure for couples presenting at younger age with lesser duration of infertility and unexplained subfertility (JPMA 57:133;2007).

Introduction

Sub fertility is an issue experienced by 18% of couples in the community and a proportion of them may require assisted conception treatment in alleviating continuing subfertility.[1] Intra uterine insemination (IUI) is a fertility procedure in which actively motile sperms are concentrated and inseminated directly in the uterus. In natural intercourse only a fraction of the sperms make it up the woman's genital tract, whereas IUI increases the number of sperms in to the fallopian tubes where fertilization takes place.[2]

Indications of IUI include unexplained subfertility, cervical hostility, mild endometriosis, antisperm antibodies and male sexual dysfunctions like impotency, hypospadias, and retrograde ejaculation.[3]

Various types of assisted conception techniques include IUI, in vitro fertilization/embryo transfer (IVF/ET), gamete intrafallopian transfer (GIFT) and intra-cytoplasmic sperm injection (ICSI).[4] Other insemination techniques such as direct intra-peritoneal insemination (DIPI), intrafollicular insemination (IFI) and fallopian tube sperm perfusion (FSP) have also been introduced.[5]

Intrauterine insemination is considered to be the least invasive and first line therapy for couples presenting with subfertility. Infective complications and formation of anti-sperm antibodies in women undergoing insemination are the possible risks of IUI.[6]

This study aimed to determine the success rate of intrauterine insemination (IUI) in couples presenting with subfertility following controlled ovarian hyperstimulation (COH) by the use of cost effective intrauterine catheter (insertion tube).

Subjects and Methods

This experimental prospective study was conducted in two centers i.e. PNS SHIFA, Karachi and Combined Military Hospital, Kharian. A total of 89 couples presenting with the complaints of primary and male factor subfertility were enrolled for IUI whereas pregnancy cycle counts to 205 as in most of the cases, repeated cycles of IUI were performed in order to achieve pregnancy. A minimum of 3 cycles were planned before a lady could be offered invasive techniques. Generally females over forty are discouraged to enter in the assisted fertilization programs but keeping in mind the specific family pressures; we also enrolled five above forty ladies in the study. Both the partners were informed about the procedure and its implications. A certificate was signed by both the partners that they were the legally husband and wife and that they had understood the whole procedure of IUI and had no objections to any of its part.

The following minimal investigations were carried out for the enrolled couples:

Complete physical examination - both systemic and local of both the husband and wife was carried out. Semen analysis with morphology and special emphasis on sperm motility was performed. Male factor was diagnosed if either the sperm concentration was <20x10^6/ml or total progressive motility < 50% or sperm morphology showing ≤10% normal forms according to the WHO criteria.[7]

All the females underwent ultrasonography of pelvis, screening for Hepatitis B, C and HIV and hormonal assay for endocrine status, antisperm antibody in both cervical mucus and serum and by hysterosalpingography for tubal patency.

Ovarian hyperstimulation was carried out with Clomiphine citrate (CC) and human Chorionic Gonadotrophin (hCG) protocol to achieve higher number of oocytes for fertilization. CC was given in a dose of 50-100mg early from day 3rd to 7th of the menstrual cycle. Follicular tracking by transvagianl sonography (TVS) started from day 9th of the cycle on alternate day till the size of the developing follicle reached up to 18 - 22 mm. At this stage injection hCG (profasi) 10,000 IU was administered intravenously. A single insemination was performed 36 to 40 hours later.

The standard swim-up technique was used for collection of motile and active sperms. Semen was collected by masturbation into a sterile container after 2-4 days of sexual abstinence. After liquefaction, the morphology, sperm count and motility were assessed and the sperm sample was centrifuged at 400 g for 15 minutes. After discarding the supernatant, pellet was suspended in pre-warmed 2.5 ml of Ham's F-10 (Sigma Chemical, St. Louis, MO) culture medium or Earle's balanced salt solution (Sigma), supplemented with human serum albumin thereafter centrifuged once more. Seminal pellet was gently over-layered with medium in the tube which was sealed, inclined at 45°C and kept at 37°C for 60-90 min in 5% CO_2. A sterile pasteur pipette was used to remove the upper layer containing actively motile sperms. A drop of it was examined under the light microscope. Motility and morphology was recorded and the specimen was kept at 37°C till dispatched to be inseminated.

IUI was performed using insertion tube of 'Copper-T 380 A' with a one or two ml syringe. First a Sim's speculum was placed in the vagina to retract its posterior wall. Anterior lip of cervix was held with Volselum forceps and uterine sound introduced to check the length and direction of uterine cavity. The insertion tube was then gently passed through the cervical canal and the sperm suspension was expelled into the uterine cavity by slow release. Insemination volumes ranged from 0.5 to 1.5 ml. The subject remained in supine position for 10-15 minutes after the procedure. Estimation of Beta human chorionic gonadotropins (b- hCG) was carried out on day 14 of IUI for pregnancy confirmation. Findings were confirmed by ultrasonography at later stages.

If pregnancy was confirmed, luteal phase support with progesterone was continued till 12 weeks of gestation, while progesterone was withdrawn on a negative test report.

Results

A total of 205 IUI cycles were carried out and 12 (15%) women conceived after first IUI cycle, 11 (13.75%) after second and 8 (10%) after third cycle (Table 1). Out of these 31 pregnancies, 3 (i.e. 9.6%) ended in miscarriage. The ongoing pregnancy rate was thus 13.3% (i.e. 28 pregnancies out of 205 IUI cycles). No case of ovarian hyperstimulation syndrome (OHSS) was reported in any patient.

Majority of the women were in age group of >35 years (n = 45, 56.25%), followed by 35 (43.8%) in age group <35 years. Out of those 31 women who conceived pregnancy, 21 (67.7%) were aged less than 35 years and pregnancy rate per cycle was also high (21 / 90 = 23.3%) in this group (Table 2). It shows a significant association (p = 0.003) of conceiving after IUI with age less than 35 years (Table 2).

Most of the women had duration of infertility of 5 years (n = 65, 81.3%). Out of those 31 women achieving conception, 29 (93.5%) had duration of infertility 5 years that indicates a significant effectiveness of IUI in shorter duration of infertility. Rate of pregnancy per cycle (29 / 172 = 16.9%) was also high in this case.

Table 1. Pregnancy outcome of IUI cycles.

Variables	Number of women	Pregnancy / cycle (%)
Age (in years):		
Less than 35	35 (43.8%)	21 / 90 (23.3%)
More than 35	45 (56.2%)	10 / 115 (16.05%)
Duration of infertility (in years)		
≤ 5	65 (81.3%)	29 / 172 (16.9%)
> 5	15 (18.7%)	2 / 33 (6.06%)
Type of infertility		
Primary	61 (76.3%)	20 / 133 (15.04%)
Secondary	28 (23.7%)	11 / 72 (15.28%)
Aetiology of infertility		
Unexplained	61 (65.1%)	15 / 89 (16.85%)
Male factor	28 (23.7%)	16 / 116 (13.79%)
Number of IUI cycles		
One	12 (43.8%)	12 / 80 (23.3%)
Two	11 (50.0%)	11 / 68 (8.91%)
Three	8 (6.2%)	8 / 57 (7.14%)

Table 2. Impact of IUI according to female characteristics.

Variables	Pregnancy		Significance
	Conceived (n = 31)	Not conceived (n = 49)	
Age (in years)			
Less than 35	21 (67.7%)*	14 (28.6%)	P = 0.003
More than 35	10 (32.3%)	35 (71.4%)	
Duration of infertility (in years)			
= 5	29 (93.5%)	36 (73.5%)	P = 0.022
> 5	2 (6.5%)	13 (26.5%)	
Type of infertility			
Primary	20 (64.5%)	21 (83.7%)	P = 0.050
Secondary	11 (35.5%)	9 (16.3%)	
Aetiology of infertility			
Unexplained	15 (48.4%)	46 (79.4%)	P = 0.002
Male factor	16 (51.6%)	12 (20.6%)	

Sixty-one (76.3%) cases in our study had primary infertility and the proportion of women who conceived was marginally significant (p = 0.05), but rate of pregnancy per cycle was slightly high in secondary infertile women (Table 2).

IUI was found more effective in case of unexplained aetiology of infertility as out of such 23 cases, 15 (%) conceived (p = 0.002) while rate of pregnancy per cycle was also higher (16.85% vs. 13.79%) in this group (Table 2).

On semen analysis, sperm count was subnormal in 25 patients (64.2%), the motility was < 50% in 22 patients (64.2%), and percentage of normal forms was < 50% in 12 (42.8%) patients. Whereas 12 of them had increase in leukocytes in the semen. None of the women or their male partners had detectable anti-sperm antibodies. Taking the sperm count, morphology and motility as variable, the semen analysis of male factor infertility couples showed a single defect in 13 subjects (20.5%), double defect in 5 (10.17%), and triple defect in 10 (16.5%).

In all the semen specimens subjected to swim up procedure the pre and post treatment value were noted down. All the three variables i.e. sperm count, motility and sperm concentration showed marked improvement after the swim up procedure.

Discussion

The practice of intrauterine insemination (IUI) with treated motile and morphologically normal spermatozoa involves bypassing the cervical mucus barrier resulting in an increased gamete density at the site of fertilization. Success rate in IUI is undoubtedly the result of better swim-up procedures enhancing the quality of a sperm sample.[8] The washing procedure is necessary to remove prostaglandins, infectious agents and antigenic proteins.[9]

The present results showed that the simplified swim-up method for recovery of motile sperm is reliable. One advantage of the method is the limited number of technical steps and the lack of multiple centrifugation steps, which besides being more practical, avoids a procedure that could potentially damage the spermatozoal cytoplasmic membrane.[10]

Our results also showed remarkable improvement in the yield of motile sperms with the procedure of swim up. The concentration of morphologically normal sperms also increased substantially due to better forward movement of normal spermatozoa. Another substantial advantage of the technique is removal of non-motile spermatozoa, leukocytes and immature germ cells. This might contribute to the enhanced sperm quality by decreased release of lymphokines and/or cytokines and a reduction in the formation of free oxygen radicals after sperm preparation. This results in better sperm fertilizing ability in vitro and in vivo.[11]

The age-related decline in female fecundity has been well documented, particularly in women undergoing IUI in primary infertility. This decline has been suggested to be a result of reduced uterine receptivity and/or decreased oocyte quality.[12] Accordingly, the success rates of IUI has been reported to decrease with advancing female age, indicating that the negative impact of age can be overcome only partly by assisted reproductive technology.[13] In our study, the success rate of IUI was reduced significantly in women aged 40 or above, which is in agreement with the results of earlier studies.[14] Keeping in view the results of multicentric studies, IUI seems to be a poor treatment option for women over 40 years of age, and they should be offered assisted reproductive technique (ART) such as ICSI after their ovarian responsiveness has been documented.[15]

We found a significant decrease in pregnancy rate (PR) with infertility duration of over 5 years compared with the PR in women with shorter infertility duration. This is in accordance with the results of many studies conducted separately[15,16] but in some studies a significant decline in success rate has been shown as soon as after 3 to 4 years' infertility. Apparently, with an increase in the duration of infertility[16], less obvious factors become more important in decreasing reproductive potential. On the other hand, some previous studies have demonstrated no correlation between increasing duration of subfertility and the likelihood of pregnancy. IUI treatment is less effective in women with a long-standing duration of subfertility.[17,18]

In a meta-analysis, the average pregnancy rate per cycle for unexplained subfertility was 18%[19] which is similar to our results. In unexplained infertility, ovarian stimulation and IUI appears to be an effective measure. A decreased fertilization rate has been suggested to be the cause of failure to conceive among women with unexplained infertility[20], which possibly can be overcome by superovulation therapy associated with an increased number of fertilizable oocytes in IUI.[21,22] The information available at present indicates that IUI should be considered for the first line of approach prior to more expensive IVF in patients with unexplained infertility.[23]

Some of the researchers suggest the technique of double insemination with the gap of around eight hours. This may lead to higher success rates after IUI in male subfertility cases.[24]

IUI when accompanied with proper ovarian activation protocol is a useful treatment option for subfertility in a selected patient category. Favourable patient characteristics for treatment success are age <35 years, duration of infertility 5 years and unexplained infertility. Most pregnancies occur during a course of three CC/hCG/ IUI cycles. This information is helpful in counselling subfertile couples entering fertility treatment, and makes it possible to carry out more precise patient selection and thereby further increasing the cost-effectiveness of IUI therapy.

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