ORIGINAL ARTICLE

Assessing the Status of Intrauterine Insemination Before Forming a Medically Assisted Conception Unit

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Summary

A survey in 1996 of our female patients suggest that the three commonest causes of infertility were endometriosis, anovulation and idiopathic which comprises of about 70% of all the patients. In the male patients, sperm morphology evaluation by critical criteria showed that abnormal morphology was present in 71% while 87% of all the semen analysis were abnormal. The objective of this study was to assess the status of IUI before proceeding to formulate patient protocols for IVF in a tertiary infertility referral unit. A retrospective study of patients data was done from Jan 1995 to Dec 1996. Ovarian stimulation by clomiphene for anovulatory and idiopathic patients was performed on couples with at least one patent fallopian tube. Ovulation induction was by an intramuscular injection of 5000 i.u of HCG after follicular maturation. IUI was performed approximately 36-40 hours later. A total of 74 couples received 114 treatment cycles producing a total of 9 conceptions. The conception rate of IUI was therefore 7.89% per cycle and 12.16% per couple with the cumulative pregnancy rate of 28.21%. Associated success features of IUI found in this study were the age of the woman and the semen parameters of the husband.

Key Words : Intrauterine insemination, Pregnancy rate, Infertility, Semen parameters

Introduction

A survey of our female subfertile patients done in October 1996 at the Department of O & G, UKM suggests that the three commonest causes of infertility were endometriosis (22.6%), anovulation (25.8%) and idiopathic (22.6%). These three groups make up 70% of all the patients. The other causes of infertility in this survey were uterine factors (16.1%), ovarian factors (6.5%) and a small number of patients had unspecified problem (6.5%).

Overall, in the male patients, sperm morphology evaluation by critical criteria showed that abnormal morphology was present in 71% with a cut off normal value of 15%[1]. 87% of our male patients also demonstrated abnormal semen parameters according to the WHO criteria 1992[2]. Altogether, male factor infertility made up 24.4% of our couples, 35.5% had female factors and 31% had both while in 9.1% the cause was idiopathic.

Three assisted conception methods (each involving some of form of ovarian stimulation) have been accepted, namely (i) timed intercourse (TI), (ii) intrauterine insemination (IUI) and (iii) in vitro fertilization / embryo transfer (IVF/ET). In the department of O & G, UKM, the first two mentioned assisted conception methods have been practised, TI is usually advised after the first consultation when the male and female factors are normal. If no conception ensues after six months then IUI is the chosen option usually offered.

The practice of IUI is assessed over 24 months before proceeding to formulate patient protocols for IVF. With this evaluation, we assess the efficacy of IUI in improving pregnancy rates within this unit and look at any associated success features.

Materials and Methods

Methodology and Setting

A retrospective study of patients' data from Jan 1995 to Dec 1996 in a tertiary referral reproductive unit. Altogether there were 74 couples who underwent 114 cycles of ovarian stimulation and IUI.

Patient Selection

All the couples were diagnosed as infertile on the basis of at least one year of unprotected intercourse. The infertility evaluation consists of an assessment of ovulation, semen analysis and confirmation of tubal patency by hysterosalpingogram or laparoscopy. The patients in this study must show no significant uterine abnormality by hysteroscopy or ultrasound evaluation and at least one patent tube. No other exclusion criteria was used on the couple.

Ovarian Stimulation for Female Patients

Two protocols were used for ovarian stimulation
Protocol A : Clomiphene citrate (CC) only in which 50-200 mg of CC was given on days 2-6 of the cycle. A step up regime was used i.e. increasing the dosage of CC in subsequent cycles until a good follicular development was seen.

Protocol B : Clomiphene citrate - human menopausal gonadotrophin (CC-HMG). 50-200 mg of CC was given on days 2-6 cycle followed by 75 IU of HMG (Metrodin, Serono) daily on day 5-9. Ovarian stimulation by CC was usually the primary choice as it is supplied by the hospital at minimal cost. If the patient showed poor follicular development, then she was put onto the second protocol. However, some patients chose to remain on CC due to the cost of HMG, which was not provided free. The ovarian response was monitored starting on day 9 or 10 by transvaginal ultrasound. The number of developing follicles and their diameters were taken every alternate day. The morphology of the endometrium and the thickness were measured too. Human chorionic gonadotrophin (Profasi, Organon or Pregnyl, Serono) 5000 IU was administered intramuscularly when the leading follicle was 16-18 mm in diameter. Cycles were cancelled if there was poor follicular response.

Sperm preparation for the male partner

Patients were asked to refrain from sexual intercourse 2 days before the HCG administration and 4 days after insemination. Semen was collected by masturbation 2-3 hours before insemination. The liquefied semen sample was quickly analysed using a Makler chamber according to the WHO criteria 1992 [2]. A commercially available discontinuos two gradient Percoll (Perception, Fertility Technologies Inc., Natick, MA, USA) in Earles based medium was used in sperm preparation. The whole procedure was performed aseptically at ambient temperature. 2.5 ml of 47.5% Percoll was layered over an equivolume of 90% Percoll in a 15 ml conical centrifuge tube. 1-2 ml of semen was layered on top of the gradient and spun at 500-600 mg for 20 minutes. The supernatant was removed leaving behind a small volume of 90% Percoll containing the sperm pellet. The pellet was resuspended into a fresh 15 ml tube containing 3 ml of Earles medium with 5 mg/ml of human semen albumin. Centrifugation was repeated at 250-300 g for 10 minutes. The resultant pellet was resuspended in 0.5 ml of the same medium. A tiny aliquot (0.05 ml) was removed for a final sperm count. The prepared sperms were incubated for an hour at 37°C before insemination.

Intrauterine Insemination

Sperm insemination was usually performed 36-40 hours after HCG administration. The cervix and the vaginal fornices were swabbed with physiological saline solution beforehand. A vaginal tenaculum is usually used to grasp the cervix to aid insemination. A 1 ml sterile syringe was attached to a 18 mm insemination catheter (Intrauterine Catheter, Kremer DelaFontaine, Paris, France) and filled with 0.4 ml of inseminate which was then introduced into the uterine cavity. The patient remained supine for 15-20 minutes after insemination.

Luteal support

As for luteal support, 5000 IU of HCG intramuscularly

was given on days 2 and 7 after insemination or 300 mg of micronized progesterone (Utrogestan, Laboratories Besins Incovesco, Paris, France).

Outcome/clinical pregnancy

Clinical pregnancy was defined by a positive urine pregnancy test of ≥ 1000 mIU of beta HCG or the presence of fetal heart beat detected by ultrasound examination. All confirmed pregnancies were entered into a computer database, along with age, fertility status, diagnosis and treatment before and during the cycle of conception.

Statistical analysis

χ^2 test was used for comparison of means and considered of statistical significant if $p < 0.05$. The cumulative probability of pregnancy and the average pregnancy rate per cycle was calculated by life table analysis as described by Cramer *et al* [3].

Table I
Number of Intrauterine Inseminations and Pregnancy Rate

No of patients	74
No of cycles	114
No of clinical pregnancies	9
Pregnancy rate per cycle	7. 89%
Pregnancy rate per patient	12.16%
Abortion rate	11.11%

Results

74 couples underwent a total of 114 cycles in 24 months (Table 1). There were 9 pregnancies in 114 cycles with an overall pregnancy rate of 7.89% per cycle and 12.16% per patient. All of the pregnancies progressed to term deliveries except for one abortion (11.11%). Only two of the deliveries were undertaken by our clinicians, the rest were by obstetricians in private practice. All were singleton babies.

Altogether 45 (60.8%), 20 (27.0%) and 9 couples (12.2%) underwent one, two and three cycles of IUI resulting in five, three and one conception respectively. All the pregnancies occur within the first three cycles (Table II).

The patients who conceived were between 28-38 years old with an average age of 31.8 years. Half of the patients (5/9) with successful IUI suffered from primary infertility while the other half (4/9) had secondary

Table II
Cumulative Conception Rate With Number of Cycles of Treatment

IUI Cycles	No of cycles	No of Conceptions	Probability of Conception
One	74	5	0.0676
Two	29	3	0.1034
Three	9	1	0.1111
Four	2	0	0.0000

Table III
Infertility Factor and the Number of Conceptions

Infertility factor	No of patients	No of conceptions
Anovulation	16	4
Male	14	2
Idiopathic	14	2
Endometriosis	11	0
Others	19	1

infertility. Eight of the conceptions occur in patients of less than 35 years of age. The cumulative probability of conception after three IUI cycles based on life table analysis was 28.21%. Only one conception took place in an older patient, a 38 year old lady who had two previous children. Table III shows the number of conceptions from IUI based on the infertility factor.

The number of prewashed sperm in pregnant cycles were higher compared to non-pregnant cycles. The post washed sperm count of the pregnant cycles were slightly lower than non pregnant cycles (Table IV). However, the differences in the sperm counts did not achieve statistical significance as analysed by Chi-square.

Analysis of our semen evaluation data performed on the day of the IUI showed that 57 men had an abnormal

Table IV
Sperm Density on Pregnancy Rate

Sperm density (x 10 ^{6}) per ml	Pregnant cycles	Non pregnant cycles
Prewashed sperm count	71.89 ± 30.86	59.9 ±36.24
Postwashed sperm count	48.60 ± 28.70	52.60 ± 39.9

Table V
Semen Profile and Pregnancy Rates

Semen Parameter	No of cycles	No of conceptions	Pregnancy rate per cycle
Normal	59	6	10.16%
Abnormal – 36 asthenozoospermia – 8 oligozoospermia – 13 oligoasthenozoospermia	57	3	5.26%

profile. The number of patients presenting with abnormal semen was not reflected in Table III which showed only 14 couples with male factor infertility as confirmed by previous semen evaluations. These 57 cycles consists of 36 asthenozoospermics (<50% progressive motility), 8 oligozoospermics (<20 x 10^6 sperms/ml) and 13 oligoasthenozoospermics. Further tabulations based on normal and abnormal semen profile versus conception showed that men with abnormal seminal parameters had about half of the conception rate per cycle compared to those who were normal i.e. 5.76% versus 10.16% (Table V).

One conception resulted from an insemination of 0.6 x 10^6 /ml motile sperms which unfortunately aborted at 14 weeks gestation.

Discussion

Intrauterine insemination (IUI) with ovarian stimulation has been a first line method in recent years for the treatment of male factor and idiopathic infertility. Previous studies had reported pregnancy rates of between 5.7% - 17.7%[4]. The average per cycle pregnancy rate of 7.89% found in our study, although low was comparable to the literature. However, a much higher pregnancy rate of 10.16% was demonstrated if the patients with abnormal semen were excluded. Many studies have suggested that men with subnormal semen have a much lower conception rate [5] and the pregnancy rate of 5.76% seen in this study agreed with the findings of Francavilla *et al* [6].

A previous study by Agarwal & Buyalos [7] have shown that most pregnancies occur in patients who were less than 30 years old or between 31-35 years old. Clinical pregnancy rates were significantly lower in patients above 36-40 years of age. In agreement with their findings, all except one of our pregnant patients were below 35 years of age. All our patients conceived within the third attempt, comparable to 85% of their pregnancies which were achieved within the first four attempts. Majority of our patients underwent two or less cycles of IUI (90.35%).

In a large study involving 546 patients and 1205 of stimulated and non stimulated cycles with IUI, a trend was seen toward increasing conception with increasing total motile sperm count[8]. We were unable to discover the same correlation as our study consisted of only 74 couples and 114 cycles. In our study, the lowest threshold for conception was 600,000 motile sperms. Brasch *et al* [8] had one conception from an insemination of 800,000 motile sperms.

There were a number of reasons for the low success rate of IUI seen in our unit. The nature of patient management in our hospital had preselected the patients who underwent IUI. Most of the patients with complaints of infertility were treated for a duration of six months in the general clinic where they underwent indeterminate cycles of CC followed by natural or timed intercourse (TI). If they do not conceive within this time, they were then referred to the MAC unit. Data from the general clinic showed that the overall pregnancy rate per patient for CC + TI and CC with natural intercourse were respectively 12.43% and 24.87% (unpublished data). It can be assumed that those couples with a milder form of infertility and hence more ammenable to treatment would have been excluded. At the same time, because MAC was a tertiary referral unit, a number of patients were referrals from other governmental hospitals with no infertility unit. Many were subfertile for a long duration of time and therefore present with a more severe form of infertility.

IUI is the only method available to infertile couples at the MAC unit currently and therefore the exclusion criteria for the patients was quite lax. Among the 74 women, 8 had showed some tubal abnormalities i.e. delayed spillage and/or kinked tube; 7 had mild uterine abnormality and 4 were over 40 years of age. Although given appropriate counselling that the chances of a conception was low, they had insisted for IUI.

Semen evaluations had shown that only 14 out of the 74 couples had male factor infertility although on the day of IUI itself 46 men (57 cycles) present with abnormal semen profile. Some studies have shown that the seminal profile fluctuates, affected by seasons, the health and mental status of the man. Therefore a diagnosis of male infertility or otherwise can rarely be established with certainty [9]. Hence, it is important to do a semen analysis on the day of the IUI itself. The patients were

given a choice to discontinue with the insemination and counselled on their chances of conception if the number of sperms recovered were below 5 x 10 ^{6} /ml. Most of the couples have chosen to continue. Low sperm and poor sperm motility does not preclude pregnancy [10] as one patient conceived on 0.6 x 10 ^{6} /ml motile sperms although she later aborted at 14 weeks gestation. Some studies have shown that low sperm numbers which is usually associated with poor sperm quality results in higher pregnancy loss [11]. As yet we do not have tests to determine those patients with male immunological infertility which had been shown to be resistant to treatment with IUI [6]. We also do not perform postcoital tests to look for cervical factors.

Infertility treatment is generally an expensive process. Ovarian stimulation by clomiphene citrate is the least expensive and one of the simplest therapies available. It requires less monitoring compared to other protocols using gonadotrophins or menotrophins. However, the usage of clomiphene citrate has been associated with a reduced pregnancy rate especially for patients age 35 years and above [7]. An antagonistic effect of clomiphene citrate on the endometrium [12] and a concomittant effect on the cervical mucus had long been recognized [13]. Financial constraints was the main reason for the use of clomiphene citrate in ovarian stimulation among our patients as most of them were in the low socio-economic group.

The data collection at the MAC unit especially the systematic follow up of the patients after the IUI was not up to mark. The probability of conception for the first IUI cycle was almost half of that for the second IUI cycle (Table II). Most studies have shown that the conception rate is the highest in the first cycle. An assumption can be made here that there was under reporting especially of early pregnancy losses. This was evident from our patients data since more than 60% of the patients do not return after their first IUI cycle. On our part, however, no attempts were made to contact them, mainly due to the lack of manpower. In view of the setting up of an IVF unit, a more efficient data management system needs to be in place. The wide discrepancy between those patients who were diagnosed with male factor infertility and those who presented with abnormal semen on the day of the IUI may be narrowed by repeated semen evaluations. To date, most of the male patients had only one or two semen analysis done. New but cost effective sperm function tests should be incorporated to provide a more accurate diagnosis.

In summary, the success rate of IUI in our unit was comparable to other studies. The status of IUI in MAC unit was viable resulting in per cycle pregnancy rate of 7.89% and a cumulative pregnancy rate of 28.21%. Among the features associated with a successful IUI was the age of the patient and normal semen parameters in the husbands. As all conceptions occur within three cycles, attempting more cycles may be futile and certainly costly for these patients. There was no difference between the pregnant cycles and non-pregnant cycles in regard to the number of motile sperms inseminated. The more severe forms of infertility seen in our population of patients justifies the move toward setting up a Medically Assisted Conception Unit. Further improvement on the various aspects discussed above would facilitate the function of the future IVF laboratory.

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