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A Clinical Study of Pregnancy Outcome Following Intrauterine Insemination in a Stimulated Cycle

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Abstract

Aim of the study: To determine the predictive factors for pregnancy outcome after ovarian hyper stimulation and intrauterine insemination.

Methods: It is a Prospective observational study done in a University-level tertiary care center. Fifty patients were studied for a period of one year. Ovarian stimulation was initiated and a single intrauterine insemination was performed 36 hours after ovulation. The primary outcome noted was clinical pregnancy and live birth rates. Predictive factors evaluated were age of the patient, duration of infertility, indication for intrauterine insemination, number of pre ovulatory follicles, and post wash total motile fraction.

Results: The causes for infertility were anovulation (50%), endometriosis (20%), male factor infertility (20%) and unexplained infertility (10%). There were single live births (50%), multiple pregnancy (20%), miscarriages like blighted ovum and missed abortion (20%), ectopic pregnancy (06%) and heterotropic pregnancy (04%) of the patients. Among the predictive factors evaluated, the duration of infertility and the total motile fraction (10-20 million) significantly influenced the clinical pregnancy rate.

Conclusion: Our results indicate that stimulated cycle with intrauterine insemination is an effective option in couples with male factor infertility. Prolonged duration of infertility is associated with decreased success. Though we had miscarriages, multiple gestation, ectopic and heterotropic pregnancies in our study, intrauterine insemination is still a boon for patients with infertility since it is cost effective when compared to *in vitro* fertilisation techniques.

Keywords: *Controlled ovarian hyper stimulation; Intrauterine insemination; Pregnancy*

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Introduction

A combination of controlled ovarian hyper stimulation (COH) with intra uterine insemination (IUI) remains an important option available to an infertility specialist globally. Common indications include cervical factors, mild endometriosis, and mild to moderate male factor infertility, ovulatory dysfunction and unexplained infertility [1]. The reported pregnancy rates per cycle range from 8 to 22% in the literature [2-4].

The cumulative pregnancy rates for stimulated cycle with intrauterine insemination vary according to the indications, and are in the range of 20–33% [4,5]. Generally, four cycles of controlled ovarian hyper stimulation and intrauterine insemination are recommended depending on the age of the patient before performing *in vitro* fertilization [3,6].

Several prognostic factors with regards to Intrauterine insemination treatment outcome have been identified, and they include patient profile, duration and type of infertility, stimulation protocol, follicular response, endometrial thickness, timing of intrauterine insemination and semen parameters like post wash motility, morphology and total motile fraction [4, 7-10].

Since ours is a tertiary care center with couples coming from different cities and towns for treatment, we decided to analyze the variables that contribute to the success of stimulated intra uterine cycles.

Aims of the study

To determine the predictive factors and pregnancy outcome following ovarian hyper stimulation and intrauterine insemination.

Methods

It is a Prospective observational study done in a University-level tertiary care center. 50 couples attending gynaecology outpatient department in Mamata general hospital, khammam, Andhra Pradesh over a period of one year were included in the study. Informed and written consent was taken from all the patients. Ethical approval certificate is obtained from ethical committee of our college before starting the study.

The study group comprised of couples with male factor and unexplained infertility, minimum to mild endometriosis and anovulation. Patency of the fallopian tubes was confirmed by diagnostic laparoscopy or hysterosalphingography in all the patients. Male factor infertility was defined as semen concentration less than 20 million sperms per ml, normal morphology less than 30% and progressive motility less than 50% before sperm preparation as per the world health organization (1992) guidelines.

Unexplained infertility included couples for whom the results of a standard infertility evaluation was normal. Minimal endometriosis patients with score 1 to 5 and mild endometriosis with score 6 to 15 by the revised American fertility society criteria were included in the study. Patients with bilateral tubal blockage, severe endometriosis and severe male factor infertility with total motile fraction in the post wash specimen of less than one million were excluded in the study.

The protocol for ovulation induction included either gonadotrophins alone or a combination of clomiphene citrate with gonadotrophin. Human menopausal gonadotrophins were used. In the clomiphene and human menopausal gonadotrophin group, tablet clomiphene citrate 100 mg was started from second day of menstrual cycle for five days along with injection human menopausal gonadotrophin 75 IU on alternate days from fifth day for three doses.

In cycles stimulated with gonadotrophins alone, injection human menopausal gonadotrophin 75 IU was administered on a daily basis from day five to nine. On day ten of stimulation, assessment of follicular development was performed using Tran's vaginal ultrasound. Once a follicle of more than 18 mm size was identified, injection human chorionic gonadotrophin 5000 IU was given as an ovulation trigger and a single intrauterine insemination was done 36 hours later. If four or more mature follicles which were more than 18mm developed, the cycle was cancelled.

On the day of insemination, the semen was collected from the husband and prepared by double-density gradient method. The post wash sample parameters were assessed. Under aseptic precautions, intrauterine insemination was carried out with a soft catheter with an insemination volume of 0.5 ml. All women were provided with natural micronized progesterone vaginal pessaries for fifteen days as luteal phase support.

If menstrual cycle was delayed, urine pregnancy test was carried out. If positive, a Tran's vaginal ultrasound was performed two weeks later, to confirm a viable pregnancy. Clinical pregnancy was defined as the presence of an intrauterine gestational sac confirmed by ultrasound. Higher order pregnancies were defined as two or more gestational sacs visualized on ultrasound examination. Women were followed till delivery and the neonatal outcome was recorded.

The variables selected were age of the woman, duration, type and cause of infertility. Parameters related to ovulation induction on Tran's vaginal ultrasonography like number of dominant follicles, endometrial thickness were also recorded. Laboratory findings like post-wash motility, morphology and total motile fraction were noted. The results were documented and analysed using appropriate statistical method.

Results

We evaluated fifty patients undergoing stimulated intra uterine insemination cycles for a period of one year. Out of them, 10 were in the first treatment cycle, 20 were in the second treatment cycle, 15 were in the third treatment cycle and 5 were in the fourth treatment cycle during the study period.

Distribution of patients in relation to age (n = 50): Majority 40% of the patients were in the age group of 31 to 35 years, 30% of them were above 36 years of age, 20% of them were in between 26 to 30 years of age and only 10% of them were below 25 years of age (Table 1).

Age in years	No. of patients	Percentage
< 25	5	10%
26-30	10	20%
31-35	20	40%
36-40	15	30%
Total	50	100%

Table 1: *Distribution of patients in relation to age (n = 50).*

Distribution of patients in relation to duration of infertility (n = 50): Most of the patients 60% had infertility for 5 to 10 years, only 20% of them were having less than 5 years of infertility and another 20% were infertile for more than 10 years (Table 2).

Duration of infertility in years	No. of patients	Percentage
< 5 years	10	20%
5-10 years	30	60%
> 10 years	10	20%
Total	50	100%

Table 2: *Distribution of patients in relation to duration of infertility (n = 50).*

Distribution of patients in relation to cause of infertility (n = 50): About 50% of the patients were anovulatory, 20% of them were having endometriosis, another 20% were having male factor infertility like oligozoospermia and 10% of the patients had unexplained infertility (Table 3).

Cause of infertility	No. of patients	Percentage
Anovulation	25	50%
Endometriosis	10	20%
Male factor	10	20%
Unexplained	5	10%
Total	50	100%

Table 3: *Distribution of patients in relation to cause of infertility (n = 50).*

Distribution of patients in relation to drugs used before insemination procedure (n = 50): clomiphene citrate along with human menopausal gonadotrophins was given for stimulation in 50% of the patients, clomiphene citrate alone in 30% and human menopausal gonadotrophins alone in another 20% of the patients (Table 4).

Drugs used before insemination procedure	No. of patients	Percentage
Clomiphene citrate with gonadotrophins	25	50%
Clomiphene citrate	15	30%
Human menopausal gonadotropins	10	20%
Total	50	100%

Table 4: *Distribution of patients in relation to drugs used before intrauterine insemination procedure (n = 50).*

Distribution of patients in relation to pregnancy outcome following insemination procedure (n = 50):50% of the patients had single live births, 20% of them had multiple pregnancy including twins and triplets, another 20% had miscarriages like blighted ovum and missed abortion, 6% of them had ectopic pregnancy and 4% of them had heterotropic pregnancy. (Table 5)

Pregnancy outcome	No. of patients	Percentage
Single live births	25	50%
Multiple gestation	10	20%
Miscarriage	10	20%
Ectopic pregnancy	3	6%
Heterotropic pregnancy	2	4%
Total	50	100%

Table 5: *Distribution of patients in relation to pregnancy outcome following intra uterine insemination procedure (n = 50).*

Out of the twenty five pregnancies that went on to term, twenty patients were followed up. All of them had live babies, out of which 12 of them had caesarian section and 8 of them had vaginal delivery and other 5 patients could not be traced. Out of ten abortions, nine were in the first trimester and one was in the second trimester. Out of the ten patients with multiple gestation, 7 had twins and 3 had triplets.

Among seven twin gestations, 5 of them had lower segment caesarian section for obstetric reasons and 2 had normal vaginal delivery. Among these fourteen babies, 12 babies survived while two babies had early neonatal death. All the three patients with triplets delivered vaginally at around 28-30 weeks of gestation. All of them had severe anaemia and pregnancy induced hypertension. Out of the nine babies, only 5 of them survived while the other 4 babies died of prematurity. No major congenital anomalies were recorded. There was no case of postpartum haemorrhage.

Three patients came with ruptured ectopic, for them emergency laparotomy and salphingectomy was done on the affected side. Two patients had heterotropic pregnancy, one of them had ruptured fallopian tube and intra uterine missed abortion for whom emergency laparotomy followed by salphingectomy on the affected side and dilatation of the cervix and evacuation of the products of conception was done in the same sitting.

Other patient had a tubal abortion and the intra uterine pregnancy continued, lower segment caesarian section was done at 36 weeks for intrauterine growth retardation and oligohydramnios with non-reassuring cardiotocography. Among all the variables, total motile fraction and the duration of infertility was found to be significantly associated with the chances of success.

Discussion

In our study, we made an effort to determine the prognostic factors that would determine the success of stimulated cycle with intrauterine insemination. Among the patient parameters, age of the patient is important as declining oocyte quality associated with increasing age is well documented [11-12]. Even more-effective treatment options like *in vitro* fertilisation cannot completely overcome the negative impact of age [13].

In our study, a trend toward reduction in success rate with stimulated intrauterine insemination cycle was noted in women with age more than 35 years, although the difference was not statistically significant. However, 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% [6,14,15].

To conclude, for women over 35 years stimulated insemination needs careful consideration and for women over 40 years it is a poor treatment option. The success rate was significantly lower with an increase in duration of infertility. An earlier study also found a significant decline in the success of intrauterine insemination therapy as the duration of infertility increased [10].

No difference was noted in the success rate with regards to the type of infertility. Among indications for intrauterine insemination, the success rate was higher in anovulatory and unexplained infertility patients as compared with endometriosis and male factor infertility, although the difference did not reach statistical significance. The trend toward lower pregnancy rates in endometriosis has been documented in an earlier meta-analysis, with the pregnancy rates reduced to half in comparison with other indications for infertility [7].

The pregnancy rate in our study for male factor infertility was marginally lower than that in previously reported studies [3,9]. Overall pregnancy rate in our study was good, but still it is low as compared with the results from other studies [3,9]. Our policy of performing only homologous insemination could be one of the reasons for lower success rates as pregnancy rates of up to 22% per cycle were documented when donor insemination was carried out [3,10].

Another important reason for lower pregnancy rates in our setting could be our strategy of aiming for mono follicular development during controlled ovarian hyper stimulation. This, while leading to lower pregnancy rates, reduces both the multiple pregnancy and the hyper stimulation rates. With the current trend of limiting the number of embryos transferred in in-vitro fertilisation cycles, ovulation induction is emerging as the prime cause for higher order pregnancies.

Earlier studies have reported an incidence of 20% twins and 39% higher order multiple pregnancies as a result of ovulation induction, outside assisted reproductive techniques [16,17]. In our study there was no case of hyper stimulation documented and a mono follicular response was observed in 71.87% of the cycles. Studies have shown that the cycle fecundity rates were higher up to 20% to 33% when superovulation protocols were used [6,8].

However, multiple pregnancy rates including higher order pregnancies also increase with super ovulation protocols. Finally, each center needs to decide regarding their own stimulation protocols and policies and try to achieve a balance between the quest for a higher success rate and acceptable multiple pregnancy rates. Studies looking at the role of antagonist in the prevention of a luteinizing hormone surge in stimulated insemination cycles have reported pregnancy rates of up to 20% to 35%, although the rise in the cost factor needs to be carefully considered [18-20].

The role of clomiphene citrate as a cost effective alternative in the prevention of a luteinizing harmone surge has been looked at in an earlier study, and promising results have been obtained [21]. Even though studies have shown an increase in the ejaculated volume, sperm count and motility with longer periods of abstinence, this has not been shown to improve the intrauterine insemination pregnancy rates [22]. The total motile fraction is an important prognostic factor for the success of intrauterine insemination.

We found a significantly higher pregnancy rate, when the total motile fraction was with in the normal range. In one of the earlier studies, the authors tried to arrive at a cut-off with regards to seminal parameters at which intrauterine insemination would be of benefit in male factor infertility [9]. When the total motile fraction was less than 5 million, sperm morphology appeared to play an important role. A pregnancy rate of 5.43% was observed with morphology of less than 30% as compared with 18.42% with a normal morphology.

Combining the finding of our study and previous reports, we believe that in male factor infertility with a total motile fraction less than 5 million, couples should be carefully counselled and the option of *in-vitro* fertilisation should be offered more liberally, especially if the female partner's age is advanced. The purpose of our study was to determine prognostic factors for predicting intrauterine insemination success and also their pregnancy outcome.

We found only two parameters significantly affecting its success, the duration of infertility and total motile fraction. In an earlier study, the authors found five prognostic factors which affected success of insemination, the number of treatment cycles, pre ovulatory follicles, age, etiology and duration of infertility [3]. A larger study on similar lines would help identify more predictors and also develop a prediction model for pregnancy following stimulated insemination cycles [23].

Once a prediction model is developed, validation studies could be carried out to prove its robustness. This could help formulate guidelines and make it easier for couples and clinicians to take important decisions regarding the next step during the course of infertility treatment.

Conclusion

Controlled ovarian hyper stimulation and intrauterine insemination is an important treatment option for varied indications, especially with advanced age. Definitive prognostic factors for predicting success will help in counselling patients regarding the modality of treatment. Significantly higher pregnancy rates were observed when the duration of infertility was less and the total motile fraction was within normal limits. Low pregnancy rates were associated with poor semen parameters, indicating that stimulated insemination is not an effective option in these clinical situations.

Many of the identified variables were not shown to significantly affect the outcome. Perhaps, a larger sample size may help in formulating a better predictive model for success of intra uterine insemination. The information could be used by couples and clinicians during counselling to arrive at a decision with regards to their treatment options. Though we had miscarriages, multiple gestation, and ectopic pregnancy and heterotropic pregnancies in our study, intrauterine insemination is still a boon for patients with infertility since it is cost effective when compared to in-vitro fertilisation techniques.

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