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Prognostic factors for outcome of pregnancy after controlled ovarian hyperstimulation and intra uterine insemination: a prospective study

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Abstract
Objective: To identify factors predicting pregnancy after controlled ovarian hyperstimulation and intrauterine insemination. **Design**: Prospective observational study. Study was conducted at Fertility unit in department of Obstetrics and gynecology in S.M.S Medical College Jaipur. **Methods**: 386 stimulated cycles were studied. Couples included in study group had at least one year of infertility and had undergone a basic infertility evaluation consisting of hormonal study, ovulation study, thyroid levels, prolactin levels, ultrasonography, and semen analysis. Ovarian hyperstimulation was done using clomiphene citrate from day 2 to day 5 of cycles and trigger for ovulation was done by injection of beta-HCG. Intrauterine insemination was done after 36 hours of controlled ovarian hyperstimulation. Outcome: Main outcome measured were studied in terms of clinical pregnancy. **Results**: In all 386 IUI cycles studied, maximum chances of pregnancy were found to be most significantly associated with age and endometrial thickness. Other factors were also studied but no significant association was found. All results were statistically analysed. **Conclusion:** Intrauterine insemination is an important option for infertile couples. Several factors predict its success rate amongst which endometrial thickness was found to be most significant.
Keywords: hyperstimulation,pregnancy

Introduction

Infertility affects more than 10% of the population and has a major psychological impact leading to depression and anxiety symptoms. Intrauterine insemination is a widely used technique. It has become the first line assisted reproductive therapeutic option for infertile couples. It is a step between the simpler ovulation induction and the more advanced in vitro fertilization. Intra uterine insemination and ovulation induction are often combined to increase the effectiveness and likelihood of infertility treatment. Ovulation induction increases the number of oocytes available for fertilization thus increasing the chances of pregnancy. Ovulation may be induced with: Clomiphene citrate Letrozole Letrozole+ HCG, Clomiphene citrate+ HCG. Intrauterine insemination is a therapeutic process of placing washed spermatozoa trans cervically into the uterine cavity. Those who benefit the most are young women with patent fallopian tubes, no ovulatory disorder, no endometriosis of moderate or severe degree and no severe degree of male factor infertility.Intra uterine insemination has also been used to treat a variety of physiological and psychological male and female infertility disorders such as severe hypospadias and retrograde ejaculation. Ovulation occurs anytime from 24 to 56 hours after the onset of LH surge with a mean time of 36 hours. After an injection of beta HCG, follicle ruptures after 36 to 48 hours later. Several prognostic factors with regard to intra uterine insemination have been identified such as patient profile, duration of infertility, type of infertility, follicular response, endometrial thickness, timing of intra uterine insemination and semen parameters; but endometrial thickness was found to be most statistically significant [1]

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Materials and method

This hospital based descriptive type of observational study was conducted in Department of Obstetrics and Gynecology, SMS Medical College, Jaipur. Written informed consent by each subject was taken before the study. All couples included in study group had at least one year of infertility and had undergone basic infertility evaluation consisting of hormonal study, hysterosalpingography, ovulation study thyroid levels prolactin levels, ultra-sonography and semen analysis Patients with known bilateral tubal factor infertility were excluded from the study.The protocol for ovulation induction included clomiphene citrate. Tablet clomiphene citrate 50mg was given from day 2 of menstrual cycle for 5 days. On day 9, assessment of follicular development was performed using transvaginal ultrasonography. Once a follicle reaches a size of 20mm, injection HCG 5000 IU was given as an ovulation trigger and IUI was performed 36 hours later under aseptic conditions using IUI catheter with a semen volume of 0.5 ml prepared with density gradient method. If menstrual cycle was delayed urine pregnancy test was carried out. Luteal phase was supported by daily vaginal administration of 200mg progesterone for 14 days. When urine pregnancy test was positive, TVS was performed 2 weeks later to confirm a clinical pregnancy which is defined as intrauterine gestational sac[1].

Results

Table 1 shows that out of 86 people who were in the age group 17-25 years only 14 achieved pregnancies with a pregnancy rate of 16.27%. Pregnancy rate was 14.11% and 6.06% in people of age group 26-35 years and 36-40 years respectively. Out of 12 people aged > 40 years only 1 achieved clinical pregnancy with a pregnancy rate of 8.33%. However, the difference was not statistically significant. (p value 0.14).386 stimulated cycles were analyzed. The overall pregnancy rate was 14.5%. 15 out of 72 patients with male factor infertility achieved pregnancy and 20 out of 93 achieved pregnancies in PCOS

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group (Table 2). So, pregnancy rate was 20.83% in male factor infertility group and 21.5% in PCOS group. In patients with unexplained infertility and endometriosis, pregnancy rate was 8.71% and 5.88% respectively. Pregnancy rate was 50.05% in case of combined male factor and unexplained infertility. The difference was statistically significant. (P<0.001)Table 3 shows that out of 219 patients in whom duration of infertility was less than 6 years 65 achieved pregnancy compared to 42 people out of 167 in whom duration of infertility was greater than 6 years. Pregnancy rate was 16.8% in first group and 10.8% in second group. However, the difference was not statistically significant.Table 4 shows that out of

27 people in whom endometrial thickness was < 6 mm, only 2 achieved pregnancy with a pregnancy rate of 7.40%. The pregnancy rate was 14.28% and 16.18% in people in whom endometrial thickness was 6-<8mm and 8-<10mm respectively. Out of 34 people who had endometrial thickness between 10 – 12 mm only 1 achieved pregnancy with a pregnancy rate of 8.33%. The difference was statistically significant. (p<0.03).Table 5 shows that out of 167 cycles which had homogenous endometrial pattern, only 22 achieved pregnancy with a pregnancy rate of 13.17%. Out of 219 cycles, 34 achieved pregnancies with trilaminor pattern of endometrium with a pregnancy rate of 15.5%.

Table1: Distributionofcases

Age (Years)	No of cycles	Clinical Pregnancy	Rate (%)	p-value
17- 25	86	14	16.27%	0.14*
26 - 35	255	36	14.11%	
36 - 40	33	2	6.06%	
>40	12	1	8.33%	

- p-value for chi-square

Table 2: Distribution of cases according to etiology

Etiology	No of cycles	Clinical Pregnancy	Rate (%)	p-value
Male factor	72	15	20.83	<0.001
PCOS	93	20	21.50	
Endometriosis	17	1	5.88	
Un explained	195	17	8.71	
M+PCOS	9	5	50.05	

p-value for chi-square test

Table 3: Distribution of cases according to duration of infertility

Duration of infertility	No of cycles	Clinical Pregnancy	Rate (%)	p-value*
< = 6	219	65	16.8	0.32
>6	167	42	10.8	

*p-value for chi-square test

Table 4: Distribution of cases according to endometrial thickness

Endometrial thickness (mm)	No of cycles	Clinical Pregnancy	Rate (%)
< 6	27	2	7.4
6- < 8	140	20	14.28
8 - < 10	173	28	16.18
10 - < 12	34	5	14.7
>= 12	12	1	8.33

Table 5: Distribution of cases according to endometrial pattern

Pattern of endometrium	No of cycles	Clinical Pregnancy	Rate (%)
Homogenous	167	22	13.17
Trilaminar	219	34	15.5

Discussion

In our study the mean age of patients, who had a positive outcome with IUI was 26.84 years while in the patients who had a negative outcome with IUI was 28.58 yrs. The age of the patient significantly affected the pregnancy outcome i.e., younger age was significantly associated with a better pregnancy outcome.Several studies have shown an association between increasing maternal age and poor pregnancy rates following IUI. Horbay et al (1991) showed a significant decline in pregnancy rate after IUI in women >36 years age. Campana et al (1996) also found that outcome of IUI was adversely affected if the woman's age was >39 years. Brzechtta et al (1997) found that increased female age >35 years negatively influenced pregnancy rates. Yang JH et al (1998) found that for

women with age >35 years the pregnancy rates with IUI were extremely low.Stone et al (1999) found that patient's age was the main determinant of pregnancy outcome. Dickey et al (2002) found significantly lower pregnancy rates with IUI in women >43 years age. Bellac et al (2008) also found that advanced maternal age had a negative effect on pregnancy rate.Demir et al (2011) showed that pregnancy rate was the highest in IUI cycles when woman was <25 years old. With decreasing costs and increase in safety IVF has become a favoured option in women with age >35 years.In our study the mean duration infertility in the positive outcome group was 6.0 years while in the negative outcome group it 7.79 years. The above table shows that increased duration of infertility negatively influences pregnancy rates following IUI. However, the results were not

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significant statistically. Mathieu et al (1994) found that duration of infertility >3 years is associated with a poor prognosis. Tomlinson MJ et al (1996) also found that duration of infertility significantly influences pregnancy rate with IUI. Nuojua-Huttunen et al (1999) stated that duration of infertility is one of the five variables that affect pregnancy outcome following IUI. Iberico G et al (2004) showed that infertility duration ³ 3 years was marginally associated with a lower pregnancy rate. Zadeh Modarres S et al (2009) stated that duration of infertility was one of the three predictive variables as regards pregnancy following IUI cycles. Kamath MS et al (2010) found that duration of infertility significantly influenced the clinical pregnancy rate in IUI cycles.There is significant consensus regarding the association between endometrial thickness and IUI results. While some researchers have found endometrial thickness to be a prognostic indicator of IUI success, others have found endometrial thickness on the day of hCG injection to have no such discriminative ability. Tomlinson MJ et al (1996) identified endometrial thickness as one of the four significant IUI variables influencing pregnancy outcome. Kolibianakis et al (2002) observed no difference in endometrial thickness between patients who did or did not achieve an ongoing pregnancy (7.6 ± 0.3 v/s 7.6 ± 0.2 mm respectively, P = 0.7). However, Esmailzadeh S et al (2006) found that the mean endometrial thickness on the day of hCG administration was significantly greater in the cycles where pregnancy was achieved. Habibzadeh V et al (2010)[2] stated that the pregnancy rate was higher in endometrial thickness 6 < ET £ 10 mm. The mean endometrial thickness in their study (with CC and gonadotropins) was 7.2 ± 1.8 mm. In our study the pregnancy rate was higher in patients with male factor infertility as compared to unexplained infertility (1 v/s 11.11%). However, the difference was also significant (P = 0.001).Several studies have tried to ascertain whether the etiology of infertility has any prognostic significance with regards to the pregnancy rates achieved following IUI. Lucette A et al (1998) found that the PR for first IUI attempts were 5.0% for andrological indication and 10.00% for idiopathic indication. They used COH with CC, no hCG was administered and percoll gradient technique was used for sperm preparation. In the group with andrological indication all patients with a sperm count <20 million/ml were included and there was no lower limit.Nuojua-Huttunen et al (1999) found a pregnancy rate of 15.3% in patients with unexplained infertility and PR of 11.8% in those with male factor infertility. They used a stimulation protocol of CC/hMG/hCG and swim up or percoll gradient technique for sperm preparation. If the progressive motile sperm count after preparation was $< 1 \times 10^6$ / ml, couples were not enrolled in IUI treatment.

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Liu et al (2006) found an overall pregnancy rate in the mild male factor infertility group to be 18.1% which was greater than the pregnancy rate in the unexplained infertility group (11.2%).Bagis T et al (2010) found a live birth rate of 14.89% in patients with unexplained infertility and 9.09% in patients with male factor infertility. Only cycles with multifollicular development were included. Kamath et al (2010) concluded that pregnancy rate per cycle of 10.6 in patients with anovulation, 5.37% in patients with male factor infertility, 7.89% in patients with endometriosis and 11.38% in patients with unexplained infertility. The difference in pregnancy rates was not significant (Chi-square = 0.494). COH was done using CC and hMG, alone or in combination with or without hCG, semen was prepared using double density gradient method.In our study we found that endometrial pattern along with thickness also affects clinical pregnancy rate. Previous studies also showed similar results. The different pregnancy rates in our study in patients with male factor infertility compared to other studies may be attributed to the lack of standardization of semen analysis and different thresholds for semen parameters for performing IUI in different studies. On the other hand, various counting chambers are used with different methodologies (eg. manual v/s computerized) to calculate these parameters.

Consequently, the variation of results among centers may well be beyond acceptable, weakening the results reported by several studies [2,3]

Conclusion

COH-IUI is an effective first line method of treatment in patients with mild male factor and unexplained infertility. Endometrial thickness with associated pattern is the most significantly associated with positive pregnancy rate. We found no statistically significant association between husband's age, patient's BMI, duration of infertility, number of preovulatory follicles on the day of HCG, type of infertility, etiology of infertility or prewash semen parameters and IUI outcome.

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