



## EFFICACY OF INTRAUTERINE INSEMINATION WITHOUT OVARIAN HYPERSTIMULATION FOR MALE OR CERVICAL FACTOR IN WOMEN AGED 40 OR OVER

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The efficacy of intrauterine insemination (IUI) for male or cervical factor by age of female partner was determined in a retrospective analysis. Patients who underwent IUI therapy for cervical and/or male factor ( $n = 281$ ) were classified by age at first IUI cycle:  $<40$  years ( $n = 232$ ),  $\geq 40$  years ( $n = 49$ ). The indication for IUI was cervical factor if a postcoital test failed to show sperm with good forward progression at time of mature follicle; male factor was diagnosed if the semen analysis demonstrated either low count, low motility, antisperm antibodies, or subnormal hypoosmotic swelling test. Intrauterine insemination was performed in either natural cycles or following ovarian stimulation for the treatment of anovulation or follicular maturation defects. Cumulative probability of ongoing pregnancy (viable at end of first trimester) following 3 cycles of IUI was evaluated. Cumulative probability of ongoing pregnancy following 3 cycles of IUI was 28.2% for the younger group and 0.0% for the older group. The age groups did not differ in terms of infertility history, use of ovarian stimulation, or baseline semen parameters. Thus, the treatment of male and/or cervical factor by IUI is ineffective for women  $\geq 40$  years.

**Keywords** age, intrauterine insemination, ovarian stimulation

A previous study found that the use of intrauterine insemination (IUI) for women  $\geq 40$  years of age was relatively ineffective for improving fecundity when compared to efficacy in younger women [4]. However, in that study the clear need for IUI was present in only 24% of the cases (6% poor postcoital tests and 18% subnormal semen analyses, according to WHO classification), whereas in 76% of the cases the use of IUI was empirical (22% for oligo-ovulation and 54% for unexplained infertility) [4]. Thus, the data merely showed that the empirical combination of ovulation inducing drugs and IUI was less effective for the older patient. These results

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did not address the relative efficacy of IUI as a treatment modality for cervical and/or male factor in women  $\geq 40$ .

The study presented herein compared pregnancy rates (PRs) in older ( $\geq 40$  years old) versus younger ( $< 40$  years old) infertile patients where there was a clear need for IUI (cervical factor or male factor). Furthermore, ovulation-inducing drugs were never used empirically but only when indicated for ovulatory disorders.

## MATERIALS AND METHODS

A retrospective study was conducted of 281 infertile couples who required IUI for cervical and/or male factors between January and November 1995. Cervical factor was determined by failure to demonstrate at least one sperm with progressive forward motion in the cervical mucus 12–16 h after intercourse despite normal semen parameters. All postcoital testing was performed at the time that the follicle was mature (i.e., a follicle with a diameter of 18–24 mm in conjunction with an  $E_2 > 200$  pg/mL). Male factor was defined as a concentration of less than 20 million/mL, progressive motility  $< 50\%$ , antisperm antibodies  $> 50\%$  as measured by the immunobead test, or an abnormal hypoosmotic swelling (HOS) test ( $< 50\%$ ).

Couples were stratified into two groups based on the female's age at the time of her first IUI cycle. Group 1 consisted of 232 couples in which the female was less than 40 years old; group 2 consisted of 49 couples in which the female was 40 years old or older. Each couple was followed for three IUI cycles unless a pregnancy occurred or the couple withdrew from treatment. The conception results of the first three IUI cycles for each couple were used to compare the cumulative probability of ongoing pregnancy following 3 IUI cycles by age. A pregnancy was considered ongoing if the fetus was viable at the end of the first trimester by sonography.

IUI was performed in either a natural cycle if the patient attained a mature follicle or in a stimulated cycle if the patient was anovulatory or had a luteal phase defect related to immature follicles. Ovulation-inducing drugs included clomiphene citrate or low-dose gonadotropins (usually starting at 75 IU per day for the first week). Percoll sperm separation was used to prepare the semen for insemination. If the male partner had either a positive test for antisperm antibodies or an abnormal HOS test, he was then instructed to ejaculate into 5 mL of Earle's balanced salt solution with 0.1 MD (+) galactose (Sigma #65388) added to a 5-mg vial of chymotrypsin (Sigma #CHY-5S) immediately prior to preparation for IUI [1]. IUI was performed 40 h after hCG injection or 36–40 h after spontaneous rise of lutenizing hormone (LH), judged by measuring urinary LH every 4–5 h once a follicle with a 17-mm average diameter was obtained. If the follicle had not collapsed by sonography at the time of IUI, the IUI was generally repeated 8–12 h later.

Life table analysis was used to estimate the cumulative probability of ongoing pregnancy after 3 IUI cycles. The logrank test was used to compare the cumulative PRs by age. Chi-square analysis and independent *t* tests were used as appropriate to compare possible confounding variables, including indication for IUI, length of infertility, proportion of patients with primary infertility and baseline hormone, and semen parameters by age groups. A *p* value of .05 was used.

## RESULTS

The 232 women in the younger group ranged in age from 21 to 39 years with a mean ( $\pm$ SD) age of  $33.0 \pm 3.8$  years. The women in the older group ranged in age from 40 to 52 years with

a mean ( $\pm$ SD) of  $42.2 \pm 2.5$  years. A total of 512 IUI cycles were studied: 410 in the younger group, 102 in the older group. A comparison of the infertility history of the age groups demonstrated no difference in the length of infertility prior to treatment (2.6 years for the younger women, 3.1 years for the older women,  $p = \text{NS}$ ,  $t$  test); type of infertility (42.3% of younger women and 39.6% of older women had primary infertility,  $p = \text{NS}$ , chi-square); or indication for IUI (in the younger group, 40.1% had male factor and used their own partner's sperm for insemination, 14.6% had male factor and used therapeutic donor insemination, 30.2% had cervical factor and 15.1% had both male and cervical factors; the corresponding rates in the older group were 40.8, 16.3, 24.5, and 18.4%, respectively).

The average baseline semen parameters did not differ by age group. The mean ( $\pm$ SD) count (per mL), motility, HOS, and strict morphology scores were  $43.5 \times 10^6 \pm 42.2 \times 10^6$ ,  $46.7 \pm 17.7\%$ ,  $62.1 \pm 15.5\%$ , and  $8.6 \pm 4.8\%$ , respectively, in the younger group and  $36.5 \times 10^6 \pm 27.6 \times 10^6$ ,  $46.4 \pm 17.7\%$ ,  $63.2 \pm 15.0\%$ , and  $7.5 \pm 5.1\%$  in the older group ( $p = \text{NS}$ ,  $t$  test). Antisperm antibodies were present in 11.1% of the younger group versus 10.2% of the older group ( $p = \text{NS}$ , chi-square). There was no difference in stimulation used in the IUI cycle by age. IUI was performed in natural cycles in 52.2% of the younger group and 51.0% of the older group.

There were 62 pregnancies in the younger group: 12 spontaneous abortions; 1 ectopic pregnancy, 3 chemical pregnancies, and 46 viable pregnancies. There were 5 pregnancies in the older group: 3 spontaneous abortions, 1 ectopic pregnancy, and 1 chemical pregnancy. Thus, there were no viable pregnancies in the older group. Based on life table analysis (Table 1), the cumulative probability of ongoing pregnancy was 28.2% for the younger group and 0.0% for the older group ( $p < .05$ , logrank test).

## DISCUSSION

We believe that this is the first study comparing the efficacy of IUI exclusively for male and cervical factor without the use of empirical ovarian hyperstimulation by woman's age ( $\geq 40$  years of age versus those  $< 40$ ). The study differs from the one by Frederick et al. [4] in that purposeful ovarian hyperstimulation [3] was not used in our study, whereas it was used by Frederick et al. in all cases. We used follicle-maturing drugs only when there was clear anovulation or luteal dysfunction related to releasing oocytes from immature follicles [2]. Furthermore, our study evaluated only couples with male and/or cervical factor, whereas 54% of the

**Table 1.** Life table analysis of cumulative probability of viable pregnancy following 3 cycles of intrauterine insemination for male or cervical factor by age

Age group	Cycle	Number of patients	Viable pregnancies	Probability of pregnancy/cycle (%)	Cumulative probability of pregnancy (%)
Women < 40 years old	1	232	28	12.07	12.07
	2	116	13	11.21	21.92
	3	62	5	8.06	28.22
Women $\geq$ 40 years old	1	49	0	0	0
	2	31	0	0	0
	3	22	0	0	0

cases used in the study by Frederick et al. had no apparent diagnosis and did not have male or cervical factor. Despite the differences in study population and use or nonuse of ovarian hyperstimulation, the conclusions reached by both studies were the same: Viable PRs in women  $\geq 40$  following IUI are very poor. Future studies are needed to determine if IVF possibly with intracytoplasmic sperm injection may produce better results for this age group.

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