

CLINICAL ASSISTED REPRODUCTION

Evaluation of Pregnancy Rates After Intrauterine Insemination According to Indication, Age, and Sperm Parameters

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Submitted: October 27, 1997
Accepted: December 23, 1997

Purpose: Our purpose was to evaluate intrauterine insemination results obtained in our clinic and identify prognostic factors for the chance of pregnancy.

Methods: A retrospective study of data from 1989 to 1996 was undertaken. Only first attempts were included in this study, except for the part on the cumulative pregnancy rates. Couples with either one-sided tubal pathology, hormonal dysfunction, idiopathic infertility, or andrological indication were selected. All women were stimulated with clomiphene citrate. Five hundred sixty-six couples who underwent 1763 cycles were included in the study.

Results: The overall pregnancy rate for first pregnancies was 6.9% per cycle and 21.4% per patient. For first intrauterine insemination attempts this was 8.8% per cycle/patient, varying between 5.0% for andrological indication and 10.6% for tubal pathology, 10.0% for idiopathic indication, and 10.3% for hormonal indication. These differences were not significant. Age did not have a significant effect either, although there were no pregnancies observed in women 40 years or older. The number of inseminated spermatozoa significantly affected the pregnancy rate: <2 million, 4.6%; ≥ 2 to <10 million, 3.9%; and ≥ 10 million, 11.3%.

Conclusions: Unless semen characteristics are insufficient, intrauterine insemination is a useful treatment for infertile couples.

KEY WORDS: age; indication; intrauterine insemination; pregnancy rate; sperm characteristics.

INTRODUCTION

Intrauterine insemination (IUI) with husband's semen is a treatment of infertility used for a variety of indications. It is often offered before the more rigorous and costly in vitro fertilization procedure. IUI involves the deposition of washed and concentrated motile spermatozoa directly in the uterine cavity. To achieve fertilization and pregnancy, the insemination has to be synchronized with ovulation, either in a natural cycle or in a cycle with ovarian stimulation. Different protocols are used for that purpose (1). Many studies report on the effects of single variables on the success rate of IUI, such as the influence of age (2–4). It has also been found that the number of motile spermatozoa influences the chance of pregnancy (2,5). Only a few studies have examined the role of indication of pregnancy outcome after IUI (6–8). None of the studies mentioned are restricted to first IUI cycles. This probably causes selection, because not all patients undergo the same number of cycles. Therefore we selected only first IUI cycles for this study.

To identify prognostic factors for IUI outcome, pregnancy rates for first IUI attempts were calculated in relation to indication, age of the woman and the man, and the total number of inseminated motile spermatozoa. We also looked at the relationships between indication and age of the woman and man and between the age of the man and the number of motile spermatozoa.

In addition, cumulative pregnancy rates were calculated based on data from our IUI program to evaluate the effect of the number of IUI attempts on conception in relation to indication.

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MATERIALS AND METHODS

Patient Selection

A total of 566 couples, who underwent a total of 1763 IUI cycles between January 1, 1989, and October 1, 1996, was included in this study. They were selected for the IUI program based on sperm characteristics, one-sided tubal pathology, hormonal dysfunction, or idiopathic infertility. All women in this study were stimulated, according to our standard protocol, with clomiphene citrate.

Definition of Indications

(1) One-sided tubal pathology: Only one patent tube present as evaluated by hysterosalpingogram or laparoscopy.

(2) Andrological: At least two abnormal semen analyses, according to World Health Organization standards (9).

(3) Idiopathic: No evident fertility disorders as investigated by the standard fertility workup schedule (10); postcoitus test negatives were also included in this group, because of the low predictive value of the test as determined by a study at our clinic (11).

(4) Hormonal: Couples in whom the woman has an irregular or anovulatory cycle but responds to clomiphene citrate administration. Some of these women belonged to the group with polycystic ovarian syndrome, as demonstrated by an increased luteinizing hormone (LH): follicle stimulating hormone (FSH) ratio.

Ovulation Monitoring

The standard protocol for IUI was to combine the inseminations with mild ovarian stimulation with clomiphene citrate (100 mg daily, cycle days 3–7, p.o.), to obtain a slight increase in number of follicles and to facilitate the detection of ovulation. The cycles of all patients were monitored by ultrasound scan of the ovaries and determination of estradiol (E_2) levels and LH levels in the serum between day 11 and day 13 of the cycle. Depending on the cycle length and the ovarian response, more frequent determinations were performed, with extremes varying from cycle day 6 to cycle day 20. When one to three follicles 16–18 mm in diameter were present and the E_2 level was in accordance with the size and number of follicles, 10,000 IU of human chorionic gonadotrophin (hCG; Profasi; Serono Benelux) were given to initiate ovulation.

When the serum LH test was positive, no hCG was administered. The time of insemination was 18 or 42 hr after hCG injection or ± 30 hr after the LH surge.

Sperm Preparation

Freshly ejaculated sperm was allowed to liquefy. Volume was determined and concentration and percentage of motile sperm were assessed in a Makler counting chamber and the total number of motile sperm was calculated. HEPES-buffered Earle's medium with 0.5% human serum albumin was added to the semen sample and mixed by pipetting. Depending on the total number of motile sperm, the mixed sample was pipetted on top of either a 1-ml 70% or a 1-ml 80% Percoll layer and centrifuged (800g, 10 min). The supernatant was removed and the pellet was resuspended in HEPES-buffered Earle's medium. Depending on the total number of motile sperm, this suspension was either pipetted on top of a 80% Percoll layer and washed two times in the medium or washed two times in the medium after the first Percoll treatment. Volume, concentration, motility, and total number of motile sperm were redetermined after processing. The sperm was kept at 37°C in an incubator until insemination took place.

Insemination and Monitoring

A 1-ml syringe was filled with Earle's medium and connected to a Frydman (MDT; Oisterwijk, The Netherlands) or a TDT catheter (MDT). After flushing the catheter, the sperm suspension was aspirated into the catheter. The catheter was passed through the cervical canal and into the uterine cavity. The suspension (less than 0.5 ml) was slowly injected, after which the catheter was withdrawn gradually. Twelve days after insemination a quantitative β hCG determination was performed on the serum. When the β hCG was positive an ultrasound was made at 6 weeks of gestation to confirm pregnancy.

Statistical Analysis

Pearson's χ^2 test was used to compare the proportion of conception and nonconception cycles in women assigned to the different groups.

Cumulative pregnancy rates were calculated for the total number of IUI cycles present in our database and for subgroups of cycles according to the indication for IUI.

RESULTS

Overall Results

A total of 566 patients underwent a total of 1763 IUI cycles in this study, which resulted in 121 first pregnancies (6.9% per cycle, 21.4% per patient). The mean number of IUI cycles per patient was 3.1, varying from 1 to 8 attempts to achieve a first pregnancy.

The mean age \pm SD of the women was 31.8 ± 4.7 years (range 19 to 46 years); the mean age \pm SD of the men was 34.3 ± 5.9 years (range, 19 to 59 years).

Cumulative Pregnancy Rates

Figure 1 shows the cumulative pregnancy rate. The total cumulative pregnancy rate reached a maximum of 31.1%, and no additional pregnancies were obtained after six IUI attempts. However, this number differed between indications: in the group with tubapathology, no additional pregnancies occurred after four IUI cycles; in the idiopathic and hormonal groups, there were still pregnancies observed in the sixth cycle. Also, the cumulative pregnancy rate after six IUI attempts differed between indications (e. g., 30.2% in the idiopathic group versus 52.5% in the hormonal group).

Pregnancy Rates in Relation to Indication

Only first IUI attempts were included in this part of the study. No significant differences in pregnancy rates between the different indications were found (Table I). The pregnancy rate in the andrological group was low (although not significantly lower) compared with the other groups. To investigate whether age contributed to this difference by a difference in age

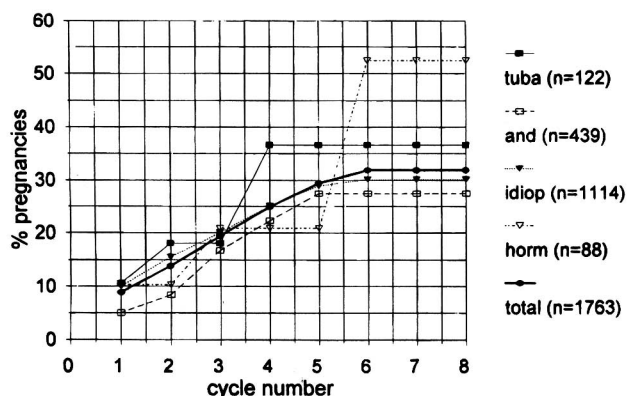


Fig. 1. Cumulative pregnancy rates after IUI in relation to indication.

between the indications, the age distribution within each indication was calculated. The only significant difference found was the higher number of women ≥ 40 years old in the tubapathology group compared with the other groups ($P < 0.01$). Although not proven to be significant, there was a tendency for the andrological group to consist of a relatively young population (40% were younger than 30 years and 80% were younger than 35 years) in comparison with the other indications (nonandrological indications: 30% younger than 30 years and 67% younger than 35 years). Both of these observations, however, cannot explain the observed differences in pregnancy rates.

Pregnancy Rates in Relation to the Number of Motile Sperm Inseminated

An increase in the number of motile sperm that was inseminated resulted in a significant increase in pregnancy rate (Table II). This is in agreement with the difference in pregnancy rate found between the group with an andrological indication and the other indication groups: the mean number of motile sperm cells inseminated in the andrological group was 8.3 ± 10.8 million, versus 30.3 ± 34.4 million in the groups without andrological factors.

To investigate whether there was a difference in the chance of becoming pregnant with the same number of inseminated motile sperm cells but belonging to the andrological versus the nonandrological groups, these groups were compared. However, there was no significant difference in pregnancy rate between them (< 2 million, $\chi^2 = 0.48$, $P = 0.49$; ≥ 2 to < 10 million, $\chi^2 = 0.29$, $P = 0.59$; ≥ 10 million, $\chi^2 = 0.42$, $P = 0.52$). This shows that there are probably no factors other than semen characteristics that are responsible for the pregnancy rates found in both the andrological and the nonandrological groups.

Pregnancy Rates in Relation to the Age of the Man and Woman

The pregnancy rates according to the age of the men and women were calculated for first IUI cycles. No differences were observed, either between the different age groups of women or between the different age groups of men (Table III). However, no pregnancies occurred in women 40 years and older.

With regard to the age of the men, two notable differences were observed. First, although the semen quality of men younger than 30 years was comparable to that of men of 30 years or older (25.7 ± 28.0 versus

Table I. Pregnancy Rates per Patient in the First IUI Cycle, According to Indication

Indication	No. patients	Age (mean yr \pm SD)	No. pregnancies	% pregnancies*
Tubapathology	47	34.3 \pm 5.1	5	10.6
Andrological	139	30.8 \pm 4.9	7	5.0
Idiopathic	351	31.8 \pm 4.4	35	10.0
Hormonal	29	31.6 \pm 5.0	3	10.3
Total	566	31.8 \pm 4.7	50	8.8

* $\chi^2 = 3.33$, $df=3$, $P=0.34$.

Table II. Influence of the Total Number of Inseminated Motile Sperm on the Pregnancy Rate with Regard to Andrological (And.) and Nonandrological (Nonand.) Indications

Total motile sperm ($\times 10^6$)	No. patients			No. pregnancies			% pregnancies		
	And.	Nonand.	Total	And.	Nonand.	Total	And.*	Nonand.**	Total***
<2	35	8	43	2	0	2	5.7	0	4.6
≥ 2 to < 10	67	85	152	2	4	6	3.0	4.7	3.9
≥ 10	37	334	371	3	39	42	8.1	11.7	11.3

* $\chi^2 = 1.35$, $df = 2$, $P = 0.51$.

** $\chi^2 = 4.55$, $df = 2$, $P = 0.10$.

*** $\chi^2 = 8.28$, $df = 2$, $P = 0.02$.

24.8 \pm 32.6 million), the pregnancy rate was half that in the other age groups. Because the partners of men younger than 30 years did not belong to the group of women of 40 years or older this cannot explain this observation either. Second, comparing the role of age in the andrological indication versus the nonandrological indication groups, no pregnancies occurred in the andrological group when the men were 40 years or older ($n = 24$). This was not observed in the nonandrological groups ($n = 77$). That no pregnancies were established in the andrological group when the man was 40 years or older cannot be explained by either the extremely low number of inseminated spermatozoa (9.3×10^6 versus 8.1×10^6 in men younger than 40

years) or the high proportion of women 40 years or older (only 2 of 24 in the andrological group, versus 9 of 77 in the nonandrological groups).

DISCUSSION

From the results of this study it is concluded that the factor with the highest impact on the chance of pregnancy after IUI treatment is the number of motile spermatozoa that is inseminated. Although other factors such as the age of the man and woman and the indication caused some differences in pregnancy rate, they did not reach significance.

The pregnancy rates found in this study are similar to those found in other studies on the outcome of IUI treatment: overall pregnancy rates of 18.7 and 21% per patient and 5.6 and 10% per cycle were reported by Campana *et al.* (2) and Frederick *et al.* (4), respectively, versus the 21.4% per patient and 6.9% per cycle found in this study. For most of the published studies it is difficult to compare IUI results in more detail, due to differences in patient selection, ovarian stimulation, definition of sperm parameters, indication, etc.

With regard to the figures for first IUI attempts, differences between indications are not significant. The somewhat lower pregnancy rate of the relatively young andrological group is not the result of an age bias. On

Table III. Pregnancy Rates per Patient in Relation to Age

Age (yr)	No. patients	No. pregnancies	% pregnancies
Woman*			
<30	180	16	8.9
≥ 30 to < 35	218	22	10.1
≥ 35 to < 40	147	12	8.2
≥ 40	21	0	0
Man**			
<30	110	5	4.5
≥ 30 to < 35	198	19	9.6
≥ 35 to < 40	157	16	10.2
≥ 40	101	10	9.9

* $\chi^2 = 2.55$, $df = 3$, $P = 0.47$, for percentage pregnancies.

** $\chi^2 = 3.16$, $df = 3$, $P = 0.37$, for percentage pregnancies.

the contrary, it is expected that younger women have a higher chance of pregnancy (12, 13). Slight differences in IUI outcome among male-factor infertility (5.45%), idiopathic infertility (12.12%), endometriosis-related infertility (6.09%), and ovulation dysfunction (5.0%) have been reported (14), but these figures are difficult to compare with our results because they do not represent only first IUI attempts.

In this study an overall significant increase in pregnancy rate was found with an increasing number of motile spermatozoa. However, when andrological and nonandrological indications were examined separately, this significance was not maintained. There was a trend toward significance in the nonandrological group. Several studies have reported on the influence of semen characteristics on IUI outcome: a significant increase in pregnancy rate was found when less than 0.5 million versus greater than 0.5 million spermatozoa were inseminated (2). A trend toward an increasing pregnancy rate with an increasing total motile sperm count was also reported. This trend reached significance when 20 million or more spermatozoa were inseminated (5). Other findings were similar to our results: a significant lower pregnancy rate was found when 2 million or fewer sperm cells were inseminated (15). However, comparisons are difficult to make because studies vary greatly in the definition of their treatment groups. In our study, the fact that there was no difference in pregnancy rates between andrological and nonandrological indications when the same number of motile spermatozoa were inseminated indicates that probably only semen characteristics are responsible for the number of pregnancies obtained. This is difficult to explain because the low number of inseminated spermatozoa in the nonandrological group should be a coincidence and factors other than semen characteristics should play a major role in obtaining pregnancies in this group. These results, however, suggest that the number of motile spermatozoa that is inseminated plays a dominant role in IUI outcome.

The influence of age on the pregnancy rate after IUI in this study starts at 40 years: women 40 years or older did not become pregnant. Again, results presented in the literature vary greatly. Agarwell and Buyalos (16) found a decrease in pregnancy rate after IUI already at 35 years of age, while Corsan *et al.* (14) reported a pregnancy rate per cycle in women 40 years or older that was less than half that in women younger than 40 years of age (6.69 versus 17.95%) but still able to become pregnant. This ability rapidly declined at 42 years of age. The influence of the age of the man was observed only in the andrological group and only when

the age was 40 years or older. This is not in agreement with the findings of Mathieu *et al.* (3), who reported a significant effect of age of the husband on pregnancy rate: increasing age proved to cause an increasingly poor prognosis for pregnancy after IUI.

From our cumulative figures it is concluded that performing more than six IUI attempts does not result in a higher percentage of pregnancies, as was also shown by Campana *et al.* (2). There are some slight differences between indications. The overall higher cumulative pregnancy rate in the hormonal group (52.5%) might be explained by the fact that the disorder that caused the subfertility/infertility is more or less removed by the clomiphene citrate and hCG administration. Many unknown factors, such as the uterine environment, unidentifiable semen characteristics, and dysfunction in the interaction between sperm and oocyte, may be involved in the idiopathic group and therefore cannot be treated adequately. This might result in the overall lower cumulative pregnancy rate (31.9%). However, the low number of six cycles (two of five in total) must also be taken into consideration when interpreting the results. Although there are differences between indications, there is no substantial evidence that we should discriminate between them in performing fewer or more attempts. This is not in agreement with the findings of Lalich *et al.* (8) and of Friedman *et al.* (6), whose results showed a significant difference between cumulative pregnancy rates for different indications. Differences in choices and definitions of indications may be responsible for this discrepancy. In our study the plateau at 31.9% after six IUI attempts might be explained by the fact that some patients are more likely to react positively to IUI treatment than others. Another explanation may be a possible negative effect (desensitization) of several clomiphene citrate treatments every other month, which might result in a decreased chance of pregnancy.

From this study it can be concluded that the number of motile sperm cells that is inseminated has predictive value for the chance of pregnancy. Indication does not play a major role in predicting the chance of pregnancy. The probability of becoming pregnant is greatest during the first six cycles. Overall it can be concluded that IUI is a useful treatment for subfertile couples unless semen characteristics are insufficient.

ACKNOWLEDGMENTS

We thank Fokke Broers for his help with the database; Paula de Boer for her help with the completion

of the data acquisition; Jo Hermans for his help with the statistical analysis; Kitty Bloemenkamp, M.D., and Harjo Verburg, M.D., for critical reading of the manuscript; and the clinicians, nurses, and technicians of the IVF Centre at the University Hospital Leiden.

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