Intrauterine insemination: evaluation of the results according to the woman's age, sperm quality, total sperm count per insemination and life table analysis

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We report on 332 infertile couples who underwent 1115 cycles of intrauterine insemination (IUI) with washed husband's semen. The indication for IUI was an abnormal post-coital test due to either a male or cervical infertility factor. The mean number of IUI cycles per patient was 3.4, the overall pregnancy rate 18.7%, and the pregnancy rate per cycle 5.6%. The cumulative pregnancy rate calculated by life table analysis showed that 16.0% of pregnancies occurred in the first three treatment cycles, while the cumulative pregnancy rate was 26.9% by the sixth cycle. The outcome of the therapy was adversely affected if the woman's age was >39 years and/or total motile sperm count per insemination was <1×10^6. No pregnancy occurred in women older than 44 years or in cases with a total motile sperm count before semen preparation of <1×10^6.

Key words: age factors/infertility/intrauterine insemination/male factor/sperm count

Introduction

Intrauterine insemination (IUI) with the husband's semen has been widely used for the treatment of infertile couples. The indications for performing artificial insemination include sperm abnormalities, cervical mucus hostility, impotence and idiopathic infertility. The value of IUI in treating couples with male factor infertility remains questionable, even though a number of reports have been published in which pregnancies were achieved with a total sperm count of 1–5×10^6 (Cruz et al., 1986; Ho et al., 1989; Francavilla et al., 1990). In a multicentre trial reporting on the use of in-vitro fertilization (IVF) and IUI, Crosignani and Walters (1994) found that both techniques were suitable for treating couples suffering from primary infertility due to oligozoospermia, asthenozoospermia or teratozoospermia. Hewitt et al. (1985) had previously reported that IVF yielded higher pregnancy rates than IUI for most indications, however, no significant differences were noted for male factor infertility without asthenozoospermia. The inability of IUI to assist in achieving pregnancies for males with asthenozoospermia has been substantiated by Yovich and Matson (1988) and Ho et al. (1989). Francavilla et al. (1990),

however, reported that the absence of teratozoospermia was an effective criterion for selecting couples for IUI with infertility due to oligozoospermia and/or asthenozoospermia.

The overall success of IUI varies, with pregnancy rates ranging from as low as 5% to as high as 66% (Allen et al., 1985). Many of the reported results, however, arise from studies composed of small treatment groups and fail to report correlations between specific variables that influence the success of treatment. There are few studies evaluating a large cohort of patients and presenting the results in the form of a life table analysis. Life table analysis accounts for patients dropping out of treatment and the length of time taken to achieve a pregnancy.

In our study, we provide an analysis of IUI results from a large population of patients. Pregnancy rates are presented (i) in relation to a woman's age and total sperm count per insemination, (ii) in relation to the absence or presence of hormonal treatment and (iii) as a life table analysis.

Materials and methods

Patients

A total of 332 couples received 1115 cycles of IUI during a 5 year period from 1989 to 1994. Treatment was performed at the Clinic of Infertility and Gynaecologic Endocrinology – WHO Collaborating Centre, Department of Obstetrics and Gynaecology, University Hospital of Geneva, Switzerland. All couples underwent extensive infertility evaluation prior to IUI consisting of at least two semen analyses, monitoring of ovulation by ultrasound and mid-luteal progesterone, a post-coital test performed in the pre-ovulatory phase and hysterosalpingography. Couples with an abnormal post-coital test according to World Health Organization criteria (WHO, 1992), due to either a male or a cervical factor, were candidates for IUI. Women had at least one patent tube, documented by hysterosalpingography, and in some cases also by laparoscopy. Women with normal ovulatory cycles did not receive any hormonal treatment. Only women with amenorrhoea, oligomenorrhoea or anovulatory cycles received hormonal treatment. In 310 cycles (27.8% of total) ovulation was induced by either clomiphene citrate or by human menopausal gonadotrophin (HMG) (or follicle stimulating hormone) combined with human chorionic gonadotrophin (HCG).

Sperm preparation and IUI

The semen sample for insemination was analysed for conventional semen parameters (volume, number, motility; WHO, 1992) and washed in Ménézo's B_2 medium (Bio Merieux SA, l'Etoile, France). During the 5 year period, a change was made in sperm preparation in that, until 1991, all spermatozoa were prepared using the swim-up technique but following 1991 spermatozoa were isolated using either conventional swim-up or the mini-Percoll technique (Ord et al., 1990). Mini-Percoll separation was used in cases where the sperm

Table I. Pregnancy rates per patient and per intrauterine insemination cycle with reference to the age of the woman

Age (years)	No. of patients	No. of cycles	Mean no. of cycles per patient	No. of pregnancies	Pregnancy rate per patient (%)[a]	Pregnancy rate per cycle (%)[b]
<30	55	143	2.6	9	16.1	6.3
30–34	116	357	3.1	25	21.6	7.0
35–39	104	377	3 6	23	22.1	6.1
40–44	47	202	4.3	5	10.6	2.5
>44	10	36	3.6	0	0	0.0
Total	332	1115	3.4	62	18.7	5.6

[a]$\chi^2 = 5.93$, df $= 4$, $P = 0.20$; trend $P = 0.25$.
[b]$\chi^2 = 7.55$, df $= 4$, $P = 0.11$; trend $P = 0.025$.

parameters were below those considered as normozoospermia (WHO, 1992). Once prepared, the final pellet was resuspended in 0.2–0.5 ml of Ménézo's B_2 medium. The insemination was routinely carried out using a simple catheter, but if the catheter failed to enter after the initial attempt a double Frydman catheter was used (Prodimed, Neuilly en Thelle, France). All techniques were carried out using sterile procedure. The IUI was performed with the patient in the dorsal lithotomy position.

Timing of insemination

In non-stimulated cycles and in clomiphene citrate-stimulated cycles, timing of ovulation was determined by urinary luteinizing hormone (LH) assay (Abbot Diagnostics, Cham, Switzerland) and inseminations were performed on the day of LH peak. Briefly, once a follicle of 17 mm diameter was observed the patient was asked to provide urine samples three times a day. The three samples were measured in the morning and the decision for insemination made in the afternoon.

In gonadotrophin-stimulated cycles, serial ultrasound measurement of follicles and analysis of serum oestradiol concentrations (radio-immunoassay) were performed to determine the timing of ovulation induction with HCG injection (Profasi, Serono; 10 000 IU). In general, HCG was given when a dominant follicle measured 17–18 mm. IUI was scheduled 36 h after HCG injection.

Statistics

χ^2 and trend analysis were used for comparisons of an overall effect within a group and single parameters within groups. Life table analysis was performed using the method described by Cramer et al. (1979) and also reported by Lalich et al. (1988). Using this analysis the cumulative chance of conception was calculated.

Results

Overall pregnancy rates

The mean number of IUI cycles per patient was 3.4, the pregnancy rate per patient 18.7% and the pregnancy rate per cycle 5.6% (Table I).

Pregnancy rates according to the age of the woman and total motility of the spermatozoa

Both the pregnancy rate per patient and the pregnancy rate per cycle showed a decline after the age of 39 years; however, a significant difference was found only when comparing pregnancy rates per cycle (Table I). When between-group comparisons were performed, a significant difference was observed in pregnancy rate per patient ($\chi^2 = 3.7$, $P = 0.05$) and per cycle ($\chi^2 = 6.1$, $P = 0.01$) when comparing the <40

Table II. Pregnancy rates after intrauterine insemination with respect to (a) total motile sperm count per insemination and (b) total motile sperm count before sperm preparation

Total motile sperm count ($\times 10^6$)	No. of cycles	No. of pregnancies	Pregnancy rate per cycle (%)[a,b]
(a) Per insemination			
<0.5	164	3	1.8
0.51–1.0	116	3	2.6
1.1–5.0	520	37	7.1
>5.0	315	19	6.0
Total	**1115**	**62**	**5.6**
(b) Before sperm preparation			
<1.0	37	0	0.0
1.1–10.0	209	8	3.8
10.1–20.0	169	8	4.7
20.1–40.0	170	15	8.8
40.1–100.0	259	9	3.5
>100.0	271	22	8.1
Total	**1115**	**62**	**5.6**

[a]For (a), $\chi^2 = 8.83$, df $= 3$, $P = 0.032$; trend $P = 0.022$.
[b]For (b), $\chi^2 = 12.6$, df $= 5$, $P = 0.028$; trend $P = 0.05$.

and $\geqslant 40$ years age groups (Table I). No significant difference was evident in patients younger than 40 years, and no pregnancy occurred in the limited sample of women who were >44 years.

When the relationship between pregnancy and total motile sperm counts was examined, we found that there was an overall significant difference in pregnancy rate per cycle in relation to both the total sperm count per insemination and total motile sperm count before sperm preparation (Table II). The pregnancy rate per cycle was significantly reduced when only $<0.5 \times 10^6$ motile spermatozoa could be inseminated compared to $>1 \times 10^6$ ($\chi^2 = 3.7$, $P = 0.05$) (Table IIa). Three pregnancies were obtained when a total of $<0.5 \times 10^6$ motile spermatozoa were inseminated. There appeared to be no obvious advantage in increasing the total motile sperm count per insemination from $1-5 \times 10^6$ to $>5 \times 10^6$, as the pregnancy rate per cycle was unchanged.

The pregnancy rate per cycle in relation to the total motile sperm count before sperm preparation also showed a significant overall difference between the groups. When IUI was performed using total concentrations of $<1 \times 10^6$ motile spermatozoa, no pregnancies resulted (Table IIb). In contrast, a number of pregnancies were obtained for patients whose husbands had a total concentration of between 1 and 10×10^6 motile

Table III. Pregnancy rates by woman's age and by total motile sperm count per insemination

Age (years)	Total motile sperm count/insemination ($\times 10^6$)									
	<0.5		0.51–1.0		1.1–5.0		>5.0		Overall	
	No. of cycles	Pregnancy rate/cycle (%)	No. of cycles	Pregnancy rate/cycle (%)	No. of cycles	Pregnancy rate/cycle (%)	No. of cycles	Pregnancy rate/cycle (%)	No. of cycles	Pregnancy rate/cycle (%)
>39[a]	144	3 (2.1)	95	3 (3.2)	408	32 (7.8)	230	19 (8.3)	877	57 (6.3)
>39	20	0 (0.0)	21	0 (0.0)	112	5 (4.5)	85	0 (0.0)	238	5 (2.5)
Overall	164	3 (1.8)	116	3 (2.6)	520	37 (7.1)	315	19 (6.0)	1115	62 (5.6)

[a] $\chi^2 = 8.75$, df = 3, $P = 0.033$; trend $P = 0.006$ when comparing different sperm count groups for the ≤39 years age group.

Table IV. Pregnancy rates with respect to total motile sperm count before sperm preparation and to hormonal treatment

Hormonal treatment	Total motile sperm count ($\times 10^6$)	No. of cycles	No. of pregnancies	Pregnancy rate/cycle (%)
No treatment	<20	317	10	3.2[a]
	>20	488	34	7.0[a]
Total		805	44	5.5
With treatment	<20	98	6	6.1[b]
	>20	212	12	5.7[b]
Total		310	18	5.8
Overall total		1115	62	5.6

[a]Values marked with superscript a are significantly different ($\chi^2 = 4.69$, $P = 0.030$).
[b]Values marked with superscript b are not significantly different ($\chi^2 = 0.01$, $P = 0.92$).

spermatozoa, with the highest number of pregnancies occurring in the group with a total motile sperm count of $20–40\times10^6$.

When comparing the role of age and total motile sperm count per insemination, we found that the highest pregnancy rates per cycle in patients aged ≤39 years were skewed to favour the couples in which the husband had a higher total motile sperm concentration per insemination (Table III). Pregnancies achieved when the male had $<1\times10^6$ motile spermatozoa per insemination were only obtained in women <39 years old (Table III). From these results, it appears that even though insemination of a low number of spermatozoa influences pregnancy results the age factor probably has a greater role.

Pregnancy rates in reference to hormonal treatment and total motility of the spermatozoa

No overall difference in pregnancy rates was evident when the group receiving hormonal treatment was compared with the non-stimulated group ($\chi^2 = 5.4$, $P = 0.14$). Couples in which the man had a total motile sperm count before sperm preparation of $>20\times10^6$ and the woman did not receive hormonal treatment had a higher chance of becoming pregnant (Table IV). However, in patients receiving hormonal stimulation, the total motile sperm count before sperm preparation did not affect the outcome of IUI (Table IV).

Life table analysis of IUI pregnancy rates

When examining the cumulative pregnancy rate over time it was noted that more than half the pregnancies occurred in the

first three treatment cycles (Table V). Overall, the cumulative pregnancy rate for all the patients who started treatment was 18.7%. No pregnancy was obtained in seven patients who were still receiving treatment after the ninth cycle. The overall cumulative pregnancy rate calculated by life table analysis was 16% after the third cycle and plateaued to 44.7% by the ninth cycle. In the majority of cases, patients who dropped out of treatment did so for personal, social or economic reasons. Thus, it is acceptable to presume that the population who gave up the treatment and those continuing treatment did not differ due to a clinical problem.

Discussion

This study describes the pregnancy rates achieved by IUI in a large cohort of patients. The value of IUI in treating couples is substantiated by these results, with a cumulative pregnancy rate of 26.9% within six attempts and plateauing at 44.7% after nine cycles. In several other studies presenting life table analyses, reported pregnancy rates ranged from 27% (Lalich *et al.*, 1988) to as high as 52% (Brasch *et al.*, 1994) after the sixth attempted cycle of IUI. As in most forms of infertility treatment, the success of IUI is largely influenced by the aetiology of the infertility. Lalich *et al.* (1988) indeed showed that the cumulative pregnancy rate after the sixth attempt could be >37% in couples where either partner had an immune factor indication or as low as 17% when male factor infertility was the indication for treatment.

One of the most important selection criteria for suitability of couples for treatment by IUI is the sperm quality. In this study, the pregnancy rate was significantly lower when a total of $<0.5\times10^6$ motile spermatozoa was used for the insemination. Even when the total number of motile spermatozoa inseminated was between 0.5 and 1×10^6, pregnancy rates tended to be lower than when $>1\times10^6$ motile spermatozoa could be used. Consequently, couples in which the male displayed severe asthenozoospermia or a combination of oligozoospermia and asthenozoospermia with a total motile sperm count of $<1\times10^6$ spermatozoa, failed to obtain a pregnancy. This confirms previous studies in which the degree of sperm motility after semen preparation has been identified as an important factor for successful IUI (Amy and Quagliarello, 1987; Yovich and Matson, 1988; Ho *et al.*, 1989).

In this study, the pregnancy rate per cycle was significantly lower for women older than 39 years. This has also been

Table V. Life table analysis of intrauterine insemination pregnancy rates

Cycle no	No. of patients	No. of pregnancies	Cumulative pregnancy rate per patients started (%)	Pregnancy rate per cycle (%)	Cumulative pregnancy rate (%)
1	332	28	8.4	8.4	8.4
2	226	9	11.1	3.9	12.1
3	179	8	13.6	4.5	16.0
4	131	5	15.1	3.8	19.2
5	91	6	16.9	6.6	24.5
6	65	2	17.5	3.1	26.9
7	37	2	18.1	5.4	30.1
8	15	0	18.1	0.0	30.8
9	10	2	18.7	20.0	44.7
10	7	0	18.7	0.0	44.7
11	5	0	18.7	0.0	44.7
12	5	0	18.7	0.0	44.7

shown by Frederick *et al.* (1994), who reported that ovarian stimulation treatment and IUI in women >40 years old had a very poor success rate. In our study no pregnancy occurred in women aged >44 years. Among women <40 years, age alone was not strongly correlated with successful IUI. Mathieu *et al.* (1995) have reported that women aged <30 years were more likely to conceive than those >35 years, although this difference was not significant. Interestingly, the same authors found that the age of the male was also important, reporting that the most significant factor contributing to the decreased likelihood of pregnancy with IUI was the age of the husband (Mathieu *et al.*, 1995). In this study, when examining the combined effects of the woman's age and total motile sperm count per insemination, the results were skewed in favour of couples in which the woman was <40 years old and the number of motile spermatozoa inseminated was $>1 \times 10^6$. Interestingly, the pregnancies achieved when the insemination was performed with $<0.5 \times 10^6$ motile spermatozoa were all obtained when the female was younger than 35 years.

There is no consensus about the role of ovulation induction combined with IUI. Several reports show improved pregnancy rates in cases of hormonal treatment (Arny and Quagliarello, 1987; Dodson *et al.*, 1987; Serhal *et al.*, 1988; Martinez *et al.*, 1990) but others do not support these data (Lalich *et al.*, 1988; Corson *et al.*, 1989). Most of these studies suffer from a small patient population and lack matched control groups and well-defined inclusion criteria. Our data showed that ovulation induction only benefits couples with an initial sperm count of $<20 \times 10^6$ motile spermatozoa.

In conclusion, the IUI data presented in this study substantiate previous studies showing that couples in which the male partner has a low number of motile spermatozoa at insemination have a decreased success rate. Women aged >40 years are also less likely to become pregnant with IUI. Life table analysis has shown that the probability of becoming pregnant is greatest during the first six cycles. These results confirm that IUI is a useful and successful method for treating couples with infertility due to either a male factor or cervical factor. IUI will continue to be an attractive option for the treatment of infertility, particularly because of its substantial cost benefits when compared to in-vitro fertilization.

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