ANDROLOGY

Sperm Motility Is a Major Determinant of Pregnancy Outcome Following Intrauterine Insemination

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Purpose: *Our purpose was to assess whether one or more sperm parameters have predictive value for the outcome of intrauterine insemination treatment.*
Methods: *Infertile couples whose normoovulatory and normomechanical female partners underwent superovulation and intrauterine insemination were investigated. The semen profile of the male partner was discounted. In 160 couples, 544 cycles were obtained, resulting in 59 ongoing pregnancies (10.84%/cycle, 36.87%/patient).*
Results: *The only parameter found to be significantly correlated with a positive outcome was the degree of sperm motility following preparation for intrauterine insemination. Close to half (47.5%) of the couples with a very good or an excellent degree of sperm motility conceived, whereas only 8.3% of those patients who had poor or fair sperm motility conceived. None of the semen characteristics, such as volume, count, percentage motility, or percentage normal morphology, were found to correlate with cycle outcome. Although there was a progressive increase in the pregnancy rate with an increase in the total number of motile sperm inseminated, it did not reach significance. Seventy percent of the pregnancies were achieved within a maximum of three treatment cycles. The spermatogram is not accurate enough as a prognostic factor for treatment outcome.*
Conclusions: *The degree of sperm motility, after appropriate preparation for intrauterine insemination, is the only parameter to be correlated with treatment outcome. For couples with a normal female partner, we suggest a maximum of three treatment cycles of induction of ovulation and intrauterine insemination, whenever good progressive motile sperm is obtained after suitable preparation. For cases with poor sperm progression, we suggest appropriate couple counseling and that an alternative assisted reproduction procedure be taken into consideration.*

KEY WORDS: conception; intrauterine insemination; sperm motility; pregnancy.

INTRODUCTION

Therapeutic intrauterine insemination (IUI) using the husband's sperm is commonly performed for male-factor infertility, as well as to enhance the probability of conception in various infertility conditions (1). Due to the heterogeneity of the sample patient population, it is difficult to indicate which sperm features have high fertilization potential. Some investigators have questioned the value of IUI for couples with regard to sperm concentration (2, 3). Confino and colleagues report that the lowest total motile sperm count at which pregnancy occurs ranges between 1 and 5×10^6 sperm (4).

Brasch *et al.* found that there was a significantly increased chance for pregnancy whenever the total motile sperm count used for IUI exceeded 20×10^6 spermatozoa (5). The majority of studies attempting to find which sperm characteristics correlated with cycle outcome included multiple female infertility problems. Thus, the results might be biased by the other infertility etiologies that were treated in parallel.

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The aim of our study was to determine which sperm features are positively related with pregnancy after IUI. For this purpose, we enrolled only normoovulatory and normomechanical patients who had undergone IUI due to male-factor or unexplained infertility.

MATERIALS AND METHODS

The study was conducted retrospectively at two infertility clinics, each of which is a tertiary referral center affiliated with the Tel Aviv University.

All patients treated with IUI during the past 5 years were reviewed. The admission criteria included a normal female partner, as assessed by a normal baseline (days 3–5) hormonal profile, ovulation as assessed by appropriate follicular development [ultrasound and estradiol (E_2) levels], and luteal plasma progesterone levels of 10 ng/ml or greater. Every patient had a normal hysterosalpingography (HSG) during the year prior to enrollment. In addition to the radiologist, every HSG was assessed by one of the authors (A.S., Y.H., or H.R.).

Inclusion criteria involved (a) patients who could not conceive spontaneously for at least 1 year previously [some had been treated empirically by the personal physician with clomiphene citrate (CC)] and (b) couples with more than 1 million sperm cells following IUI preparation. Couples with any female infertility problems were excluded.

Each couple was offered several cycles of induction of ovulation and IUI. Induction of ovulation was conducted with either CC or human menopausal gonadotropin (hMG). There were no strict criteria for choosing either agent. Generally, CC was the first drug of choice. Patients who did not conceive with CC were offered several additional cycles of hMG and IUI.

Ovulation monitoring was done by ultrasound surveillance of follicular size and serum E_2 levels. The monitoring started 3–4 days after the last tablet of CC or 5–6 days after the initiation of hMG administration. All the treatment files were available for review, and only cycles with a good ovulatory response were enrolled. Cycles with premature luteinization or inadvertent ovulation before an IUI treatment was planned were excluded from the study. The IUI treatment was given whenever the dominant follicle was at least 18 mm in diameter, and serum E_2 levels were appropriate. Inseminations were performed 24 and 48 hr after human chorionic gonadotropin (hCG) (10,000 IU) administration.

Pregnancy was diagnosed by positive serum β-hCG levels, and patients were followed up by vaginal ultrasonography until a fetal heartbeat was detected. In this study, only intrauterine pregnancies with positive fetal heart beats confirmed by ultrasound were reported.

Laboratory Procedures

Semen samples were obtained by masturbation. Following liquefaction and counting of the initial sample, Ham's F-10 medium (Biological Industries, Beit Haemek, Israel) supplemented with 1% human serum albumin was added (3:1), followed by centrifugation. The sperm pellet was resuspended in 3 ml of fresh Ham's F-10 medium and recentrifuged. Finally, the pellet was suspended in 0.45 ml of Ham's F-10 medium. In some cases, preparation of semen with Percoll 40/80 was performed. A two-layer discontinuous Percoll gradient was prepared by layering 1-ml aliquots of 40% upper and 80% lower isotonic Percoll (Pharmacia, Uppsala, Sweden). Up to 1 ml of the ejaculate was then layered onto the Percoll gradient and centrifuged for 20 min at 300*g*. The sperm pellet was collected, resuspended, and washed one more time, after which 0.45 ml of fresh Ham's F-10 medium was added. Sperm variables of the prepared suspension were evaluated and IUI was performed promptly. In each treatment, the sperm sample was assessed before and after preparation for morphology by strict criteria, degree and percentage of motility.

With an optical microscope at a magnification of 15×40, the grade of motility was assessed as follows: Grade 1 (poor)—spermatozoa with nonprogressive movements, mainly head movements; Grade 2 (fair)—very slow progressive movements; Grade 3 (good)—progressive but mainly nonlinear movements; and Grade 4 (excellent)—rapid, linear trajectories, sperm movements. The relative proportion of the spermatozoa with different degrees of motility was noted, and the final score was calculated respectively.

Statistical Analysis

The statistical evaluation was performed by a qualified biostatistician, and the data were analyzed by Statistical Analysis System (SAS), Version 6.10 for Windows. Multiple parameters were analyzed in those couples achieving pregnancy and those not conceiving. The two-sample nonparametric Wilcoxon score, followed by chi-square analysis, was used for comparison of intergroup means. The Mantel Hendzel chi-square test was applied to check the trend of proportions.

Estimated relative risk was based on a 2 × 2 contingency table with a 95% confidence interval. The results are presented as mean ± standard deviation, and the level of significance is $P < 0.05$.

RESULTS

A total of 544 treatment cycles was performed in 159 couples, and 59 pregnancies were achieved. The pregnancy rate per treatment cycle was 10.80%, with 37.10% of the patients achieving pregnancy. Of the viable pregnancies, 59.32% were achieved in up to two treatment cycles and 69.5% in up to three treatment cycles. Only 16.95% of the pregnancies were achieved following more than four cycles. Failure to conceive occurred in 71.28% of those who received more than three treatment cycles.

Patients without previous pregnancies were more likely to become pregnant ($P = 0.0154$) than patients with a previous pregnancy, regardless of the outcome of the previous pregnancies. All the other female variables, such as age, follicle stimulating hormone levels (Table I), and the protocol of induction of ovulation, were similar in both groups.

Although there was a trend for an increase in pregnancy rates in parallel with an increase in the number of inseminated spermatozoa (Fig. 1), this did not reach significance. Only the degree of sperm motility post-preparation for IUI correlated significantly with the treatment outcome (Fig. 2). Patients with good and excellent sperm motility, at the time of IUI, had a significantly higher chance of achieving pregnancy than patients with either fair or poor motility, irrespective of the total number of motile sperm inseminated. Forty-seven and five-tenths percent of couples achieved pregnancy whenever the sperm motility at the time of IUI was excellent, 28.57% when it was good, and only 8.33% whenever the degree of motility was fair or less ($\chi^2 = 0.005$, Fisher exact test = 0.00425). For a better than good sperm motility degree at the time of IUI, the relative occurrence of pregnancy was 2.775, with a confidence interval of 1.338–5.775.

None of the sperm parameters (Table II) analyzed by the sperm analysis (i.e., volume, count, percentage motile spermatozoa, degree of motility, or the percentage normal spermatozoa as assessed by strict criteria) were correlated with the treatment cycle outcome. We could not recognize any cutoff value for these parameters and the probability of achieving pregnancy. Nor could we find a correlation between all these factors combined (as calculated by multiplying all of them: "total functional sperm count") and the probability of conception.

Thirty-six pregnancies were achieved after CC induction of ovulation and 23 after hMG induction of ovulation. Six of the latter women had received several previous cycles of CC and IUI. Four couples achieved spontaneous pregnancy during the interval between treatment cycles. All of them had previously had three or four treatment cycles with a good or excellent degree of sperm motility after sperm preparation for IUI.

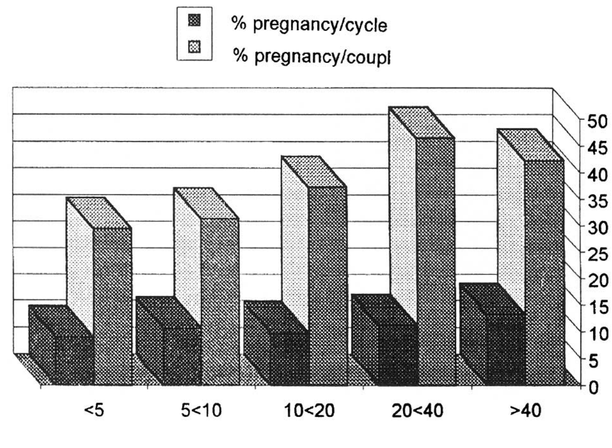

Fig. 1. Relationship between the total number of inseminated motile spermatozoa and the pregnancy rates.

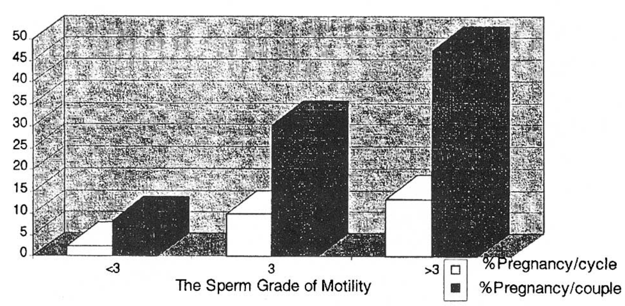

Fig. 2. Relationship between the motility grade of inseminated spermatozoa and the pregnancy rates.

Table I. Female Patient Characteristics[a]

	Age (yr)	FSH[b] (IU/L)	LH[c] (IU/L)
Pregnant	28.84 ± 4.84	7.32 ± 2.46	5.43 ± 2.26
Nonpregnant	30.13 ± 4.99	7.33 ± 2.60	6.57 ± 2.76
P value	NS[d]	NS	NS

[a] Values expressed as mean ± standard deviation.
[b] Follicle-stimulating hormone.
[c] Luteinizing hormone.
[d] Nonsignificant.

Table II. Male Follicle-Stimulating Hormome (FSH) Levels and Spermatograms for Pregnant and Nonpregnant Couples[a]

	FSH (IU/L)	Volume (ml)	Concentration ($\times 10^6$)	% motility	% normal	IUI TMC[b]
Pregnant	5.32 ± 2.41	2.95 ± 1.75	45.72 ± 40.48	39.19 ± 10.58	10.4 ± 7.52	34.16 ± 30.09
Nonpregnant	6.36 ± 3.89	2.56 ± 1.34	53.36 ± 63.59	36.15 ± 13.28	12.65 ± 11.09	29.41 ± 31.57
P value	NS[c]	NS	NS	NS	NS	NS

[a] Values expressed as mean ± standard deviation.
[b] Total motile count.
[c] Nonsignificant.

DISCUSSION

Methods of assisted reproduction are increasingly being applied to patients with long-standing infertility. Such methods are designed to maximize fecundity by the use of ovulation induction, which increases the number of available oocytes, in combination with techniques that increase the number of functionally competent spermatozoa at the site of fertilization. The washing procedures are necessary to remove prostaglandins, infectious agents, and antigenic proteins. Another substantial advantage of these techniques is the removal of nonmotile spermatozoa, leukocytes, or immature germ cells. This may be an important factor in enhancing sperm quality by decreasing the release of lymphokines and/or cytokines and reducing the formation of free oxygen radicals after sperm preparation (6).

A wide range of pregnancy results was reported after intrauterine insemination performed for varying indications. Ho *et al.* found a significant difference in postwash total motile sperm counts in the cycles of pregnant versus nonpregnant women, but their study comprised only 15 patients (7). Brasch *et al.* also found an increasing percentage of conception with an increasing total motile sperm count (5). They found a significantly higher chance for pregnancy when the total motile sperm count used for IUI exceeded 20×10^6. Although it seems logical to find a correlation between the total number of motile spermatozoa and the pregnancy rates, the cutoff value of 20×10^6 is very intriguing. Huang *et al.* found a similar trend toward an increased success rate with an increased total motile sperm count, but in their study, significance was found when the total motile sperm count exceeded 5 million (8). Differences in the criteria for the sperm preparation technique may explain the different cutoff values in these two studies. Brasch *et al.* used different preparation techniques ("glass-wool filtration" or "simple sperm wash") for normospermic cases, and this may account for the reduced percentage of spermatozoa with a high degree of motility, necessitating a larger amount of total spermatozoa (5). The main criticism of the work of Brasch *et al.* is the inclusion of couples with a wide spectrum of female infertility pathology, including tubal factor (5). Fracavilla *et al.* (9) analyzed 86 couples treated with IUI and found that the total motile sperm count was not predictive of the pregnancy rate if the normal sperm morphology was greater than 50%.

In our study, in which the female infertility factor was neutralized, the differences in the sperm characteristics become more significant. Our study provides evidence that within a sufficiently large group of couples, the degree of motility of inseminated sperm is the major predictive factor for the success rate in IUI treatment. Pregnancy rates of about 9% per cycle and almost 30% per couple were obtained even when less than 5 million spermatozoa were inseminated. These figures were not statistically different from those for cycles in which more than 20 million motile sperm were inseminated (12.26%/cycle and 43.83%/couple). The most acceptable explanation for the studies by Brasch *et al.* (5) and Fracavilla *et al.* (9) is that their two predictive variables for cycle outcome are well correlated with a high degree of motility after a specific value. In other words, it is more likely to have sperm with a higher degree of motility whenever there are more than 20 million motile sperm cells or whenever more than 50% of them are normal.

Our finding that a relatively low count of total motile spermatozoa was sufficient to achieve pregnancy may be explained by the use of controlled ovarian stimulation in cases with normal female ovulation. Thus the relatively higher number of released oocytes may compensate for the lower sperm count.

It is important to mention that patients with a low sperm density are usually referred directly for in vitro fertilization (IVF) and, in extreme cases, for intracytoplasmic sperm injection (ICSI) treatment. In view of our results, it is worthwhile to perform a pretreatment sperm preparation and to evaluate the degree of motility. Whenever the degree of motility is high, we recommend attempting three cycles of ovulation induction and IUI before more sophisticated assisted reproduction techniques, such as IVF, are attempted. However, if the sperm motility following preparation for IUI remains poor or fair, then IVF is required as the initial attempt. Further studies are required to evaluate the efficacy of conventional IVF in these cases versus ICSI as the first procedure of choice.

The rationale behind the use of ovarian stimulation in IUI is to increase the number of oocytes available for fertilization and to correct subtle unpredictable ovulatory dysfunction. Arici *et al.* showed that the addition of active ovulation management that includes CC stimulation increases the pregnancy rate per cycle (10). In our group of normomechanical and normoovulatory patients, we did not find an advantage for induction of ovulation with hMG over CC. Bypass of possible hostile cervical mucus as a result of CC treatment may be a reasonable explanation for this finding. Most probably, the appropriate sperm preparation and the timing of IUI are the most important "nondependent" factors to determine the success rate for these patients.

Four pregnancies were achieved during the treatment-free cycle, all in patients with a previously high degree of sperm motility at IUI. Because our policy was to offer consecutive treatment cycles once the patient status allowed it, we wonder if alternative bimonthly treatment is a more judicious approach.

We conclude that the chance of pregnancy, in infertile couples in whom the woman has neither ovulation disturbances nor tubal pathology and has undergone induction of ovulation and IUI, is directly related to the degree of sperm motility after preparation for insemination. In these couples, CC seems to be equally beneficial as hMG.

Therefore, we recommend a trial of three cycles with either CC or hMG and IUI whenever the degree of sperm motility is good, and we suggest immediate referral to an alternative assisted reproductive technology procedure for cases with a poor degree of motility.

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