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## The Use of Therapeutic Donor Insemination to Demonstrate the Inadequacy of Present WHO Standards for Normal Motile Density in Distinguishing Fertile from Nonfertile Males

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In a previous study 135 infertile couples were evaluated to determine the pregnancy rate in 6 cycles. Included were all females who had a female factor(s) identified and thought to be fully corrected. Although a semen analysis was performed, no therapy was offered to the male partner for this time period. During the 6 months, males with normal motile densities (MD) according to the World Health Organization (WHO) standards (minimum of  $10 \times 10^6/\text{ml}$  motile sperm with  $> 50\%$  normal morphology) showed a pregnancy rate of 83% as compared to 69% in those couples with semen specimens below WHO standards. The differences, however, were not statistically significant. These data make unreliable previous statistics which suggest the percentage of male factor as a cause of infertility in this population. They were based solely on determining what percentage of men in infertile couples have motile sperm counts below WHO standards. It had already assumed this to be the cause of the infertility. The data also provided serious questions as to the validity of performing semen analyses on patients and predicting male factor problems based on the results with the exception, perhaps, of the extremely poor motile densities.

We therefore considered the possibility that in couples who failed to conceive after 8 cycles despite all female factors having been corrected, males who exhibited subnormal semen parameters might be those with a

greater likelihood of not achieving a pregnancy during the next 8 cycles. When a couple has had 8 cycles to achieve a pregnancy without success, it has been the experience of many that continuing on the same therapy will result in only a very small percentage of pregnancies. Theoretically the failure in these unexplained cases might be related to either an occult male or female factor problem, or possibly both. A priori one would think that those with subnormal semen parameters (despite the fact that these levels do not predict infertility during the first eight cycles of exposure after the correction of female factors) might certainly have problems with male fertility potential whereas, in men with levels above the minimum requirements by WHO standards, the cause of infertility may be related more to an occult female factor problem.

To test the hypothesis that if the semen analysis is not predictive of infertility during the first 6–8 months, this would at least predict the cause of infertility in those who failed during that time, we initiated a study using a donor probe. It was reasoned that men with a subnormal spermogram would, in all probability, respond with a high pregnancy rate following therapeutic donor insemination (TDI) whereas those with normal semen analyses would demonstrate a much lower pregnancy rate following TDI. We report, herein, the pregnancy rates following TDI in couples who failed to conceive after 8 cycles when all known female factors had been corrected. All couples were separated into two groups, one in which the male partner had subnormal spermograms and one group with normal spermograms. Further evaluation included 70 additional couples who also failed to achieve pregnancies after 8 corrected cycles in which all males had normal semen parameters but where the hamster ova penetration test was either normal or subnormal, and the response to TDI also evaluated.

### *Materials and Methods*

In study one, 88 couples who had a minimum of 12 months of infertility were selected. The requirement was that at least one infertility factor be identified and corrected in the female partner. Luteal phase defects were evaluated by late luteal phase timed endometrial biopsies in two consecutive cycles and dated according to the criteria of Noyes et al. [2]. Ovulation was treated by either clomiphene citrate, human menopausal gonadotropins or bromocriptine for hyperprolactinemia. Adequacy of therapy was evaluated by demonstrating a mature follicle by sonography [3] and also an adequate level of estradiol. The postcoital test was evaluated after at least 10 h after intercourse; an abnormality was considered if there were less than 3 sperm per high-power field with good linear progressive motion. The cervical factor was treated with either guaifenesin [4] or

high dose estrogen and human menopausal gonadotropins (hMG) [5, 6]. Women who had laparoscopies and were diagnosed with endometriosis were included only if it was felt that after fulguration or vaporization there was no disease remaining. Those having tubal occlusion or adhesive disease were only to be included if it was felt that the problem was corrected following surgery.

Semen analyses were performed using a Makler chamber. Men with extremely low motile densities  $< 2.5 \times 10^6/\text{ml}$  were eliminated from the study. TDI was performed at mid-cycle in the female partner with the timing based on follicular maturation studies using ultrasound, estradiol, and progesterone criteria. The pregnancy rates after 8 cycles were then determined in groups that appeared to have normal semen analyses during the previous two baseline specimens evaluated versus those with subnormal semen specimens.

In study two, 70 men with unexplained infertility but semen analysis in two consecutive measurements also considered normal were treated with TDI before considering in vitro fertilization. These men had hamster ova penetration test performed with a technique described by Yanagimachi et al. [7]. Similarly, the pregnancy rate was determined in the female partner of those males having normal hamster tests versus those who fell below the level of 10% of the eggs penetrated. Two inseminations per cycle were performed in each female.

### *Results*

The pregnancy results of the couples who failed to achieve a pregnancy after 8 months despite correction all female factors and subsequent treatment by TDI can be seen in table 1. The data do not support the initial hypothesis that a higher pregnancy rate is expected in men who had the lowest motile densities (during the initial 8 months). In fact, there were no statistical differences between the groups.

The data, however, do show that the motile density was not particularly predictive of a normal male in the sense that if this were a good indicator, we would not have found a high pregnancy rate in the group of failures during the first 8 months. There was, however, a respectable rate in both the subnormal and the normal males of 65 and 62%, respectively. Table 2 demonstrated that poor hamster ova penetration tests were not better than lower motile densities at predicting which couple would achieve a higher pregnancy rate following TDI.

In a group of 200 patients selected following the correction of all factors after 8 cycles and offered TDI but refused, there were 142 men considered as having a normal semen analysis and 58 men with a substandard analysis. A total of 34 patients achieved a pregnancy during the 8 months (17%) following continuation of the same therapy that had corrected all

*Table 1.* Pregnancy rates following therapeutic donor insemination correlated with the motile densities of the male partner in couples failing to conceive after 8 cycles of all female factors corrected

	Motile densities, millions/ml	
	WHO standards ( $< 10 \times 10^6/\text{ml}$ )	normal WHO standards ( $\geq 10 \times 10^6/\text{ml}$ )
Number of couples	15	73
Number pregnant	13	53
% pregnant	86.6	72.6

*Table 2.* Pregnancy rates during 8 cycles in couples conceiving after 8 cycles of all factors corrected according to whether the hamster ova penetration test was normal or subnormal (all men with normal motile densities)

	Men with subnormal hamster test	Men with normal hamster test
Number of couples	20	50
Number pregnant	13	31
% pregnant	65	62

the factors during the first 8 months. Fisher's exact test revealed no significant differences comparing TDI pregnancy results among the groups with normal or poor hamster ova penetration tests ( $p = 0.51$ ) or comparing the pregnancy results from TDI in couples with previous low versus normal motile densities ( $p = 0.21$ ).

### *Discussion*

It has been estimated that the male contributes to infertility in 40–50% of all cases; these figures, however, are based on WHO standards. The data presented herein do not challenge the fact that the male is a cause of infertility even when the motile density is not extremely high. What this study does challenge is the fact that the male can be identified by the

standard semen analysis. By demonstrating a high pregnancy rate following TDI in men whose semen specimens were subnormal vs. normal, whether it be motile density or the hamster ova penetration test, the data confirms that methods of evaluating male fertility potential cannot even predict the subfertile male who has failed to achieve a pregnancy after 8 cycles, even with all the female problems corrected. Thus, the results of this study underscore the need to find other tests that will better help us identify subfertile men. This study and its findings further emphasizes the extreme importance of identifying and correcting all female factors even in couples where the males who are thought to be subnormal since they may still achieve a high pregnancy rate after aggressive therapy of the female partner.

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