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Can abnormal semen parameters truly identify the subfertile male?

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INTRODUCTION

Normal semen parameters are frequently determined by establishing the mean values for a fertile group of men and then allowing two standard deviations from the mean to determine the normal range of low values. Most clinicians have seen pregnancies achieved despite very subnormal semen parameters in the male partners, but it is usually assumed that this is an exceptional case. The present study was designed to evaluate what lower levels for semen parameters (motile density, standard morphology and strict morphology) are able to distinguish the normal from subfertile male by choosing couples with a minimum of 1.5 years of infertility where a female factor is identified and corrected, and then determining the 6-month pregnancy rate in relationship to the various subgroups of couples determined by semen parameters. The male partner would not be treated at all during this 6-month period.

MATERIALS AND METHODS

General selection of female factors and treatment

The female counterpart had initially been diagnosed as having either anovulation, a luteal phase defect (LPD), cervical factor, or endometriosis. Anovulation was diagnosed by the presence of amenorrhea or by the failure of the patient to demonstrate a level of serum progesterone over 4 ng/ml despite careful monitoring in those women who did menstruate.

LPD was diagnosed by two consecutive out-of-phase endometrial biopsies obtained 12–13 days postovulation. The cervical factor was established if poor quality mucus existed at the time that a mature follicle was demonstrated by ultrasound (18–24 mm diameter) and serum estradiol level (minimum of 200 pg/ml).

Motile sperm density

A total of 281 consecutive infertile couples (infertile for a minimum of 1.5 years), in whom the female partner was initially found to have an infertility factor were selected for the study. Two baseline semen analyses obtained after 48–72 h from last ejaculation were averaged in the 281 men. The sperm count was measured using a Makler counting chamber. An additional requirement for inclusion in the study was that all female infertility factors be considered fully corrected. The number of pregnancies achieved within six cycles of correction of the female problem was ascertained.

To determine if motility density is a factor in rate of pregnancy, the couples were separated into five groups based on each male partner's motility density, ranging from <2.5 to $\geqslant 15 \times 10^6$/ml. These groups were: group 1 ($<2.5 \times 10^6$/ml); group 2 ($\geqslant 2.5-<5 \times 10^6$/ml); group 3 ($\geqslant 5-<10 \times 10^6$/ml); group 4 ($\geqslant 10-<15 \times 10^6$/ml) and group 5 ($\geqslant 15 \times 10^6$/ml), the first three groups are considered subnormal by World Health Organization standards.

Standard sperm morphology

A total of 145 couples with infertility (either primary or secondary) were evaluated in this study. Pregnancy rates in 6 months were calculated and compared to those with morphology $<50\%$ normal vs. those $\geqslant 50\%$. The groups were divided into those with motile density $\geqslant 10 \times 10^6$/ml and those below this value.

Strict sperm morphology

Two retrospective studies were conducted to evaluate 223 couples. In each of the couples there were two baseline morphology evaluations performed on the male partner. This was done to evaluate the correlation between sperm morphology and *in vivo* conceptions. In couples for whom all the female infertility factors were considered corrected, the pregnancy rates were determined and then correlated with results of

Table 1 Correlation of motile density and pregnancy rates during a 6-month interval

Motile density ($\times 10^6$/*ml*)	*Number of couples*	*Pregnancies*	
		n	*%*
<2.5	32	7	22
$\geqslant 2.5-<5$	13	9	69*
$\geqslant 5-<10$	31	25	81*
$\geqslant 10-<15$	34	27	79*
$\geqslant 15$	171	139	81*

*$p < 0.001$ compared to group 1

morphology evaluations in the males. A patient was considered pregnant only if there was evidence of a gestational sac by ultrasonography performed at 7 weeks gestation.

A second study was performed as a prospective investigation. A total of 34 couples with normal morphology and only $\leqslant 4\%$ were matched with infertile couples with $> 14\%$ normal morphology. In this group, all female factors were not corrected. After identifying a male with poor morphology of $\leqslant 4\%$, the next infertile couple where the male partner had a morphology $> 14\%$ was enlisted in the study; this latter group comprised the controls. χ^2 analysis and Fisher's exact tests were performed to evaluate the statistical significance of the results.

RESULTS

Motile densities

The number and percentage of pregnancies in 281 infertile couples during a 6-month interval (beginning from the first cycle in which all female infertility factors were corrected) were analyzed according to the motile densities of the male partners (Table 1). When the motile density was less than 5×10^6/ml, 36% (16/45) of the women conceived in comparison to 81% (191/236) when the motile density was $\geqslant 5 \times 10^6$/ml. When the comparison was made between couples for whom the motile density was $< 2.5 \times 10^6$/ml and those with motile density of $\geqslant 2.5 \times 10^6$/ml, a statistical significance was found in the number of pregnancies achieved ($p < 0.007$; χ^2 analysis and Fisher's exact test, as appropriate). No statistical differences were seen comparing group 2 ($\geqslant 2.5 \times 10^6$/ml but $< 5 \times 10^6$/ml) to any of the groups except group 1 ($< 2.5 \times 10^6$/ml).

Table 2 Correlation of 6-month pregnancy rates with Kruger strict test for sperm morphology and motile density (MD) (retrospective study)

	Kruger score (% normal)			
	≤4 (n = 28)	*5–14 (n = 119)*	*>14 (n = 76)*	*Total*
Group 1 (MD $< 10 \times 10^6$/ml)				
Total	18	45	35	98
Number of pregnancies (%)	10 (56)	15 (33)	8 (23)	33 (34)
Group 2 (MD $< 10 \times 10^6$/ml)				
Total	10	74	41	125
Number of pregnancies (%)	4 (40)	54 (73)	38 (93)	96 (77)

Standard morphology

There were 117 patients whose sperm motile densities were $\geq 10 \times 10^6$/ml; 95 had normal morphology and 83 female partners (87%) conceived within 6 months; 22 men had subnormal morphology and 18 female partners (82%) conceived within 6 months. There were 28 patients whose motile densities were $< 10 \times 10^6$/ml. Interestingly, all 20 men with normal morphology achieved pregnancies (100%), but so did 6 of 8 (75%) whose morphology was <50% normal.

Strict morphological criteria

The correlation of pregnancy rates in 6 months with sperm morphology was evaluated using the strict criteria of Kruger and colleagues[1] (Table 2). Included in the retrospective study were 129 pregnancies grouped for comparison according to morphological results as follows: 50% conceived when the morphology was ≤4%; 58% conceived when the score fell between 5 and 14% and 61% at >14% ($p = 0.45$ NS, χ^2 analysis). In the group with subnormal motile densities of $< 10 \times 10^6$/ml, it is interesting to note a statistically lower pregnancy rate ($p = 0.03$, χ^2 analysis) in the group with the highest score (>14%) compared to the group with lower scores of ≤4%. However, in the group with normal motile densities the opposite was seen in the 93% pregnancy rate in the group >14%, this was statistically better than the ≤4% group with a 40% pregnancy rate ($p < 0.007$, Fisher's exact test).

A significantly higher pregnancy rate overall ($p < 0.001$) was found in the normal group (46/125, or 77%) compared with the subnormal motile density group (33/98, or 34%). However, normal sperm morphology did

not reduce the detrimentral effect of subnormal motile density, since the 23% pregnancy rate in the group with subnormal motile density, but normal morphology had the lowest pregnancy rate of all groups, including subnormal motile density and subnormal morphology.

The prospective study produced similar results. The 41% rate of pregnancy after 6 months in female partners of men with subnormal morphology, despite not all female factors being corrected, compared to 29% in female partners of men with scores $>14\%$, further reduces the credibility of the use of morphological evaluation in predicting the subfertile male *in vivo*. The abortion rates in the female partners of men with low scores was 7% compared to 2% in those with normal scores (chemical pregnancies without ultrasound confirmation were excluded from this study). It would appear that these data do not support the strict criteria test for morphology as an effective method of distinguishing the fertile from the subfertile male *in vivo*. Sperm motile density seems to be a more reliable parameter for predicting male fertility potential.

DISCUSSION

It would appear that the motile sperm density does not distinguish fertile from subfertile men, except, possibly, when that value is extremely low ($<2.5 \times 10^6$/ml). These findings underscore the need to select other alternative tests that better evaluate the fertile potential of spermatozoa.

Paulson and Wacksman[2] previously reported a significant improvement in semen parameters in oligozoospermic men following clomiphene citrate therapy; the pregnancy rate, however, was only 23%. Since Check and Rakoff found some defect in all 10 partners of the 10 oligozoospermic men that they treated with the same clomiphene citrate regimen, they attributed the low pregnancy rate of the Paulson and Wacksman report to possible inadequate correction of some of the infertile factors in the female partner[3]. They did, in fact, report 90% pregnancies within 8 months of therapy and attributed the rise in success not only to improving the male factor, but to the concomitant correction of the female factor(s) as well[2]. However, the data from the present study cast some doubt as to whether the increased pregnancy rate was exclusively related to the treatment of the female, or perhaps totally unrelated to the male therapy. Similarly, doubts about the efficacy of varicocelectomy may be drawn and may explain the wide range of pregnancy rates reported (24–53%)[4].

Previous data by Jeyendran and co-workers[5] failed to find a useful predictability of sperm morphology for fertilization capacity with *in vitro* fertilization (IVF). The possibility that the large number of spermatozoa

in contact with the oocyte (at least 50×10^3) may overcome all but the most severe abnormalities, whereas since only 300–400 sperm reach the oocyte *in vivo*, abnormal morphology may serve a much larger role in male subfertility. Indeed, for many years sperm morphology has been considered the most important semen parameter to predict fertilization potential[6,7].

The importance of the present study was the fact that the female factors were meticulously corrected, so that a true assessment of male factor could be made. The morphological system used for this study followed World Health Organization (WHO) guidelines.

Kruger and colleagues[1] described a fertilization rate of only 7.6% during the IVF cycles in which normal morphology was $<4\%$ and the morphology index was $<30\%$; however, a 64% fertilization rate was reported when the normal morphology was $>4\%$. If such poor fertilization occurs *in vitro*, an *in vivo* pregnancy should be almost impossible. However, using $\leqslant 4\%$ as the cutoff for our *in vivo* study, there were 14/28 pregnancies (50%). These findings did not require the majority of patients to be at the 4% mark because had we used $<4\%$ as the criteria there would have been an even higher pregnancy rate ($10/19 = 53\%$). We allowed 1% higher because of the predicted greater difficulty in achieving *in vivo* pregnancy. In no instance where the test was $\leqslant 4\%$ did the morphology index, including slightly amorphous forms, show $>30\%$.

Oehninger and colleagues[8] evaluated the IVF pregnancy outcome in accordance with the strict criteria evaluation scores. Their data confirmed the original Kruger study, in that the normal ($>14\%$) group had 94% fertilization compared to only 44.5% in the poor Kruger group ($<4\%$). The normal group had a 44% pregnancy rate compared to only 8.5%/cycle in the lower group.

Although a statistical difference was found in our study in the $>10 \times 10^6$/ml group with normal morphology scores compared with $<4\%$ ($p = 0.007$, Fisher's exact test) and thus was similar to the findings by Kruger, the failure to demonstrate similar trends in the $<10 \times 10^6$/ml group lessens the credibility of the test, especially as a means to predict whether a given individual is fertile or not. Lowering the motile density seemingly negates the adverse effect of poor sperm morphology.

At least *in vivo*, a low morphology result does not ensure a true male factor problem. Correction of all female infertility factors, even if sperm morphology is very poor, is therefore strongly suggested. Sperm morphology, even using Kruger's strict criteria as the best semen parameter to distinguish the fertile from subfertile male, cannot be supported by these data.

These data indicate the need for the development of better tests of sperm function and physiology to better distinguish the fertile from subfertile male.

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