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MALE INFERTILITY

THE INVESTIGATION OF MALE INFERTILITY*

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How do we know if an investigation result is relevant to subsequent male fertility?

There are two ways doctors have tried to answer this question. Firstly the result of the test has been related to the time taken by the man to make his wife conceive. The second approach has been to compare the result with a control fertile population (for example, note how the control population has been defined in Table I). This latter method is the way most infertility has been evaluated and while the inferences may be generally true for a large population they are not necessarily true for an individual.

There are, however, problems with both of these approaches. Firstly it is difficult to identify an appropriate control population. Secondly conception depends, of course, on both man and woman, but this introduces another set of variables and there may sometimes be further confusion because of doubts about paternity. As if all of this is not difficult enough many of the laboratory investigations are of questionable accuracy.

These multitudinous variables create one of the most interesting and perhaps most complicated problems of data interpretation in medical practice. It is for this reason that it has been so difficult to evaluate laboratory investigations of male infertility and so easy for arbitrary diagnoses to be made which have little to do with fertility. For example "oligozoospermia" is not a diagnosis but is a description of findings from semen analysis. Most clinicians find it difficult to give an exact prognosis to a man with oligozoospermia, and in most cases we do not know the cause.

In order to illustrate the problem let us examine more closely two widely reported measurements from standard semen analysis[1]: sperm density and sperm mor-

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phology. Different laboratory technicians report a wide range of values when counting sperm from aliquots taken from the same sperm samples. The coefficient of variation of 41.7% which has been reported from such a study would be unacceptable for any other laboratory technique[2]. Evaluation of sperm morphology is time consuming and allows a label of teratospermia to be applied to some samples, but does this relate to fertility? In reality there is a wide range of different normal morphology for human sperm — a feature we share with gorillas — and what is normal or abnormal in any one sample is highly debatable.

TABLE I

Comparison of Sperm-agglutinating Activity in Serum and Seminal Plasma between Fertile and Infertile Men when the Samples are tested by the Tray Agglutination Test (TAT)[5]

	Serum TAT titer		Seminal plasma TAT titer	
Group	A	B	A	B
No. of men	151	645	52	378
No. agglutinations	137	518	52	310
4	2	2	5	
8	8	25	22	
16	3	19		4
32	1	20	14	
64		15	10	
128		10	6	
256		13		3
512		9	1	
1024		4		1
2048		11		2
	A v B $p < 0.001$		A v B $p < 0.01$	

Group A are men attending requesting vasectomy. In all cases these men claimed fatherhood of at least two children and at the time of testing they had at least one child under the age of two years.
Group B are men who are complaining of a marriage with primary infertility.

When multivariate statistical analysis is applied to the semen measurements we get surprising results. If we wish to advise a man about his fertility based on the semen analysis we get little or no information from measuring sperm morphology, little information from measuring sperm volume unless it is very low (<0.5 ml), and the chance for future fertility only deteriorates substantially when the numbers of sperm are much lower than currently accepted limits (Table II).

TABLE II

The Percentage Chance of Conception in the Next Year (normal wives)

Azoospermia		12	24	48	96
Sperm present		0	0	0	0
	Motile Density				
	0	0	0	0	0
	0.5	16	12	9	6
Millions of motile	1	25	19	14	9
sperm/ml	2	34	26	19	13
	5	36	28	21	14
	10 +	37	28	21	14

FSH measurement is a barometer of testicular damage and gives similar prognostic information to sperm density measurement. The assay techniques for FSH are some of the most accurate, applied to infertility clinic samples however and semen analysis, results backed by FSH measurements give surer information. Gonadotrophin and testosterone measurements are vital to confirm a diagnosis of pituitary insufficiency and are useful to monitor the effects of specific treatment. As screening tests these are useless, as the diagnosis of pituitary insufficiency and androgen insufficiency can be made on clinical grounds. Indications for gonadotrophin and testosterone measurement are delayed puberty, lack of virilization or testis atrophy.

Antisperm antibodies have been detected more frequently in infertile men compared with a control fertile population but controversy remains about their effect on fertility (Table I). Current methods of measurement[3] rely on agglutination or immobilization of donor sperm samples by serum or seminal plasma from the patient and these tests may be measuring a number of different antibodies of which only some are relevant to fertility. There have been many attempts to make more accurate assay procedures, eg the ELISA assay, but so far these are not clinically applicable because of problems with high background levels of activity. Agglutination tests give positivity in 20% of men attending our infertility clinic (Table I) and if these antibodies are in fact relevant to fertility then this group of men may represent one of the largest potentially treatable male problems.

There is increasing realization that current seminology techniques give little prognostic or scientific information, and there is a search for other ways to assess fertility. Two new tests are worthy of mention. The first is the hamster egg test where the fertilizing ability of sperm is judged by their ability to penetrate hamster eggs from which the zona pellucida has been removed[4]. The zona pellucida is the species-specific barrier which surrounds the ovum. The second type of test involves accurate measuring of constituents within spermatozoa. Flow cytometry measurement of DNA gives indication of the numbers of sperm as well as quality. These two new tests are important because in one case we are measuring something that has not formerly been possible, namely fertilizing ability, and in the second case there is an enormous improvement in accuracy. The results of these new tests have yet to be evaluated in relation to the clinical outcome in terms of pregnancy and the place of these new tests in the infertility work-up has yet to be defined. There is, however, a need for better tests for male fertility, and the current hope is that these new techniques may in part fulfill this need.

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