Correspondence

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DNA probes or microvillar enzymes or both for prenatal diagnosis of cystic fibrosis

SIR,

Now that at least two DNA probes tightly linked to the cystic fibrosis (CF) gene are available,^{1,2} it makes sense to offer first trimester prenatal diagnosis to high risk couples when this is possible. The question that has to be considered is whether this should be combined with second trimester diagnosis based on measurement of amniotic fluid microvillar enzymes.³

In the most favoured situation a pregnancy will be fully informative for DNA analysis. This means the availability of DNA samples from both parents and an affected index child, a phase relationship that is unambiguous, and enough time to work up the family before chorionic villus sampling. If recombination frequencies between pJ3.11, met, and the CF gene remain as low as reported,^{1,2} DNA based prenatal diagnosis will be more accurate than that using microvillar enzymes. Posterior odds on either an affected or normal fetus will be sufficiently high to enable clinical decisions to be made immediately. The advantages of a first trimester termination of pregnancy are so great that they probably outweigh the possible benefit of being able to confirm the diagnosis on an abortus after a second trimester termination.^{3,4} If a fetus is deemed to be normal after DNA diagnosis, microvillar enzyme analysis two or three months later will either confirm already substantial odds or throw the whole situation into hopeless confusion. I believe that the temptation to 'make assurance doubly sure' should be resisted.

At the opposite extreme are those cases where DNA based methods cannot be used. There may be

no living affected child for phase determination (my estimate from our prenatal series is 20 to 30% of cases), or both parents may be homozygous for all the markers, or the work up may be started too late. Here one would obviously go straight to 17 or 18 week amniocentesis.

A more difficult situation arises when a pregnancy is only partially informative for DNA analysis. Even when using two markers, each with two alleles, there are a surprising number of these, including, for example, a quarter of pregnancies where both parents are each heterozygous at each marker locus. The common feature of these partially informative pregnancies is that a chorionic villus sample will either show the fetus to be unaffected or to have a 1:1 risk of CF (assuming, of course, that we are only dealing with pregnancies with prior odds of 1:3). What should we do in the latter case?

At first sight the sensible thing seems to be to let the pregnancy go to the second trimester and then do an amniocentesis. Much depends on the sensitivity and specificity of microvillar enzyme analysis. If, as I estimate, there is a false negative rate of 5% and a false positive rate of 5% at 17 or 18 weeks of gestation, the odds on a normal test indicating an unaffected fetus are 19:1. Lower sensitivities will decrease these odds (table). But even at 19:1, there is a 5% recurrence risk of an affected infant. Many mothers, having undergone both first trimester chorionic villus sampling and second trimester amniocentesis, will regard this degree of reassurance as less than adequate. They should be made aware of these facts before the first trimester prenatal diagnosis is attempted.

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TABLE Posterior odds after microvillar testing of a pregnancy with a 50% chance of a CF child.

Microvillar sensitivity (%)	Microvillar specificity (%)	Posterior odds on	
		Affected fetus	Normal fetus
95	90	9.5:1	18 :1
95*	95*	19 :1	18 :1
90	95	18 :1	9.5:1
90	90	9.5:1	9.5:1

*Most likely sensitivity and specificity.

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