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Commentary: Preimplantation diagnosis raises a philosophical dilemma

J A Raeburn

Preimplantation genetic diagnosis followed by implanting healthy embryos offers high risk couples the option to decrease the risk of disease in their offspring without the dilemma of a prenatal diagnosis which may be followed by a termination of pregnancy. If the technology of preimplantation diagnosis were easy or inexpensive (which it is not) the approach would supplant prenatal diagnosis for several single gene disorders.

Ethics and basis of test

In principle the ethics of selecting healthy embryos to implant do not differ from those of early prenatal diagnosis with the selection of unaffected fetuses. However, because genetic tests before implantation can remove the need for abortion they are a preferred approach for couples who are offered the choice (L Jenkins and J A Raeburn, unpublished data, 1994). Cui *et al* describe and evaluate the technology required to carry out preimplantation diagnosis of cystic fibrosis in carrier couples (who have a one in four risk of having affected offspring).¹ The general reader does not require detailed knowledge of the relevant technology and scientific principles but ought to be aware of the possibilities and implications.

The basis of preimplantation testing is that single cells are obtained by biopsy from pre-embryos formed in vitro. The relevant gene sequence is then amplified by the technique of polymerase chain reaction, in which oligonucleotide sequences of about 24 bases long—which flank the relevant part of the gene—are used to amplify both the common cystic fibrosis mutation, $\Delta F508$, and the normal gene sequence. If the pre-embryo genotype is homozygous normal the two copies of the normal sequence in the cell (one copy from each parent) will be amplified. If the pre-embryo is of carrier genotype both a normal gene and a cystic fibrosis gene will be present and both will amplify, producing a mixture of normal and cystic fibrosis sequences. If the pre-embryo is abnormal (homozygous for the cystic fibrosis gene) only the cystic fibrosis sequences will amplify. Cystic fibrosis sequences are

clearly distinguishable from normal by having a three base pair deletion, which leads to a different electrophoretic mobility.

Carriers are not "abnormal"

The wonder of polymerase chain reaction techniques, and the likeliest cause of error, lies in the ability to amplify a single copy of the relevant sequence rapidly. Thus, though single cells contain only one copy of the gene conformation from each parent—or at the most two copies of each if DNA synthesis has occurred—polymerase chain reaction can in a few hours replicate with precision the target stretch of DNA by as much as a millionfold. The danger is that the pre-embryo cell could be contaminated with other DNA, thus invalidating the amplification procedure (and the whole test). To minimise this error Cui *et al* (backed by mathematical models) have analysed the effect of contamination in different circumstances. The risk of fetal misdiagnosis would be lowest if only identified normal homozygotes were implanted.

Therein lies the dilemma. Heterozygotes for cystic fibrosis mutations are not "abnormal," as would be implied by any decision not to implant them. Thus preimplantation testing carries the danger of discrimination. Selection before implantation is so straightforward conceptually that it could easily lead to "technological stigmatisation." Should we select only normal homozygotes, or should we counsel couples that in a small percentage of situations carrier embryos may not be distinguishable from abnormal?

BMJ readers will have strong views about this because all are heterozygotes for recessive mutations which in the homozygous state could be lethal. Well informed couples may or may not choose to accept some low degree of risk of having a cystic fibrosis pregnancy. That decision must not be based on technological aspects alone.

¹ Cui KH, Haan EA, Wang LJ, Matthews CD. Optimal polymerase chain reaction amplification for preimplantation diagnosis in cystic fibrosis ($\Delta F508$). *BMJ* 1995;311:536-40.