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Genetic screening of in vitro fertilization (IVF)–embryo transfer (ET) patients

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Although it is not customary that a couple undergoing investigation and therapy for sterility is also screened for genetic defects, such an approach might be envisaged in IVF–ET for several reasons:

1) The procedure is time-consuming and expensive not only for the couple concerned but also for society and for the scientific community. Much research is still being done to improve the techniques and a lot of money has been spent already since the first experiments were started[2]. Therefore, it could be argued that there are more important issues to spend money for than IVF–ET. But the wheels cannot be turned back, and we have to face the facts and try to make the best of it. This means that, when IVF–ET becomes a routine treatment for sterility, risks should be kept as low as possible. This can be accomplished to a certain extent by genetic screening and selection of candidates.

2) Another argument in favor of a genetic evaluation of patients for IVF–ET is the psychological burden of this procedure for the prospective parents as well as for the physicians involved. This implies that there must be the greatest possible reduction of risk to the fetus, and this, again, can be accomplished by a genetic screening of the couple, among other measures.

Selection of patients for IVF–ET should consider the following genetical aspects:

1) Seriously debilitating multifactorial traits should not be present in the couple or in more than one close relative. Among common multifactorial traits some present serious handicaps, whereas others are of little medical importance. In some cases it is open to debate how serious the ensuing handicap is in personal and social terms. In these, the wish of a couple to conceive a child (even by means of IVF–ET) may be greater than their fear of the respective disease. Cleft lip and palate, pyloric stenosis, club foot and diabetes are examples of this type

of handicap. Other malformations, such as: hypospadias, congenital heart disease or neural tube defects, and systemic diseases, such as mental and neurological disorders (schizophrenia, affective psychosis, multiple sclerosis) should be regarded as contraindications for IVF–ET[6,7]. When there is a clustering of mental retardation in the respective families, and it is impossible to establish a diagnosis or an exact mode of inheritance, the couple should be alerted as to the possibility of mental retardation in their offspring.

2) IVF–ET should not be performed in a couple who has already had a child with an autosomal recessively inherited disease because of a 25% recurrence risk. In a consanguineous marriage with such a disorder in a close relative the risk for their offspring could also be substantially increased over population risk, and IVF–ET may be contraindicated under these circumstances. Most autosomal recessive diseases are severely debilitating disorders.

3) Dominantly inherited diseases are quite varied as to their disabling capacity. Therefore, decision for or against IVF–ET will depend on the appreciation on the part of the prospective parents of these factors, and also on the objective judgement of the treating or advising physician or geneticist[6,7]. A dominantly inherited syndrome of minor malformations without mental involvement – for example in one of the prospective parents – will certainly not present any difficulties in decision-making. Serious diseases such as neurofibromatosis Recklinghausen, tuberous sclerosis or porphyria, however, may offer considerable difficulties in arriving at a decision, especially because of their variable expressivity. Examinations and tests for microsymptoms are available for some of these disorders and should be performed whenever the suspicion of heterozygosity in one of the parents exists; this means when there is a close relative or familial clustering of the disease.

In dominant disorders with low penetrance, for example otosclerosis, generations may be skipped and a seemingly healthy parent can be a carrier of the gene. A careful family history and sometimes specific tests will help in the evaluation of carrier risk.

Dominantly inherited diseases with a late age of first manifestation present a particular problem. In the case of severe disorders, such as Huntington's chorea, myotonic dystrophy, cystic kidney, and polyposis coli, IVF–ET should probably not be performed if one of the parents is a potential carrier of the gene.

4) In a woman with a brother, maternal uncle or grandfather with a serious X-chromosomal recessively inherited disease, IVF–ET should only be performed when reliable tests for carrier detection exist. In the most serious X-chromosomal disease, namely Duchenne muscular dystrophy, only about 80% of carrier females can be detected, so these tests are not considered reliable enough.

If the husband suffers from an X-chromosomal recessive disease all his daughters will be carriers. So men with a serious X-chromosomal recessive disorder and normal capacity of reproduction (for example hemophilia) should not be granted IVF–ET because of the severe burden on a female of knowing that she is a 100% carrier of such a disease*.

When there is a family history of mental retardation one should be alert to the possibility of X-linked mental retardation. This recently newly discovered not too rare disease is – as a rule – transmitted from unaffected females to about half of their male offspring. Sometimes, however, males can be unaffected carriers and transmit the disorder via their daughters to their grandchildren. In some of these families a cytogenetic marker, the fragile X, can be found in a proportion of mitoses, and unaffected carriers can thus be identified[4]. This examination may sometimes be warranted before decision for IVF–ET is made when there is a family history of mental retardation affecting mainly males.

5) The danger of other chromosome abnormalities in children conceived by IVF–ET does not seem to be substantial. However, it is probably wise not to perform this procedure in women over 40. If it is done, prenatal diagnosis can be offered to these women as it is in normally conceived pregnancies. Prenatal diagnosis should actually be made available to all women undergoing IVF–ET to rule out chromosomal abnormalities induced by the procedure[1,3]. However, this is not considered imperative on the basis of experience so far with IVF–ET. If prenatal diagnosis is not envisaged for some reason, it would be wise to study the couple's chromosomes before initiating IVF–ET.

6) Although the problem of teratogenesis is not a genetic problem in the strict sense it is dealt with by medical geneticists almost everywhere in the world. Therefore, it seems to be warranted to mention a few situations where IVF–ET should not be done because of a known substantial risk to the fetus. Chronic alcohol abuse and regular consumption of drugs by the parents should alert the physician to the possibility of fetal damage, and IVF–ET should be denied to such couples[5].

Moreover, an epileptic woman should be tried on the least teratogenic antiepileptic drug compatible with her condition, and therapeutic measures for any other disease should be kept at a minimum when IVF–ET is considered.

* *Note added in print:* The rapid progress in the application of recombinant DNA to medical genetics has enabled many laboratories throughout the developed countries to detect carriers of some serious X-linked disorders with a very high probability.

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