Opinion on embryo research aiming to achieve pre-transfer genetic diagnosis for wich a moratorium was declared in 1986

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Opinion

After time for reflection provided by the moratorium, and taking into account scientific knowledge acquired in recent years, which has made it possible to gain a better understanding of the problems involved, the National Consultative Ethics Committee for Health and Life Sciences has reached the following conclusions :

1.Medical indications for a pre-transfer genetic diagnosis are exceptional for infertile couples who could benefit from in vitro fertilisation;

2.Couples at high risk of conceiving a child affected by a severe genetic disease can benefit from existing widely used prenatal diagnosis methods which have already proved reliable;

3.Pre-transfer genetic diagnosis would lead to misuse of indications for medically assisted reproduction and subjecting fertile couples to the constraints and hazards of these methods;

Research on embryos to be re-implanted may lead to serious impairment of the human genetic heritage.

As a consequence, the Committee reiterates the ethical considerations in its previous Opinion and recommends that pre-transfer genetic diagnosis should not be undertaken.

In a few years time, knowledge may have progressed and new possibilities arise which would modify the situation. It would then be necessary to reconsider what ethical rules should apply.

Report

In its Opinion dated 15th December 1986, the National Consultative Ethics Committee proposed a three year moratorium for research on the embryo.

The specific limited object of the moratorium must be kept in mind. The sole concern is research aiming to achieve pre-transfer genetic diagnosis, i.e. relating to chromosomes, genes, or gender.

The end date set for the moratorium was a few months ago, but no harm was done by delay since it gave more time for in-depth reflection.

A consideration of events during this period leads to the following conclusions.

Has the moratorium been observed ?

According to information received, it seems the moratorium was respected by French research teams. Their research programmes did not include as a priority subjects covered by the moratorium. In fact, they had more important problems to solve in order to improve medically assisted reproduction techniques which demanded a great deal of their attention.

Work done abroad on subjects covered by the moratorium

Some work on human embryos was done for the development of genetic diagnosis techniques :

- mostly research involving evaluation of sex determination techniques using surplus embryos. Two methods were tried : either DNA analysis after gene amplification, or nucleic acid hybridisation *in situ* with fluorescent probes able to recognise Y chromosomes on interphasic nuclei;

- in the field of single-gene disease diagnosis, some recent work based on an analysis of enzymatic activity (HGPRT) responsible for the Lesch-Nyhan syndrome, demonstrated that at the four or eight cell phase, enzyme activity is still of maternal origin. No work has been published on specific diagnosis for genetic disorders using DNA analysis of human embryonic cells.

As far as we know, there has been no application of single-gene disease diagnosis followed by re-implantation. However, quite recently (April 1990), there have been reports on the use of gene amplification and DNA analysis of the Y chromosome on human embryos *in vitro* for the purpose of gender determination followed by re-transfer of female embryos for women who are carriers of x-linked diseases.

Animal research in genetic diagnosis work

Sex determination

In animals, sex determination of the embryo before transfer is beginning to be used commercially, in particular for cattle. DNA analysis with a specific Y chromosome probe after gene amplification is performed on a sample of about ten cells taken from a six or seven day old embryo (blastocyst comprising about 120 to 200 cells). Results are available five or six hours after sampling so transfer the same day is possible.

Technically, results are satisfactory (80% of embryos are sexed) but costs are high which is the main obstacle to the method becoming widespread. Several industrial partners are in the process of grouping together to form a pilot unit in France. Freezing sampled embryos should contribute to the industrialisation of sex determination technology. Research on cows and mice, embryos of which withstand freezing, show that the survival rate of embryos removed by biopsy and then frozen greatly depends on their initial morphological quality.

esults become poor (survival rate as low as 10 to 20%) when embryos whose survival rate, without biopsy, is as low as about 50%.

The human embryo belongs to this latter group and biopsy before freezing is simply therefore a technical achievement.

Gene abnormality diagnosis

Several studies have shown that it is technically possible to diagnose a gene abnormality on the basis of a few cells taken from an embryo. However, there is no evidence so far that such a diagnosis can become routine followed by transfer of the embryo to a female host with reasonable chances of success. The example of the transgenic mouse, carrier for thalassemia major, is more than anything else designed to serve as a model for as yet hypothetical somatic therapy.

Direct chromosomal diagnosis (mouse)

Results are poor and in practice not applicable to human embryos. In attempts to overcome difficulties which make presently available techniques unreliable, several possibilities are being researched :

1. Development of in vitro culture techniques using one (or two) cells taken from the embryo so as to obtain a sufficient number of cells for a reliable diagnosis. In depth research is essential in this case;

2. Transfer of a cell from a whole embryo beyond the time frame presently used for reimplantation (about four cells) with the aim of sampling several cells for genetic diagnosis (as is done for bovine embryos). Co-culture methods would need to be used here and these have not yet been fully evaluated.

Human embryo genetic research with no potential individual benefit

Such research may be of medical interest, in particular in order to understand vast differences in development aptitude which have been observed in eggs of identical appearance after *in vitro* fertilisation.

However, the two following facts must be taken into consideration :

1. Differences that may be observed between several species of mammals and human beings in the first phases of development are secondary compared to common mechanisms which depend essentially on sequential use of information: maternal transcriptions, proteins contained in the oocyte before fertilisation. Differences are chronological in nature; developmental phases are identical : segmentation, activation of the embryonic genome, moving into differentiation, loss of totipotency, cellular organisation, withdrawal from pellucid zone.

Animal embryos (mammalian) are therefore good models for human embryos.

2. Events which lead to the first phases of animal development are not fully understood at present. Molecular aspects are only just beginning to be better known but the small amount of material which can be derived from each embryo is a limitation.

Research therefore requires the use of a great many embryos. Only a few mammalian species can supply demand : mice, guinea-pigs, rats, and perhaps rabbits and some

agronomic species. Therefore, researchers cannot claim to be doing fundamental research using only human embryos.

It has been noted, however, that in medically assisted reproduction centres, researchers are not generally concerned with scientific investigation based on the use of animal models. They compensate by offering projects which simply aim at making technical improvements as has been the case during the three years of the moratorium.

In this way, the human embryo becomes an instrument unnecessarily and in the long term this is detrimental to the prospects for research on the human embryo. The impending advent of new technologies such as nuclear transfer with a view to embryonic cloning induce strong feelings of rejection in public opinion whereas these technical instruments could have helped to better understand some essential problems.

Human embryo genetic research with potential benefit

What are the possible medical indications for genetic diagnosis before transfer ? We shall only consider indications which might be available in the near future, that is in practical terms those techniques which use DNA analysis after gene amplification using one, or preferably, several cells.

Gender determination for X-linked disorders

Progress in genetics over the last few years is such that it is possible, for a large number of x-linked diseases, to make a reliable prenatal diagnosis of the abnormality, thereby sorting normal and abnormal foetal males. Therefore gender determination as such is excluded since it would lead to an elimination of all males, normal or affected. This is the case for Duchenne's myopathy, hoemophilia, and other, rarer, diseases. Possible indications of using only gender determination for other x-linked diseases are becoming exceptional.

Specific diagnosis of gene abnormalities

Prenatal diagnosis of single-gene diseases has progressed considerably :

- firstly because of early chorionic villus sampling so that diagnosis at 10 or 12 weeks of pregnancy is now possible and early elective abortion can be performed;

- secondly because of progress in molecular biology, specific probes for mutations, and gene amplification.

As it turns out then, concurrently with research on pre-transfer diagnosis possibilities, safe and speedy methods of early prenatal diagnosis have developed so that in medical terms the question arises of whether pre-transfer diagnosis has much to offer particularly since its reliability when it is applied is not proven. Rules governing the application of a diagnosis technique are not identical to those governing research. Only totally reliable techniques can be considered.

It should also be noted that potential demand for single gene disease diagnosis is low because these are mostly rare disorders. In 1989, for the whole of France, about three hundred molecular biology prenatal diagnoses were performed. Potential demand for pre-transfer diagnosis would represent a tiny fraction of them, so that a maximum annual figure of only a few units is likely.

Convenience diagnosis

Gender choosing of a future child springs to mind. Chromosomal diagnosis based on chorionic villus sampling already provides sex determination at nine to ten weeks of pregnancy, i.e. within elective abortion legal limits.

Obstetricians and cyto-geneticians have found that such requests are exceptional and that the landslide effect that was feared has not occurred. Perhaps of course this is simply due to an ethical attitude on the part of physicians involved in such diagnosis. Care must be taken regarding possible consequences of excessive media attention given to research on pre-transfer gender diagnosis which could provoke an increase in demand.

One last point deserves attention

We refer to medical constraints attendant on pre-transfer genetic diagnosis which would lead to fertile couples using medically assisted reproduction techniques.

It would be a deviation of the indications for medically assisted reproduction if fertile couples entered into this hazardous and constrictive domain.

The medical situation would be the following : in the case of *in vitro* embryo diagnosis and re-implantation of embryos found to be normal, it is only in 20% of these cases that pregnancy will follow a normal course until delivery despite the fact that the implanted egg is normal. These are the (favourable) success rates for IVF-ET (in vitro fertilisation and embryo transfer) so that it is necessary to test a large number of embryos and freeze them in view of later transfers, in case of failure or intention to have a second child.

With *in utero* prenatal diagnosis as it is now performed, in the by far most frequent case of autosomal recessive diseases or x-linked conditions, in 75% of situations, the foetus is normal and normal pregnancy is followed by delivery of a normal child. In this way, instead of physical and psychological trauma due to prenatal testing and elective abortion, there would be physical and psychological trauma due to IVF-ET for a fertile couple who would be disappointed by a succession of failures.

We have found that workers in medically assisted reproduction centres are mostly cut off from genetic research and do not have a clear view of technical difficulties in the application of diagnosis methods nor of the genetic aspects of medical indications.

Efforts should be made to improve information and training in this respect.