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I. The moral status of the pre-implantation embryo

ESHRE Task Force on Ethics and Law

In this first statement of the ESHRE Task Force on Ethics and Law, the focus is on the pre-implantation embryo. This embryo is owed respect as a symbol of future human life. The basic ethical principles which govern the practical way embryos should be treated are outlined. Specific items of concern are pre-implantation genetic diagnosis, freezing, donation and research. The usefulness and safety of these specific issues, together with the ethical concerns, are presented with a view to protect the vulnerable infertile couple as well as the future child.

Key words: ESHRE/ethics/human embryo/moral status

Introduction

The creation of the Task Force on Ethics and Law was approved by the Executive Committee of ESHRE in December 1998. Its purpose is to evolve general ethical considerations which may be a useful reference for the patients and for the members of our society, while keeping up to date information on the legislation in different states.

The Task Force on Ethics and Law addresses the ethical aspects of the practice of medically assisted procreation. The initial document composed by the task force is put on the web for comment by all ESHRE members. After consideration of the reactions, the final document is prepared. This document is approved by the ESHRE Executive Committee before publication.

Basic principles

We wish to establish a code of ethical practice in assisted reproductive technology for all those who have a duty of care towards infertile patients, rather than to take part in a theoretical philosophical debate about the nature of the embryo. In our multicultural societies, respect of personal autonomy means both obtaining the participants' consent and the avoidance of references to religious beliefs concerning the nature and status of the zygote, the embryo and all the intermediary pre-implantation stages. It is essential to respect the personal convictions of all participants, the intended parents, which may include gamete providers, and the carers.

However, both in therapy and research, consent is not sufficient in the broader societal context. The issues, including their long-term consequences, need to be made public and evaluated periodically. It is in the public interest to establish boundaries that respect this special biological entity, the embryo, and reflect a responsible attitude, especially towards the child resulting from assisted reproductive technology. Thus the child's welfare and our responsibility are of utmost concern, as well as the respect due to the entity embryo because it is human and has a specific symbolic significance, before as well as after its implantation.

Nevertheless, we take into account the fact that this entity cannot achieve its potential to become a fetus and then, potentially, a child unless and until it is transferred into the uterus. Indeed, if there is no further development of this entity into a potential child because the in-vitro stage is not followed by an in-vivo stage, we think that, while aware of the different attitudes concerning the status and nature of the embryo which has led to much debate, it may be treated differently before and after implantation. In all cases we underline the respect owed to the human embryo. Because the entity embryo and the terminology used to describe the different stages of its development has led to several debates we start with definitions concerning these biological events.

Definitions

The term embryo (including pre-implantation, pre-embryo, conceptus, etc.) is often used for all the previous stages. The fact that the term embryo reduction is also used after 10 weeks of pregnancy adds to the confusion, as the transition from embryo to fetus is a matter of terminology.

We describe here an approach to the biological sequence of events according to our current knowledge. These definitions are based on in-vivo developments and may not necessarily reflect in-vitro events, but our concern in this first task is the embryo prior to its implantation:

- the zygote results from the fertilization of an oocyte by a spermatozoon;
- cleavage refers to mitotic division of the zygote and results in blastomeres;
- further cleavage to 12–16 blastomeres forms a solid ball of cells called a morula, about three days after fertilization. Its centrally located cells, called the inner cell mass, will form the embryo;

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- development of a cavity in the morula converts it to the blastocyst stage;
- gastrula: gastrulation and the formation of the triliminar embryonic disc follows;
- neurula: the neural plate is closing to form the neural tube;
- embryo has classically referred to the early stages of development, after formation of the embryonic disc in the second week until the end of the eighth week.

However, in order to avoid confusion and specialized terminology which may lead to uncertainty in the public mind, and with the knowledge that there are many other definitions for the entity resulting from fertilization during development to the fetus, we have decided to use the generic term 'embryo' which refers to the stages from fertilization to the formation of the embryonic disc. This is preferable to the term pre-embryo, as this terminology has sometimes been understood as representing a wish to lessen the symbolic value of this entity.

It should be clear that *in vivo* the embryo may perish, split into several entities, become neoplastic or progress outside the uterus, all of which prejudice its potential. However, the main point is that the pre-implantation embryo is human and deserves our respect as a symbol of future human life.

Thus, the following remarks apply only to the pre-implantation embryo or the embryo before it is transferred into a uterus, the actual step that may lead to the birth of the child. The semantic variations in legal definition of the embryo are a reflection of the principled arguments concerning this entity. They are summarized below.

Overview of the situation in Europe

We are aware that there is a lack of consensus at European level concerning the status of the embryo, reflected by the different national legal definitions given to this entity. The complexity of deciding on this status is in turn reflected by the fact that legislation in assisted reproduction techniques is absent in several countries, or does not give a legal definition of the human embryo. For instance, Belgium, Greece, Italy and Luxembourg are currently lacking legislation, contrary to Denmark, Finland, France, Ireland, the Netherlands, Portugal, Spain, Sweden and the UK. Furthermore, in countries where there is an explicit legal definition of the human embryo, this often varies considerably. In Austrian law, cells capable of development rather than the embryo are mentioned, defined as 'inseminated ova and cells developed from them'. German law defines the entity as 'the fertilized human egg cell capable of development, from the moment of fusion of the pronuclei', while in Spanish law the pre-embryo (the group of cells resulting from the fertilization of ovum until the implantation and formation of the primitive streak) is distinguished from the embryo (process of organ formation) and the fetus. Finally, the British legislation defines the embryo for the purpose of the Act as 'live embryo where fertilization is complete, including an egg in the process of fertilization'.

Items of concern in the practical field

Pre-implantation genetic diagnosis (PGD)

Usefulness and safety: the aim is to obtain the birth of a healthy child in a family at high risk of genetic disease, and to spare the woman the distress of a therapeutic abortion or induced premature delivery after amniocentesis. Furthermore, it may allow the screening of pre-implantation embryos at risk because of maternal age or a known high cancer risk.

From the existing limited experience, the technique seems to have an acceptable degree of accuracy and seems to be safe for the offspring.

The ethical concerns related to the technique of PGD are:

- the destruction of affected pre-implantation embryos: the purpose of PGD is to avoid the birth of diseased children or children who might develop serious disease later in life. We are aware that the main problem resides in the definition of what constitutes a serious illness. This is traditionally evaluated with regard to the illness's incidence and gravity, but increased knowledge of the genetic input in multifactorial diseases is going to render this assessment even more complex. Extensive genetic counselling and psychological support is mandatory;
- since in some cases the accuracy of the technique is not sufficient, some non-affected pre-implantation embryos are destroyed. This applies for instance in the case of sex selection for sex-linked genetic disease;
- in all cases, we are aware of the risks of abuse for non-medical reasons. Information and consent of the couple, public transparency and the respect of professional guidelines will limit abuse.

Pre-implantation embryo freezing

Usefulness and safety: the main professional concern in assisted reproduction technology is the achievement of healthy pregnancy (preferably singleton) and a healthy child. In view of the high number of oocytes retrieved with the current stimulation protocols and the high incidence of multiple gestation obtained with multiple embryo transfers, it is necessary to reduce the number of transferred pre-implantation embryos and thus it is useful to cryopreserve supernumerary pre-implantation embryos. There is no evidence that cryopreservation is not a safe procedure for the future child.

The ethical concerns related to the technique of freezing are:

- the inevitable loss of pre-implantation embryos which do not survive cryopreservation despite the best professional standards;
- the fate of frozen pre-implantation embryos if abandoned;
- the length of storage of the frozen pre-implantation embryos.

Considering that the cryopreserved pre-implantation embryo is not a full person and considering the pre-implantation embryo as a step to the achievement of a parental project, we do not object to the disposal of the pre-implantation embryo, to the donation to a couple in need or to the donation for research. Joint consent of both gamete providers is imperative in all cases. The disposition in case of disagreement will be discussed in the second statement of the task force.

Two main practical problems remain: continuation of storage, which should be linked to the continuing wish of both intended parents and its duration which should be linked to the biological age of the recipient of the frozen–thawed pre-implantation embryo(s).

Donation of pre-implantation embryos

Usefulness and safety: some couples may both be affected by total sterility, and therefore in need of pre-implantation embryo donation. Pre-implantation embryos specifically offered for donation may be given after appropriate medical screening of the donating couple.

The ethical concerns related to the technique are general to the donation of gametes and embryos (to be published at a later date) and specific to the donation of pre-implantation embryos. Confirmation of the couple's intention to donate should be obtained. After the end of the cryopreservation period, totally abandoned embryos may be destroyed or used for research, as long as the couple involved was forewarned of this eventuality. They should not be donated without specific consent.

Research

The embryos used for research can be divided into two categories: supernumerary pre-implantation embryos donated for that purpose by couples undergoing treatment, and embryos created for the specific purpose of being submitted to research, as for instance to test the viability of a frozen–thawed oocyte to fertilize.

Usefulness and safety: pre-implantation embryo research was necessary for the advent of IVF, and is necessary for the continuation of the care of infertile couples to an ever-improving standard. It is also useful in other fields linked to reproduction (e.g. contraception) and for fundamental research.

Research embryos should not be transferred to achieve a pregnancy. However, in the transition between research and therapeutic application of the technique, there must be reasonable indication that this technique will not harm the child to be.

Ethical issues linked to the technique: the creation and the possibility of research on pre-implantation embryos specifically created for the purpose is appropriate only if the information cannot be obtained by research on supernumerary zygotes. Embryo research should be preceded by animal research if there is a suitable animal model available. This means that, if this is not possible, one may have direct access to pre-implantation embryo research. After the end of the cryopreservation period totally abandoned embryos may be used for research as long as the gametes providers were forewarned of this possibility.

The 14 days limit for research on pre-implantation embryos is generally accepted because beforehand there is no fetal tissue differentiation, and after 14 days it would be difficult to find an acceptable limit. Nevertheless because it is arbitrary, it may have to be re-evaluated in specific cases.

Specific issues in research

Gene therapy

We accept the principle of somatic cell gene therapy.

Germ cell gene therapy is currently rejected by most authorities because of the fears of unforeseen iatrogenic genetic damage to future generations. However, if this method was the only possible way to cure a serious genetic disease, it could be explored in human embryos after thorough experimentation in suitable animal models and approval by the mentioned process of public transparency and scientific evaluation.

Cloning

There are two kinds of cloning: therapeutic, which may allow the generation of stem cells *in vitro*, with their potential ability to repair damaged tissues. Because of the potential in curing serious disease we consider this technique acceptable.

The second is reproductive cloning, which can be achieved by embryo splitting or by somatic cells nuclear transfer.

The ESHRE statement issued in February 1997 declared a 5 year voluntary moratorium on cloning human beings but indicated that research using human cells would be a necessary step following animal research, including mammals, on cell differentiation and nuclear cytoplasmic interactions.

Embryo stem cells

Embryo stem cells can be used for their potential ability to repair damaged tissues. They may come from aborted fetuses or research embryos. In the case of aborted fetuses the separation principle (i.e. separate consent for a termination of pregnancy and for the use of any tissue) should apply. The comments on research pre-implantation embryos and cloning apply to the second source. Because of the huge potential in curing devastating diseases the method is considered ethically acceptable.

Conclusion

The Society believes that the above described principles allow us to protect the vulnerable infertile couple, to allow them the optimal chances of becoming parents and protect the future child of this couple, while showing respect to all pre-implantation stages of the embryo.