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STEERING COMMITTEE ON BIOETHICS
(CDBI)

THE PROTECTION OF THE HUMAN EMBRYO *IN VITRO*

Report by the Working Party on the Protection
of the Human Embryo and Fetus
(CDBI-CO-GT3)

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Report on the protection of the human embryo *in vitro*

I. General introduction on the context and objectives of the report

Reflecting on ethical questions concerning the protection of the human embryo *in vitro* and the use of medically assisted procreation have formed an important part of the Council of Europe's work in bioethics for nearly fifteen years. The extent of this reflection is a measure of the complexity and difficulty of the ethical questions concerned, of the significant scientific developments that have taken place over that period, and of the evolution of opinion on these difficult matters.

In 1989, the Ad hoc Committee of Experts on Bioethics (CAHBI), the predecessor to the current Steering Committee on Bioethics (CDBI) issued a report on human artificial procreation. Although not a legally binding text, that report set out a number of principles that were useful as a source of guidance to member States in an area which was still at a relatively early stage of development.

In 1992, the CAHBI, and then the CDBI, began its work to develop a framework convention, setting out common general standards for the protection of the human person in the context of the biomedical sciences. That work culminated in the opening for signature of the *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine* (Convention on Human Rights and Biomedicine; ETS 164) in April 1997.

Article 14 of that Convention sets out the general principle of prohibition of the use of techniques of medically assisted procreation for the purposes of sex selection except in very restricted health-related circumstances. Article 18 of the Convention is a general provision concerning research on embryos *in vitro.* The general standards set by the Convention on matters such as consent, professional obligations and standards and the prohibition of financial gain from the human body and its parts, as such, would be as relevant to medically assisted procreation as they are to other health care interventions.

The need to undertake a more wide ranging reflection on questions concerning the protection of the embryo *in vitro* and the use of medically assisted procreation lead to the setting up in 1995 of a Working Party, chaired initially by Mr Jean MICHAUD (France) and then by Professor Daniel SERRAO (Portugal), to examine these questions. (The membership of the Working Party, as well as the experts not members of the Working Party who contributed to the report, can be found in Appendix IV).

To confront the different opinions on these questions and to contribute to the reflection to be undertaken by the Working Party, a symposium on medically assisted procreation and protection of the human embryo was organised on 15 – 18 December 1996 (see the proceedings of the symposium on the web site: http://www.coe.int/bioethics).

The birth of Dolly the sheep in 1997 lead to worldwide concerns about the possibility of the reproductive cloning of human beings. These concerns were addressed by the Working Party which was then entrusted with the task of preparing a draft additional Protocol to the Convention on cloning. The *Protocol to the Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings* (ETS 168) was opened for signature in January 1998.

After the symposium, to further assist the reflections of the Working Party, a comparative study of the position of the then member States, and those States having observer status with the CDBI on relevant issues was conducted and published in 1998 (see document CDBI-INF(98)8 *Medically assisted procreation and the protection of the human embryo: comparative study on the situation in 39 States; Cloning: comparative study on the situation in 44 States*).

Whilst on many of the issues covered by this report there is a broad consensus at European level, on other matters a considerable diversity of opinion exists, which makes it difficult to identify common approaches at the present time. In this context, the elaboration of a report on the protection of the human embryo *in vitro* was considered as a useful step to progress in the ethical discussion around these issues. The Working Party started the elaboration of this report in September 2002.

Its purpose is to aid reflection on these topics, by outlining the various existing positions on the subjects covered by the Report and the arguments on which those positions are based, without taking a stance on

the issues raised. The Report provides a brief introduction to the scientific issues involved as an aid to understanding of the ethical questions raised, but does not intend to provide a comprehensive scientific review of the relevant topics.

In developing laws and regulations concerning *in vitro* fertilisation, it is recognised that legal questions within the field of family law, for example concerning the parentage of a child to be born, will need to be considered. However such questions, which are beyond the scope of the protection of the embryo, are also beyond the scope of this Report.

The Report is organised in four main sections. The first section addresses issues of principle concerning the protection of the human embryo *in vitro* that are relevant to all of the topics discussed in this report. It is then followed by three sections discussing the issues raised respectively by *in vitro* fertilisation, by research on the embryo *in vitro* and by preimplantation genetic diagnosis.

II. General concepts

A. Biology of development

Fertilisation occurs 24 hours after ovulation in the upper segment of the Fallopian tube. The male and female pronuclei come together in the ovum, and the two sets of chromosomes – one from the male and one from the female gamete – join. The single-cell zygote then undergoes cleavage through a series of mitotic divisions. The first cleavage of the zygote occurs in the tube, 1.5-2.5 days after fertilisation (see fig. 1, in Appendix I).

The two cells (blastomeres) of the embryo possess equal potential for development, that is both blastomeres are totipotent. Each blastomere is still able to form an entire embryo and then a fetus on its own, with all cell types required for differentiation into foetal tissues and extraembryonic membranes after fertilisation. By 3-4 days, the multicellular morula is formed. Blastomeres in the mouse embryo are not totipotent after the 2-cell stage, but sheep and cattle blastomeres are totipotent even at the 8-cell stage, with human embryos perhaps intermediate. At all stages up to implantation, the human embryo is surrounded by a non-cellular transparent membrane, the zona pellucida. By 5 days the blastocyst is formed (see fig. 2, in Appendix I). A fluid-filled cavity (the blastocyst cavity, or blastocoele) is formed among the blastomeres. At one of its poles an agglomeration of cells is noted (the inner cell mass – ICM). The outer one-cell layer of the blastocyst forms the trophectoderm. Thus for the first time in the developing human embryo two different cell types appear: the functions of the trophectoderm are the nutritional supply and the implantation of the embryo, while the ICM contains all the cells that will generate the fetus. The cells of the ICM are pluripotent. They are not totipotent because they cannot make a fetus on their own.

At 6-7 days the embryo separates from the zona pellucida “by hatching” and begins implanting through the uterine epithelium and more deeply into the uterine wall. The trophoblast, differentiated from the trophectoderm, establishes contact with uterine cells and maternal blood vessels, building up the placenta. At the beginning of the second week the primitive (embryonic) endoderm cells separate from the rest of the ICM to line the blastocoele cavity. This primitive endoderm (hypoblast, an extraembryonic tissue) gives rise to the yolk sac endoderm (see fig. 2, in Appendix I). The remaining ICM cells are now called the epiblast or ectoderm.

During days 7-14 the blastocyst becomes more deeply implanted in the uterine endometrium. The amniotic and exocoelomic cavities are formed. The primitive streak is formed in the midline, at the posterior end of the ectoderm. The precursor cells of foetal endoderm and mesoderm split off from the ectoderm and migrate through the primitive streak. Gastrulation is characterized by the formation of three definitive embryo layers: ectoderm, endoderm and mesoderm which are required for further organogenesis.

B. Philosophical views on the “nature” and status of the embryo

The status of the embryo is fundamental to the ethical controversy about the protection to which it should be entitled. Different assumptions about the status of an embryo have led to different conclusions about the appropriate protection of the embryo *in vitro* both in terms of its starting point and its level. These different arguments have been combined in various ways. As a result of these combinations different moral positions

on the status of the embryo are defined. Four main moral positions can be identified. However, among individuals or groups that would broadly accept a particular position, there may be variations in the status accorded to an embryo, and hence the distinctions between positions are not necessarily as sharp as they might appear. Some people may therefore not recognise their own views in any of these four positions. Nevertheless, attempts are often made to draw clear boundaries, not least because such boundaries are necessary for the development of clear and enforceable legislation.

The four main moral positions on the status of the embryo

The two more opposite positions

They are both clear, simple and unambiguous.

In the first case, a fertilised egg is regarded as a human being. Therefore, in principle a fertilised egg, or an embryo, has inviolable value (as do all human beings), and a right to life. Therefore, nothing should be done to prevent, or make difficult or impossible, the further development of the embryo. If natural processes may jeopardise such further development, there may be an obligation to attempt to counteract such processes, in the same way that there may be an obligation to counteract life-threatening diseases of individuals. However, in the same way that there can be no obligation on a State to ensure implementation of all forms of life-prolonging treatment, such an obligation cannot be absolute.

Because each fertilised egg or embryo has equal value, it follows that any form of selection between individual fertilised eggs or embryos is impermissible. Those who support this position consider that in principle termination of pregnancy or embryo research that entails the destruction of the embryo would be unacceptable. The only possible exception may arise when the continuation of pregnancy poses a definite threat to the life of the mother.

In the other position the embryo is considered to have very little or no moral value. Hence, it is not considered to need any particular protection, nor would it be regarded as having a right to life.

In consequence, those who hold this position consider that in principle it may be acceptable to carry out research that may entail the destruction of the embryo. If, for some reason, a selection between embryos or fertilised eggs has to be made, it should be done on the basis of the interests at stake, and fertilised eggs as such have no interests; the interests concerned are those of the other stakeholders. Thus this position leaves the embryo without any protection.

The "gradualist" positions

Holders of these types of positions note that both the sperm and the egg are living entities before the fertilisation process, and consider that the fertilised egg is gradually developing into a human being. The embryo is considered to have significant, but not absolute, value. With regard to the right to life, a range of opinions may be held; some may consider that the embryo has a right to life, whereas others will refer to a right to develop.

Holders of gradualist positions consider that the rights of the embryo are reinforced in the course of the development process. Hence, other rights or interests, such as the health of the mother, may override these rights provided they are stronger. Critics of the position express concern that a gradualist position may undermine respect for human dignity and the equal moral value of persons because of the variable degrees of protection afforded to the embryo/fetus. In a gradualist position, if a selection has to be made between embryos for some reason, this should only be made on the basis of stronger and overriding interests.

As has been indicated, within the gradualist position different shades of opinion exist about the implications of the position for the protection of the embryo which differ on the period at which a maximum level of protection is granted. Two positions can be considered.

In the first case, as development is a continuous process, entitlement to rights and protection increases progressively throughout development, with full protection and rights being applied at the time of viability. The interests and rights of others should also be taken in to account, and hence there may be ethical dilemmas arising from conflicts of interests.

Therefore, under certain conditions it may be acceptable - for example - to use post-coital contraception, select between fertilised eggs, conduct embryo research and perform abortion. In clarifying the nature of those conditions sharp borderlines often need to be drawn (such as the stage of development after which embryo research is prohibited). Particular stages in embryonic development, such as the development of the primitive streak, have been retained as determinant criteria. However, some consider such conventional borderlines relatively arbitrary, given the continuous nature of the developmental process. Even the time of viability may vary depending on the technical assistance (such as intensive care) that may be available.

In the other position, as with the first gradualist position, entitlement to rights and protection increases progressively throughout development, but full rights are only achieved at birth. Again, the interests and rights of others may also be taken in to account and hence it may be justifiable to conduct – for example – embryo research. Holders of this position may find abortion acceptable at a later stage of pregnancy than would holders of the preceding position. Some people consider that the arguments used to support this position could also be used to support infanticide, and that therefore the application of this position may lead to a "slippery slope".

In conclusion, it can be seen that in most of the positions taken on the status of the embryo, the embryo is considered to warrant at least some level of protection.

These different positions are supported by various arguments based on, amongst other things, biology, potential, and personhood, which can be reviewed.

Basis of the assumptions

Fundamental to the assumptions about the status of the embryo is the question of when an individual life begins and when it begins to matter morally.

Arguments based on biology

This type of argument identifies a key point as the moment when a unique human being begins to exist. At the moment of fertilisation a new unique entity, in particular with regard to its genetic make-up, exists. For some, it is from this moment on that reference can be made to a unique human being.

Others considered that the defining moment comes later in development. During a certain period that ends approximately fifteen days after fertilisation and before the appearance of the primitive streak, the embryo subsequently develops in a manner that could lead to the formation of one, two or three individual embryos. Those who hold this position consider that it is only at the end of this period when the embryo has lost this potential, that reference can be made to a unique human being.

Those taking the first position argue that whether a genetic identity is ultimately shared – for example by twins – is not important, given that it is already clear that at least one individual human being with a unique genetic identity is in the process of development.

Also, given that the proportion of pregnancies which lead to a monozygotic multiple pregnancy is only a small fraction of all pregnancies, it can be argued that it is disproportionate to focus on the abstract possibility of such an outcome when it will not be relevant in the great majority of cases.

Philosophical arguments based on "potentiality"

At the basis of these types of argument is a view that an embryo and a human being at a later stage of development may be considered different but are related through development. However, from this position different arguments can be developed, which may even be in opposition.

One argument suggests that whilst an embryo and a human being at a later stage of development ("a person") may be considered different, the embryo has the potential to become a person. Because it has this potential, it should be respected as if it was already a person, and hence selection between embryos for the purposes of determining which should have the chance to live (for example, by being placed in the uterus in *in vitro* fertilisation) would be as unacceptable as a corresponding selection among persons.

On the other hand, others would stress that if “a” has the potential to become “A”, they are not ontologically the same. They would therefore argue that just because a has the potential to become A does not mean that we should treat a as if it was already A.

Further, in nature many fertilised human eggs do not implant successfully in the uterus. Given the frequency of such natural loss, it could be argued that it is incorrect to suggest that all fertilised eggs are potential human beings, as this takes no account of the actual probability of such an outcome. However, the fact that nature may appear to provide limited protection for a fertilised egg or early embryo does not necessarily mean that we should take the same approach. Man is a moral agent, whereas nature is not.

Implantation in the uterus is only one of the events that have to happen if an embryo is to fulfil its potential to become a person. Some of these events reflect the process of natural development, but others may depend on the existence of technical support – such as surgery or neonatal intensive care – to enable the fetus to survive.

Arguments based on personhood

In these arguments, “mere” membership of the human species is distinct from the concept of personhood. Here, the term personhood is being used as a definition of a member of the human species worthy of moral respect. This implies that membership of the human species is insufficient as a basis for moral respect, but that some additional qualities are required.

Such a viewpoint has the implication that there might be two categories of members of the human species, one of which could be used, or instrumentalised, for the benefit of the others (i.e. for the “persons”).

Within such approaches, the nature of the additional qualities required for personhood is clearly central. Given that the qualities are to be used as the basis for according moral respect, it may be considered that the relevant qualities must themselves have a moral basis. For example, a distinction made on the quality of “height” would be inappropriate, as it is difficult if not impossible to see why a person’s height of itself should make a moral difference as to the treatment to be accorded to the person. Stronger justifications could be made for qualities such as “autonomy” considering that autonomy may be the basis for the moral judgments made by an individual, and hence enables the person to act as a moral agent.

However, members of the human species could not be considered to attain any complete autonomy until a considerable time after birth. Further, some individuals may never acquire complete autonomy – for example persons with profound learning disability. Other individuals may develop such autonomy, but as a result of disease, such as dementia, or a severe head injury, may subsequently lose it partially or completely.

Such an approach clearly has wider ramifications than the appropriate treatment of the embryo and fetus. If being entitled to moral respect were equated with entitlement to legal protection, the legal implications would be of considerable complexity. It can also be argued that such an approach fails to respect the most vulnerable members of society.

In contrast, others argue that all human beings possess human dignity, which is worthy of moral respect, by virtue of being human. Although all those taking this position would agree that living, born human individuals possess human dignity, differences of opinion exist as to whether, or at what stage, an embryo or fetus possesses human dignity. Some of these differences derive from the biological arguments about the existence of a specific individual as discussed above.

Finally, other positions based on the identification of a clear point when an embryo or fetus becomes morally worthy of protection derive from several cultural traditions which refer to “successive animation” of the embryo and fetus. Although the details of such approaches are beyond the scope of this report, an illustration of the approach would be the belief that an embryo/fetus is animated by a series of progressively higher souls throughout its development. Another interpretation argues that “successive animation” should not be equated to chronological animation.

In some traditions, a further distinction has been made in which, for example, the intellectual soul is considered to begin at 40 days for males and 90 days for females. It has been suggested that this distinction may have cultural roots in that the cultures concerned required women after birth to undergo 40 days of purification for boys and 90 for girls. Biological knowledge has however shown that development was a progressive process.

Embryo created by nuclear transfer

A more recent aspect of the debate concerns the very nature of the embryo. With regard to *in vitro* cloning of embryos to enable the development of organs and tissue from stem cells – independently of any position taken on the moral acceptability of this process – arguments based on the method used have been developed to counter the objection that embryos are actually being created.

It has been argued that an embryo cloned by the method used to create Dolly the sheep (cell nuclear transfer) cannot be considered the same as an embryo defined as the completed union of sperm and egg cells. The cloned embryo is the result of the introduction in an enucleated egg cell of the nucleus of a somatic cell and does not involve a fertilisation process with gametes. The view expressed then is that notwithstanding their development potential, the different origin of "natural" and "cloned" embryos means that they need to be considered differently.

On this view an embryo that does not arise from natural reproduction (or an imitation of it, as in *in vitro* fertilisation) would not be an embryo with the rights that may be attached to that status (as discussed above). Whether or not the product of cell nuclear transfer is an embryo is a key question in particular for those who have strict positions against any interventions on embryos *in vitro*. If the status of the embryo derives from its developmental potential, the status of a "cloned" embryo would be the same as that of a "natural" embryo. However, if its status depends on its originating from a "natural", albeit assisted fertilisation, as well as on its developmental potential, the status of a "cloned" embryo would be different.

If in fact a cloned embryo was not actually capable of developing into a born human being the situation might again be different. If the cloned embryo lacked full developmental potential, some of the arguments used to support the status of an embryo would be inapplicable, as would fears about the development of cloning for babies. However, some might have concerns about the use of egg cells in this way and consider this an inappropriate manipulation of fertility. At present, the many philosophical and moral questions raised by cloning have not been answered. Furthermore, scientific knowledge and technical expertise arising from work with embryonic stem cells derived from "natural" embryos, where this is permitted, may affect answers to some of the questions about stem cells derived from cloned embryos.

C. The protection of the embryo

Even if positions differ on the status of the embryo and the creation of embryos *in vitro*, there is general agreement on the need for protection. Measures taken to ensure that protection and the level of protection may however vary, in particular depending on the stage of development and on whether the embryo concerned is part or no longer part of a parental project. Furthermore, not all countries have adopted specific legal instruments. More detailed information on the protection of the embryo in specific circumstances is provided in the other sections of this report.

However, two positions can be generally identified. In both cases, measures provided usually offer protection of the embryo *in vitro* from the fertilisation stage onwards. The aim in general is to ensure optimal conditions for fertilisation and embryo culture, and respect for good medical practice (see Chapter III. *In vitro* fertilisation). One of the aims of protection is to ensure that the embryo is not subjected to experimental procedures that could damage it or put at risk its developmental potential.

In the first position, maximum protection is granted starting from the completion of fertilisation. Any manipulation of the human embryo *in vitro* that does not directly serve its preservation is prohibited. Creation of embryos *in vitro* for any purpose other than establishment of a pregnancy is also prohibited (see Chapters III. *In vitro* fertilisation and IV. Research). Such an approach precludes any human embryo research projects and derivation of embryonic stem cells. Furthermore, the removal of a totipotent cell capable of dividing and developing into an individual human being would be unacceptable. A cell from the 8-cell stage of the embryo has to be removed if preimplantation genetic diagnosis (PGD) is to be carried out. If such cells are regarded as potentially totipotent, PGD may then not be allowed. However, problems may arise if the woman is unable to continue with the parental project.

If at the same time termination of pregnancy is permissible, such a degree of protection for embryos is considered by some people as being disproportionate to the degree of protection accorded to the fetus after implantation.

In the second position, protective measures applied do not always imply such prohibitions. In these countries, other views are expressed for example with regard to preimplantation diagnosis (PGD), not least because the cells of the 8 cell stage embryo are not considered to be totipotent (see Chapter V. Preimplantation diagnosis). Furthermore, the number of embryos created by IVF in one treatment cycle may not be limited and embryos not transferred may be cryopreserved.

If the embryo is to be cryopreserved, specific protective measures aim at ensuring proper methods of freezing and thawing and uninterrupted supply of liquid nitrogen. Those embryos that are no longer part of the initial parental project and are not being donated for transfer to another couple may be subject to different measures of protection than those that are part of such a project. The measures may vary in different circumstances.

Cryopreservation of these embryos is usually limited in time. One argument given in support of such a decision takes into account the interests of the embryo itself, which is not to be cryopreserved but to develop. Even though this is not in the scope of the report, economic considerations may be relevant to such a choice. However, some people would question the legitimacy of such limitation and would favour permanent cryopreservation as a duty to the embryos to ensure that they are not destroyed.

In certain countries, these embryos that are no longer part of a parental project may be donated for research, which may include the derivation of stem cells. The measures provided to protect embryos donated for research (where such research is permitted) are aimed particularly at ensuring that the research aims are appropriate and that the embryos are maintained under appropriate conditions for as long as is consistent with the aims of the research project (see Chapter IV. Research). Permissible research aims are often strictly limited.

D. Commercialisation of the embryo and its parts

There is a well-established principle that a person cannot be bought or sold. In the same way that people are not generally regarded as a good it is difficult to see why an embryo should be so regarded.

To a certain extent, this principle has been extended to the human body, be it the body of a person alive or already deceased. In legal terms, the human body is classically considered as « *res extra commercium* ».

It could be suggested that liberal economic theory accepts the principle that all goods have a price. Hence, any human organ on embryonic stem cell used for someone's benefit should be paid for at a price proportional to the benefit. However, not everything that would benefit an individual or society, whether an object or a service, necessarily has a market price, and the usefulness of an object, even if necessary for a market price to exist, is not measured by its price, the latter being more directly determined by the rarity of the object or by its production cost.

The principle of non-commercialisation of the human body is stated in Article 21 of the Convention on Human Rights and Biomedicine as follows : "*The human body and its parts shall not, as such, give rise to financial gain*". The use of "*as such*" makes clear that technical acts (such as sampling, testing, storage or culture) on those items may give rise to reasonable remuneration. Similarly, when a tissue has been transformed by a process of work and skill in to – for example – an immortal cell line, that process of work and skill can be the subject of remuneration.

E. The destiny of the embryo

Independently from the principle of non-commercialisation, the question is raised as to who can decide over the embryo's destiny.

If an embryo *in vitro* exists, it is advisable to have legal clarity on the person or persons who may decide the destination of that embryo.

Although as was shown in Section II. B. above, there may be some disagreement about when exactly life begins, it can be argued that at the very least it can be inferred from the Convention that the embryo or its parts should not, as such, be commercialised.

In that respect, it should be recalled that contrary to an organ, tissue or cells coming from the body of a single individual, in the case of an embryo resulting from the fusion of gametes coming from two different persons, more complex questions would be raised with regard to the rights of those individuals.

The central involvement of those whose gametes have been used to create the embryo as part of a parental project means that whilst such a parental project exists, the interests of that couple in determining the use of that particular embryo will be greater than any interest others may have in that embryo. However, the State might choose to place limits to that control, for example by specifying a maximum period of storage in a cryopreserved state for an embryo. The reason for such limits might be, for example, that the state of scientific knowledge at the time is such that the safety of more prolonged storage for the embryo, or the effects of a prolonged storage period on a future child, is not known.

If there is no longer a parental project, the question of the rights to determine further use of the embryo will arise. As noted previously in this report, different views on the status of the embryo may lead to different conclusions about the protection to which it is entitled. Thus, the State may choose to limit certain uses of embryos in all cases – for example by specifying that embryos may not be used for research, or may not be destroyed. As a result of the general principles laid down by the State for the protection of all embryos *in vitro*, there may or may not be a range of options offered to the parent couple for the destiny of an embryo once it is no longer part of the initial parental project – for example disposal, donation for transfer into another woman, or use in research, within any possible constraints of the scope of the consent given by any third party whose gametes were donated and used in the creation of the embryo concerned for the parental project.

It would be possible to argue that once there is no longer a parental project, then the interests of each member of the parent couple in the subsequent use of the embryo are lessened, and the interests of others might be given a greater importance. Hence, there might be a greater role for others in determining the ultimate fate of the embryos. On the other hand, for an embryo to be used for a purpose with which the members of the parent couple did not agree – particularly if this was use in IVF by another person – would be likely to be highly traumatic for the persons concerned. It is therefore usually considered that the parent couple should have the right to choose the final fate of the embryo and its parts within the options laid down by the State.

Where a State bans the use of embryos *in vitro* for purposes other than procreation by the couple concerned, the question of commercialisation will not arise. Where the use of embryos for other purposes can be authorised, the principle of non-commercialisation can be dealt with as part of the authorisation procedure.

F. “Freedom of procreation” and instrumentalisation of women

The concept of “freedom of procreation”, which is sometimes used as a slogan, and questions concerning instrumentalisation of women, are not directly relevant to the protection of the embryo. However, they are relevant to the social context in which decisions about the protection of the embryo are taken. Further, they raise issues such as the right to non-interference in reproductive choices and the legitimacy of controlling access to medically assisted procreation (MAP), which have to be taken into account when considering the protection of the embryo *in vitro*. These issues will not be developed here but may be briefly mentioned considering their relevance to the general reflection around medically assisted procreation in particular.

One approach to “freedom of procreation” interprets it as a right to non-interference in reproductive choices. Arguments in favour of women’s moral rights to freedom of procreation have highlighted the possible consequences for a woman’s self-realisation and for her social situation of having a child early in life, or of having a child with severe health problems.

The social influences on women, and questions concerning social reforms to improve women’s quality of life, including economic and other issues that are relevant to the timing of procreation, are beyond the scope of this report. Issues concerning freedom of choice in the field of reproductive medicine, and of the impact of

progress in this medical field, are relevant to wider questions concerning women's self-actualisation, but cannot offer a comprehensive answer to such questions. Nevertheless, we can note that at present, lifestyles - such as balancing maternity with work - appear to be leading women in Europe to, on average, give birth at a later age than in previous generations. Similarly, the average age of women using IVF appears to be increasing. Because the risk of infertility increases with age, and the success rate of IVF declines with age (particularly over the age of 40), women may not be able to achieve their procreative aims.

As this report highlights, free and informed consent plays a central role in all ethical considerations, and in choices made about the use of techniques of medically assisted procreation (MAP). However, some have argued that social pressures on women may limit the extent to which their choice is "free", and have suggested that in some situations a woman could be instrumentalised by others. Other parts of this report highlight situations where there is a risk of instrumentalisation of women.

However, some would reply that, without necessarily having to recourse to the notion of "social pressures", the current way of life largely influences the decision of some women to delay maternity. While the possibility for young women to pursue their studies is viewed positively, other economic and social conditions, such as those concerning work or housing have a decisive impact in limiting the choice of when to have a child. Those supporting these views argue that efforts should be made to improve these conditions.

Concerns about the possible limits to women's free choice have highlighted the risks and constraints to women of assisted procreation procedures, which have to be set against the probability of a successful outcome of those procedures. Ensuring that appropriate procedures are in place to ensure that consent is truly free and informed, as discussed in Section V.D, helps to address such concerns.

International legal texts, such as the European Convention on Human Rights, refer to "the right to found a family" rather than the right to procreate. However, the question of freedom of procreation may be considered in the context of respect for private and family life.

Taking into account the distinction generally made with respect to human rights, the "freedom of procreation" as a possible right of both men and women, could be claimed as a more defensive - negative - right or as a positive right. In the first case, a woman or a man should be protected against interventions that inappropriately interfere in the process of reproduction without her or his consent. Such interference can occur directly or indirectly either by intervening in the process of natural procreation or, more commonly, by hindering access to MAP techniques. There is a well-established doctrine in both legislation and case-law to the effect that in order to be justified, any restriction on fundamental rights must fulfill a number of specific conditions, including the following: it must correspond to a legitimate aim (e.g. protecting another fundamental right), it must be necessary in a democratic society (or in other words fulfill a pressing social need), the means of restriction used must be proportional to the objective pursued, and the restriction must be provided for by law. On the other hand, a positive right would entail unlimited access to medically assisted reproduction, with in particular the resulting economic consequences.

International legal texts regard the right to found a family mainly as a negative right, and hence that restrictions on the right must be justified in accordance with the principles described above. Although such principles are relevant to decisions on categories of persons who may have access to the techniques of medically assisted reproduction, such texts are not seen as conferring a general right of access to medically assisted reproduction in the sense of requiring a State to make such treatment widely available. Generally speaking, the principle of equitable access to healthcare implies also that choices need to be made for a fair allocation of limited resources. However, some would argue that the concept of freedom of procreation, even if regarded as a negative right, also appeals for the solidarity of society with the case of those suffering from infertility.

In current national legal systems, a person's access to medically assisted procreation (MAP) is often subject to certain restrictions (see replies to the 1998 questionnaire on medically assisted procreation and the protection of the human embryo[1]). For instance, several countries restrict such access to heterosexual couples, denying it to single women or homosexual couples, while other countries permit MAP for the latter

[1] CDBI/INF (98)8 *Medically assisted procreation and the protection of the human embryo: comparative study on the situation in 39 States; Cloning: comparative study on the situation in 44 States*

categories. Without wishing here to go into the merits of either of these solutions, we might point out that restrictions on medically assisted procreation are much more numerous and widespread than those on natural procreation. The latter involve actual physical interventions and so are no doubt considered too intrusive to be anything other than exceptional, whereas MAP restrictions concern medical services provided by professionals, regulation of which does not impose the same level of constraint.

In conclusion, we can note that it is important that questions concerning the protection of the embryo *in vitro* are not seen in isolation. Rather, wider social conditions, and the opportunities and choices open to members of a society will need to be taken into consideration as forming a background to medically assisted procreation and the reflection on the protection of the embryo**.**

III. *In vitro* fertilisation (IVF)

A. Presentation of the procedure

In vitro fertilisation and embryo transfer (IVF-ET) is a medical treatment intended to restore fertility. Infertility is a disease of the reproductive system that affects the male, the female or both. Infertility affects about 10% of the reproductive age population in western societies. In these days, approximately 5% of infertile couples in treatment use IVF.

In vitro fertilisation (IVF) is usually the treatment of choice for women with blocked, severely damaged, or absent Fallopian tubes. IVF is also used to circumvent infertility caused by endometriosis or a male factor. Many programs also use IVF to treat couples with unexplained infertility or long duration infertility which has failed to respond to other infertility treatments.

IVF is a complex biological procedure in which we can identify four steps in the method:

Obtaining gametes

Retrieval of mature oocytes

In rare cases, oocyte retrieval can be carried out during a spontaneous cycle. Then, only one oocyte can be obtained. In most cases, it follows an ovarian stimulation during about 12 days with ultrasound monitoring and hormonal control to identify the most appropriate moment for the oocyte retrieval. An average of 9 oocytes are obtained per treatment cycle. However, this may vary depending in particular on the response to hormonal treatment. Almost 90% of collected oocytes are mature. Gametes may also be obtained from a donor in those countries where such donation is allowed (utilised in only 1% of IVF in these countries).

Hormonal stimulation allows the recovery of several oocytes which increased the pregnancy rate per cycle. However, it involves the creation of an embryo which may not be immediately transferred to the uterus. Furthermore, there is a risk of ovarian hyperstimulation syndrome and concerns have been expressed with regard to the potential risk of breast **or** ovarian cancer development.

A number of births have been reported from mature oocytes following freezing and thawing. This method is however still experimental. The possibility to conserve in particular ovarian tissues, in case of treatment leading to sterility (e.g. radiotherapy for cancer treatment), is considered promising but would require *in vitro* gametogenesis.

Obtaining and treating spermatozoa

Male gametes (spermatozoa) are obtained from the patient's partner or donor ejaculate in more than 90% of the cases. After collection, sperm is treated in the laboratory to keep and concentrate those spermatozoa with best mobility and normal morphology.
Spermatozoa can also be obtained by surgical means from vas deferens, epididymis or testes. In some cases spermatozoa are freeze stored prior to fertilisation. In 5% of the cases, spermatozoids come from a donor, in countries where such donation is allowed.

Fertilisation and culture of the embryos

In most cases, one or more oocytes and spermatozoa at an appropriate concentration (50.000 to 100.0000 per ml) are brought together. When spermatozoa are in insufficient number or are functionally deficient,

fertilisation can be assisted through intra cytoplasmic sperm injection (ICSI) (see Special IVF procedures below).

The process of fertilisation leads to the formation of a fertilised egg with normally two pronuclei, one female and one male. After 15 to 17 hours, the peripheral cells of the fertilised oocytes are eliminated to check the result of the process and detect possible abnormality (one or more than two pronuclei). The first cellular divisions of the embryo usually occur the day after. The embryo can then be transfer into the uterus or cryopreserved. The vast majority of embryos formed *in vitro*, that do not present polyploidy (more than two pronuclei and as a consequence too many chromosomes) and no other morphologically assessed anomalies (about 60%), are cultivated in artificial media and transferred to the uterus on the second-third day after fertilisation. In certain cases, culture can be prolonged for 3 to 4 days until preimplantation stage (blastocyst) (see special IVF procedures below).

Embryo transfer

Embryos formed *in vitro* are introduced through the cervix to the uterus. Ultrasound guidance can be used, in certain cases, for proper placement of the embryo in the cavity.

In order to minimize the risk of multiple pregnancies, the number of embryos transferred is generally two or three per attempt. However, this number may be increased to four in certain countries or reduced to one in few others. With the improvement of the techniques, the tendency is however to transfer fewer embryos. If not transferred in the first treatment cycle, the embryos are frozen for a future transfer, either if the treatment fails or if the couple wants another child. Some countries however, do not allow the creation of more embryos than can be transferred in one treatment cycle (see Section III.C).

IVF future development

Knowledge acquired and improvement of the different technical steps of the procedure has led to an evolution in IVF programmes. Currently, a decrease in the number of created embryos and in the number of embryos transferred can be noted, which has been made possible by the improvement of the ability to evaluate *in vitro* the implantation and development capacities of the latter.

Access to medically assisted procreation techniques, in particular IVF, continues to develop in the majority of European countries. However, it seems important to highlight, in this context, the importance of socio-economical aspects, which could contribute to disparities encountered between these countries – disparities that have another dimension if, beyond the European level, we consider a North-South perspective.

Special IVF procedures

Intra cytoplasmic sperm injection (ICSI)

ICSI is aimed at facilitating the fertilisation process in case of a male infertility problem related to a very low number of spermatozoa or functional deficit of the latter. A spermatozoid is injected into an oocyte specially prepared by eliminating the layer of peripheral cells. Spermatozoa come either from ejaculated sperm or from epididymis fluid or from testis biopsy, which may all have been previously frozen. The pregnancy rate after ICSI is about 30 to 40%. Embryo creation rates are 60 to 70% with spermatozoa coming from ejaculated sperm, 45 to 50 % for those coming from epididymis fluid, and 30 to 45% when testis biopsy is used.

Injection of germ cells (spermatid, spermatocyte), when spermatogenesis is blocked, remains experimental and much debated with regard to the risks for the future child.

Co-culture and assisted hatching to improve implantation success

Culture of embryos *in vitro* with embryotrophic factors can be prolonged until blastocyst stage. This enables the identification of embryos with development problem not kept for transfer. Among them, about 40% present cytogenetic abnormality. The implantation rate of the remaining blastocysts is almost doubled compared to transfer of an embryo two or three days after fertilisation. By diminishing the number of embryos transferred at that stage, it allows a reduction of multiple pregnancies.

Assisted hatching

Implantation requires the opening of the zona pellucida which envelops the fertilised egg (see figure 2, in Appendix I). In certain cases, the zona pellucida seems to thicken and to harden, making this process difficult. A hole created in the zona pellucida, either mechanically or chemically, seems to solve this

problem. However, further research needs to be done in this field to specify the indications and to improve the techniques.

Gamete donation

Sperm donation

IVF with sperm coming from a donor is usually considered in case of unsuccessful attempts with artificial insemination with sperm coming from a donor (male infertility) or in case of infertility problem in both man and woman.

Oocyte donation

It is mainly considered in cases of early menopause, following treatment affecting fertility, or abnormal gonad development often related to genetic diseases (e.g. Turner syndrome), successive failures of homologous IVF, and risk of transmission of severe diseases. Donated oocytes, in contrast to sperm and embryos, may not be previously frozen (see paragraph on cryopreservation).

The embryo created after oocyte donation may have then been frozen or just created, donor and recipient cycles being then synchronised. The pregnancy rate per cycle after transfer is around 20 to **4**0%.

Results of IVF

The results of IVF may vary according to the indications (Fallopian tube problem, male fertility problem, endometriosis, absence of ovulation, male and female infertility problems, etc.) and the age of the woman. Furthermore, results may also vary from one medical team to another and from one period to another with the same medical team. In this context, general statistics on IVF when it comes to evaluating the chance of success for an individual couple, may not be relevant. However, they are interesting for evaluation of the techniques in terms of general risks and efficiency.

The success rate of IVF is 20 - 25% pregnancy per oocyte retrieval. This success rate is similar to the chance that a healthy reproductive couple has of achieving a pregnancy that results in a live born child in any given month. When considering pregnancies per transfer, the success rates are on average: 25 - 29% for standard IVF, 26 - 30% for ICSI, 15 - 16% for standard IVF with previously frozen embryos and approximately 40% with donated oocytes.

The patient's age is one of the most determinant criteria influencing the success rate. Indeed, the implantation rate decreases with age: by almost 10% per embryo at 38 years old, to reach less than 3% at 42 years old.

Cryopreservation

Embryos can be cryopreserved in liquid nitrogen at -196º C in straw or glass flasks, for a period of several years. The majority of states that have regulations on this topic, allow embryos to be kept frozen up to five years. This technique has been routinely used for nearly 20 years with successful transfer, and avoids the need for further ovarian stimulation treatment and oocyte retrieval attempts. No harmful consequence to the resulting child caused by freezing and cryopreservation of embryos has been noted to date.

IVF team

IVF teams are usually multidisciplinary and combine in particular the different clinical and biological competencies and skills necessary to carry out the different steps of the procedure.

B. Critical discussion on IVF

The possibility of obtaining gametes - the man's sperm and the woman's oocytes - has made it possible to devise solutions based on medically assisted procreation for infertile couples who want a child or couples who have a risk of passing on a particularly serious disease to their children. Although artificial insemination in human beings has been practised for two centuries, the first *in vitro* fertilisation goes back a mere quarter of a century.

Fertility problems and difficulty in having a child have been recognised as calling for medical help and for the establishment of research and clinical institutions in this field. However, society, which is involved when new technologies are instituted and may have to provide financial resources, is not required to ensure totally unconditional access to these technologies. IVF has now become an integral part of clinical practice in

reproductive medicine in many European countries and all countries where IVF is provided insist by law on strict control and on specific conditions.

However, three major arguments have been expressed against IVF. One concerns the destruction of embryos resulting from embryo research carried out to develop and improve IVF methods. Two others make reference to “nature“. The first such argument opposes any form of technical interference in the “natural process“ of procreation. The second argument suggests that IVF provides a lower level of protection for an individual embryo than does “nature“. On this view, in “nature“ there is usually only one embryo per cycle that may potentially implant in to a uterus whereas in contrast in IVF several embryos are transferred to a uterus. However, it is probable that only one of them will actually implant and therefore, it is argued, the protection (in terms of protection of the potential for development) of each individual embryo is lower than that provided by “nature“.

But others note that the protection of the embryo provided by “nature“ is not absolute. “Nature”, from the perspective of the embryo, could not then be considered ideal. Hence, it may be possible to manipulate “nature“ to the benefit of mankind. It is interesting in this context to note that “nature“ also constitutes a reference point for the development and improvement of IVF, the aim of which is to get as close as possible to the optimal conditions offered by nature for the creation and development of the embryo. Furthermore, it has been stressed that if this technique is a means to respond to infertility problems, it does not treat their cause.

In the current critical discussion around IVF, other arguments are now developed which, besides the results, risks and benefits of the methods, take into account social context, in particular the evolution of the mode of life and its influence on infertility problems, as well as psychological aspects.

In the countries where it is allowed, fertilisation outside the body was developed as a therapeutic response to infertility situations that were previously impossible to remedy. Initially, IVF was used as an answer to sterility due to blocked Fallopian tubes: the gametes were brought together *in vitro* to achieve fertilisation and the embryos obtained were transferred. The use of hormonal treatment to stimulate ovulation and the monitoring of such treatment helps to optimise the egg harvest, the time at which the gametes meet in order to produce embryos and the synchronous preparation of the endometrium for the transfer of the embryo. The results of this practice have made it easier to decide when to use surgery in cases of sterility caused by blocked Fallopian tubes and to avoid operating and re-operating to no purpose.

Simplification of the method in both biological and clinical terms has made it possible to extend the indications for IVF to include the failure of treatment for other causes of female infertility such as endometriosis, certain types of ill-explained infertility and infertility caused by moderately serious male factors, particularly after the failure of artificial insemination.

A bare ten years ago, microinjection of sperm into the oocyte cytoplasm (ICSI), was to male sterility the therapeutic revolution that IVF was to sterility of tubal origin 15 years previously. It now enables nearly 70% of couples who only recently would have had to resort to an outside sperm donor to conceive a child which is biologically 100% their own.

However, when IVF and particularly ICSI are used to overcome an infertility (or subfertility) problem in men, women may be subject to invasive interventions despite the absence of a personal cause for an infertility problem. Although in many instances infertility problems whether of male or female origin, are felt as a “couple problem“, concerns have been expressed about such situations and the possible difficulties in ensuring full respect for the autonomy of the women and that she is really making a free choice to undergo the interventions.

Results

As a result of medically assisted procreation, nearly 2% of children in France, for instance, are born every year following IVF or ICSI, from nearly 7,000 couples. These results are considered by many people as real scientific progress, offering infertile or sub-fertile couples a fertility (ability to conceive per cycle) comparable to that provided by nature to fertile couples (who have already had a child). They could also be considered to reflect an ethical progress on the basis of the principle of beneficence, in relieving these couples of anxiety, supporting their autonomy in their desire for a child and sparing them any feeling of being different, and maximising benefits to what is considered to be a health problem.

However, with regard to these results, it is also suggested that the success rate of IVF is relatively low and is perceived as being associated with more and more difficulties by the couples over the course of a number of failed attempts.

Risks

It has been suggested that IVF entails risks for the women, in particular due to the hormonal ovarian stimulation treatment and in particular a higher risk of cancer. However, on the latter, scientific studies carried out so far have failed to demonstrate such implications and the knowledge acquired has enabled substantial improvement of treatment and limitation of its secondary effects.

More frequent premature birth and risks attached to such early birth have been linked to the use of IVF. It is argued however that IVF methods are not responsible. The two main reasons put forward are the more advanced age of women involved in IVF procedures and an increase in the proportion of multiple pregnancies. The latter should however now be more limited given the improved success of transfer which enables the number of embryos introduced in the uterus to be decreased.

There seems to be wider agreement however on the fact that not all prerequisites, in particular very limited preclinical studies, were fulfilled before ICSI was introduced in clinical practice. In that respect, concerns are currently expressed with regard to the potential use of non-mature spermatozoids (e.g. spermatid).

In general, the limited health related data on children born after such procedures have been a reason for scientists to suggest improved follow-up of those children, whilst being conscious of the need to prevent any stigmatisation.

One specific concern has been expressed regarding the health, and in particular the fertility, of children born from ICSI when this technique is used to overcome certain types of male infertility. If the infertility has a genetic cause, it is likely that a male child born as a result of ICSI will carry the same genetic abnormality. Hence that child will have to face the same fertility problems as did his father beforehand. Therefore, some have argued that it is wrong to bring a child in to the world that will have what might be regarded as a form of disability.

On the other hand, others consider that the problem does not affect the health of the child as such and methods may exist that would ameliorate the effect of the problem. Hence for them, the extent of the problem is not sufficient to justify interference with the autonomy of the parents in the desire to have their own biological child.

Finally, it has to be noted that the possibility to create an embryo *in vitro* opened the door to new techniques enabling intervention on and/or selection of the embryo as well as to research. This raises other related issues which are further developed together with the arguments supporting the different positions expressed in the following chapters.

C. Number of embryos created for IVF

IVF consists of fertilising *in vitro* the oocytes from the group of follicles developed after hormonal ovarian stimulation treatment. Current folliculogenesis physiology data suggest that ovarian stimulation treatment targets a set of follicles whose maturity is such that they have receptors essential for hormonal action. These follicles begin to develop nearly 70 days before ovarian stimulation by intra-ovarian mechanisms, about which little is known as yet.

The ovarian stimulation treatment does not therefore affect the ovary's reserve, since it concerns only follicles that have already begun to develop; in other words, it is not in itself likely to speed up the onset of the menopause.

But, this also means that:
- it is not possible to predict the size of the group of follicles that would develop for a given cycle;
- the quality of the oocytes and the number of oocytes harvested vary from one cycle to the next for the same woman subjected several times to the same ovulation stimulation treatment.

The number of embryos obtained[2] (see Section III. A) and their "ability to develop"[3], the receptiveness of the endometrium and hence the likelihood of a pregnancy and resulting birth of a child, are therefore difficult to predict precisely.

Several oocytes suitable for fertilisation are therefore harvested each time from an ovary from the group of follicles (oocyte retrieval) that has been stimulated for IVF. Their number depends on various factors, including the natural intra-ovarian mechanism which leads to the development of a certain number of follicles and the quantity of hormone given to the follicles already recruited.

It sometimes happens that the number of embryos obtained is larger than the number that can reasonably be transferred at the same time if multiple pregnancy is to be avoided, as multiple pregnancy may have tragic consequences for the couple concerned and the children, with a risk of a miscarriage, often at a late stage, or a somewhat or even very premature birth. The embryos that are not used for an immediate transfer may be cryopreserved after freezing (see Section III. A).

In certain countries (e.g. Germany, Austria), however, the law prohibits the creation by IVF of more embryos than can be transferred in one treatment cycle. Their number is then limited to a maximum of three embryos to reduce the risk of multiple pregnancy. To create more embryos is prohibited by penal law.

The possibility of freezing embryos means that there are, strictly speaking, no oocytes that are not used (unless some are not fertilised in order to avoid producing embryos), that would possibly be cryopreserved. The difficulty of estimating the fertilisation rate and therefore the number of embryos that will be obtained in advance means, however, that:

- either too few oocytes are used in the fertilisation procedure and the embryonic transfer rate or the pregnancy rate per transfer procedure is reduced;

- or that too many embryos are transferred, with the result that the couple is inevitably exposed to the risk of multiple pregnancy.

But in those countries where the number of embryos per cycle is limited, such as Germany, if more "embryos" are created, in small numbers, by accident they would be frozen before the fertilisation of the oocytes is completed. At that stage, until the complete fusion of the two pronuclei and termination of the fecundation process, they would not be considered as embryos, according to the definition in the law.

In the countries where cryopreservation of embryos is allowed, the possibility of freezing embryos with a view to their subsequent transfer applies in the case of nearly 94% of embryos. In these countries, it is required that couples be traceable and embryos be clearly identified in relation to the parent couple.
It should be noted that oocytes, unlike spermatozoids and embryos, cannot as yet be routinely cryopreserved without there being an unevaluated risk to the unborn child. Research is carried out however in this field which, if successful, would make it possible to limit cryopreservation of embryos.

The tendency today is to reduce the hormonal input used to stimulate the ovary and therefore the number of oocytes produced. The number of embryos transferred each time – even reduced to one in certain cases – tends also to be reduced, limiting thereby the risk of multiple pregnancy. However, the creation of more embryos than can be transferred at once is considered, where allowed, as good IVF practice, given the current state of our knowledge.

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[2] Fertilisation rate, ratio of the number of embryos obtained to the number of oocytes fertilised

[3] This is assessed optically, and sometimes also by prolonging culture of the embryo until it reaches the blastocyst stage of development

A remaining problem that is not solved by legislation nor regulation in several countries, is the time-limit that should apply to storage of embryos (see Section II. C).

However, other concerns are raised by the future of these embryos when they are no longer kept as part of a parental project. The fate of those embryos whose parents have decided not to go ahead is usually decided by the parental couple, in accordance with what is legally possible: the embryos may simply no longer be stored, they may be used for authorised research, or they may be donated to another couple.

It is the question of the future – outside of a parental project - of embryos created in large numbers by IVF with the aim of a higher success rate of the whole procedure, which led certain countries to favour the limited creation of embryos per treatment cycle. The question of the number of embryos to be created is then not considered primarily with a view to the success of the treatment and the individual needs of the couple, even if these needs are accepted as high ranking needs. Rather, it is considered from the point of view of general values in society (often claimed as based on the country's Constitution in particular) and of the assessment of the outcome for embryos that are not longer part of a parental project. The individual demand to have a child with the help of society, as understandable and morally acceptable as it is, is not considered as a strict negative nor positive right (see Section II.F.). Hence, in this context, the solidarity of society is not demanded on the basis of rights but only by more or less accepted compassion.

Aneuploidy screening

Where there is no limitation on the number of embryos created by IVF per treatment cycle, an appropriate number of these embryos can be selected with a view to benefit from the best likelihood of implantation and development. When carried out, such selection is done on the basis of observational criteria without any intervention on the embryos. However, in certain countries, in the case of women with a history of repeated miscarriages or IVF failure, a cytogenetic analysis, involving a more invasive procedure (biopsy of one or two cells), can be carried out to detect potential types of aneuploidy which would affect the ability of the embryo to develop or to implant.

Such aneuploid embryos contain an abnormal number of chromosomes, leading almost always to failure of implantation or miscarriage. In general, the frequency of aneuploidy appears to be rather high in human embryos, and increases with advancing maternal age. Aneuploidy may be identified in embryos *in vitro*, using the techniques of biopsy and fluorescent in-situ hybridisation (FISH). The aim of the procedure is to improve the success rate of IVF, and it has been shown to reduce the rate of miscarriage. The possibility to select embryos free from aneuploidy makes it also possible for fewer embryos to be transferred and therefore enables a decreased risk of multiple pregnancy.

However, although the technique has been implemented in a number of clinics around the world, it is still in the early stage of development. Furthermore, aneuploidy may affect some cells of the embryo but not all (mosaicism), leading to both positive and negative errors in diagnosis.

Ethical concerns have also been expressed with regard to such a screening procedure, in relation to the very principle of selection of embryos and to the actual invasive procedure involved (biopsy). In that respect, preimplantation diagnosis (PGD) and aneuploidy screening can be considered as being comparable in some respects, and argumentation developed around PGD be considered equally relevant to aneuploidy screening (see Section V.B). However, it has also been argued that a fundamental difference between both procedures would justify them being considered differently from an ethical point of view. Indeed, PGD is aimed at identifying a genetic condition in an embryo which may not affect its development in the uterus and the ultimate birth of a child, but could lead to a disease or disorder in this future child. Aneuploidy screening is aimed at identifying embryos which would, on the contrary, naturally not develop or implant and is therefore directly relevant to the success of the IVF procedure.

D. Information and consent

Respect for autonomy of persons is one of the fundamental ethical principles in medicine. It includes respecting the self-determination and choices of autonomous persons and protecting those persons with diminished autonomy. The rule of free and informed consent is directly linked to this principle. Article 5 of the Convention on Human Right and Biomedicine lays down the following basic rules on these points:

> "*An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it.*
>
> *This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.*
>
> *The person concerned may freely withdraw consent at any time*."

As pointed out in the Explanatory Report to this Article: " *This rule [of informed consent] makes clear patients' autonomy in their relationship with health care professionals and restrains the paternalist approaches which might ignore the wish of the patient*."

Article 6, paragraphs 3 to 5 of the Convention, adapts the requirements of information and consent to persons of full age who do not have the capacity to consent.

The request for free and informed consent is an integral part of the requirements applied to IVF.

However in this context several points can be stressed, in particular regarding the type and form in which information is communicated, as well as with the consent, including its scope and length of validity.

<u>Information</u>
It is agreed that informed consent requires prior communication of objective information in particular on the procedure, including a description of the entire process and of interventions involved and a forecast of its possible duration, the implications and risks involved, the expected results (in terms both of failure and success), as well as to possible existing alternatives.

Concerns have been expressed however in relation to the amount of information provided. This is the case in particular for information on the possible future of embryos which may be no longer kept as part of the initial parental project (e.g., in accordance with national legislation, the possibility of donation, research, end of storage). If it is agreed that such implications need to be referred to, concerns are expressed that, as they may not be directly relevant to the consent requested – indeed, consent would be requested for any decision with regard to the future of such embryos if the parental project ends - they might actually be a source of confusion. Hence, it is argued that the difference between this information and that directly related to the consent requested should be made clear to the person concerned and possibly be communicated at a different time.

In practice, further information is also given on legal provisions applicable, such as situations where the consent could be invalidated (e.g. separation of the members of the couple) or where authorisation by a judge would be required (e.g. sperm donation in France). Where appropriate, information on legal effects (e.g. in terms of filiation) is also provided.

The way and form in which information is provided is also determinant to enable the provision of free and informed consent. The rule of free and informed consent implies that any information be given in a non-directive way and in comprehensible terms to the person concerned. There is agreement on the need for the person who would be giving this information to have appropriate knowledge and skills to present it in clear and suitable words for the persons concerned.

With regard to IVF, a difference is generally made between the information which is common to all cases (the procedures involved in IVF, their chronology, the legal provisions etc.) and the information which is tailored to each individual situation and concerns clinical and biological aspects. If in practice the first type of information may be given in written form, this is usually not the case for the second category. The latter is usually communicated by a member of the medical team.

Independently of the information provided prior to consent, it is also agreed that during treatment the persons concerned also have the possibility to seek and obtain additional information and be informed of any developments and intermediate results in the procedure; in particular, where appropriate:

- the number of oocytes actually removed;
- the number of embryos obtained;
- the number of embryos to be transferred;
- the development of the pregnancy.

Consent

With regard to the consent, concerns have been expressed in relation to the form in which it should be given. In this respect, it has been argued that express consent in written form should be requested considering in particular possible disagreement between the persons concerned regarding alteration of the initial decisions or possible legal implications.

Furthermore, in accordance with internationally agreed principles, consent may be freely withdrawn at all times. However, professional obligations and standards may be relevant to the immediate action to be undertaken by the professional where such withdrawal would seriously endanger the health of the woman and/or embryo or fetus.

Consent is usually requested from both members of the couple concerned. However, due to her biological role in the procreation process, the woman will be much more physically involved in the procedure in being submitted to invasive interventions. Even though both consents are equally valid with regard to the IVF procedure as a whole, this might be seen as supporting a difference in practice in the way both consents might be regarded. In particular, an intervention on the woman's body would not be carried out without the woman's consent. This is particularly relevant when considering consent in relation to prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD). In the first case, the procedure would involved an invasive intervention on a pregnant woman whereas in the other the intervention is carried out on an embryo *in vitro*. In the first case, discussion would be primarily between the physician and the woman concerned. With PGD, both members of the couple would be involved and discussion will generally take place with the multidisciplinary medical team.

With regard to the future of embryos which would not have been transferred at the end of the parental project, it is agreed that the decision always remains subject to the consent of the parents who initiate the project, even if the embryo is not the product of their own gametes (in the case of sperm donation for example). However, embryo donation may be subject to some conditions that the couple should be informed about prior to the beginning of the IVF procedure.

The following outcomes may be considered, provided that they are permitted by law:

- embryo donation to another couple;
- permission to use the embryos in a biomedical research project;
- end of storage.

However, the difficulties which the couple could face in taking such decisions as well as the irreversibility of certain procedures once undertaken have to be acknowledged. Taking these elements into account, support has been expressed in favour of imposing a period of reflection between the communication of information in relation to the different outcomes, seeking consent and the time frame following consent in which such consent may be withdrawn.

E. Embryo "donation"

In certain countries, couples who went through an IVF procedure where embryos were created using their gametes have the possibility to "donate" one or more of these embryos to another couple for transfer. Such embryo "donation" is not authorised in certain countries.

In those countries where it is authorised, it usually only concerns embryos created by IVF for a parental project, that are no longer part of this initial project. However, in a few countries, creation of embryos for donation is authorised.

It should be noted that the concept of “donation” occasionally raises a problem as it entails the underlying idea of “property”. In France, for example, the choice was therefore made not to use the word “*don*” (donation) but “*accueil*” (reception).

Most ethical concerns expressed around “donation” of embryos are related to the respect for the dignity of the human being. It is argued that the practice could lead to the instrumentalisation of the embryos which could be considered as mere means to respond to infertility problems without treating the cause of these problems. In this respect, for the holders of this position, embryo donation is seen as increasing the ethical problems raised by sperm and oocyte donation, and creation of embryos purely for donation is considered by some totally unacceptable. For this reason, concern is also expressed with regard to the possibility of creating, by IVF, more embryos than necessary for the success of an IVF procedure.

Those supporting the principle of embryo donation oppose to such arguments, that “embryo donation” is in fact respectful of human dignity, and benefits the embryos in giving them the possibility to develop in appropriate conditions which are strictly defined, rather than destroying them (see Section III.D). For the holders of this position, provided that strict conditions are respected in particular for the protection of the future child, embryo donation could be considered as an alternative to embryo destruction while giving an acceptable answer to a couple with infertility problems.

In the countries where embryo donation is allowed, it usually remains an infrequent practice. In the United Kingdom for example, where embryo donation is allowed, many couples with infertility problems would prefer to receive a donated oocyte than a donated embryo.

If donation has often been viewed in a similar way as adoption, the fundamental debate remains in certain countries as to whether it should also follow the same legal regime – adoption could then be considered for any embryo- or if, on a legal level, it should rather be considered closer to gamete donation – with the possibility to define criteria to pair the donor and recipient couples.

The main conditions defined for embryo donation are the absence of financial gain, health protection measures and legal protective procedures. The prohibition of financial gain on all parts of the human body as such is a fundamental principle laid down in Article 21 of the Convention on Human Rights and Biomedicine. Couple are requested to go through a certain number of tests to check in particular the presence of certain conditions which could affect the future child’s health or the recipient woman and would therefore preclude donation. Finally, formalities are carried out to ensure that the legal terms of the donation and their consequences are known particularly in relation to legal filiation. Independently from the consent of the donor couple, the consent of the recipient couple (or woman in countries where donation to single woman may be permissible) is requested. Embryo donation often involves a decision by an authority or a guarantee that the relevant substantive and legal conditions are met.

Besides those conditions on which there is general agreement, the question of anonymity of the donation has recently been questioned. The anonymity of embryo donation is generally the rule. It is argued that respect of this rule is aimed at protecting both the donor and recipient parents as well as the future child as information on identity of the donor and recipient parents could only be a psychologically disruptive factor for themselves and the child. It is further argued that biological filiation is less relevant for the establishment of the parental bond and the development of personal identity than social filiation.

However, argumentation around anonymity has been developed supporting the opposite view on the issue. In that respect, a parallel can be drawn with the discussion on anonymity in the case of adoption. Two main reasons have been put forward against anonymous donation. The first one is the risk of psychological suffering for the child in the search for his or her origin. The second is based on the development of genetic applications for medical purposes and therefore the importance for the child to have access to information about his or her biological parents, including genetic details, which can be determinant for his or her health. Considering the importance of these data, those who support the principle of anonymity may also consider that access to non-identifiable information relevant to the health of the child.

IV. Research

A. Introduction to research on the embryo

The question of whether, and if so under what conditions, to permit research on the embryo *in vitro* is one of the most sensitive ethical questions that need to be addressed. At present, different member States of the Council of Europe have resolved this question in different ways. Other States are contemplating the development of legislation on this matter.

Although the question of the status of the embryo (discussed in Section II.B above) is fundamental to resolving the question of embryo research, in this section other issues that will also impact on the debate on embryo research are discussed.

B. The principle of "freedom of research"

It has been **said** that any regulation that restricts research simultaneously impacts on freedom of scientific research. However, research may also have the potential to infringe fundamental rights. Therefore agreement has been reached at international level on the need to respect a balance between the need to protect fundamental rights and to protect the freedom of research. This is clearly stated in Article 2 of the Convention on Human Rights and Biomedicine, which affirms the primacy of the interest and welfare of the human being over the sole interest of society or science. Article 15 of the Convention applied this principle to research in stating that "*scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of this Convention and the other legal provisions ensuring the protection of the human being*." As mentioned in the Explanatory Report in relation to the latter, if *"freedom of scientific research is justified not only by humanity's right to knowledge, but also by the considerable progress its results may bring in terms of health and well being of patients*", it is "*not absolute… it is limited by the fundamental rights of individuals …which protect the human being*".

However, there are differences in the method used to protect freedom of research from one country to another.

In some European countries such freedom is explicitly enshrined (like other fundamental rights) in the Constitution. Sometimes science and research are both mentioned together, whereas in constitutions that deal exclusively with "scientific freedom", the latter is seen as also covering research (as the basic scientific working method). Furthermore, a number of constitutions expressly require the State to develop and promote science.

In other countries, freedom of scientific research is not explicitly protected but can be indirectly derived from protections of individual freedom (of action), freedom of opinion, freedom of intellectual creation and/or academic freedom. However, it may be agreed that if freedom of thought and freedom of opinion should be as wide as possible, research, and particularly experimental research, is not comparable to the expression of an opinion.

The diversity of situations in approaches to the "freedom of scientific research" may in part arise from different conceptions of the scope of the concept. For instance, freedom of intellectual creation and to state one's views can be seen as distinct from scientific experimentation, even though the latter is usually considered an integral part of any broad definition of science. Hence, a distinction between basic or fundamental research and experimental or applied research is often made, with restrictions in particular being applied to the latter. However, this distinction is not absolute. Many types of basic biomedical research do not only involve contemplative speculation, but experimental methods. Such basic research may also entail a requirement to obtain bodily materials to be used in the research, bringing in to question issues concerning the rights and protection of those from whom material has been obtained.

Moreover, there are a variety of interpretations of the scope of the personal protection contemplated in the concept of freedom of scientific research.

C. Embryonic stem cells: scientific aspects

Stem cells are cells which have the unique capacity to renew themselves and to differentiate into specialised cell types. Based on their origin, three main categories of stem cells can be identified: adult, foetal and embryonic stem cells. Stem cells are not totally undifferentiated cells and can differentiate, depending on their origin, into one or more tissues.

The presence of adult stem cells has been shown in different tissues of adult organisms and it is probable that a large number of tissues contain such cells. They have the capacity to differentiate into a limited number of specialised cell types. However, recent studies seem to indicate the presence in the adult organism of stem cells which would have a much higher capacity for differentiation.

Fetal stem cells can be obtained from fetal tissues or umbilical cord blood. Like adult stem cells, their capacity to differentiate seems more limited than that of embryonic stem cells. Research on these cells with a view to therapeutic applications concerned mainly stem cells obtained from fetal nervous tissue and haematopoietic stem cells from umbilical cord blood.

Embryonic stem cells (ES cells) are derived from an embryo at the blastocyst stage (5 – 7 days). They have the ability to differentiate into a wide variety of tissues (pluripotence). However, they cannot on their own make an embryo.

Current knowledge on embryonic stem cells mainly results from research carried out animals. The isolation and manipulation of mouse ES cells is now a routine procedure. These cell lines can be induced to differentiate both *in vitro* and *in vivo* (in mice) into recognizable tissues and various cell types (from ectoderm, mesoderm and endoderm).

ES cell differentiation can be prevented by growing the ES cells on a layer of feeder cells, which produce a factor or factors that prevent differentiation and maintain ES cell proliferation and pluripotency. A factor that is able to substitute for feeder layer activity was isolated in 1988: leukaemia inhibitory factor (LIF). ES cells can be maintained for long periods in the absence of feeder layers using LIF in the culture medium, but eventually they accumulate aneuploidies or other chromosomal aberrations.

History

In 1981, the first two reports were published concerning the derivation of embryonic stem (ES) cells from the inner cell mass (ICM) of 3.5 day old mouse blastocysts. When ICM cells were cultivated *in vitro*, they gave rise to cell lines that were capable of indefinite self-renewal. These ES cells were capable of differentiating into many cell types: ES cells while in culture gave rise to the stem cells of adult tissues, haematopoietic, muscle, nerve, stratified squamous epithelia, intestine, etc.

The first report concerning human ES cells was published in 1998, by Dr J. Thomson and colleagues. The cell lines expressed cell surface markers characteristic of ES cells. Four cell lines tested produced teratomas when grown in immunocompromised mice. Embryos were cultured to the blastocyst stage, 14 ICM were isolated, and five ES cell lines originating from five separate embryos were derived. Four of the cell lines were cryopreserved after five to six months of continuous undifferentiated proliferation. The other cell line retained a normal karyotype after six months of culture and has now been passaged continuously for more than eight months (32 passages)…" (Thomson et al., 1998). Human ES cell lines have since been made in other countries, including Australia, Sweden and Israel.

Interest in stem cell study and its possible applications

The following examples are among the arguments put forward to support the potential benefits of studying such cells:

- ES cells are in a state of instability similar to that of pre-cancerous cells and could serve as a model for finding out more about how a cell becomes cancerous;

- if it could be controlled, the potential for differentiation of ES cells *in vitro* would make it possible to establish models for pharmacological cell studies which are lacking today because they are restricted to animal tissues and human cells which are usually different from the normal type;

- on the therapeutic front, there are prospects of a branch of regenerative medicine that could generate substitute tissues for degenerative and metabolic diseases and those involving cell necrosis, which are incurable today.

Current limits

Knowledge about stem cells, either embryonic, adult or foetal, still remain limited, in particular when it concerns differentiation mechanisms, their isolation (adult stem cells) or determination of their culture conditions. Futhermore there is, with embryonic stem cells, a significant risk of tumour (teratoma) development when transplanted into a host organism. Finally, the risk of immune rejection of cells coming from a particular organism when transplanted into a different one remains an important problem when considering the potential use of stem cells for therapeutic purposes.

Reports have shown the possibility of deriving stem cells intended for cell-based therapies in various human diseases. However, a large number of scientists seem to agree on the difficulty, in the current state of knowledge, to take a position on the comparative interest of the different stem cell types with regard to possible therapeutic applications.

However, the issue of the use of human embryos to derive ES cells and its ethical acceptability remains at the centre of the debate on stem cell. (see Section IV.D).

D. Use of embryos that are no longer part of a parental project for research (including for collection of stem cells)

The permissibility of research on the embryo

There are two central ethical concerns about the use of embryos that are no longer part of a parental project for research. The first concerns the ethics of using an embryo for any purpose other than procreation and the second is that such research will result in the destruction of the embryo. These concerns form the starting point for critical reflection, and for the need to justify such research.

The central philosophical and juridical question is whether or not there are benefits that may be achieved, or values served, by destructive embryo research that outweigh considerations of the good of the embryo. As discussed in Section II.B, positions on the status of the embryo differ. For certain people, there is no good, that can be achieved that could outweigh the status accorded to the embryo, or in other words that could outweigh its good.

In such contexts, it is argued, that rather than choosing between two different methods of destroying an embryo that was no longer part of a parental project (research or the usual procedure), it would be better to ensure that there were no such embryos in existence, and hence the ethical dilemma would be avoided (see Section III.C).

However, for those who take a gradualist position – as is the case with States that permit research on embryos that are no longer part of a parental project - the status of the early embryo is seen as a status "between" the understanding of the embryo as a part of "human life" and as a human person with human rights. **T**his has lead to the principle of "respect for human life", which is a constant and to be respected throughout the period in which the embryo/fetus is developing (see Section II.B). Such respect provides recognition of the embryo as more than merely a part of the human body or a bundle of cells. However, the question of a "right to life" is separate, and for holders of a gradualist perspective, the extent to which an embryo or fetus can be considered to possess such a right will progressively develop.

This principle means that, for those who hold it, "respect for life" can**,** under certain circumstances, be outweighed by the "good" of health. For those, the fact that such outweighing can take place is not necessarily in conflict with recognition of the dignity of the embryo; that dignity can be seen as fundamental, even if it does not entail a right to life. The outweighing of respect for the life of the embryo by other potential benefits to humankind is supported by the fact that embryos that are no longer part of a parental project will inevitably die. In contrast, this could be seen by others as a consequentialist approach. This raises however, the question of whether the end would justify the means.

A distinction may also be made between embryos which were created in the setting of IVF treatment with the aim of utilising only those most likely to develop after transfer (in other words, in situations where it

would always have been envisaged that not all of the embryos would form part of a parental project), and embryos created to be all transferred. The latter might occur in countries whose law prohibits the creation by IVF of more embryos than can be transferred in one treatment cycle (such as Austria and Germany) when, for example, a mother died during treatment. In such systems, the aim is that embryos should only be used for procreative purposes.

Proponents of such an approach also note that**,** if some use the term "embryo" before the appearance of the primitive streak (after about 15 days (see figure 2, in Appendix I)) and then refer to "fetus", other researchers use the term "pre-embryo" to make a distinction between early stages of embryonic development and the later ones, and that this might be considered as a way of "disguising" that the subject of research is in fact an embryo. Indeed the term "pre-embryo" is not used in research on other mammals than the human being. Some people, holders of a gradualist approach, might in turn argue that the term "pre-embryo" is a practical way of distinguishing different stages of embryonic life which may warrant different levels of protection.

Purposes of research on the embryo

If research on the embryo *in vitro* is not ruled out in principle, the question arises as to the aims of research that might justify the use of an embryo. Research on embryos that are no longer part of a parental project is established in several European countries. Not all of these countries have legislation about this practice. However, whether or not there is a law, there seems to be general agreement that such research must be for what might be broadly described as health purposes, whether directly (applied research) or indirectly (basic research, the results of which would have a potential direct benefit for human health).

Earlier forms of legislation, such as the United Kingdom's 1990 Human Fertilisation and Embryology Act, took a relatively narrow view of health purposes and permitted embryo research only for purposes that, in broad terms, might be considered to concern reproductive health and the reproductive process (including assisted procreation). More recently however, speculation about the potential for research on embryonic stem cells to lead to treatments for diseases unrelated to the reproductive process (such as Parkinson's disease) has lead certain countries to allow using embryos that are no longer part of a parental project for wider health purposes.

Research into human reproduction and medically assisted procreation

There are two main types of research in this field using embryos that are no longer part of a parental project:

- *research which relates more specifically to the improvement of medically assisted procreation techniques, in particular IVF treatment and procedures*. This may include studies designed to improve fertilisation, or investigations of prolonged culture, freezing and the viability of the embryo; or the development of embryonic analyses for diagnostic or therapeutic purposes. The results of the latter may assist potential future parents who carry or have a genetic disease in their desire for a healthy child, and recognises the suffering and dilemmas that they may experience as a result of the risk of having a child with that disease. Such suffering may result from their actual experience of a child or a relative with the relevant disease. The recognition of this issue by law or practice is the background of research for improvement of PGD.[4]

- *basic research, for example certain embryonic development studies, particularly at molecular level in the early stages of development, in respect of which little is known about significant differences between human beings and animals*. Such research could also be seen as serving wider health purposes, which are discussed further below.

It is generally agreed that an embryo that has been the subject of research must not be subsequently transferred to the uterus of a woman. Exception is made for research which is confined to observation of the development of the embryo where it is usually supposed that the risk to either the embryo or the mother posed by the research would not be any greater than if the research had not taken place. Another exception implies however a more invasive intervention on the embryo, in countries where preimplantation genetic diagnosis is allowed and considered as a research procedure (see Chapter V).

[4] There is some variability between countries on whether or not certain procedures which are being developed are considered as research for the purposes of the relevant legislation. This has, for example, been the case with the development of PGD in some countries.

In contrast, with other types of research the possibility of an adverse effect on the embryo or its subsequent development may be considered much greater. Nevertheless, it is also argued that if some potential improvements in IVF are to be of benefit in clinical practice, the transfer of embryos that have been subject to a research technique would, at one stage, be necessary.

Recent research purposes

Producing an exact, brief, definition of health purposes is difficult. However, such purposes clearly serve – immediately or at length - the health of concerned patients. Over very recent years, increasing attention has been focused on the potential for research on embryonic stem cells or ES cells to lead to benefits for human health. Potential benefits have been suggested in the treatment of patients suffering from Parkinson's disease, diabetes, and for those who may require an organ or tissue transplant. Others point out that these are just hopes, and that what is in fact being promoted is more research – in which embryos may be used. They draw the parallel with gene therapy, from which much has been hoped over the last fifteen years, whereas the results have been, in clinical terms, very limited.

In this difficult debate, the importance of being clear about what is a fact, and what is merely a hope, has been emphasised, as have the dangers of predicting dates by which therapeutically useful interventions will be available. On the other hand, others have emphasised the importance of the freedom of research, as discussed earlier in this report (see Section IV.B).

Obtaining embryonic stem cells entails extracting them from an embryo, which will be destroyed by this procedure[5]. At present knowledge of embryonic stem cells is limited. However they have two key properties: plasticity (the ability to differentiate into blood, brain, liver or muscle cell lines depending on the culture conditions *in vitro*) and the capacity for self-renewal (the ability to replicate themselves almost indefinitely) (see Section IV.C).

The potential benefits of studying such cells were mentioned in Section IV.C. However, it is clear that there are still many questions to be answered in relation to human beings about ways of renewing ES cells and how to direct them at will to form differentiated tissues and to control their proliferation. Beyond this, questions about the interaction between ES cells and the immune system and any harm that might be caused by transplanting such cells would require investigation.

Moreover, there are increasingly high hopes of using, for therapeutic purposes, stem cells from umbilical cord blood and from adult tissues. Certain recent studies suggest that progenitor cells, particularly from adult bone marrow, behave very similarly *in vitro* to ES cells. For those who do not consider research on the embryo acceptable, this has led to suggestions that we should not study ES cells until the hope of achieving the same benefits from adult stem cells has been exhausted. Others, who do find embryo research acceptable in certain circumstances, but only if the results cannot be achieved by any other method, have also taken this position.

In contrast, given the current state of our knowledge, a number of arguments are given that suggest that the adult source cannot be considered as an alternative to the embryonic source[6] and therefore it has been suggested that both ought to be studied. Proponents of this position point to the suffering of patients with disease that might be alleviated by the results of ES research, and that to delay conducting such research might prolong suffering. On the other hand, it has been argued that consideration of the rights of patients who can be probably healed by cell transplantation is inappropriate, as any relevant rights they could have can only exist in the future, given that a number of scientists estimate that the possibility of therapy utilising cell transplants is likely to be a minimum of 10-15 years in the future. Further, it may be ethically problematic to hold out such future promises to patients suffering from serious diseases, as this does not help them cope better with their disease in the present. Moreover, there can be no right to be healed by an immoral means. In contrast, if the embryo that will be destroyed in the relevant research has any rights, those rights exist now. If a patient in the future may be helped by a therapy developed as a result of research conducted now, the specific identity of that individual is not known – and so there is no one to whom we could be said to have a specific duty – whereas there will be a specific, identifiable embryo that is destroyed by the research.

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[5] There are a few countries (e.g. the United Kingdom, Japan) where the production of embryos by fertilisation or by cloning for this purpose is provided for by law; a few others are considering it; elsewhere such research is only done using embryos which are no longer part of a parental project.

[6] For example: lesser division potential; small quantity in any tissue; possibly absent from certain tissues; would also require genetic modification in the event of a genetic disease.

Regulation of research

As is evident, the ultimate resolution of the question of the permissibility of research on embryos which are no longer part of a parental project depends centrally on the conclusion drawn on the status of the embryo. It is important that the arguments both for and against such research are fully discussed in reaching such conclusions.

Those States which have concluded that research on these embryos may be permissible have clearly recognised the ethical dilemmas involved. Both the procedures and the institutions involved in such research are subject to regulations, and the individual research projects are both authorised and supervised by the relevant competent body.

A final question concerning the regulation of research may be briefly raised. Whilst a State may choose to ban embryo research completely, if it does so the question arises as to whether it should permit on its territory techniques, or use of materials or even results that have been developed or produced using such research carried out in another state where they are allowed. Should, for example, research that has made ICSI[7] or PGD[8] possible and is essential before such techniques are put into practice, continue in some countries and then benefit others which have already condemned such research? If so, is there a duty to inform patients who might benefit from the techniques in clinical practice of the means by which the technique has been developed?

Import of embryonic stem cell lines

For countries in which research on embryos is forbidden, such as Germany, the question of whether or not the import of embryonic stem cell lines should be permitted has raised difficult questions. The issue of import of stem cells may also arise in countries in which the scientific resources to develop embryonic stem cell lines are not yet available.

As noted previously, it has been argued that it is important to continue the promising experiments with stem cells and animal models using both embryonic and adult stem cell lines.

Certain countries with strict positions with regard to embryo research have taken the decision to allow import of embryonic stem cells from other countries. This was the case in France with a Governmental order in February 2000 (this possibility has however been suspended since then**.** The issue is now being reexamined in the framework of the revision of the bioethics legislation of 1994).

Another example is Germany. According to the German Embryo Protection Act, the production of human embryonic stem cells is prohibited in Germany. The German Stem Cell Act, which entered into force on 1st July 2002, poses a general ban on import and use of human embryonic stem cells. An exception is made only for publicly and privately funded research purposes subject to strict conditions and approval by a government agency.

As noted in the previous section, there are different approaches to the creation of embryos in the context of IVF. In some countries there is essentially an acknowledgment that embryos will exist that may not form part of a parental project, in that more embryos are created than can be replaced in the uterus in a single cycle and which may not be transferred in the future. In countries such as Germany and Austria legally the number of embryos created shall not exceed the number which can be transferred within one treatment cycle, and therefore it is not intended that any such embryos should exist. As a result, it is estimated that in Germany less than 70 stored embryos are thought to exist that are no longer part of a parental project, by contrast to the remainder of Europe, in which more than 100,000 such embryos are thought to exist and to be cryopreserved.

Current discussion and decisions with regard to embryonic stem cells show the difficulty in finding an appropriate balance between the wish to keep an active role in a research field the results of which are suggested as potentially determinant in terms of medical progress and to benefit from these potential applications whilst seeking to maintain a generally highly restrictive approach to the question of embryo

[7] Intra cytoplasmic sperm injection

[8] Pre-implantation diagnosis

research. Current legal initiatives taken in several European countries acknowledge the wish for coherence in the approach taken.

E. Creation of embryos for research (including for the collection of stem cells)

To deliberately create an embryo for the purposes of a research project is prohibited by the Convention on Human Rights and Biomedicine (Article 18(2)) and is widely regarded worldwide as not ethically acceptable. It would involve using the embryo purely as a means to an end. This degree of instrumentalisation of the embryo is rejected even by many of those who accept the use of embryos which are no longer part of a parental project for properly regulated research. As seen in Section IV.D above, it is argued that unless such an embryo is to be transferred to a uterus, it will in any case not survive, so to use it for worthwhile research that might bring benefit or help to reduce suffering might be regarded as a better option than just discarding it. This argument would not apply to embryos created for research, since they would not have existed had it not been for the research project. However, it is argued that certain specific research intended to benefit human health cannot be carried out on existing embryos and requires creation of embryos outside of a parental project. It is on that basis and subject to very strictly defined criteria and purposes that in the United Kingdom and in Belgium, for example, creation of embryos for research has been authorised.

The status of the embryo itself, once it has come into existence, is presumably the same whether it was created directly to alleviate infertility (IVF) or to avoid the birth of babies with serious disorders (PGD) - or for research aimed ultimately also to alleviate infertility or to avoid or treat serious disorders or illness. In principle, all embryos that are created, for whatever purpose, have the capacity to develop. The range of views on the status of an embryo were reviewed earlier in this report (see Section II.B).

The proximate intention in creating an embryo may, of course, differ: on the one hand the birth of a baby, and on the other hand to create an embryo that will be destroyed in the course of the research. When more embryos are created than can safely be transferred to the uterus in a single cycle, it is almost certain that some of those embryos will perish, but it is hoped that this will reinforce the chance of a successful parental project. When embryos are deliberately produced for research, the hope for beneficent consequence is both less direct and more long-term.

From the proportionality point of view, there are research projects that are considered worthwhile and necessary that cannot be carried out on embryos that are no longer part of a parental project. There are several examples. Cryopreservation of embryos today is safe and relatively efficient. It would be preferable on both clinical and ethical grounds to be able to cryopreserve unfertilised oocytes, for instance for young women who are receiving cancer treatment that is likely to endanger their fertility and who wish to preserve some reproductive potential. Unfortunately chromosome stability is lower in oocytes than in embryos, so that to develop optimal methods of oocyte freezing and thawing it is necessary to fertilise the experimental oocytes and then test the resulting embryos for normal cleavage chromosomes and patterns. This entails their destruction, but the alternative is to transfer embryos derived from experimentally frozen oocytes directly to the uterus, thus in effect subjecting the fetus and mother to experimentation. Similarly, embryos derived by intracytoplasmic sperm injection (ICSI) of immature, as opposed to mature, spermatozoa require to be tested for normality before ICSI with immature spermatozoa is introduced into clinical practice. This would require the creation of embryos which would not be subsequently transferred into a uterus.

A significant proportion of international research into human reproductive biology now concerns the early stages of fertilisation leading to the conception of embryos which need to be analysed by invasive techniques. The creation of embryos is thus an integral part of such research, or necessary for analysing the results of such research. It is argued that, in such cases, embryos created could be considered as having been created “by research” as distinct from “for research”. For some people this is a significant distinction, with some considering that the creation of embryos for non-procreative purposes is only acceptable in the context of research on fertilisation.

The tens of thousands of embryos cryopreserved in Europe at the present time make it unlikely that there would be any need to fertilise donated oocytes specifically in order to derive new stem cell lines. It is argued however that, at some stage, it might become relevant that the frozen embryos come, in the vast majority of cases, from a selected sample of the population with fertility problems, and they are often of poor developmental potential since the embryos appearing most likely to develop will be transferred to the

woman's uterus first. Also as IVF becomes more efficient and fewer oocytes are recovered, the number of embryos that no longer form part of a parental project could fall and fewer could be cryopreserved.

In countries which have authorised the creation of embryos for research, the relevant regulations have laid down restrictions on the procedure. As with research on embryos that are no longer part of a parental project, such regulations aim to ensure that the aims of the research project are worthwhile and cannot be achieved in any other way. In practice, the number of embryos that have been created for research purposes are extremely small compared to the number initially created for reproductive purposes.

Oocyte donation

Concerns have also been expressed about the risk of instrumentalisation of human beings and, in particular, donors of oocytes for the purposes of this type of research (e.g. improvement of fertilisation and cryopreservation technique for oocytes). Given that the research may not benefit the donor of the oocytes, it has been suggested that there are analogies with research without potential benefit on persons not able to consent. On the other hand, from the perspective of certain patients, it could be argued that participation in this research involves no greater risk or degree of instrumentalisation than any other research project. From the perspective of donors, if a donor is given all the necessary information about the risks that may be entailed in donating oocytes, and about the ways in which their oocytes will subsequently be used, the donor should be in a position to choose whether or not to give free and informed consent. However, some concerns have been expressed about the risk of commercialisation, in particular for women in difficult financial situations who might be tempted to sell their oocytes. The possibility of oocytes being diverted from the purpose for which they were originally obtained has been suggested. However, if a woman has given such consent it may be inappropriate to regard her as being instrumentalised. In this respect, the accuracy and extent of the information given will clearly be vital. In this context, it has sometime been suggested that after having given consent, the couple/woman should be given time to reconsider their/her decision. Similarly, it has been proposed that consent be requested by somebody else than the doctor in charge of the treatment. Furthermore, in general, the imperative need to make sure that the consent of the couple/woman is free, has been stressed.

Cloning

Arguments are also developed in favour of a possible future category of embryos created for research by somatic cell nuclear transfer, a procedure leading to cloning. As noted previously, there is debate about the moral significance of different methods of creating an “embryo” (see Section II.B). In this case, the definition of an embryo is taken to be the earliest stage of development, rather than the product of fertilisation of an oocyte by a spermatozoid. At present there is little evidence that such a procedure would work in the human. If it did work, one possible line of research which could be considered worthwhile, might be the production of embryonic stem cell lines from patients suffering from rare and poorly understood metabolic or genetic diseases, to provide material to study the biochemistry or physiology of the disease. A further aim might be to derive embryonic stem cell lines from individual patients suffering from degenerative diseases, with the aim of therapeutic use of the stem cells on the same individual, thus circumventing the risk of transplant rejection. However, it is argued that the difficulties already met with embryonic stem cells (e.g. control of differentiation and of proliferation) would first need to be solved before considering such a technique. Furthermore, this approach, sometimes misleadingly termed "therapeutic cloning" (see below), seems unlikely to be developed for clinical use for economic reasons. The chief objection to "therapeutic cloning”, in addition to the more fundamental objection, namely the ethical unacceptability of creating embryos for research and the resulting instrumentalisation of the embryos, is that it would facilitate the development of "cloning for babies" (often termed "reproductive cloning"). “Reproductive” cloning is almost universally rejected on ethical grounds and is prohibited in several European countries (as well as by the Council of Europe's "Additional Protocol to the Convention on Human Rights and Biomedicine on the prohibition of cloning human beings").

Those who have concerns about the use of embryos in research have also highlighted what might be described as “language politics” with regard to ES cells. In particular, they express concerns about the term “therapeutic”. The term “therapeutic” is only used because the intention is to derive embryonic stem cells which could potentially be used for therapeutic purposes. But for those who believe that the product of cell nuclear transfer is an embryo, the fact that the purpose of the procedure of “therapeutic” cloning is not to produce a baby is to ignore the fact that the embryo so produced does indeed have that potential and therefore its creation does raise ethical concerns. Further, they would argue that the term “therapeutic” is also misleading, given that there is nothing therapeutic about the cloning procedure itself and that, at present, there is no guarantee of producing a result of therapeutic use. It is argued therefore that it would be more accurate to refer to “cloning for stem cells” and in the same way to talk about “cloning for a baby”

rather than “reproductive cloning”. Finally, others anxious not to use misleading terminology have proposed that reference be made each time to the purpose of the cloning: research, therapeutic, reproductive.

V. Preimplantation diagnosis (PGD) (for genetic diagnostic purposes)

A. Presentation of PGD: procedures and conditions

Preimplantation genetic diagnosis (PGD) allows the detection of genetic defects before implantation. PGD was initially developed to offer an alternative to prenatal diagnosis for couples at risk of transmitting a particularly severe genetic defect, avoiding the difficult decision of whether or not to terminate a pregnancy.

The first indication for PGD was the detection of specific genetic anomalies that will lead to the development of a genetic condition in a future child (including sex-linked diseases), or chromosomal abnormalities which would lead to early miscarriage or major health problems in the child. PGD indications have recently evolved to include improving IVF success for infertile couples by screening embryos for common or age-related aneuploidies. The practice of screening for aneuploidy is discussed in Section III.C. Clinical PGD applications started in 1990 in England and since then it has been offered in a very large number of countries, but by a limited number of centres.

PGD procedure

PGD procedures combine an *in vitro* fertilisation and a genetic analysis of the embryo obtained in order to select and transfer to the uterus of the women only embryos not affected by the abnormalities concerned. The first part of the procedure is hence no different from normal IVF/ICSI treatment, producing for these usually fertile couples, sufficient embryos to give a high probability of obtaining unaffected embryos, even in situations where the risk of an embryo being affected is 25 to 50%. The vast majority of PGD cycles use ICSI to avoid contamination with “foreign” DNA coming from other spermatozoa. The biopsy on the embryo is carried out three days after fertilisation by gentle aspiration of one or two cells (blastomeres) or, less often, on the fifth day by biopsy of the trophectoderm (future placenta) of the blastocyst (embryonic stage just before implantation). An alternative to blastomere biopsy is the biopsy of the first and/or the second polar body. Such a strategy has the advantage of avoiding the pick up of embryonic material, but the major limitation comes from the fact that only the maternal genome can be analysed. Most PGD procedures are carried out on blastomeres.

The genetic analysis, according to the indication, can be performed by two different techniques:
1) PCR (polymerase chain reaction) which amplifies the small amount of DNA obtained from the blastomeres determines the presence or absence of the gene defect involved by molecular analysis.
2) FISH (fluorescent *in situ* hybridisation) identifies particular chromosomes with a specific colour to look for suspected numerical or morphological chromosome abnormalities.

In all cases, only unaffected embryos are transferred. The others may be donated for research in countries where such research is allowed.

Regulation

In some countries PGD is regarded as a research technique, whereas in others it is considered as clinical practice. Considerable legal differences exist among countries, ranging from total bans to the almost complete absence of any regulations. In the majority of countries offering PGD, an authority regulates and ensure respect for good practice, for PGD as well as for prenatal diagnosis (PND).

PGD requires a multidisciplinary medical team which combined the necessary competencies and skills to carry out the different steps of the procedure. It should be possible for the couples to be offered adequate independent and non directive counselling and psychological support before and after PGD.

PGD results

Preimplantation genetic diagnosis is used for couples at risk of transmitting a severe genetic disease, usually identified on the basis of family history or the birth of affected children. Technically embryos can be checked for more than twenty genetically determined monogenic diseases, as well as for chromosomal

abnormalities[9]. The biopsy of blastomeres is successful in 97% of cases and a diagnosis obtained in 86% of successfully biopsied blastomeres[10].

The scientific and medical information that is presently available suggests that the use of PGD does not pose a risk to the health of the future child. However, because the technique has been in use for relatively few years, a follow up of children born after the use of PGD has been suggested to establish the position in relation to safety more clearly.

PGD' future development
Most centres offering PGD have tests for the most frequent genetic disorders. The advances will now come in the ability to develop diagnosis for rare diseases and in the improvement of the existing diagnosis.

However, an increasing range of potential uses for PGD is being suggested. As well as gender selection for a range of purposes, these have included using PGD to screen for susceptibility to certain cancers, and more controversially for HLA matching with an existing sibling. The latter is discussed further in Section D below. Fears have also been expressed about the possibility of "designer babies", although the term is misleading. Rather than a potential child being "designed" as such, a selection would be made on the basis of particular characteristics – that may have nothing to do with health, such as hair colour, if the genetic basis of the characteristics is known – and only embryos with the desired characteristics would be replaced in the uterus and hence have a chance to develop.

B. Ethical aspects and social consequences, in particular the issue of eugenics

Preimplantation diagnosis (PGD) can be seen by some, as an anticipatory form of prenatal diagnosis (PND) even if each has its own indications. If seen as such it does then raise ethical issues which are common to other types of prenatal diagnosis, in particular when it comes to discrimination and stigmatisation. However, as PGD implies creation of embryos by IVF, intervention on embryos and their selection for transfer, additional concerns are expressed in relation to the status of the embryo and reference is made to eugenics.

The consequences of PGD and PND procedures for the couple and in particular the mother, are very different. PND is carried out during pregnancy. As a result of the test the couples have the dilemma of whether or not to terminate the pregnancy if the relevant genetic abnormality is present. Preimplantation genetic diagnosis (PGD) offers the possibility of identifying affected embryos before the pregnancy is established. Only unaffected embryos will be transferred to the uterus. This technique obviates the need for screening for this purpose during a pregnancy, and therefore avoids the physical and psychological trauma associated both with the consideration of a possible termination and, where such an outcome is chosen, with the termination itself. However, PGD results are currently routinely controlled by a later PND.

Without access to PGD couples that are aware that they are carriers of a genetically transmitted disease, and wish to avoid passing on that disease to a child, will be faced with the options of choosing not to have a child or to undertake PND and possible termination of pregnancy. For those who would find termination of pregnancy unacceptable, this may mean giving up the hope of having a child that is biologically their own. The potential benefits of PGD to such couples are to enable them to consider a pregnancy without the

[9] The ESHRE PGD Consortium steering committee, Geraedts J, Handyside A, Harper J, Liebaers I, Sermon K, Staessen C, Thornhill A, Vanderfaeillie A, Viville S, Wilton L. ESHRE preimplantation genetic diagnosis (PGD) consortium: data collection III (May 2001). Hum. Reprod. 2002; 17 : 233-246.

(Indication for PCF diagnosis for 2001)
Central core disease, Charcot-Marie-Tooth 1A, Charcot-Marie-Tooth 2A, Crouzon syndrome, FAP-Gardner, HD-exclusion, Huntington's disease, Marfan's syndrome, Myotonic dystrophy, Neurofibromatosis, Osteogenesis imperfecta I, Osteogenesis imperfecta IV, Stickler syndrome, Tuberous sclerosis, Beta-thalassemia, CDG1C, Cystic fibrosis, Epidermolysis bullosa, Gaucher's disease, Hyperinsulinemic hypoglycemia PHH1, Sickle cell, Spinal muscular atrophy, Tay-Sachs disease, Agammaglobulinemia, Alport syndrome, Duchenne's muscular dystrophy, Hunter's syndrome MPSII, Spinal and Bulbar muscular atrophy, Alport syndrome, Fragile X syndrome, Oro-facial-digital syndrome type 1, MELAS, CF+FRAXA, CF+XL mental retardation

[10] Hum. Reprod. 2002 17: 3260-3274.

anxiety associated with the risk of passing on a serious genetic disease to allow them to have children who are both biologically their own and free from that specific disease.

On the other hand, a number of concerns have been expressed about the practice which are discussed below. Indeed, to those who regard an embryo as a human being with a right to life from the moment of conception (see Section II.B), PGD is objectionable because it involves a morally impermissible selection amongst those with an equal right to life.

There has also been debate about the capacities of the blastomere removed from the embryo and subjected to the process of genetic testing. If such a blastomere was totipotent, or in other words itself had the capacity to form an embryo, to undertake testing that would result in the destruction of the blastomere could be regarded as equivalent to destroying an embryo, and, for certain people, a human being. However, most scientists consider that a blastomere derived from the embryo at the 8-cell stage is pluripotent (i.e. has the capacity to differentiate into different tissues but no longer the capacity to form an embryo) rather than totipotent.

Others have pointed out that if an embryo with a genetic abnormality is allowed to mature and be born alive, the abnormality may not necessarily result in a disorder or disease in the person concerned. Genetic variations (alleles) have a penetrance factor, which is a measure of their effectiveness or power. For example, the allele that causes Huntington's disease has a 100% penetrance, so that if someone has the allele, s/he will – assuming they live long enough – develop the disease. Other genetically determined conditions have a much lower penetrance: for example, 15% for left-handedness. Thus it is argued that many embryos will be destroyed even though the abnormality that they carry would never have caused a disease or disorder if PGD were to be allowed for such low penetrance conditions.

PGD has also aroused particular concern with regard to its social consequences and in particular the possibility of eugenics (see below).

Assumptions underlying PGD

The assumption underlying prenatal diagnosis, and therefore PGD as a particular category of such diagnosis, is that certain conditions or characteristics are classified as diseases or malformations or otherwise unwanted. This emphasises the need to clarify relevant concepts – for example of disease, normality, genetic variation, and eugenics. In particular, there needs to be clarity about the misleading notion of "genetic perfection", in contrast to the reality of genetic "abnormality" as an integral part of the characteristics of all human beings. Clarifying these concepts will mean that underlying conceptions of disease and quality of life are made explicit, and that reasons for and against the potential approaches to the indications for PGD can be considered. Questions concerning the status of the embryo, and ensuring the voluntary basis of decision-making will also be relevant in such debates.

The distinction between diseases, disorders and characteristics warrants scrutiny. If it could be considered morally acceptable to use PGD for severe genetic diseases, some concerns are expressed with the possibility of using PGD to select an embryo on the basis of certain characteristics.

This may give rise to several kinds of risks: in particular, a risk for children with those characteristics (handicap, for instance) that are born to be or feel stigmatised, and a risk of pressure on the parents who, since the technique is available, could have arguably avoided a child with this particular handicap or genetic disorder.

Some people are already arguing that the current use of PGD will lead to discrimination and stigmatisation. Others have expressed concern that the use of PGD will have such negative social consequences, or at least that it is not unlikely that PGD will lead to such consequences.

The problems of definition and classification should be considered in this context. In many countries PGD is only allowed for diagnosis of severe genetic diseases. But differences are met in how the seriousness of a given disorder is classified. Certain patient's organisations have objected to the use of PGD and other methods for prenatal diagnosis on the ground that they undermine the equal value of human beings, and have stressed that notions like "severe genetic diseases" are social constructions.

It has been replied that one must distinguish between a particular genetic disease and the person having that disease. That the disease is negatively valued, and that it is desirable and legitimate to try to avoid it,

does not mean that the person having the disease is negatively. In that way there is no conflict of interest between attempts to eradicate (or diminish the prevalence of) a disease and help to those who suffer from it.

However, it has been stressed that the use of PGD, even though this is not intended, will have stigmatising consequences because it will reduce the number of people with certain genetic diseases. Social pressure may be enough to exert the effect. If the values underlying these definitions, classifications and social and reproductive practices are more generally supported in society, such evaluations may lead to more obvious and straightforward discrimination - which in its turn may increase the pressure on future parents to use PGD and other similar techniques to avoid embryos with certain diseases or characteristics.

The risk of widening the indications, so that the method is first used to avoid children with severe genetic diseases, and then less and less severe diseases are included as time goes by, has been stressed. Some argued that the risk cannot be excluded, particularly as increased weight is attached to respecting the autonomy of the couple/woman. If the method can be stigmatising and discriminatory when used restrictively, it may be even more so when the indications are wider.

As will be seen below, in the context of eugenics issues have arisen about the promotion of desirable characteristics. It can be noted that human beings can seek to improve their own capabilities, for example by training in sports, or parents the capabilities of their children by providing them with extra facilities for education. Some people have questioned whether the difference between undertaking such activities, and conducting PGD – should the genetic basis of the characteristics sought ever be sufficiently elucidated – with the aim of producing a child who has the potential to develop high capabilities in certain fields, is morally relevant.

The reference to "eugenics**"**

The term "eugenics" arouses strong emotion, and it is particularly important to try to clarify what is meant by the term. Eugenics involves selection on the basis of genetic characteristics. Some people would argue that any selection of human beings, each with certain rights, is eugenics - the question of eugenics in relation to PGD being thus mainly related to the question of the status of the embryo (see Section II.B). However, others would consider that not all selection involve eugenics. Eugenics presupposes that a selection is made on the basis of some type of genetic characteristic and that the moral basis in terms of the purpose and/or consequences of the selection is unacceptable, involving discrimination and stigmatisation of certain individuals or groups. Furthermore, eugenics has been historically associated with the notions of coercion and third party influence in reproductive choices. This notion is therefore perceived as a strongly negatively-valued term.

A distinction has traditionally been made between positive and negative eugenics. In the first, parents with what is considered to be a good genetic heritage are encouraged to produce children. In the second, people with what are considered to be "bad genes" are dissuaded or prevented (sometimes by compulsory sterilisation) from having children.

Concerns have been expressed about the morality of eugenics on two grounds. Firstly, because it undermines respect for human dignity and for the equal value of human beings. The second ground is more historically based. In the context of PGD, it has been suggested that we should learn from past experiences and for the potential for a progressive increase in the scope of the indications for PGD to lead to the practice of eugenics.

In the context of PGD, it is clear that although the practice is used to prevent the passage of a serious disorder to a child, there is at least the possibility of using the technique for the purpose of selecting "positive" qualities, rather than purely the absence of diseases or disorders. Furthermore, it is the choice of an individual couple which is supposed to be taken freely without the intervention of a third party. The question is therefore whether or not PGD is always, or may be in some circumstances, a eugenic practice. Eugenics is usually also used as a term for a practice which may be applied to all members of a particular group. However, questions of discrimination and stigmatisation of individual members of a particular group are also important, whether or not any forms of intervention are applied to that group as a whole. The need to address such discrimination at a European level is highlighted by Article 11 of the Convention on Human Rights and Biomedicine, which prohibits discrimination on grounds of genetic heritage. Similarly, at a global level, Article 6 of UNESCO's Universal Declaration on the Human Genome and Human Rights states: "*No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity*". These concerns have lead

countries to develop laws and guidelines to reduce the risk of eugenics, and of undermining respect for human dignity. In some countries, explicit restrictions have been placed to the effect that PGD must only be used for couples with serious, progressive, hereditary diseases which can lead to premature death and where no cure or treatment is currently available. Other countries have not considered it necessary to require that the disease be "progressive" or that it specifically lead to premature death and have only referred to the high probability for the child to be born with an incurable serious genetic disease. Some other countries have taken a more flexible approach, limiting the use of PGD for the purposes of establishing whether an embryo might suffer from a serious genetic condition.

Three different approaches can be taken with regard to the diseases concerned:

- *a fixed list of diseases for which PGD is allowed*
This is the least flexible approach. As our knowledge of the genetic basis of disorders increases, such a list would need to be regularly reviewed if it was to remain appropriate. Equally, as the possibility of treatment for different disorders develops there may be a need to review whether the indication remains appropriate. Determining the criteria for inclusion on the list may be problematic for the same reasons discussed in relation to the second potential approach. A specific list would give rise to particular concerns about discrimination and stigmatisation of those suffering from the conditions concerned.

- *PGD only used for serious non-curable diseases, but no fixed list*
The difficulty with this approach is determining how, or by whom, the seriousness of a disorder should be determined. Even within a single genetic disorder, the way in which the life of an individual is affected by that disorder may vary considerably. Another issue is whether or not the views of the couple concerned should be taken into account in determining the seriousness of a disorder. Those who have experience of a disorder within their family, or who already have one or more affected offspring, may have different views about their ability to cope with a child with that particular disorder. A rigid approach may make it more difficult to take individual perceptions into account. Furthermore, geneticists may also have different views on precisely which conditions are "serious". This might mean that a couple might be able to obtain PGD for a particular condition in some places but not in others.

- *examination on a case-by-case basis, on the assumption that what is a serious disease will vary to different people, as will their ability and willingness to cope with various diseases*
This is the most flexible approach and enables a more individualised approach to be made to the couple. However, the results may be criticised as being somewhat arbitrary.

In relation to the restrictions placed on PGD, the coherence between the protection offered to the embryo *in vitro* (the subject of PGD) and the fetus *in vivo* (the subject of PND) within an individual national system has also been questioned. For example, if PGD is only permitted for a very restricted range of disorders, but PND and subsequent termination of pregnancy can be undertaken for a broader range of disorders, this could be interpreted by some as suggesting that the embryo is offered a higher level of protection than the fetus. For those who take a gradualist approach, as described in Section II.B above, and consider that the protection and rights afforded to an embryo/fetus increase throughout the process of development, this would appear anomalous.

<u>The importance of voluntariness</u>
Autonomy is an important value, and it provides the basis of the requirement of free and informed consent. Voluntariness – an expression of autonomy - is generally considered crucial in health care, and is emphasised in Article 5 of the Convention on Human Rights and Biomedicine.

Concerns have been expressed that health care professionals, including genetic counsellors, whether consciously or unconsciously, may transmit social pressures and "eugenic attitudes" to patients. Hence, influence could be exerted on the choices made by a couple, diminishing the voluntariness of consent and leading to eugenic consequences in the sense that the purpose – as well as the effect – of the selection will be to reduce the number of people with certain genetic diseases, or with an increased risk of getting certain hereditary diseases.

Although it is generally considered vital that individuals make a voluntary choice about undergoing PGD, concern has been expressed about particular cases in which there has been a request for affected embryos only to be selected for replacement in the uterus. Such requests may derive from a desire that the child of a couple affected with a disorder may "fit in" to the family or social culture where s/he will be living (for

example in to the “deaf community”). However, it would then generally be argued that the welfare of the potential child should be given paramount importance and the impact the relevant disorder may have on the child in terms of that child’s functioning and opportunities as a whole should be considered.

C. Selection of sex

As has been noted above, it is possible to use PGD to select the sex of the embryos that will be replaced in the woman’s uterus. There are three main reasons why this may be considered desirable:

i) for medical reasons

This is the most straightforward indication. Where a genetic disease is linked to gender, rather than the need to identify the specific gene responsible for the disorder, it would be sufficient to identify the presence of the relevant sex chromosome as a basis for selecting embryos that will be free of the disease. Such an approach does not raise differences in principle from selecting on the basis of the presence of a specific gene. Article 14 of the Convention on Human Rights and Biomedicine permits the use of medically assisted procreation techniques for the purpose of choosing a future child’s sex if the aim is to avoid a serious hereditary sex-related disease. PGD could be considered as part of such techniques.

However, as noted in the previous section, defining what constitutes a “serious” disease is not straightforward. The same issues discussed in Section V.B would also apply to gender linked disorders.

ii) for societal reasons

In some societies children of one sex may be considered inherently more desirable than children of the other sex. Alternatively, it may be considered particularly desirable for the first child to be of a particular sex. In such societies, it is usually a male child that has been preferred. Concerns have been raised about the identification of fetal sex during pregnancy in such countries using non-invasive techniques such as ultrasound, as there have been reports of healthy female fetuses subsequently being aborted. The existence of such preferences raises issues concerning discrimination on grounds of sex in such societies. It can be argued that permitting sex selection in support of such preferences is likely to reinforce discrimination and be contrary to human dignity and the respect for equality to which all human beings should be entitled.

In contrast, it has been argued that the use of PGD in such situations may prevent termination of the fetus at a later stage of pregnancy, and from a gradualist approach to the rights and protections of the embryo and fetus this might be considered desirable. Nevertheless, to allow PGD to be used in this way could also be seen as an implicit endorsement of the practice of terminations of fetuses of an undesired sex, and of the discrimination that such practices reflect. Furthermore, Article 14 of the Convention on Human Rights and Biomedicine would prohibit the use of medically assisted procreation techniques for this purpose.

iii) for family balancing

When a couple has one or more children of a particular sex, they may desire to “balance” their family by having a child of the opposite sex. This might be seen as a variant of the social reasons discussed above, but in this case it has been argued that the risks of reinforcing discrimination, or of the approach leading to eugenic practices, are considerably reduced. This is because the sex of the first child will not be deliberately chosen, and PGD is only used to choose a child of the “opposite” sex, rather than being used in a systematic way to select embryos of a specific sex.

Given that the risks to the values of society should be limited or non-existent, if parents wish to exercise their autonomy by choosing to have a balanced family some argue why should they not do so? On the other hand, the deliberate selection of embryos with particular characteristics may give rise to fears about instrumentalisation of a child and of a slippery slope to selecting children on the basis of other characteristics. For example, if two children of the family were good at sport would it be acceptable to select – should this be technically possible – a future child on the basis of potential for musical talent? It could also be considered, with regard to the proportionality principle, that implications for the parents of not having

access to a such procedure for family balancing would be limited with regard to the possible risks of extending such selection.

Worldwide the morality of family balancing continues to be debated, and there is a greater divergence of views on this issue than on sex selection for other social reasons, which is generally regarded as unacceptable. Article 14 of the Convention on Human Rights and Biomedicine would however prohibit the use of medically assisted procreation techniques for this purpose.

D. PGD use for immunocompatibility analysis

Another application of PGD has been found which although it may serve a health purpose for the embryo itself also has another purpose. An example might be the situation where a child of a family suffers from an extremely serious illness, such as Fanconi anaemia. A treatment has been developed that involves the removal and transplant of blood cells from the umbilical cord of another child free of the illness and having matching HLA in order to prevent problems arising from rejection of the transplant. PGD could be used in order to establish whether a future child would meet these criteria. Consequently, *in vitro* fertilisation is also necessary, although the question of parental infertility does not arise. PGD in this situation has two objectives: to ensure HLA compatibility with the existing child, and to confirm that the future child is free from the relevant illness.

Some argue that this is a distortion of the original purpose of PGD. It is argued that the unborn child, sometimes referred to as a "designer baby" (although as noted previously this term is misleading) will not be conceived for his/her own sake, but for another person's benefit. This is the first ethical objection. However, a parent might answer that they desire to have another, healthy, child in any event. Some commentators have emphasised the importance of the motivations of the parents in determining whether PGD in a specific situation would be ethically acceptable.

However, more practically, it would be very difficult to truly establish what the motivations of the parents might be prior to initiating the procedure. For example, in a situation where PGD was undertaken and those embryos that were found to be free of disease were not HLA compatible with the existing child, if the couple refused to permit the transfer of any of those embryos it could be inferred that their original motivation – whatever they might have said previously – was not purely to have a healthy child. Although it may be difficult to establish the exact motivation of the parents, as with all IVF treatment, it is generally agreed that non-directive counselling should be undertaken to ensure the welfare of any future child is carefully considered. In particular, parents need to consider in advance their potential reactions should an umbilical cord blood transplant be undertaken, if it failed to produce a benefit.

A second ethical objection highlights the fact that in such circumstances if an embryo was found to be healthy but not HLA-compatible, transfer to the uterus could not assist the existing child – the question raised then would be the fate of that embryo. The options might include transfer to the uterus in any event, conservation for a possible transfer at a later moment or destruction. If the latter were the case, it is argued that this would be a clear "instrumentalisation" of the embryo.

In addition, if an embryo was transferred that was both free of the illness and HLA compatible, there are potential concerns about the welfare of the future child. For example, should it prove impossible to obtain the umbilical cord blood – or a sufficient amount of it – the parents might seek to have bone marrow removed from the child to be used in the treatment of the sick child, or indeed to commence a further PGD/IVF procedure for the purpose of obtaining another embryo to obtain the necessary material to treat the sick child. Again, concerns about instrumentalisation arise.

It should also be noted that umbilical cord blood transplants could be used to treat a wide range of diseases, including some that are not genetically based. In such cases, some would consider it desirable to use PGD purely for the purposes of establishing HLA compatibility. Unlike in the first example, where PGD could be considered to offer potential benefits for the embryo concerned by establishing that the latter did not carry a serious disease, in such a case PGD would offer no benefits to the embryo.

Some argue that the duty of family solidarity means that it is appropriate to use PGD in this way to promote such solidarity. Further, it is argued that the duty of social solidarity means that society should not make it impossible for a parent to access a life saving treatment for his or her child. In contrast, others argue that to

use PGD in this way, particularly when it serves no health purpose for the embryo concerned, is a distortion of both PGD and of medically assisted procreation, and that furthermore the use of such techniques for these purposes would involve an unacceptable instrumentalisation of a child.

VI. Conclusion

This report aimed at giving an overview of current positions found in Europe regarding the protection of the human embryo *in vitro* and the arguments supporting them.

It shows a broad consensus on the need for the protection of the embryo *in vitro*. However, the definition of the status of the embryo remains an area where fundamental differences are encountered, based on strong arguments. These differences largely form the basis of most divergences around the other issues related to the protection of the embryo *in vitro*.

Nevertheless, even if agreement cannot be reached on the status of the embryo, the possibility of re-examining certain issues in the light of the latest developments in the biomedical field and related potential therapeutic advances could be considered. In this context, while acknowledging and respecting the fundamental choices made by the different countries, it seems possible and desirable with regard to the need to protect the embryo *in vitro* on which all countries have agreed, that common approaches be identified to ensure proper conditions for the application of procedures involving the creation and use of embryos *in vitro*. The purpose of this report is to aid reflection towards that objective.

APPENDIX I

Figure 1

Chronology of embryo development until implantation

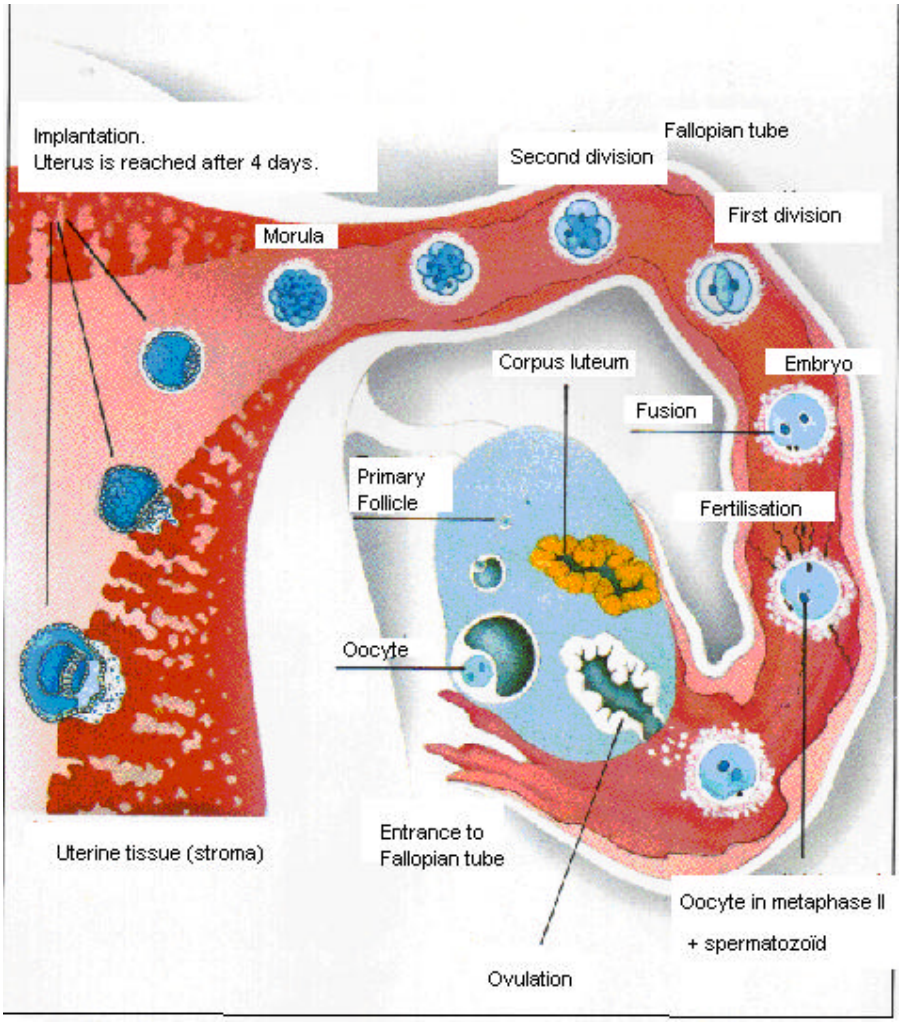
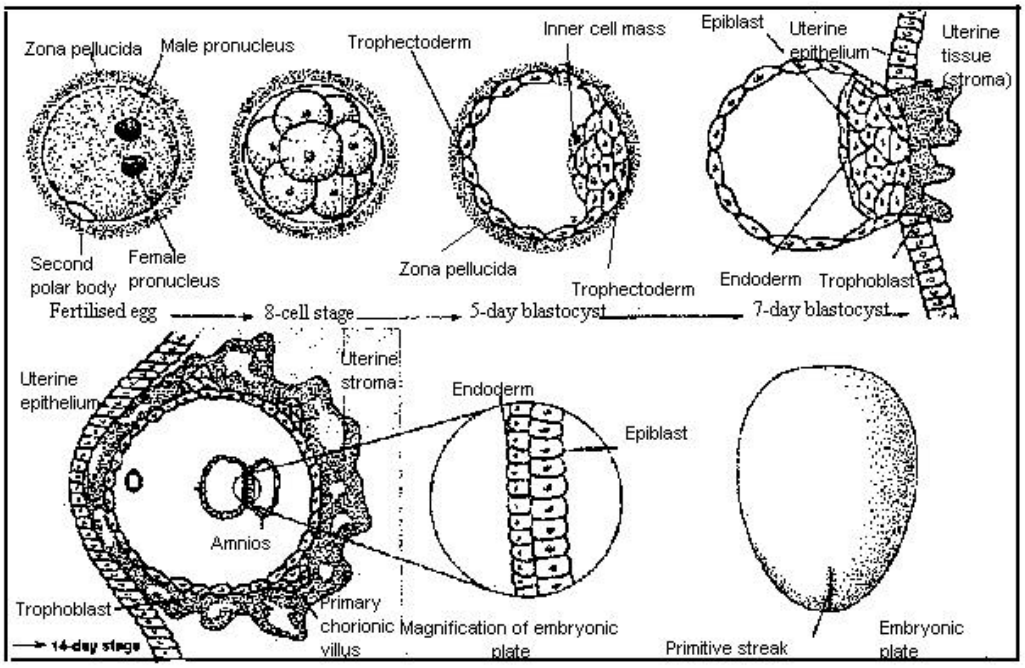


Figure 2

First stages of embryo development



APPENDIX II

Glossary

- **Aneuploidy** a condition in which the number of chromosomes in the cell differs from the normal number.
- **Blastomeres** cells into which an embryo divides during cleavage stage.
- **Blastocyst** the stage normally reached 5 to 7 days after fertilisation; the stage at which implantation process in the uterus begins.
- **Embryonic stem cells (ES cells)** embryonic cells that can proliferate indefinitely and differentiate into many different tissues.
- **Cell nuclear transfer** cloning technique where the nucleus of a cell from the organism (e.g. animal) which we want to clone is transferred into an oocyte whose own nucleus has been removed.
- **Cell differentiation** the progressive restriction in potential cell fates, until acquisition of a specialised function is achieved.
- **Endometriosis** presence of endometrial tissue (normally restricted to uterus) in abnormal locations such as Fallopian tubes, ovaries or the peritoneal cavity.
- **Fertilisation** begins when the male gamete penetrates the oocyte and ends when male and female chromosomes come together to form the zygote.
- **Folliculogenesis** the entire maturation process of the follicle in the ovary.
- **Implantation** process which lasts about one week, beginning when the blastocyst attaches to the wall of the uterus of the woman and ending when the embryo is fully embedded in the wall of the uterus**,** or exceptionally in an extrauterine place.
- **Inner cell mass** group of cells in the blastocyst which would make up the fetus and some of the surrounding membranes.
- **Karyotype** analysis of the number, size and shape of an individual's chromosomes.
- **Meiosis** the process by which germ cells (i.e. reproductive cells from the ovary or the testes) divide to produce haploid gametes (i.e. which contain only one set of chromosomes which results from the recombination between the maternal and paternal chromosome set).
- **Monozygotic** derived from one zygote.
- **Ovarian hyperstimulation syndrome** results from an overstimulation of the ovary by hormonal treatment. In its moderate form, it is characterised in particular by enlarged ovaries due to big ovarian cysts. In its more severe form it can be potentially life threatening.
- **Oocyte** the mature oocyte, also called ovum or egg, is the female gamete, possessing a genome reduced by half (haploid genome), ie normally 23 chromosomes.
- **Oocyte in the process of fertilisation** the result of the penetration of a male gamete into an oocyte; it contains two nuclei (pronuclei), a male pronucleus containing the set of chromosomes of the male gamete, and a female pronucleus, containing the set of chromosomes of the female gamete.
- **Penetrance factor** the frequency with which persons carrying a genetic characteristic responsible for a disease show signs of the disease.

- **Polyploid** which contains three or more sets of chromosomes rather that the normal two sets (more than 46 chromosomes in human beings).

- **Pronuclei** the haploid nuclei of the oocyte and the spermatozoa after fertilisation but before the **dissolution** of their membrane and the first division of the fertilised egg.

- **Pluripotent** a cell possessing the potential to become any tissue in the final organism.

- **Somatic cells** all body cells that are not part of the germ line.

- **Spermatid** haploid (one set of chromosomes) germ cell resulting from the second meiotic division of spermatogenesis which will then differentiate into spermatozoa.

- **Spermatocyte** diploid (two sets of chromosomes) germ cell which will undergo two meiotic divisions to give haploid spermatids.

- **Totipotent** a cell from which an entire organism can be formed.

- **Zygote** the final stage of fertilisation, the single cell formed when the two sets of chromosomes, one from the male gamete, the other from the female gamete, have joined.

APPENDIX III

Selected European reference documents

- Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine (Oviedo, 4.iv.1997) ..... *ETS n° 164*
http://conventions.coe.int/Treaty/EN/WhatYouWant.asp?NT=164&CM=7&DF=

- Additional Protocol to the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, on the prohibition of cloning human beings..... ..... *ETS n° 168*
http://conventions.coe.int/Treaty/EN/WhatYouWant.asp?NT=168&CM=7&DF=

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APPENDIX IV

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