The Parliamentary and Scientific Committee

INFORMATION FOR MEMBERS
FROM THE
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Briefing Note
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In Vitro Fertilisation and Embryo Research

Following the Warnock Report of 1984 and the 1987 White Paper, the Government has introduced the Human Fertilisation and Embryology Bill containing provisions on research involving human embryos. Parliament is asked to decide between two options set out in Section 11 of the Bill which determine whether the Human Fertilisation and Embryology Authority(HFEA) is empowered to grant licences for research involving human embryos less than 14 days old.

This question involves substantial ethical and religious considerations. An understanding of scientific aspects of human fertilisation and embryology may assist Parliamentarians to come to grips with these considerations. Some of the relevant science and technology is described in this note.

THE STATUS OF THE EARLY EMBRYO

An important issue relates to the status afforded the fertilised egg and the early (pre-14 day) embryo or conceptus[1]. Some argue that these should have the status of a human being from the moment of fertilisation, since the fusion of egg and sperm produces a unique genetic combination which, if it develops normally, will develop into a child. Others point out that it is not possible to establish with certainty whether an early embryo will become a child; neither is it capable of any continued existence independent of the mother. Thus, while some legal protection should be provided, it is argued that this should not be such as to prevent the benefits to others which research may provide.

Science alone cannot resolve this question, but a clearer understanding of the early developmental process of the fertilised egg may provide illumination to allow individuals to reach their own decision.

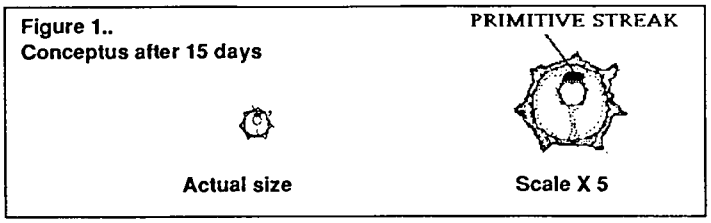

Figure 1..
Conceptus after 15 days

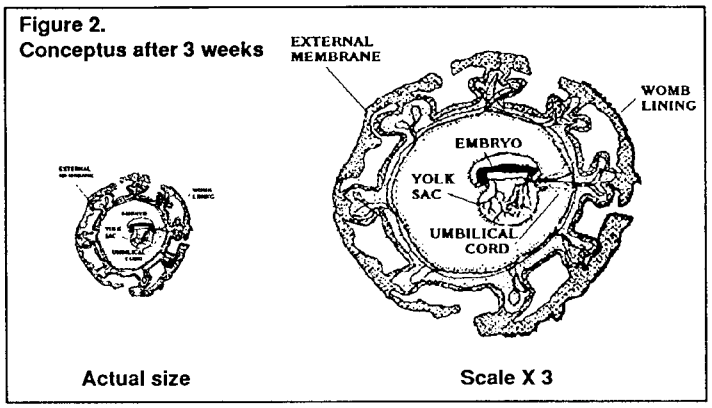

Figure 2.
Conceptus after 3 weeks

Figure 3.
Embryo at end of 4th week
(without surrounding tissues)

Early Human Development

After the egg has been fertilised, it divides into two cells, then four, eight and so on. The conceptus (the total product of the fertilized egg) initially remains unattached, passing down the Fallopian tube into the uterus. Around the 6th or 7th day, it starts to implant into the wall of the uterus - a process which takes about a week. At this stage, most of the conceptus consists of cells which develop into the life support structures of the placenta, the umbilical cord, and the amniotic sac.

The first cells whose specialised function is to form the fetus (or fetuses), develop separately at around the beginning of the third week. These cells organise themselves along a line in the conceptus and are called the "primitive streak" (Figure 1). From this point, growth

1. There has been some ambiguity in terminology in previous discussions. Medical/scientific debate often uses the terms:
   Conceptus - the whole of the developing egg, which includes the surrounding membranes and tissues (Figure 1 and 2)
   Embryo - the developing baby within the conceptus (Figure 2)
   Pre-embryo - the pre-14 day conceptus
The Bill uses the term 'embryo' in the wider context as the product of conception from the completion of fertilisation. Except for Figure 2, which illustrates the more specific use of the word, embryo is used here in the same context as the Bill - i.e. embryo and conceptus have the same meaning.

of all tissues in the conceptus continues; Figure 2 shows its development at the end of the third week. By the end of the fourth week (Figure 3), the embryo alone (excluding the surrounding support tissues) is a few mm long. At this stage, a little tail is visible, tiny buds mark the places where the arms will grow, and the future position of the head is marked by a bulge.

The Success Rate of Human Reproduction

Human reproduction has a low success rate relative to other mammals. The exact rate is difficult to determine, but most work suggests that between 25 and 75% of fertilised eggs proceed through pregnancy to a live birth. Most losses appear to be through failure of the conceptus to implant during the first fourteen days after fertilisation.

Some argue that this uncertainty over whether a fertilised egg will or will not succeed in developing into a child born live, has important implications for the degree of protection that should be afforded the fertilised egg and ensuing conceptus under law. Others argue that the same unique genetic combination is present at all stages, and that to attempt to distinguish between any one stage of development and the next is an artificial exercise.

The Significance of 14 Days and the Primitive Streak

The option allowing licensing of research places an absolute upper limit of 14 days' development after the start of fertilisation, or the appearance of the "primitive streak" -which generally coincides with the completion of implantation. As described above, this comprises the first differentiation of cells which develop into the fetus, and is taken by some as marking the onset of a discrete human existence. In most cases, only one primitive streak will form which can go on to develop into a single child. In rare cases, two streaks may form which can develop into identical twins. In other cases, the conceptus fails to develop fetal cells at all. This "blighted ovum" usually fails to implant properly and is lost, but very occasionally it may develop into an abnormal growth which has to be surgically removed.

The 14 day or primitive streak limitation would therefore restrict research to the conceptus before the fetal cells start to develop separately. There is no possibility of the embryo having any consciousness because the development of the central nervous system does not begin until late in the third or early in the fourth week.

At the current state of technology, the 14-day option would be hypothetical because no conceptus has successfully developed *in vitro* for more than 8-9 days.

TABLE 1 Success rates in IVF in the U.K. (1987)

	Treatment cycles	Egg collections	Embryos transferred	Pregnancies	Live births**
Number	8899	6983	14941	980	760
Overall success rate(%) *	-	-	-	11.0	8.5

*per treatment cycle **Subsequent neonatal deaths 21

IN VITRO FERTILISATION TECHNOLOGY

Most embryo research to date has been with the objective of improving IVF techniques. An understanding of current IVF technology is thus relevant.

IVF to produce "test-tube babies" was first successfully applied over 10 years ago to overcome a range of causes for infertility[2] which affect some 10-15% of married couples. Over 2000 children have been born in the UK as a result of this technique. IVF involves removal of eggs from the woman, fertilisation with the partner's sperm in a test-tube or glass laboratory dish, cultivation in a nutrient mixture for the first few days as a growing conceptus, and return to the woman's uterus in the hope that the conceptus will implant and develop via a normal pregnancy.

This is a simple procedure in principle, but has a relatively low success rate. Returns to the Interim Licensing Authority which oversees all IVF facilities, are summarised in Table 1 which show that treatment succeeds in giving rise to a live birth only around one in ten attempts. This low rate arises from difficulties in several key steps in the procedure including

- ovarian stimulation may produce eggs which are immature and not as readily fertilised
- difficulties in getting efficient fertilisation *in vitro* without causing fertilisation by more than one sperm
- problems in determining the optimum growth medium for the conceptus
- low rates of implantation on return to the woman after culture
- slightly lower rates of success for conceptuses implanted after freezing.

For these reasons, clinics collect several eggs at once. Eggs suitable for fertilisation cannot be stored at present, so are all fertilised. Two or three of these are returned to the mother to compensate for the low

2. The main causes of infertility found in a study in Bristol were :

Sperm defects /deficiency	24%	Ovulatory failure	21%
Blocked Tubes	14%	Endometriosis	6%
Unexplained	28%	Mucus defects	3%
Other male infertility	2%	Coital failure	6%
Other causes	11%		

implantation rate - a practice which gives rise to a multiple pregnancy rate of over 20% (compared with the normal rate of only around 2%). Excess fertilised eggs can be frozen to provide reserves in the event of the first set not implanting successfully.

Much research has already gone into developing the existing techniques used for IVF. This has inevitably involved fertilisation using eggs and sperm from consenting donors, culture, and study of the resulting conceptuses in order to define and develop procedures which have a better success rate.

IVF has clearly brought benefits to those it has helped have children. However, some have criticised it as technologically and emotionally demanding, expensive and inefficient, as well as introducing the ethical difficulties associated with the creation of excess embryos. Critics suggest increased emphasis on the development of more "natural" techniques, for instance by transferring the egg to the woman's uterus for fertilisation through sexual intercourse. However, this has not been shown to be effective, although research to pursue this possibility is planned.

Since the Warnock report, additional techniques have been developed which allow fertilisation inside the woman's Fallopian tubes using eggs and sperm collected in the manner usual for IVF. These methods therefore offer treatment for some causes of infertility, without recourse to fertilisation outside the body. However, the causes of infertility are varied and it is accepted that IVF remains the only available technology for several causes of infertility, including blocked tubes, and male sterility due to low sperm counts or sperm which have difficulty reaching or penetrating the egg.

RESEARCH INVOLVING HUMAN EMBRYOS

Research and its Control

Following the Warnock Report, the Voluntary Licensing Authority (now renamed the Interim Licensing Authority [3]) was set up in 1985 to apply the controls envisaged in the report. Up until April 1989, the ILA had approved 53 research projects which are summarised in Table 2. The majority of these are aimed at investigating the reasons for failure of IVF described earlier and bringing about an improvement. Several projects are related to the diagnosis of genetic defects, and one to the development of a contraceptive vaccine.

TABLE 2 Research Involving Human Embryos Approved by the ILA 1985-9

Subject	Objectives	Number of Projects
IVF	Improve efficiency of -egg and sperm collection -fertilisation -culture of fertilised eggs -embryo storage -embryo implantation -tests for embryo viability	41
Diagnosis genetic disorders	Embryo biopsy Tests for x-linked genetic diseases (inc. Lesch-Nyhan's disease)	11
Contraception	Vaccine development	1

In considering applications, the ILA applies criteria developed in the Warnock report and retained in the Bill. These include the banning of certain categories of research; namely modification of the genetic constitution of fertilised eggs/embryos, cloning, growing the conceptus beyond 14 days and growing the human embryo in another species. The ILA also does not approve research which is just for scientific curiosity (eg to study conceptus development) or which could be pursued by alternative means, eg using animal models. Work must be both scientifically valid and clinically relevant.

Supporters of continued controlled research suggest that the main areas of potential future benefit fall into the same categories as existing research[4] i.e.

a. Improving treatment of infertility
b. Developing more effective contraceptive techniques
c. Screening for genetic abnormalities before implantation.

One of the subjects to attract much effort is the pre-implantation diagnosis of certain genetic diseases. Recently it has been shown that a single cell can be removed from the conceptus at the 8-16 cell stage without affecting its subsequent *in vitro* development, and this provides sufficient DNA to carry out tests for sex and for the presence of certain genes responsible for genetic disorders (See POST Briefing Note 4). While this is not appropriate for congenital malformations (such as neural tube defects), there are many disorders that are caused by failure of a single gene, including thalassaemia, muscular dystrophy, Huntington's chorea, cystic fibrosis, Lesch-Nyhan's and Tay Sachs diseases.

Supporters of this work point out that where both couples are carriers, there is a 1 in 4 chance of passing

3. The ILA is jointly sponsored by the Medical Research Council and the Royal College of Obstetricians and Gynaecologists and comprises 18 members, of whom half are lay members. It produces guidelines for local ethical committees, clinical practice and research. It also considers licence applications to conduct any research involving human embryos. The ILA visits all centres before issuing any licence and also conducts review visits.

4. The Bill includes the additional purposes of research into the causes of miscarriages and congenital disease, as well as increasing knowledge about the creation and development of embryos.

on the genetic disorder to their children. Currently, prenatal tests can be carried out after 8 weeks' pregnancy at the earliest, at which point a positive result may lead to a difficult decision on whether to terminate the pregnancy. Using IVF and pre-implantation screening, it would be possible to select for replacement only those conceptuses shown to be free of the genetic defect, thus avoiding the trauma of abortion.

How Necessary is Human Embryo Research?

Critics of the use of human embryos argue that the protection of the embryo is paramount and that it is improper to conduct research, regardless of the potential benefits to others. Some have also questioned the benefits obtained from such research and whether embryos need to be used at all.

In response, it has been pointed out that maximum use of animal models and other (non-embryo) human tissue already takes place. Nevertheless, promising procedures still have to be validated before they can be applied in clinical practice. For instance, diagnostic tests can be developed using a range of human cells. Before such tests can be applied to preimplantation diagnosis however, it has to be demonstrated that human conceptuses can survive the procedures and develop normally before a clinician would replace them in a woman.

The Medical Research Council and the Royal Society strongly support the option allowing controlled research up to 14 days. They and others point to the continued problems of infertility and the shortcomings of current techniques, and that avenues of potential improvements would be curtailed, if research were to be banned. It would also not be possible to extend the role of pre-implantation diagnosis for serious genetic diseases as an alternative to prenatal screening and abortion (currently this can determine sex which can be of use in relation to sex-linked diseases such as haemophilia and muscular dystrophy, but its potential is expected to expand as probes for other single gene defects become available). Opponents of research however question the real utility of these anticipated developments and do not, in any case, believe that they justify the use of human embryos.

Would 'Spare' Embryos Suffice if Research were allowed?

Much research to date has used human eggs which have been donated by women undergoing sterilisation, who have consented to the procedures involved after counselling on any risks involved. The eggs are fertilised *in vitro* as part of the experimental procedure. In addition, fertilised eggs and conceptuses formed in IVF treatment may exceed the numbers required, and some of these have been donated for research. It has been suggested that research could be accepted on such 'spare' embryos, while opposing research on those created from donated eggs and sperm.

Arguments have been raised against the usefulness of this suggestion. The main one is that the source of such 'spares' is likely to decline as more couples exercise the option of freezing excess embryos for potential use at a later time. Also, it is anticipated that future research on IVF techniques (if this takes place) may reduce or even eliminate the generation of excess fertilised eggs. For instance, if unfertilised eggs could be stored, only those needed for the single course of treatment would need to be fertilised.

A second point is that much of the research envisaged relates to the fertilisation process itself and the early development of the conceptus; these stages are completed by the time any decision is taken on whether excess embryos could be donated for research. It has thus been suggested that the decision whether or not to allow controlled research on human embryos, should be made on the basis that donated eggs, as well as 'spare' embryos, could be used in any research licensed by the HFEA.

Developments in other countries

This issue has been debated in a number of countries. Only a few have enacted laws; others have not yet acted on the recommendations of relevant national review committees. Table 3 provides a partial summary.

Table 3 : Some National Positions on Human Embryo Research

Australia	One state law allows research on 'spare' embryos; one restricts research to that not detrimental to the embryo
Canada	Proposal to limit embryo research to infertility treatment
Germany	Draft law prohibits research; yet to pass Bundestag
France	White paper would allow research on 'spare' embryos
Netherlands	Proposal to control research via national committee
Norway	Law prohibits research and freezing of embryos
Spain	Law allows research on 'spare' embryos
Sweden	Proposal to control embryo research up to 14 day limit
USA	No Federal law. Louisiana prohibits creation of embryos for research. Most states have no applicable laws

FURTHER READING

Additional details and background information are available from POST, 16 Great College Street, Westminster, tel 222-3912/7085.

The ***Parliamentary Office of Science and Technology*** has been set up by the Parliamentary and Scientific Committee to inform Parliamentarians on scientific and technological matters underpinning current issues.