REPRODUCTIVE TECHNOLOGIES

Reviews infertility treatment
Where is the science going?
What ethical issues are raised?
How could they be dealt with?

POST note 48 January 1994

POSTnotes are intended to give Members an overview of issues arising from science and technology. Members can obtain further details from the PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY (extension 2840).

Recent public consultation on the future possibility of using foetal ovaries in infertility treatment has brought home how far reproductive technologies allow 'natural' constraints on human reproduction to be by-passed. There have been calls for Parliament to debate the ethical issues raised by this and other aspects of infertility treatment.

This briefing note summarises the relevant science and the issues involved.

TREATMENT FOR INFERTILITY

Differing estimates suggest that 6-15% of couples seek help at some stage because of difficulties conceiving, although only around 4-7% of women are permanently and involuntarily sterile. Infertility can arise from a variety of causes, including:-
Male: sperm defects/deficiency and other causes.
Female: ovulatory failure, blocked tubes, endometriosis, mucus defects and uterus defects.

Some infertility can be avoided (e.g. by early treatment of pelvic infections, reducing excess alcohol or tobacco use), but many cases can only be overcome by treatment. Surgery or drugs are effective with many women, while male infertility has been circumvented by donor insemination (DI) for 50 years or more. But to overcome some causes of infertility, techniques for fertilisation outside the woman's body had to be developed, giving rise to in-vitro fertilisation (IVF)- first carried out successfully in Oldham in 1978, and covered by the Human Fertilisation and Embryology Act in 1990 (**Box**). Much research has been needed to improve the various steps involved in IVF and the chances of a successful outcome:

Sperm collection and storage presents few problems, since most IVF uses the partner's sperm. Where donated sperm is used, it is frozen and stored for 6 months or more to reveal any HIV infection in the donor; there are some local shortages of donated sperm, particularly amongst minority groups.
Egg collection still requires hormonal stimulation, intensive daily monitoring, and extraction of mature eggs under anaesthesia or sedaion with the attendant discomfort and risks. Eggs are not routinely preserved by freezing, although this is becoming possible.
Fertilisation in vitro is now fairly routine although research was necessary to define the right conditions.

❒ CURRENT LEGISLATIVE POSITION

The Human Fertilisation and Embryology (HFE) Act was passed in 1990, establishing the Human Fertilisation and Embryology Authority (HFEA) which took over from the Interim Licensing Authority regulation of all treatment and research centres involved in:-

- any fertility treatment involving donated eggs or sperm, or embryos created outside the body;
- storage of eggs, sperm or embryos;
- research on human embryos (up to the statutory limit of 14 days).

The activities above can be carried out only under licence from the HFEA, and licensees must adhere to HFEA codes of practice covering the techniques allowed, staff qualifications, clinic standards, consent, counselling, criteria for the suitability of donors and consideration of the welfare of the child, and policy on storage and disposal of eggs, sperm, and embryos. The HFEA ensures compliance with the code.

HFEA guidance is applied at local level by clinicians with the help of ethical committees which have been established by most IVF clinics to look at individual cases. In deciding whether or not to offer treatment, the HFEA states that centres should take into account both the wishes and needs of the people seeking treatment and of the needs of any children involved. Clinicians will also take account of professional guidance from the Royal College of Obstetricians and Gynaecologists; in addition the British Medical Association has a Committee on Medical Ethics which may influence professional views. The BMA's view is that the needs of the child are more important than the 'right' to have children.

Embryo culture and transfer. Providing the right mixture of energy and nutrients to mimic development in the mother took many years' work, and research continues on this stage. Biochemical tests may help assess the chances of successful implantation, but most decisions on which embryo(s) to transfer are still taken 'by eye'. Up to 3 embryos are transferred to the woman[1].

The outcome of the above research has been that the success rate of IVF has risen steadily (see **Table 1**) - in 1987, less than 1 in 10 attempts led to a live birth, while today the average is nearer 1 in 7, and over 10,000 children have been born through UK IVF. There remain however large variations in the success rates between different clinics (as well as between age groups and causes of infertility), and the HFEA is considering how more information on this might be made available.

Other techniques include Gamete Intra-fallopian Transfer (GIFT), which attempts fertilisation in the body by

1. Depending on the consent conditions, any surplus embryos would be frozen for future transfers, others' treatment, research within the statutory limit of 14 days age or allowed to perish.

Table 1 SUCCESS RATES FOR IVF TREATMENT (Source:HFEA)

Year	Patients	Treatment Cycles	Pregnancies	Live Births	Miscarriages	Ectopic pregnancy	Perinatal deaths
1987	7,488	8,899	980	760	216	65	21
1991	12,135	13,156	2,186	1,604	389	64	37

placing eggs and sperm into the fallopian tubes (controlled studies show success rates are lower than IVF). GIFT is subject to HFEA licensing only where donated eggs or sperm are involved (Box).

RECENT DEVELOPMENTS

New ways to allow men with reduced fertility to use their own sperm include **'micromanipulation' techniques** to collect sperm from close to the testes (Micro EpididymalSperm Aspiration); alternatively, the sperm can be **'micro-injected'** into the egg. Techniques at an earlier stage include **'zona drilling'** to reduce the barrier posed by the egg protein shell (zona pellucida).

There is a **shortage of eggs** relative to demand and the HFEA recently launched a consultation paper on three **new sources of ovarian tissue**.

The first considers **patients donating ovaries.** For example, a woman facing sterility due to surgery, chemotherapy etc., might choose to have her ovaries removed for later use. Under some circumstances, ovarian tissue might be replaced when she had recovered from her illness; alternatively the ovaries could be used as a source of eggs for IVF. The current technical constraint is that, of the thousands of eggs in a woman's ovaries, only a few are near enough the 'ripe' stage to be successfully matured in the laboratory and fertilised (this has been done in S Korea). Scientific understanding of the processes by which the bulk of the eggs mature is still limited, and attempts to use immature eggs have had a very low success rate (3 pregnancies out of 38 transfers in S Korea); moreover, lab-based maturation seems to lead to significant numbers of eggs with chromosomal abnormalities.

Similar considerations apply to the use of **ovaries donated from cadavers**, subject to specific consent to take genetic material. Ovaries would need to be removed speedily to avoid deterioration, and there is less opportunity to screen the donor's genetic background than with a live donor. There is thus concern that the risk of genetic abnormalities could be increased, and research would have to address this and other points before such material could be used safely.

The third possibility raised was to use **foetal ovaries** from abortions, still births or miscarriages. Although foetal ovaries have been transplanted to restore the fertility of sterile mice, this technique is not remotely possible in humans at present, and would raise very substantial scientific challenges in addition to the ethical concerns outlined later. Ovary development proceeds through several stages whereby 7 million or so germ cells are laid down by the 5 month old foetus, after which they are progressively destroyed so that ~2 million are left at birth, and ~200,000 at puberty. Research would have to establish why so many primordial eggs are wasted naturally (e.g. is it a means of selecting and destroying cells with genetic errors?), and then develop means of culturing and maturing the very immature eggs (which could require up to year in culture) before they could be used. There are also serious questions on how to check that the foetus was not suffering from a genetic disorder which would normally have led to a miscarriage, but which could now be transmitted to the next generation[2]. Experts in the field do not see such questions being answered inside 10 years, if then, and there is currently no research underway in the UK on using human foetal eggs pending the outcome of the HFEA consultation.

Pre-implantation diagnosis. In the last few years, a new capability to 'test' embryos *in vitro* has been developed - one or two cells can be removed from the embryo at the 8-16 cell stage, without any effect on subsequent development and the genetic makeup of the removed cell can then be investigated (**Figure 1**).

Research outside the UK also throws up scientific developments with ethical implications. For instance, work at George Washington University in the USA showed that embryos could be split to generate **'clones'**[3] which could continue growing.

ETHICAL AND OTHER ISSUES

Applications of Infertility Treatment

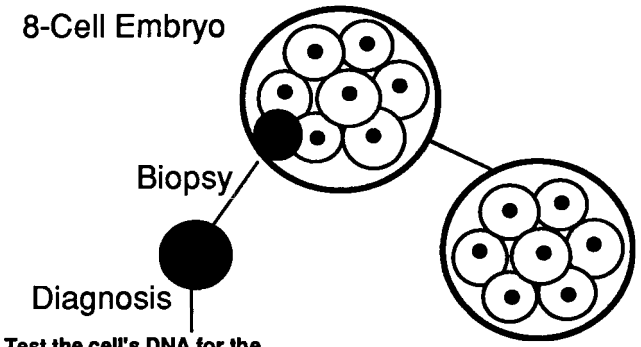
Age. A woman's fertility declines markedly after 35 and ends altogether with the menopause. IVF allows such constraints to be by-passed, and Italian clinics have impregnated women in their late 50s and early 60s, using eggs donated from younger women. UK guidelines specify that female **donors** should not be over 35, but the prospective mother's age is one of a number of factors "to be borne in mind" in meeting the statutory duty to consider the welfare of the child. In practice, local ethics committees appear not to have supported the procedure for post-menopausal women (except for cases of premature menopause).

Some argue that each case should be judged on its merits according to the woman's physical and psychological health, and that there should be no fundamental objection to IVF for older women. Others believe the physical risks of pregnancy to the woman and foetus have been underplayed and that the child is not well

2. There are already 5,000 or so genetic disorders known and more may be discovered in future; it is thus impractical to screen any egg or embryo for all such disorders.

3. Cloning by embryo splitting is not actually prohibited by the HFE Act, but the HFEA has said it would not issue licences for such work.

FIGURE 1 PRE-IMPLANTATION DIAGNOSIS



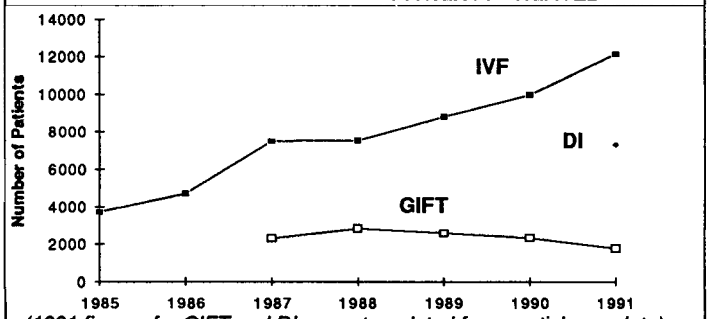
served as a teenager by having a mother in her 70s, and that 'natural' limits to child-bearing should not be circumvented. Irrespective of UK practice, the recent case of a woman declined treatment in the UK but successfully impregnated in an Italian Clinic, shows the permeability of national regulations. Within the EU, only some Member States regulate IVF, and the Government has indicated its wish to see greater consistency within the EU. Given the global availability of IVF, even if there were EU harmonisation, patients unhappy with local restrictions would still have opportunities to find treatment.

Physical Characteristics. The HFEA Code of Practice (Box) encourages prospective parents to choose donors to match their own genetic makeup (height, race, hair colour etc). However, recent publicity over a case in Italy where a 'black' woman chose a 'white' donated egg because of concerns over racial discrimination shows it is equally possible to select a child well outside the genetic range of the social parents. HFEA guidance is that the clinician should not allow such 'social' choices, and donated material should be selected as far as possible to match parental physical characteristics.

The HFEA's consultation paper on **ovarian tissue from live donors, cadavers or foetuses,** raises the ethical issues involved and invites comment by 1 June 1994. As mentioned earlier, while the first two sources are a realistic prospect in the near future, the HFEA consultation on foetal ovaries is well (10 years or more) ahead of any medical capability. Some consider it appropriate to anticipate such developments and encourage debate now; others see the question of using foetal ovaries as so far ahead that debate would be better focused on the use of ovaries from patients and cadavers. If there is a wider debate, many scientists see it as important that the contribution of research on foetal egg development to understanding the origins of genetic disorders should be recognised and not obscured by concerns over the potential future implications for IVF treatment[4].

4. The HFE Act requires that any research involving the creation, keeping or using of a human embryo can only be carried out under a licence from the HFEA, and for the specific purposes specified in the Act. However, eggs are only covered when they are 'mature eggs of a woman', so research on immature eggs and ovarian tissue would not need a licence under the Act, until used in attempts to create an embryo.

FIGURE 2 TRENDS IN NUMBER OF PATIENTS TREATED



(1991 figures for GIFT and DI are extrapolated from partial year data)

Nevertheless, the debate has started. Some point out that foetal tissue can already be used in research and therapy under the guidelines of the Polkinghorne Report, and conclude it would be better to use foetal ovaries for some 'good' purpose than see them go to 'waste'. Others point out that the Polkinghorne report did not cover germ-line tissue, and that this raises wholly new issues. Primary questions concern the psychological effects on the child of knowing its 'genetic mother' was an aborted foetus which had been unwanted by its 'grandmother'. Difficult issues of consent would also be raised, since the foetus cannot give consent, and procedures under the Polkinghorne report might not be appropriate.

Some argue that the potential beneficial uses warrant trying to resolve these issues, but others see the effect of the debate reducing the foetus to a source of 'spare parts' and believe the use of foetal material should be ruled out on ethical grounds. Indeed, some Church leaders see these ethical concerns as merely a magnification of those already existing over the use of donated genetic material in general, and believe that reproductive technologies should be limited to assisting couples to have their own children **without** the use of donated eggs or sperm. On this however, DI and egg donation are long-established and widely applied techniques, and many see their basic acceptability as having been resolved by the passage of the HFE Act.

Relevant to this debate is that the number of patients involved in IVF and DI is growing (**Figure 2**) and, of the 20,000 or so patients treated in 1991, the 7,300 DI patients and a small proportion of the IVF patients (2-3% for eggs and 3-4% for sperm) relied on donated sperm or eggs. The great majority (~90%) of treatments are carried out privately, and not all NHS districts offer IVF treatment.

Another issue surrounding IVF has been its tendency to produce **multiple births.** Guidelines introduced in 1987 limit eggs or embryos transferred to 3, and this has eliminated births through IVF of quads and higher. However, the number of twins from IVF has actually risen (24.5% of IVF births in 1991; 16% in 1987) and triplets have remained not uncommon (4.6% of IVF births in 1991; 6.1% in 1987). Improved success rates have thus undermined to some extent the measures to

reduce multiple births, and the HFEA is keeping this aspect under scrutiny.

On the issue of **donor confidentiality**, the HFEA keeps records of the identity of egg and sperm donors, but confidentiality is preserved except where a genetic abnormality in the child could be traced to a failure by the donor to disclose required genetic information. Under the Act, the Government is empowered to make regulations on what information can be given to a child seeking to find out more on its genetic origin, but these have not yet been formulated.

Sex Selection and Genetic Screening

Some clinics claim to be able to **separate sperm** to allow couples to select the sex of their child. There is much scepticism over the efficacy of methods currently offered in the UK, but patents have been awarded to a US company for a process which gives 80%+ success rates in animals. Sperm sorting is currently outwith legislation (when not donated), and there is the future possibility of home sorting and insemination kits without even the need for medical supervision.

Pre-implantation diagnosis also allows the sex of an embryo to be screened. **Sex selection** can be used where there is a risk of x-linked diseases such as Duchenne Muscular Dystrophy - here by selecting a female embryo there is no risk of the child developing the disease in later life. However, some parents might wish to choose the sex of their child for 'social' reasons. The HFEA carried out a consultation exercise during 1993 and concluded that grounds for sex selection should be limited to avoiding serious diseases.

The genetic material (DNA) of the separated cell (Figure 1) can also be screened for any gene whose composition is known. Many genetic disorders are caused by a defect in a single gene, including thalassaemias, muscular dystrophy, Huntington's chorea, cystic fibrosis and Tay Sach's disease. Using IVF and pre-implantation screening, it is possible to select for replacement only those embryos shown to be free of the genetic disorder[5]. This technique has been applied at Hammersmith Hospital to screen embryos for cystic fibrosis and other genetic disorders in cases where couples had a high risk of having an affected child.

As the Human Genome Project proceeds however (POST Briefing Note 15), many more genes will be discovered and there are public visions of 'designer' babies where the embryo is selected for physical traits, intelligence etc., as well as freedom from genetic disease. There are however, major technical constraints to broadening the basis for embryo screening, and the prospect of parents being given a 'menu' of characteristics to choose from remains in the realm of science fiction. Firstly, it would only be possible to choose between different embryos, so the choice will remain between genetic combinations 'nature' has thrown up. Secondly, most physical traits (e.g. intelligence, height) are expected to involve more than one gene, be difficult to predict exactly and be difficult to screen for. Clinicians thus expect pre-implantation diagnosis to remain restricted to serious single-gene genetic disease.

TABLE 2 SOME POINTS FROM DANISH CONSENSUS CONFERENCE

- adoption should be seen as an alternative to infertility treatment, and couples counselled accordingly when receiving information on IVF etc.
- more emphasis on researching and addressing the causes of infertility
- infertility is not a societal problem but a personal one; the costs of treatment should be properly quantified and involve a user contribution
- anonymity of donors should be lifted in the interests of the child
- technology which makes it possible to use eggs from aborted foetuses should be prohibited
- at least one of the social parents should be a genetic parent
- it is better that society should set the limits for technological development than technology setting the standards for everyday practice.

Developing Public Debate

There have been many calls for a wide public and parliamentary debate on the ethics of reproductive techniques, with two main lines of argument. One wants to develop ethical boundaries within which science and medicine should be required to operate. The other would evaluate each ethical issue as and when scientific developments made it practicable.

Some believe in addition that there are sufficient ethical issues emerging from the new biology (e.g. the ethics of patenting life forms or human gene sequences) to justify establishing a national bioethics forum to provide a common framework of guidance and principles within which the specialised agencies such as the HFEA could operate. The Government has preferred up to now to establish *ad hoc* committees to address specific questions (e.g. that on Gene Therapy established in 1989). But others have seen a need for a national forum for some years and set up the Nuffield Council on Bioethics in 1991; this issued a report recently on the ethics of genetic screening, and is also looking at medical and scientific use of human tissue.

Official national bioethics committees have been set up in Australia, France, Denmark and other countries, and Canada has a Royal Commission on reproductive technologies. Another model for encouraging public debate has been the 'consensus conferences' of Denmark and the Netherlands, where a lay panel (representative of society at large) reaches conclusions after being briefed by technical, medical, legal and other experts. A recent conference in Denmark reached a number of 'conclusions' with respect to infertility treatment, some of which are illustrated in **Table 2**.

5. This is seen by many doctors and patients as preferable to avoiding serious genetic disorders by prenatal testing and selective abortion; however, some would argue that the moral status of the foetus and embryo are the same and that there is thus no difference on ethical grounds between discarding an embryo or abortion.