

HUMAN FERTILISATION AND EMBRYOLOGY AUTHORITY REPORT: PREIMPLANTATION TISSUE TYPING

Introduction

1. Preimplantation tissue typing is a new technique which allows the selection of embryos in order to bring about the birth of a child who can provide a matched tissue donation to an existing sibling, either as the sole clinical objective or in combination with preimplantation genetic diagnosis (PGD) to avoid a serious genetic condition in the resulting child.
2. The first reported use of preimplantation tissue typing was in 2000 in the United States, when PGD was used to avoid the birth of a baby with an inherited condition called Fanconi anaemia. During the embryo selection process, a second test, to identify the tissue type of the embryo, was carried out in order to ensure that the resulting baby was both free from the genetic condition in question, but whose cord blood could also be used in a tissue donation to an existing sibling with the same condition.
3. Following detailed consideration of the issues raised by this innovation, the HFEA produced an interim policy on preimplantation tissue typing in November 2001. The policy is described in the next section.
4. Three years on, after a period of public and professional discussion, the HFEA took the decision to review the interim policy. The Authority's Ethics and Law Committee (ELC) was asked to conduct the review, by carrying out research into scientific and clinical developments, expert views on cord blood and bone marrow transplantation, legal developments, academic literature and public attitudes. This report outlines the findings of the research which was taken into account during the development of the new policy.

The 2001 interim policy on preimplantation tissue typing

5. In November 2001, following the birth of Adam Nash (the first baby born following preimplantation tissue typing), the HFEA established a policy on preimplantation tissue typing. This policy followed detailed consideration of the issues by the HFEA's Ethics Committee. The Authority recognised that the decision to pursue this procedure was a highly personal one and was likely to involve complex motivations. It was persuaded that preimplantation tissue typing would not necessarily compromise the welfare of the child born as a result of the procedure because there was no reason to suppose that such a child would necessarily suffer emotional or psychological harm as a result of knowing that they were conceived, at least in part, in order to be a tissue donor to a older sibling. The Authority therefore agreed that in principle the procedure was ethically acceptable but that safeguards should be put in place in order to prevent unacceptable uses of the procedure.

6. However, the HFEA took a cautious view of the current state of the science involved, in particular what little was known at that time about the consequences of removing one or two cells from the embryo (known as embryo biopsy). As a result, the Authority stated that the procedure would only be acceptable if applications for tests were considered on a case by case basis and certain conditions were met:

- (a) the condition of the affected child should be severe or life-threatening, of a sufficient seriousness to justify the use of PGD;
- (b) the embryos conceived in the course of this treatment should themselves be at risk from the condition by which the existing child is affected;
- (c) all other possibilities of treatment and sources of tissue for the affected child should have been explored;
- (d) the technique should not be available where the intended tissue recipient is a parent;
- (e) the intention should be to take only cord blood for the purposes of the treatment, and not other tissues or organs;
- (f) appropriate implications counselling should be a requirement for couples undergoing this type of treatment;
- (g) families should be encouraged to participate in follow-up studies and, as with PGD, clinics should provide detailed information about treatment cycles and their outcomes;
- (h) embryos should not be genetically modified to provide a tissue match.

7. The purpose of setting out these criteria in this way was to express the circumstances in which the Authority would consider preimplantation tissue typing to be a necessary or desirable use of licensed assisted conception treatment and therefore fulfil the condition at paragraph 1(3) of Schedule 2 to the 1990 Act that requires any activity authorised by a licence to appear to the Authority to be 'necessary or desirable for the purpose of providing treatment services'.

8. The Authority had doubts about the desirability of using PGD to select on the basis of tissue type alone (and not in order to avoid a particular genetic condition) because of the possible risks, both physical and psychological, to the child born as a result of the procedure.

9. In 2001, there was no evidence available about the possible health risks to the resulting child from embryo biopsy. This led the Authority to take a precautionary approach. The benefit of PGD, when it is performed both to avoid a particular genetic condition and to select for tissue type, is that it brings about the birth of a child without a particular genetic condition. This benefit outweighs any concerns about the possible risks associated with embryo biopsy. However, when PGD is performed for tissue typing alone, the procedure does not bring about the birth of an unaffected child where an affected one might have been born. In this circumstance, the theoretical risk of embryo biopsy to the resulting child was enough to convince the Authority that PGD for tissue typing alone would not be a desirable use of the procedure.

10. Taking into account these possible risks, the HFEA took the view that preimplantation tissue typing, performed for the sole purpose of providing a tissue matched donor, was not a desirable use of PGD.

Reviewing the 2001 Interim Policy

11. Following a court case challenging the Authority's powers to license preimplantation tissue typing and a sustained period of public and professional debate on the issue, the Authority asked its Ethics & Law Committee (ELC) to review its policy on the use of the technique. The timetable of the review was:

December 2003	Ethics and Law Committee recommends a review of preimplantation tissue typing
February-May 2004	Desk research started and views of experts gathered
April 2004	Scientific & Clinical Advances Group reviews the latest evidence on risks associated with embryo biopsy
June 2004	Research is reported to Ethics and Law Committee
July 2004	Authority considers recommendations from the Ethics and Law Committee

12. The research conducted in the course of the review included:

- consideration by the Scientific & Clinical Advances Group of the latest evidence relating to the risks associated with blastomere biopsy and implications for the resulting child;
- expert psychosocial evidence and literature review concerning the experience of families and children in sibling cord blood and bone marrow donation;
- expert evidence and literature review concerning current practice in cord blood and bone marrow donation for a range of conditions;
- research into case law relating to consent and authorisation for procedures involving minors;
- review of statements and opinions of UK, foreign and international ethics and advisory bodies relating to preimplantation tissue typing;
- commissioned research into public opinion on issues related to embryo selection for tissue type and sibling cord blood and bone marrow donation.

Risk associated with embryo biopsy

13. As indicated in paragraph 9, the lack of evidence relating to the effects of embryo biopsy on any child resulting from a biopsied embryo was a material consideration in the Authority's 2001 decision. Whilst there is known to be some risk of damage to the embryo as a result of the biopsy procedure (<5%), such damage usually renders the embryo non-viable. In the majority of cases, where the embryo continues to develop following the biopsy, the development of the embryo and subsequent development of the fetus and child is thought to follow a normal path.

14. As well as existing published studies, the HFEA reviewed evidence collected by the European Society of Human Reproduction and Embryology's

PGD Consortium and unpublished evidence from a paediatric follow-up study of more than 60 children born following embryo biopsy at one UK centre. These studies showed consistently that the sample of children studied did not show a significant increase in incidence of serious abnormalities at birth, or, where information was available, at 1 and 2 years of age. Nevertheless, there are as yet no long-term follow-up studies of PGD offspring available. Whilst it is clear that further follow-up work is required, **the HFEA took the view that the risk to the resulting child associated with embryo biopsy is not enough to warrant a policy which distinguishes between cases in which preimplantation tissue typing is used in combination with PGD for serious disease and where discovering tissue type is the sole treatment objective. However, the latest evidence should be considered in relation to each application.**

Families' experience of sibling bone marrow and cord blood donation

15. Bone marrow donation from one sibling to another is an established procedure in the United Kingdom. Although there is limited evidence relating to the long-term psychosocial outcomes for those involved, the experts whose opinions were canvassed indicated that bone marrow donation within a family tends to intensify family relationships, but it does not necessarily change them for the worse.

16. With particular reference to cases in which a child is conceived to be a tissue donor, experts pointed to concerns about the welfare of the child as well as the welfare of the mother undergoing IVF at an already stressful time. However, there was no indication that the concerns relating to the child's welfare would differ depending on whether the condition of the affected child was heritable or not.

17. Issues relating to the potential risk to the psychological welfare of the child arising from knowledge of the circumstances of their conception were examined carefully. It was concluded, firstly, that there was no evidence that being conceived in this manner is necessarily injurious to the psychological welfare of the child and, secondly, that, in the absence of relevant empirical information, consideration of these concerns, whilst important, was merely speculative and should not therefore prohibit the use of the technique. Having considered the further evidence provided by the experts canvassed, **the Authority found no evidence that was transferable or relevant to the issue of preimplantation tissue typing that adverse psychological effects would result from the procedure. However, the Authority wished to recommend that these issues be carefully and sensitively addressed, with counselling being available from appropriately qualified counsellors, and that follow-up studies of children and their families be strongly encouraged.**

18. Those who provided the expert evidence on the psychological welfare of sibling bone marrow donors were also asked whether there were any additional considerations relating to preimplantation tissue typing that should be taken into account. They drew attention to a variety of other factors,

including the demanding family situation into which the child would be born and the donor child's relationship with the affected sibling and with other family members. In considering these responses, however, **the Authority found that these other issues would be best assessed in consideration of the circumstances of the families involved and that therefore applications for preimplantation tissue typing (both as the sole objective or in conjunction with PGD) should include submissions from the clinical team responsible for the care of the affected sibling.**

Current state of the art of cord blood transplantation in context of alternative therapeutic options

19. The Authority is only required to address itself to the issue of whether preimplantation tissue typing can be a necessary or desirable use of the technologies of assisted conception – and not to the appropriateness of different treatment options for a child affected by a particular medical condition. However, the HFEA considered it relevant to understand the reasons why preimplantation tissue typing might be an appropriate treatment and the limitations of this as a treatment strategy.

20. **Related cord blood transplantation:** Expert opinion was sought from paediatricians and haematologists working with cord blood and bone marrow transplant patients in the UK. Written responses were obtained along with a report of a discussion on preimplantation tissue typing at the UK Childhood Cancer Study Group meeting in May 2004. These indicated that the technique was considered suitable for the treatment of certain conditions. Current literature reports on the successful outcomes for both children and adults when cord blood is used to treat blood malignancies, immunodeficiency, bone marrow diseases and storage diseases.

21. **Related bone marrow transplantation:** Bone marrow transplantation is a well-established procedure for the treatment of certain conditions. Depending on the condition to be treated, there is evidence that closer human leukocyte antigen (HLA) match is generally more important for successful treatment using bone marrow transplantation than when cord blood is used.

22. Both expert opinion and the literature reviewed indicated that related donors were preferable to unrelated matched donors. Although experts pointed to important advances in transplantation using related donors who are not an exact tissue match, this is only advised for the treatment of certain conditions, such as those affecting the immune system, in which the condition is life threatening. For patients with many other conditions, such as the haemoglobinopathies (diseases of the blood), the use of related donors is not recommended because of lower success rates and a higher risk of significant complications. Where no matched donor already exists in the affected child's family, the birth of a tissue-matched sibling therefore remains the best opportunity for treating the affected child in many cases.

23. **The HFEA requires that any application submitted to carry out this procedure must be fully supported by the clinical team treating the sick**

child. They will be expected to give consideration to every other appropriate treatment before applying to the HFEA, for example the availability of alternative sources of tissue for treatment of the affected child. The HFEA regards preimplantation tissue typing as a last resort.

Legal research

24. ***R. (on the application of Quintavalle) v. HFEA***: Following the HFEA's announcement of its policy decision in December 2001, the interest group Comment on Reproductive Ethics (CORE) sought permission to apply for judicial review, claiming the decision was *ultra vires* the 1990 Act. The claim was initially successful but an appeal, in which the HFEA was joined by the Department of Health, was allowed in May 2003. As the law stands following the decision on the appeal, the HFEA has the power to license preimplantation tissue typing, with or without PGD to avoid serious disease. CORE has since successfully petitioned the House of Lords which will hear its appeal in March 2005.

25. **Consent**: Young children are not usually old enough to be legally competent to consent to their own medical treatment. However, a medical procedure may be carried out, with the consent of a holder of parental responsibility, if it is considered to be in the best interests of the child, a test which is often interpreted broadly, to include the child's psychological well-being. If a medical procedure, such as a bone marrow transplant, would save the life of a sibling, it is likely to be in the best interests of the child, since to lose a sibling is psychologically damaging. When there is a disagreement, perhaps between the doctors and the parents, the case can be referred to the court.

26. The HFEA does not have the power to impose a condition on a license that would prohibit any future attempt to obtain bone marrow, should a cord blood donation fail. However, the Authority noted that obtaining bone marrow for the treatment of siblings from children from the age of one year was a relatively routine treatment strategy where no other matched donor was available. The Authority also noted that, under common law, the best interests test applied by the courts when considering the type of medical procedures that may be performed on a child, is very much higher when such treatment gives no health benefit to the child concerned. As such, solid organ donation is extremely unlikely to be held to be in a child's best interest. Having considered typical arrangements for decision making with respect to child bone marrow donors, **the Authority found that existing arrangements were sufficient to protect the welfare of the child in these circumstances.**

Opinions of ethics committees and advisory bodies

27. Since the HFEA's landmark policy decision to permit PGD with tissue typing in November 2001, many ethics committees of professional bodies, foreign regulators, and other national and international bioethics committees have delivered opinions and produced guidance on the use this technique.

The HFEA's decision has also been the subject of considerable discussion in the academic literature.

28. **Committee opinions:** The majority of those committees that have addressed the subject agree with the HFEA that tissue typing combined with PGD for serious disease should be permitted, although many have disagreed with one or other of the HFEA's licensing criteria. In particular, many bodies discuss whether preimplantation tissue typing should be restricted to cases in which embryos are at risk from the genetic disease affecting the existing child.¹ There is also some suggestion that the procedure may be permissible, subject to certain safeguards, where the intention is to use bone marrow from the resulting child and not merely cord blood. Additionally, some feel that a decision of this sort should rest with the parents of the child concerned and not with regulators, whilst others would seek guidance from Parliament.

29. **Academic articles:** More thoroughly and consistently argued positions were found in the academic and professional journals. Arguments discussed included reproductive autonomy, 'procreative beneficence' and the moral value of parental motivation, child welfare and the instrumentalisation of the child, and the 'slippery slope'.

30. The Authority reviewed the now considerable literature on preimplantation tissue typing but concluded that, despite the volume of literature that had accumulated, **there were no significant new arguments that it had not previously taken into account.**

Research into public opinion and debate

31. In order to probe the way in which public opinion on this and related issues is formed and influenced, and to identify significant thresholds in public acceptance of new reproductive technologies, the HFEA commissioned a market research company, Opinion Leader Research, to conduct a series of workshops with members of the public. Six groups, each comprising 6-8 individuals (two groups having direct interest in either genetic disease or assisted conception) were convened to discuss the issues and to develop their opinions on the use of assisted reproductive technologies. The same individuals were then brought together for a half-day workshop with invited experts to explore their views further.

32. Participants' initial feelings were broadly in favour of the use of any technique which could save the life of a child, as long as the risks were well managed. Their primary considerations tended to be for the families involved

¹ For example, the Medical Ethics Committee of the BMA suggests there is no morally significant distinction between tissue typing as an adjunct to PGD and tissue typing alone and concludes that both should be available. However, the International Bioethics Committee of UNESCO, the French National Ethics Committee for Life Sciences and Health and the Infertility Treatment Authority in Victoria, Australia, (which has recently produced guidance on the use of the procedure) consider it unacceptable to select an embryo on the basis of tissue type alone. The Danish Council of Ethics considers it unethical for PGD to be used to obtain compatible tissue type at all.

(the affected child, donor, and parents) and their initial cautious approval tended to be confirmed by more sustained consideration of the issues. They were generally reassured by the views of the experts from whom they heard. Those without children tended to approach the issues with slightly more scepticism than those with children or those with experience of infertility or disability. The majority of participants agreed that regulation is important but indicated a need for the benefits of technology to be more widely communicated and for decision makers to take into account both the views of experts in all relevant disciplines (medicine, psychology, ethics, etc.) and the views of the wider public.

33. Generally, participants did not consider it to be important whether the condition affecting the existing sibling was hereditary or not, although they thought the justifiability of the procedure would depend on the seriousness of the condition and should be addressed on a case-by-case basis. Many had greater reservations about the use of the procedure to produce a bone marrow donor, but these concerns tended to diminish in the light of more information about the procedure provided by the invited experts. **The Authority concluded that the research into public opinion formation had been extremely helpful in discovering the values that informed people's opinions on preimplantation tissue typing and had helped to draw their attention to the wider context within which particular reproductive decisions are made.**

Future developments

34. Centres abroad are understood to have received applications for preimplantation tissue typing where the existing child is not currently symptomatic but is in remission, for example, from certain sorts of cancer. In these cases, should the existing child relapse, there is likely to be insufficient time to go through the process of creating a tissue-matched sibling. If such a sibling existed already, tissue that could be used in treatment would then be at hand if and when required. Whilst different arguments are likely to be required to justify preimplantation testing in cases such as this, some have stated that the argument that the child is instrumentalised by being selected in this way is diminished since in this case the use of the child as a donor is merely conditional. Having considered such cases, the Authority agreed that there was no objection in principle to applications being considered in the same way as for cases in which the affected child was symptomatic at the time of the application.

35. Efforts in related areas of biomedical science, such as the management of disease, the use of combined cord or mismatched transplant tissue, the use of peripheral blood stem cells or therapeutic cloning to derive stem cells for treatments, may provide viable alternatives to the use of tissue from matched siblings in the future.

36. The Authority also considered a number of other scenarios, including the very rare circumstance in which preimplantation tissue typing might be used to produce a child who could donate tissue to a genetic parent. **The**

Authority concluded that the use of the procedure to produce a donor for a parent raises distinct and significant issues and recommended that this matter needed further consideration.

Conclusion

37. The Authority used the research summarised above to inform the review of its policy on preimplantation tissue typing. The findings of the research indicate that in none of the areas considered, in particular the risk associated with embryo biopsy and the psychological implications for the child, would the use of preimplantation tissue typing necessarily be an undesirable use of the technology. **Balancing the likely benefit of preimplantation tissue typing - to the sick sibling, the new baby and the family as a whole - against a better understanding of the possible physical and psychological risks to the child to be born, the Authority concluded that preimplantation tissue typing should be available, subject to appropriate safeguards, in cases in which there is a genuine need for potentially life-saving tissue and a likelihood of therapeutic benefit for an affected child.** However, each application for such a procedure will be considered on a case-by-case basis and the policy as a whole will be kept under review as new information and evidence continue to emerge.