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ARTICLE

Ethics of PGD: thoughts on the consequences of typing HLA in embryos

R.G. Edwards

Chief Editor, *Reproductive BioMedicine Online*, Duck End Farm, Dry Drayton, Cambridge CB3 8DB, UK

Abstract As with so many fields of study associated with assisted human reproduction, many ethical issues are raised by the practice of preimplantation diagnosis of inherited disease (PGD). Some are part and parcel of assisted conception, e.g. the rights of human embryos *in vitro* and of embryologists to establish them, carry out research and discard them. Others unique to clinical PGD were discussed at an earlier meeting on PGD (Edwards *et al.*, 2003). Recent developments in PGD are discussed briefly in this Commentary, especially the ethics of designer babies. 

KEYWORDS: embryos, ethics, Fanconi's anaemia, HLA typing, PGD

Foundation ethics of assisted conception and PGD

Embryo research was essential from the outset of IVF to identify the optimal conditions of culture, clarify the nature of any anomalous forms of growth *in vitro* and produce the highest quality embryos in attempts to alleviate various forms of infertility. The moral principle involved decisions as to whether embryos growing *in vitro* for several days deserved full recognition as human beings. PGD took many of these issues one step further, as embryos were discarded because their anomalies were considered too severe to transfer them to their mothers. Virtually all practices introduced in the early days of IVF and later of PGD led to fervent debates on the rights and wrongs of using human embryos in this way. Yet the current widespread practices that developed from the early work were later legitimatised for medical purposes by governments world-wide. Many observers queried these legislative decisions and insisted that human life begins at fertilization. They overlooked the broad evolutionary outlook that life began only once and is continued as its spark is transmitted through successive generations via the gametes. Any decisions about the beginnings of human life will therefore be arbitrary and involve selecting a point where human life and dignity become paramount. Embryos are lost by the dozen *in vivo* and *in vitro*, and many are

abnormal or carry disease genes. The only approach to curing various forms of infertility on a mass scale and averting the birth of children with serious forms of inherited disease involved IVF and its derivatives, including stem cells. Yet strict doctrines imposed in some countries restricted assisted conception and embryo research, and were recently renewed to forbid many aspects of IVF and embryo research, as in Italy (Benagiano and Gianoroli, 2004). This Act of Parliament forbids the aspiration of more than three oocytes for fertilization *in vitro* and imposes other severe restrictions on embryo research and many aspects of PGD. Its rules closely follow the opinions of the hierarchy of the Roman Catholic Church even though Italy, like most other countries, has an Abortion Act that permits fetuses much older to be aborted for societal reasons.

Beliefs that fertilization signifies the onset of human life are not accepted by some moral philosophers, who reject it as a significant moment. They prefer to base their opinions on the onset and dignity of human life on the stage of embryonic development, or stress the significance of the brain at the beginning and end of life. Some point out that brain death is usually equated with the end of life, so brain formation and its level of activity should reflect ethics at the onset of human life (e.g. Lockwood, 1985). Alternative stages included the characterization of the onset of human characteristics such as implantation, fetal movements

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or feelings of pain. Legislators in many governments have also conformed to human rights increasing with age and stage of development, as clerical authority has been increasingly questioned worldwide. Hard and fast rules do not exist to establish a basis for making ethical decisions about the exact stage when a human embryo acquires the rights of an adult. Most professionals working in assisted conception and PGD share the ethical opinions of these philosophers and of the consenting governmental legislation based on arbitrarily defined stages of growth. They are in the front line of medical care, well aware of and prepared for the needs of their patients for abortions and for fetal reduction in multiple pregnancies, whether embryos were conceived *in vitro* or *in vivo*. In effect, they base their ethics on a clinical imperative that accepts the paramount need to adopt procedures that are ethically debatable while safeguarding the perceived health of their patients. PGD has passed through all these stages and is accepted by many legislators. The UK Government has moved further than most by passing an Act in the British Parliament permitting studies on therapeutic cloning of human embryos to overcome host versus grafts against donated stem cells. In the USA, work on human embryos is forbidden in state-run laboratories and clinics, while private clinics can decide their own ethical stances. The practice of PGD is therefore widening in both countries, and in many others, but based on very different forms of gaining legislative consent.

Clinical imperative is a powerful doctrine, immediately accepted by many patients and professionals alike. A strong argument offered by many clinicians insists that any unwarranted restriction of scientific and clinical research must be rejected if it restricts the access of their patients to the most recent scientific advances. It challenges religious stances formulated over many centuries. Copernicus often wins today, as extreme religious opposition is overcome. PGD currently offers a highly relevant example, since it is more complex than IVF in accepting some embryos for transfer to their mothers while rejecting those embryos identified as carrying severe genetic defects. Once again, the clinical imperative prevails despite this need for a selective rejection of human embryos. This aspect of PGD strikes hardest at those people who were born with these inherited diseases, since many of them feel they have also been rejected by society. This extremely sensitive issue must be met by doing all possible to alleviate the symptoms of their disease.

PGD introduces even wider ethical implications, including some that have not reached the stage of legislation (Edwards *et al.*, 2003). Unknown risks still attach to the removal of one or more blastomeres from cleaving embryos, since some reports indicate that this procedure reduces implantation rates. Modern PGD

also raises novel ethical questions, in that many genes can be identified by removing a single blastomere from an embryo. Many late-onset genes can be identified, which will influence the health of parents in their older ages. Disclosure of information thus becomes a highly significant matter of privacy when PGD reveals serious conditions inherited from one parent. Afflicted parents may have no desire to know their future fate, especially if it involves a debilitating illness. Information about the genetic nature of a parent may also be valuable to an insurance agency or even a supermarket trying to increase its sales. Protecting confidentiality on data gained from embryos is not easy when so many professional groups are involved in the diagnosis, reporting and deciding of these complex cases. Wider ethical implications also include who should decide the final outcome. Patients are often consulted, and sometimes play the major role in decision-making. While generally acceptable, this approach can be flawed, as when a deaf couple elected to transfer an embryo carrying the genes for deafness rather than choosing an embryo free of this disorder. This case must be the first occasion when PGD was used to conceive a disabled child. It sets a poor precedent for later patients facing complex familial decisions, and also questions the responses of scientists and doctors who agreed with the parents' decision.

Ethics of HLA typing

The HLA typing of human embryos involves even further complexities. It is usually done more from the benefit of a potential recipient than offering any help to the embryo itself, since it involves using grafts of cord blood from a newborn PGD child to save the life of a sick elder sibling carrying a familial disease gene. This procedure raises further queries about the exact status of human embryos and the reasons for their conception *in vitro*. Immense amounts of information on the numerous HLA antigens can be gained today by the genetic amplification of DNA from single cells. It has become possible to characterize specific inherited disorders in an embryo, and then attain a detailed classification of its HLA groups. Embryos carrying familial disease genes are rejected, and disease-free embryos are selected for HLA typing. Those found to have a close HLA match with those of a previously born sibling with an inherited disease are then transferred to the mother. At birth, cord blood haemopoietic stem cells are collected and grafted to the sick sibling.

The initial example involved a family with a young child suffering from Fanconi's anaemia. The parents wished for a second child free of this inherited condition. They also wished to cure their firstborn child of its anaemia, but matching stem cells could not be found from haemopoietic registries. A wider selection

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of donors, preferably closely related to the firstborn child, was needed. In young couples, IVF offers many embryos which share familial genes with previously born siblings, and these could be tested by HLA typing them for their similarity with those of an elder sibling. These embryos would thus be compatible and free of Fanconi anaemia. HLA types were accordingly measured in a number of embryos to identify those most closely matched with those of the sick elder sibling. Compatible embryos were transferred to the mother, and at birth, haemopoietic stem cells purified from the infant's cord blood were donated to the sibling. Within days, the donated stem cells were repairing the disease to offer permanent functions in the recipient's haemopoietic system (Verlinsky *et al.*, 2001).

Diverse and novel ethical issues emerged from this study concerning the parents, the sick child, and the use of embryos for this purpose. Considerable numbers of embryos were needed to identify one closely matched with the elder sibling. Were the parents stimulated repeatedly in order to identify the few highly compatible embryos? Was the PGD embryo produced and used for someone else's benefit? What are the longer-term implications of this form of treatment? Moral outrage was expressed about these facts, although many onlookers considered this criticism as minor in comparison with the enormous happiness in the delivery of a disease-free child and the saving of a child's life from a devastating disease. In essence, the progress of this case offered another example of the dominance of the clinical imperative in ethical decisions. It could also be applied in further diverse forms of curing illness in an existing child, or even in a parent, relation or an unrelated family member. Similar cases could well include the treatment of thalassemia, leukaemia and immunodeficiencies in elder children or parents. The success of the case in curing the elder sibling, and the birth of the second normal child has certainly stimulated the wider uses of this form of treatment, often referred to as 'designer babies'.

However, the ethics do not end here. There are now two children to consider. The younger child who developed from a PGD embryo is free of Fanconi's anaemia, and its unwitting gift of cord blood caused it no harm, a situation morally acceptable to most observers. The elder sibling, desperately ill at a few years old, was saved due to its HLA-matched gift of normal cord blood stem cells from its newborn sibling. This child clearly and unknowingly had a very large stake in this form of treatment. Vested interests of the parents included clearing Fanconi's disease from both their children. Even though the younger child was used to help its sibling, it was much desired by its parents entirely for its own sake (Verlinsky *et al.*, 2001). This situation may not hold as many other couples are

attracted by the possibilities of repairing an existing child. They could be tempted to have another child purely for this benefit and not because they desired another baby. The moral dilemma thus stands on the exact desires of parents for another child.

What if the elder sibling suffered from a less clearly defined disease than Fanconi's anaemia? Situations are known where childhood diseases may not be inherited and arise through environmental factors. The UK HFEA has indeed declined a request for a designer baby since the potential recipient child might have suffered a relapse and was not a clear-cut genetic case. Should the same designer principles still apply in these cases? This authority has given its consent if available evidence showed the second child was wanted by its parents and in its own rights, but withheld it if there was any risk of parents having other motives or requiring a designer child for its 'spare parts'. Other complex situations could also emerge. Some designer babies may be unwanted after their donation and fostered at birth. Others may be retained within the family in case the cord blood stem cells fail to provide permanent grafts and the recipient requires a later bone marrow graft. This would need the consent of the PGD baby or its guardian. Lack of the necessary PGD techniques in particular clinics has also brought a refusal of care. All these matters are highly sensitive, involve delicate investigations into parents' motives and extremely difficult, since a child's life may be at stake.

Feelings ran high over this case for other reasons. The donor embryo clearly could not give consent, and this matter may loom large in later life when the second offspring realizes someone else gave this consent on its behalf. Unusual aspects of the rights of embryos and newborns are raised. Some states in the USA appoint a warden to represent the interests of the embryo, fetus and child in such complex situations, and wardens' decisions may conflict with those of the parents. Presumably the donor child will be glad to be alive, and when adult, it may also applaud saving its elder sibling's life, at least if family matters are proceeding well. But other circumstances could cast a shadow on this happy scenario. Many parents may claim they need another child to add to their family but really wish to provide a moral cover for their need for a designer baby. Difficulties such as these led the HFEA, and no doubt other regulatory agencies, to examine each request on a case-by-case scenario.

Some philosophers might well ask why HFEA or ethical committee consent was needed anyway for these cases, since taking such a decision outside the family might be interpreted as an unlawful curtailment of parents' rights. This situation has already arisen when the HFEA declined a request for a designer baby to help an elder sibling. The parents simply migrated elsewhere to find a consenting

clinic. Patient tourism (and clinical tourism) of this kind arises frequently in relation to numerous human complaints, including the sexing of their embryos for family balancing by means of PGD or through the use of sperm selection techniques. Elements of design requiring similar ethical analyses arise in other situations. Grafts of ooplasm or mitochondria from one oocyte to another might overcome some genetic disorders in the recipient, or give great satisfaction to a parent wishing for a sportsman son. Cloning involves donation, which must be accepted openly and transparently. HLA matching could be applied to produce cord blood stem cells to alleviate other forms of haemopoietic disease. Non-haemopoietic diseases may also be cured if haemopoietic stem cells in cord blood could be transformed into stem cells for brain, muscle, myocardium, liver etc. It may not be difficult to induce such transgenic changes in these stem cells in the near future. Stores of widely differing stem cells could be established for most body tissues, cryostored at birth for the later use of the newborn child.

Consideration must be given to an item of potential significance in overall stem cell therapy. When used for regrafting irradiated or anaemic recipients, or to mend a damaged heart or a malfunctioning brain, attention to recipients usually concentrates on the particular organ under study. Yet if stem cells do undergo spontaneous transgenesis, their potential for linear differentiation may be widened epigenetically and confer a pluripotency enabling them to colonize

numerous tissues in recipients. Their actions would then be a matter of chance, with profound consequences for the recipient. This possibility also applies to HLA typing.

Will the clinical imperative continue to carry sufficient weight to gain permission for new advances in reproductive medicine, PGD and stem cells? Perhaps not, as in the case of human reproductive cloning and other extreme situations, so it is essential to maintain current professional approaches to regulatory and legislative authorities. Science is not sacrosanct, although for the present it has enabled wide new aspects of assisted conception to be introduced and thousands of patients to achieve their own forms of happiness.

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