

OPINION

Ethical considerations on preimplantation genetic diagnosis for HLA typing to match a future child as a donor of haematopoietic stem cells to a sibling

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Recently, several requests were made by couples with an affected child who wanted preimplantation genetic diagnosis (PGD) to select embryos in the hope of conceiving an HLA identical donor sibling. This article considers the ethical arguments for and against the application of PGD for this goal. Only embryos HLA matched with an existing sibling in need of a compatible donor of haematopoietic stem cells would be transferred. The main arguments are the instrumentalization of the child, the best-interests standard, the postnatal test for acceptability and the experience of the donor child. It is argued that conceiving a child to save a child is a morally defensible decision on the condition that the operation that will be performed on the future child is acceptable to perform on an existing child. The instrumentalization of the donor child does not demonstrate disrespect for its autonomy or its intrinsic worth.

Key words: ethics/haematopoietic stem cells/HLA matching/preimplantation genetic diagnosis/transplantation

Introduction

In 1998, the Centre for Medical Genetics was for the first time contacted by a couple who asked for IVF and selected embryo transfer after preimplantation genetic diagnosis (PGD) in the hope of conceiving an HLA identical donor sibling. Since then, several similar requests have been made. Moreover, the media attention and the public debate on the recent Nash case will certainly contribute to the awareness in the general public of this procedure (Verlinsky *et al.*, 2000). In order to be prepared for this evolution, the ethical arguments for and against this solution are analysed. The increasing insights in molecular genetics and the further development of PGD as well as the growing understanding of diseases in which fully matched haematopoietic stem cell transplantation (HSCT) will be required will very probably lead to a growing number of requests. We will concentrate on HLA typing of embryos with the intention of using haematopoietic stem cells (HSC) from the umbilical cord blood or the bone marrow of a future donor child to save an existing recipient sibling.

Haematopoietic stem cell transplantation (HSCT)

A number of malignant and non-malignant diseases are treated by means of bone marrow transplantation and are considered

standard transplant indications according to the guidelines of the European Organisation for Blood and Marrow Transplantation (EBMT) (Goldman *et al.*, 1998). Allogeneic HSCT is the only known cure for most of these diseases. The risk:benefit ratio may differ significantly depending on the disease type. The use of the procedure should be evaluated carefully for each disease and for each patient.

Allogeneic HSCT requires the availability of an HLA-matched donor who may be an HLA-identical sibling or, alternatively, a volunteer-unrelated donor. An individual has two different HLA haplotypes, co-dominantly inherited from each parent. The chance that a particular sibling is HLA identical is theoretically 25%. Taking into account the increasing tendency towards small families in Western countries, the chance of having an HLA-identical sibling is no more than 15%. Several millions of HLA types are stored in many national 'Registries' and the chance of finding a fairly compatible donor through a donor search in these registries is around 75% (Hensley-Downey and Gluckman, 1999; Tiercy *et al.*, 2000). A third possibility of obtaining compatible HSC is from cord blood, given at birth and cryostored in cord blood banks on a voluntary basis (Gluckman and Locatelli, 2000). Cord blood transplantation allows for more HLA-incompatibility between patient and donor and although not precisely known from

literature data, the chance of finding cord blood suitable for transplantation is probably more than 50%. Finally, parents or siblings who are HLA haplo-identical may be HSC donors under certain conditions (Hensley-Downey, 1999).

In order to determine whether it is worthwhile to create a child as an HSC donor, we have to consider the success rate of HSCT for the affected child. In general, the outcome after allogeneic HSCT is determined by the transplant-related mortality, which can vary between 10 and 50% and is mainly due to graft-versus-host-disease, graft failure and infections. These complications are related to several prognostic factors such as age and disease status of the patient, number of HSC grafted and, most importantly, the degree of HLA compatibility between patient and donor (Beatty *et al.*, 1985; Sullivan *et al.*, 1991; Sasazuki *et al.*, 1998). HLA mismatches are increased in case of HSCT using unrelated donors, unrelated cord blood or haplo-identical donors (alternative donors) and this generally translates into a higher incidence of transplant-related morbidity and/or mortality (Szydlo *et al.*, 1997). If the patient survives the transplant procedure, there is still the possibility of leukaemia-recurrence. The overall success rate of a HSCT in a child with a sibling donor is substantially higher than HSCT performed with alternative donors. These considerations offer a clear rationale to support the parents' request.

Moreover, the time restrictions are important for rapidly progressing and/or well developed diseases. It may take several months for the practical development of a specific diagnostic multiplex PCR at the single cell level and even later on the multiplex PCR will have to be specifically designed towards each family. The IVF cycles can start only when the diagnostic test for preimplantation biopsy has been developed. Given the success rate of IVF, the establishment of a pregnancy may take several cycles. Add to this 9 months of pregnancy and we are talking of a delay of approximately 1.5 to 2 years. Presumably, a multiplex PCR procedure could be developed independently of the present case, which would shorten the preclinical development time needed for future cases.

In summary, whereas the advantages of using a related donor compared with an unrelated donor are clear, the main practical obstacle in these cases is the time needed to create a matched sibling. In addition, a number of ethical problems have to be addressed.

Specificity of PGD as opposed to prenatal genetic diagnosis

Different methods can be used to obtain a child whose haematopoietic cells could be donated to a sibling: the parents can go on having children until a match is found, they can opt for prenatal genetic diagnosis or they can try PGD (Handyside *et al.*, 1990). All methods have pros and cons, both medically and ethically. PGD is necessarily preceded by IVF. In the course of a normal IVF cycle, a large number of embryos can be obtained. Precisely this number facilitates the selection. With several embryos to choose from and with a theoretical chance of 1 in 4 of finding a match, the probability that at least one embryo will have the desired characteristic is high. With this procedure the selection can be carried out before and not during pregnancy and without having to recur

to abortion in case the fetus does not have the required genotype. Given the chance mentioned above for a match, there is a considerable risk that a woman who relies on prenatal diagnosis will have to undergo one or more terminations of pregnancy. PGD may be easier on the couple (and especially on the woman), both physically and psychologically. Before the existence of PGD, natural conception followed by prenatal diagnosis (and possibly termination of pregnancy) was the only alternative. A survey carried out (Kearney and Caplan, 1992) revealed that several cases are known where babies were created specifically to serve as a bone marrow donor and where parents were prepared to abort if the fetus was not a match (Norton, 1994). It can be argued that the ethical problems in these cases are greater than when PGD is performed. This is mainly due to the increasing moral value attributed to the embryo at later stages of development (Clark *et al.*, 1989).

The availability of a large number of embryos is especially important when the HLA typing is an additional selection criterion. This was the situation in the recently debated Nash case (Verlinsky *et al.*, 2000). This couple has a 6-year old daughter with Fanconi anaemia who would have died in the next few years if no suitable donor could be found. However, PGD would always have been an option for this couple if they had wanted another child not inflicted with Fanconi anaemia. The first selection, appropriately labelled preimplantation genetic *diagnosis*, was directed at those embryos that did not have the anaemia (and so for this part there was a strict medical indication). The second selection, which would more correctly be called preimplantation genetic *typing*, is performed on the first set of unaffected embryos and is used to classify the embryos according to their HLA types.

According to the opponents of PGD in general, the availability of several embryos is responsible for lowering the indication threshold for selection (Testart and Sèle, 1995). Thus the sliding down the slippery slope has already started. Originally, PGD was developed to test embryos for serious genetic illnesses and to eliminate the risk of a child born with such a disease. In this case, however, there is nothing wrong with the embryos that are biopsied. The selection is made for a characteristic (i.e., the HLA genotype) that is only useful to others. Since the embryo itself does not benefit by the selection, the criterion should be seen as a social one. Ultimately, the opponents argue, this will lead to the direct choice by the parents of other characteristics of the child. Not surprisingly, the Nash child was labelled as a 'designer baby' in the newspapers. The danger of the slippery slope is, according to the opponents, much more real for PGD than for prenatal diagnosis due to the absence of a restrictive barrier. Abortion functions as such a barrier for prenatal diagnosis for 'futile' characteristics. The moral and psychological impact of an abortion is sufficiently high to prevent prenatal testing and abortion for trivial reasons. However, the psychological and practical barrier in the case of PGD is arguably as high as abortion, i.e., the necessity of having an IVF treatment.

The appeal for medical assistance is crucial in the present discussion. If parents decide to take the chance and to have another child the 'natural' way, this concerns no one except themselves. It would be inconceivable to forbid or to obstruct

this reproductive plan. However, if the parents want to guarantee the outcome, medical collaboration is required. The responsibility of the physicians increases in proportion to the biotechnical intervention and contribution. The question is no longer solely whether the parents can justify their decision to make another child but whether the physicians should help them to have a child with specific features. Should the medical staff carry out the IVF treatment and the genetic testing for this goal?

Instrumentalization of the child.

The main ethical argument against this kind of request is the instrumentalization of the future child. The child becomes an instrument to cure another child. One of the fundamental rules underlying Western moral thinking is the Kantian imperative. The second formulation of the categorical imperative goes as follows: 'Act in such a way that you always treat humanity, whether in your own person or the person of any other, never simply as a means, but always at the same time as an end' (Kant, 1964). It is not always clear how it should be decided when someone is treated as a mere means and no longer as an end-in-himself (Drebushenko, 1991). It is generally agreed that using someone as a means is not unethical. In fact, we do it all the time. An action should only be condemned when it treats a person *solely* as a means. When does an act instrumentalize a person? Parents frequently decide to make another child as a companion and a playmate for the first one. Is the second child hereby treated as an instrument? And how should we evaluate the 'replacement' child? Suppose the transplantation is not successful and the affected child dies. The new child can fill the void left by the dead child. Is the wanting of a child to replace another child less or more instrumentalizing than wanting a child that can also save the life of a sibling? When the parental decision is evaluated with this possible scenario in mind, it seems at least acceptable to decide to have another child who can possibly save the life of the existing child. It could even be argued that parents who want to have another child anyway, have an obligation to try this last possibility of saving their sick child.

The parents' decision to conceive and select a certain embryo would fail to show respect for the future child if their only reason for creating the child was its tissue. What kind of action would demonstrate or allow this conclusion? The parents could give up the child for adoption after taking the tissue or they might neglect the child when they keep it. Robertson argues that even when the parents give up the child for adoption because it lacks the right tissue, this would still be ethically defensible and fall within the range of the right to reproduce (Robertson, 1994). The child will have a normal and reasonably happy life. The only difference with the 'normal' situation is the raising of the child by adoptive parents. The child given up for adoption need not be harmed compared with the same child that would be raised by its genetic parents. Our indignation and repugnance of this parental decision is caused by the fact that this act shows beyond doubt that the sole motive for having the child was its tissue. While it could be argued that the child is not harmed by its having

been given up for adoption, it most certainly is wronged by being treated in this way. The parents' behaviour would be a blatant demonstration of disrespect. However, this discussion is mainly theoretical. Given the psycho-logic of the parental concern demonstrated by their efforts to save the recipient child, it is highly unlikely that they will not treat the intended donor child as an equal to the existing child (Sharpe, 1990).

The best-interests standard

The standard approach of the problem of the acceptability of a medical intervention is to request the informed consent of the patient. If no consent can be obtained because the candidate donor is incompetent due to age or lack of mental capacities, we rely on the best interests of the person. A major problem for most cases in which incompetent persons are volunteered as organ or tissue donors is the demonstration that the intervention serves their best interests (Ross, 1994). This standard can be considered as a operational reformulation of the Kantian imperative that a person should always also be treated as an end. Being treated as a person can be identified with 'respecting his goals, desires, values etc'. When it can be shown that the act serves an interest of the donor candidate, he or she is not treated solely as a means. Showing this is not always easy or even feasible. The defenders of the intervention refer to the family context to determine the interests of the donor child. The child will certainly have an interest in growing up in an intact family. The child once born will benefit if his or her older sibling survives. If the situation of a possible child that can serve as a donor is compared with the situation of a child that is unsuitable as a donor, the former has an advantage compared with the latter. The child that cannot donate will see its sibling die and will grow up in a family that is marked by the death of a family member. However vague, the underlying idea is that the social, emotional and psychological interests of a person depend on the happiness in the family in which he grows up (Savulescu, 1996). The relationship between donor and recipient functions in an indirect way: it explains why the donor has an interest in the wellbeing of the recipient. To the extent that the wellbeing of the others is part of one's own wellbeing, the person is helping himself. According to this scheme, every donor who gives to someone close to him, is behaving selfishly. Moreover, this condition changes the decision to volunteer a child as a donor into a paternalistic act intended to benefit the donor child. This is, euphemistically speaking, a strange construction. Would we say to the child that is proposed as a donor 'We're doing this for your own good'? Since it is impossible to bring forward medical benefits in case of organ or bone marrow donation, one concentrates on the psychological and social benefits for the donor as a consequence of his relationship with the recipient and/or other family members. This looks very much like a rationalization to explain what we feel to be the right decision (Dwyer and Vig, 1995). The most obvious solution to this problem is that we accept that the wrong standard is applied. The intervention can be justified even if it goes against the interests of the donor child.

One is struck by the artificiality of the moral justification

in this construction. The parents obviously do not intend to benefit the new child by selecting the HLA genotype. Their concern is for the existing child. But why should the act be to the donor's advantage? Or, if the weaker criterion is used, why should the intervention not be against the donor's interests? (Delany, 1996). In ordinary life, parents with more than one child frequently make decisions by which one child is harmed to benefit the other (Ross, 1994). Suppose one of the children has special needs and has to go to a special school. If the parents decide to move in order to be closer to this special school, they harm the other sibling who is losing his friends and familiar environment. This problem cannot be solved in a way that both children benefit. The dilemma for the parents is that they have to balance the interests of both their children. They judge that the sacrifice of the healthy sibling is justified by the gains of the needy child. The parents decide that one child must suffer a small disadvantage in order to help his sibling a lot. In fact, it can be argued that refusing this use (e.g., not agreeing to the bone marrow donation of one child if there is a serious chance that its sibling can be saved) would be an unacceptable neglect of the sick child's interests.

Can good parents subject one of their children to the harm caused by bone marrow donation in order to save the life of another child? There is no doubt in our minds that good parents can take this decision. Giving bone marrow is a sacrifice that does 'not exceed the ordinary sacrifices family members make and expect from one another' (Jecker, 1990). There is general agreement that bone marrow donation represents a very low risk and inconvenience to the donor. The considerable benefit to the recipient in conjunction with the low risk for the donor renders donation (related and unrelated) of bone marrow ethically appropriate (Ethics Committee of the UNOS, 1992). The more serious the harm (pain, risk of the intervention, non-regenerability of the tissue etc.) for the donor child, the more difficult the decision becomes. The donation of a kidney constitutes a difficult borderline case. When treatment is possible with the umbilical cord stem cells, no intervention or risk is imposed on the donor child. While this aspect of the use has no impact on the question whether the selection of the embryos is in principle acceptable, it changes the balance at least in that sense that the subsequent use is not against the interests of the child.

The postnatal test to determine the acceptability of making a child

A possible criterion to determine the acceptability of a motive for the selection of the embryo is the 'postnatal' test: it is ethically acceptable to make a child for a certain reason if it is acceptable to use an existing child for the same reason. This test is a necessary but not a sufficient condition for the child's creation. There are still the child's needs to be considered, e.g. the need to be loved for its own sake and the need to be cared for in stable and warm personal relationships. So if taking bone marrow from an infant is acceptable when the child exists (and came into existence independently of this decision), it is acceptable that one of the motives for making the child is to have bone marrow. The postnatal test makes a link

between the intention and the act. This argument has been presented in the context of the debate on the acceptability of creating embryos for research. 'Typically, to argue that an *intention to do x* is immoral, presupposes that *doing x* is immoral' (Gerrand, 1993). If it is permitted to use an existing child as a bone marrow donor, then how can it be wrong to intend to use it as a bone marrow donor at the time of its conception?

A stringent standard should be maintained for the acceptability of medical experiments on, and organ donation by, minors. But if the parents can decide that an existing child should have an operation in order to give bone marrow to a sibling, then it is difficult to argue that they should not desire, as part of their set of motives for having a child, a child that can give bone marrow to a sibling. There is nothing wrong with 'being conceived to be used for *x* unless 'being used for *x* is the sole reason for the conception. It follows from this criterion that parents cannot want a child for a certain reason if this means that something will be done to the child that is not allowed. If taking a kidney from an infant to save its sibling is unacceptable, it makes no sense to help parents to have a matching kidney donor.

Experience of the child

The experience of the future child is an objection against most non-conventional applications of the new reproductive technologies. What is it like to have a mother who could be your grandmother? How does an adolescent experience having lesbian parents? How does it feel when you are told that you were created in order to save your sibling's life? This argument is little else than a reformulation of the moral position the person adopts. A person that disapproves of the motive for procreation, will also believe that a child will feel hurt and diminished when informed of the reason for his existence. The connection between the moral position and the presupposed feelings and experiences is demonstrated by the fact that the same argument is used by the proponents. Being informed of the fact that you were conceived to help your sibling may give the child a greater sense of self-esteem and self-worth. There are few things as valuable as saving the life of a primary other. Compared with most other persons, who are conceived by accident or without any conscious thought at all, this child already has a reason to exist. The child may feel proud of its role in attempting to save its sibling's life (Thomasma, 1992). And is it not more devastating for your self-concept to be told that you were an 'accident'? Does this information about your conception take away the meaning and value of your life?

It could be argued that a heavy burden is placed on the donor child. The transplantation may fail and this may give the child a fundamental sense of unworthiness and deficiency and a feeling of not being able to live up to the expectations. The psychological impact of bone marrow donation among siblings should indeed not be underestimated (Packman, 1999). However, the impact depends on the conscious experience of the donor child of the donation. In the cases we consider, the donor is much too young to have any understanding of what is happening. The psychosocial effects will have become

diluted by the time that the child is able to understand the action in which it took part. Moreover, it is very likely that the child will later agree ('hypothetical consent') with the decision his parents made for him for he will then have come to value his relationship with his sibling (Redmon, 1986).

Counselling

During counselling the probabilities and uncertainties concerning the embryo selection, the pregnancy and the transplantation should be stressed. The parents should not leave the clinic thinking that the sick child is saved from the moment that their request for PGD is granted. Moreover, 'side issues' of the proposed treatment should be considered beforehand. Parents should think about the fate of the remaining non-matched embryos, about the possibility that few embryos are obtained, no matching embryos are found or no pregnancy follows.

The most important element to be verified to justify the centre's collaboration are the parents' intentions regarding the future child. There is no fail-safe way to predict with absolute certainty the future attitude of the parents. Still, a psychologist trained in fertility counselling who has experience in talking to patients about their future offspring might be able to notice contradictions and inappropriate feelings in the parents' attitude towards the new child. The parents should be questioned about how they see their new family, how they think the donor child will react when it is informed about the special circumstances surrounding its conception, how they evaluate the risks for both siblings and about the impact on the family when the engrafting fails.

Conclusion

Conceiving a child to save another is a morally defensible decision on the condition that the operation that will be performed on the future child is acceptable on an existing child. There are no indications that parents who ask medical assistance to obtain an HLA compatible sibling do not intend to love and care for the new child. The instrumentalization of the donor child does not demonstrate disrespect for its autonomy and its intrinsic worth. If the sick child will die without transplantation, the creation of a sibling with matching tissue can be considered. Still, the conditions in the present case are almost optimal: no cure without transplantation, high success rate of transplantation, considerable advantage of using an HLA-identical sibling compared with alternative donors and slow progression of the disease resulting in sufficient time to wait for the birth of the donor child. A more general discussion of this solution is needed in order to determine whether a similar approach would be justified for other conditions.

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