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Taskforce 9: the application of preimplantation genetic diagnosis for human leukocyte antigen typing of embryos

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This 9th statement of the ESHRE Taskforce on Ethics and Law considers ethical questions and specific dilemmas concerning preimplantation genetic diagnosis for human leukocyte antigen typing of embryos. This application is particularly complex because the interests of the sick child needing a transplantation should be balanced against the interests of the future donor child who may result from the technique. It is concluded that, if parents intend to love the child, the creation and use as a donor is not inherently disrespectful.

Key words: ethics/HLA typing/PGD/transplantation/welfare of the child

Introduction

In a previous statement on preimplantation genetic diagnosis (Shenfield *et al.*, 2003), the ESHRE Task Force on Ethics and Law already presented a short analysis of the present issue. However, some members of ESHRE thought that it deserved further detailed analysis, which hereby follows.

Scientific background

The facts

Transplantation of haematopoietic stem cells (HSCs, i.e. cord blood or bone marrow) is the standard treatment in cases of neoplastic (e.g. leukaemia) or congenital (e.g. β-thalassaemia, sickle cell anaemia) diseases affecting the haematopoietic and/or the immune system. Transplantation may also be appropriate for some rare metabolic diseases (e.g. adrenoleukodystrophy). Cord blood collected at birth is an established source of HSCs. If no human leukocyte antigen (HLA) identical donor is available in the family, preimplantation genetic diagnosis (PGD) can be used to select an embryo that is (i) HLA identical and/or (ii) free of disease-related mutations. The overall success rate of HSC transplantation with an HLA-matched sibling is significantly higher and has fewer complications than transplantation with HSCs from an unrelated donor. However, although HSC transplantation with an HLA-identical donor is currently the best treatment option for the affected child (advice from a transplantation haematologist is required), other treatments, such as stem cell transplantation, may supersede this in the future. Whether the affected child can be helped by umbilical cord blood depends, among other factors, on its age/weight. Cord blood may be sufficient for young children below 25 kg, while older children will need a bone marrow transplantation.

Treatment alternatives

Some couples may consider natural conception, followed by prenatal diagnosis for HLA and possible termination of pregnancy, when the fetus is not HLA compatible. In specific circumstances (e.g. when no specific multiplex PCR exists), this alternative may give a higher chance of obtaining a suitable donor within a limited time period.

Furthermore, in a number of cases, this solution could be avoided by increasing the number of available unrelated cord blood samples. This option requires the development of cord blood banks for public use.

Safety

Based on the available data and the limited number of children born, there is no evidence for the time being that embryo biopsy has a deleterious effect on the health of the future child. The incidence of abnormality after PGD is comparable with that in IVF/ICSI children.

Efficiency, accuracy and limitations

There are several limitations at different stages of the process of conceiving and using an HLA-matched child to cure a sibling.

(i) A minimal time period is needed for the procedure. When transplantation is indicated, a delay of 12–18 months between decision making and treatment should be taken into account. This point is especially important for fast progressing or far advanced diseases and may differ between leukaemia

and inherited diseases. The speed of the procedure depends, amongst other things, on the availability of molecular information (HLA markers and mutations of the disease), the time needed for the development of a test at the single cell level and on the success rate of the IVF cycle.

(ii) A high number of embryos (and therefore several IVF cycles) may be necessary to obtain a pregnancy and a live birth. The theoretical chance of finding an HLA-matched unaffected embryo in cases of a recessive disease is three out of 16. The limited number of published cycles for this application confirms the low theoretical chance.

(iii) The misdiagnosis rate of PGD may be in the range of 1–5%, although further data may reveal slight variations for different methods and indications.

(iv) The chance of obtaining a pregnancy in IVF is limited by several factors, and in particular by the advancing age of the mother.

(v) The success rate of HSC transplantation depends on the type of disease and may vary between 90% (thalassaemia) and various lower rates in certain leukaemias. If treatment with cord blood fails, there may be a need for bone marrow transplantation afterwards.

General ethical considerations

Society

In society, there is a presumption that parents will act for the benefit of their children. This presumption underlies their right to make decisions about what can or should be done with their children. In some cases, the interests of two siblings may conflict. The dilemma for the parents is that they have to balance the interests of both children. They may judge that the possible harm to the future healthy sibling is outweighed by the probable gains for the sick child. Moreover, the acceptability of this balance can be argued by referring to the notion of hypothetical consent: the future sibling on whose behalf the decision to donate is made will agree with the present decision when he/she becomes autonomous.

The children's interests

For the sick child, the benefits are obvious since transplantation of stem cells from cord blood is the treatment of choice and offers the only chance of cure.

For the future child, although there may be some psychological benefits for the donor child, no medical benefits result from the donation. However, the risks and inconveniences of HSC donation for the donor are considered as minimal. These risks are outweighed by the benefits for the receiving sibling whose life can be saved. This is a decision to be made by the fully informed and counselled parents.

The parents respect the child's autonomy if his/her use as a donor is not the only motive for the parents to have the child. They should intend to love and care for this child to the same extent as they love and care for the affected child. If this condition is fulfilled, the future child is not created merely as an instrument for the benefit of the older sick sibling. The lack of instrumentalization is even more obvious when the parents request PGD primarily to avoid having another child affected by the same disease and the wish for HLA matching is only added afterwards.

The use of a child as a donor of HSCs in itself is not considered disrespectful towards the child. This is demonstrated by the fact that the parents may volunteer an already existing child to serve as a bone marrow donor for a sibling. One way to check whether the interests of the future child are respected is by applying the postnatal test: if it is acceptable to use an existing child for a certain reason, it is also acceptable to create a new child for the same reason.

The responsibility of the physician towards the future child

Since the parental project to conceive a child to cure a sick sibling is morally acceptable, the collaboration of the physician in the project is also morally justified. The team involved has the responsibility to provide full information, genetic counselling and implication counselling to the future parents (e.g. the possibility of the affected child dying before the birth of the sibling).

Specific ethical considerations

(i) Based on the above considerations, the use of PGD for the creation of an HLA-matched sibling to cure a sick child suffering from a serious non-genetic disease (e.g. some forms of leukaemia) is also acceptable.

(ii) Given the low chance of success of the procedure (see 'Facts'), it may be inappropriate to recommend the technique in cases of advanced maternal age and/or poor ovarian reserve. In practice, the physician must evaluate and explain the chances of success for each specific case. The team may conclude that the technique is not advisable if the chance of delivering an HLA-matched child given the specific circumstances is estimated as very low. Decision making should take place in a multidisciplinary team including paediatricians, haematologists, geneticists and psychologists.

(iii) Parents should be urged to think about the disposition of the remaining healthy embryos that are not HLA compatible. In these cases, the options should be restricted to freezing for future reproduction by themselves, donation for research or disposal. Donation to other couples is not advisable until sufficient information about the health of children after embryo biopsy is available.

(iv) The creation of a child for the purpose of harvesting non-regenerative organs is extremely difficult to justify in view of the risks involved for the donor child. Since solid organ donation by children or incompetent adults is not considered morally acceptable because of the more than minimal risk for the donor, creating a child in order to obtain an organ for a sibling is not acceptable either.

(v) In order to collect reliable information on the fate of the children and the families that apply this technology, careful follow-up should be performed. Present concerns about the psychological and social consequences for the donor

sibling can only be corroborated or refuted by empirical research. It is therefore advisable to collate a register of such donations for this purpose.

(vi) Given the relevance of parental motives for the moral evaluation, the parental intentions regarding the upbringing of the future child and the coping capacity of the parents should be discussed by a psychologist before the start of treatment.

Acknowledgements

1. Liebaers was consulted as an external expert.

References

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