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COMMENTARY

Clinical guidelines for IVF with PGD for HLA matching

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Abstract Preimplantation genetic diagnosis (PGD) for human leukocyte antigen (HLA) typing is an established procedure for conceiving a child who may donate cord blood or haematopoietic stem cells for transplantation to save an ill sibling. Haematopoietic stem cell transplantation (HSCT) from related matched donors improves overall survival compared with unrelated or non-matched donors. Since HSCT from related matched-donors is unavailable for 70% of patients, IVF for PGD-HLA is a relevant clinical option. Recent success of HSCT after PGD–HLA, and excellent health and family support of the children born, suggests that debate over this kind of 'designer baby' and 'gift of life' should subside. Discussions about IVF for PGD–HLA should be held with families when a related matched-donor is unavailable, when HSCT can wait at least 9–12 months, within weeks of diagnosis irrespective of prognosis, and when the mother is of reproductive age. Related half-matched egg donors may also be considered. National and international collaborations should be established, and couples choosing this modality should be referred to experienced IVF and PGD centres. Clinical guidelines will improve physician and patient awareness of IVF for PGD-HLA and its role in advancing the clinical care of children in need of HSCT.

KEYWORDS: bone marrow transplant, cord blood, hematopoietic stem cell transplantation, human leukocyte antigen matching, inherited and acquired hematological disorders, PGD

The gift of life

Conceiving a child just to provide a match bone marrow to cure a living sick child? The world was shaken in 1990 when the Ayala family from California did just that in order to save their daughter who was suffering from leukaemia. As the chance to conceive a matched child is 1:4, they felt blessed to spontaneously conceive with a matched baby. In spite of the controversy on 'baby farming', the sisters and their parents had an amazing journey of hope, survival and happiness (Alby, 1992; Quigley, 2011).

The story of such a unique 'gift of life' had a major turn in 2000, when Adam Nash was born unaffected for Fanconi anaemia and human leukocyte antigen (HLA) matched to his 6-year old sister, after IVF with preimplantation genetic diagnosis (PGD) for the mutation and HLA typing (Verlinsky et al., 2001). This was done so that a related healthy sibling could be matched for a girl suffering from bone marrow failure secondary to Fanconi anaemia. Therefore, PGD was used to identify the embryos that were unaffected from Fanconi anaemia to avoid another affected child, and, out of the unaffected ones, HLA typing was used to select the embryo/s that matched the sick child. These matched unaffected embryos were transferred and a healthy boy was born. Cord blood of the girl's healthy matched brother was used for haematopoietic stem cell transplant (HSCT), which was successful and the girl was cured (Grewal et al., 2004). This first case of this new application of PGD, published by Verlinsky

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et al. (2001), instigated a worldwide debate on the issue of 'saviour siblings' (Ingerslev and Hindkjaer, 2012; Madanamoothoo, 2011; Shenfield et al., 2005; Soini et al., 2006). Although the debate is still ongoing in some countries, it has subsided significantly worldwide. In some countries, the treatment has been approved and is routinely offered to families in need (Fernandez et al., 2014; Harper et al., 2012; Kahraman et al., 2011; Kuliev et al., 2005a, 2005b; Rechitsky et al., 2006; Samuel et al., 2009; Tur-Kaspa, 2012; Van de Velde et al., 2009). More than 10 years after the first 'saviour baby', still less than 35% of parents of children with Fanconi anaemia are offered PGD by any healthcare professional, and only 70% are aware of PGD for HLA as a reproductive option (Zierhut et al., 2013).

The study published by Kahraman et al. (2014) describing 44 out of 48 successful HSCTs (92%) after PGD for HLA to cure, save an ill sibling, or both, and previously published cases, may serve as a proof of concept. Although outcome of HSCT from mixed non-matched donors has improved dramatically recently, related-matched donor for HSCT, and thus IVF for PGD-HLA, is here to stay. Clinical guidelines on the role and usage of PGD for HLA will assist in incorporating it into routine clinical care and will help parents in their reproductive decision-making process.

PGD for HLA

Preimplantation genetic diagnosis is the genetic testing of embryos obtained by IVF before transferring them into the uterus to achieve conception with a healthy child, and has been established worldwide as a clinical service. The American Society for Reproductive Medicine, the European Society for Human Reproduction and Embryology, the European Society of Human Genetics, and the Preimplantation Genetics Diagnosis International Society, support PGD as an option for couples at risk of having children with heritable and debilitating genetic diseases who wish to avoid the difficult dilemma of possibly terminating the pregnancy with an affected fetus or delivering a sick child (Preimplantation Genetic Diagnosis International Society (PGDIS), 2008, Practice Committee of Society for Assisted Reproductive Technology and Practice Committee of American Society for Reproductive Medicine, 2008, Soini et al., 2006; Harper et al., 2012). In 2000, PGD for HLA was added to the expanding indications of PGD. As it is considered ethically and clinically justified to test children for HLA typing for possible HSCT to save their siblings (Policy Statement, 2013), we argue that the same rule may apply for embryos before implantation.

Kahraman et al. (2011, 2014) summarized their experience with 242 couples who underwent 461 IVF cycles for PGD with HLA typing. Their data may assist physicians in consulting such couples. A total of 3973 embryos were biopsied, of which 90% were diagnosed successfully. For HLA matching plus mutation testing, 12% of analysed embryos were found as both disease-free and HLA compatible (versus 19% expected). For the HLA-only testing group, 17.0% of analysed embryos were found as HLA-compatible and transferrable (versus 25% expected). In 60% of cycles, at least one suitable embryo could be transferred, resulting in an ongoing pregnancy rate of 30% per transfer. Ninety healthy and HLA compatible children were already born. One HLA non-identical baby was born as a result of a misdiagnosis out of 91 babies (1.1%). Forty-four sick children have already been cured by HSCT from these HLA matched born siblings. Graft failure occurred in four additional children with beta-thalassemia where a second HSCT was planned (92% success rate). Although such results clearly support the clinical use of PGD for HLA, its limitations should be properly communicated to families before starting treatment. They should have realistic expectations for the overall success of this approach, and should be informed on the possible risks and complications of IVF, intracytoplasmic sperm injection, PGD, PGD error rate and pregnancy outcome. They should also receive information on the experience and IVF success rates of their particular clinic, with or without PGD, the chance of have a matched embryo (as described above) and the fact that even if an HLA matched embryo is available, the transfer might not necessarily result in pregnancy, and further IVF-PGD cycles may be needed. Additional aneuploidy testing may further decrease the percentage of available embryos for embryo transfer, but the pregnancy rate per embryo transfer may improve (Rechitsky et al., 2006; Tur-Kaspa, 2012). As indicated by Kahraman et al. (2014), stem-cell dose obtained from umbilical cord blood was frequently insufficient, and extra time was needed for the child to gain sufficient weight to be able to donate his or her bone marrow cells. All of these limitations might increase the time it will take for the ill sibling to undergo the transplant, other than the fact that 9 months are required for delivery of a successfully implanted embryo. When the chance to conceive with a matched child and the number of oocytes to be retrieved are very low because of diminished ovarian reserve, advanced maternal age, or both, egg donation from a half-matched relative of the mother may be considered (Tur-Kaspa *et al.*, unpublished data).

To justify PGD for HLA, related HSCT must result in a significantly better clinical outcome over unrelated or non-matched HSCT (Samuel et al., 2009). About 70% of patients who need a transplant do not have a suitable donor in their family. When there is no related HLA matched donor, matched unrelated donors might be identified in national or international donor registries. The Center for International Blood and Marrow Transplant Research showed a superior overall survival when using an HLA-identical sibling donor compared with an unrelated matched donor for leukaemia as well as for non-malignant conditions (Horan et al., 2012; Pasquini and Wang, 2013). The overall benefits of related-matched HSCT compared with matched unrelated HSCT are as follows: decreased risk of graft versus host disease, improved long-term disease-free survival in malignant conditions, superior overall survival, decreased post-transplant morbidity and decreased risk of treatment failure (Horan et al., 2012; Pasquini and Wang, 2013; Samuel et al., 2009). If unrelated HSCT in conjunction with a novel transplant protocol demonstrates long-term similar outcomes to related-matched transplant for all diseases, then PGD for HLA may no longer be needed (Li et al., 2012).

To whom PGD-HLA should be offered?

PGD–HLA should be offered to anyone with a condition that requires matched-related HSCT. Creating an HLA-matched child to an existing sick sibling in case the sibling needs