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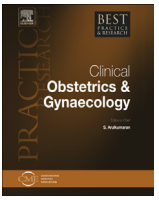

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Pre-implantation HLA matching: The production of a Saviour Child

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Pre-implantation genetic diagnosis (PGD) requires the use of assisted reproductive technology (ART) to create several pre-implantation-stage embryos, followed by biopsy of embryonic cells for genetic testing and transfer of selected embryos to the womb to establish a pregnancy. HLA typing of ART-created embryos was first reported in 2001. The aim is to establish a pregnancy that is HLA-compatible with an affected sibling who requires haematopoietic stem cell transplantation. HLA-typing can be performed with or without PGD for the exclusion of a single-gene disorder. Haematopoietic stem cells collected from the umbilical cord blood or the bone marrow of the HLA-matched donor sibling born, or a combination of both sources, are used for transplantation and cure of the affected sibling. The procedure is multistep and technically challenging. All specialists involved must aim to adequately support and counsel prospective parents. Results have so far been encouraging, with many documented positive outcomes of affected children being cured.

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Evaluating the clinical needs of pre-implantation HLA matching

Clinical value of HLA-matched donors

The first allogeneic haematopoietic stem cell transplantation (HSCT), pioneered by Donnall Thomas, was reported in 1957, and the momentous and successful transplantation of the one millionth-patient was achieved in December 2012 [1,2]. Today more than 70 diseases are treated with blood stem cell transplantation for the replacement of abnormal haematopoiesis and reconstitution of the bone marrow (BM), such as acute and chronic leukaemia, lymphoma, aplastic anaemia, Fanconi anaemia, severe congenital immunodeficiencies and haemoglobinopathies, including sickle cell anaemia and thalassaemia major [3–5].

Stem cells for transplantation are usually obtained from the BM, peripheral blood or umbilical cord blood (UCB) of an allogeneic (non-self) donor with matched human leukocyte antigen (HLA) tissue type, the latter so that the donor material is not recognized as foreign by the recipient's immune system. Umbilical cord blood transplantation (UCBT) from an HLA-identical sibling was first introduced for haematopoietic reconstitution in a patient with Fanconi anaemia in 1989 [6]. UCBT has been associated with a lower incidence of complications, although for particular diseases, it has been recently proven to be as effective as bone marrow transplantation (BMT) [7]. Cord blood collection, however, may not be able to collect an adequate number of cells for cryopreservation and subsequent transplantation. Overall, the major constraint for the HSCT is the availability of an HLA-matched donor. Within a family, if there is only one sibling, the probability of an affected child having an HLA-matched sibling is 25%, whereas if there are two siblings, this chance increases to 43.7%. It is generally mentioned that only 30% of patients can find a suitable donor within their family, while a recent study demonstrated that the likelihood of having a sibling match ranges from 13% to 51%, depending on patient age and ethnicity [8]. In the absence of a matched sibling, a matched unrelated donor may be searched for in national or international donor registries. There are now more than 29 million voluntary stem cell donors worldwide, but finding an unrelated matched donor is very difficult, especially for patients with rare HLA allotypes and haplotypes.

HSCT from matched related donors shows superior outcomes with fewer complications (risk of rejection and graft-versus-host disease, GvHD) and higher overall survival than HSCT from matched unrelated donors, despite considerable progress towards improving outcome for both related and unrelated donor transplants, achieved through advances in HLA typing and high resolution allelic matching, modifications of transplant conditioning regimen and improved supportive care treatment.

When a patient fails to find a matched donor, alternative sources include the use of a related haploidentical donor or mismatched unrelated donor. However, these options cannot guarantee equivalent success compared to transplantation with a complete HLA match [9].

Apart from the stem cell source, donor category and degree of histocompatibility, additional factors affecting the HSCT outcome include the pre-transplant clinical status and the recipient age at transplantation [7]. Planning for HSCT should, therefore, consider the urgency to transplant and the likelihood of a clinically beneficial outcome.

Clinical value of HLA typing through PGD

In the past, failure to find an HLA-matched donor to cure an affected child often led parents to try natural conception for an HLA-matched baby; there are some reports of performing prenatal diagnosis to identify the HLA status of the unborn baby [10,11].

In 2001, an HLA-matched pregnancy was achieved using new expertise known as pre-implantation genetic diagnosis (PGD). PGD, first reported in 1990, requires the use of assisted reproduction technology (ART) to create several pre-implantation stage embryos, followed by biopsy of embryonic cells for genetic testing and transfer of selected embryos to the womb to establish a pregnancy [12]. Pre-implantation HLA typing can be offered as a sole indication when the affected child requires transplantation to treat an acquired disease or in combination with PGD to concurrently avoid the risk of producing another affected child. In some countries, for ethical reasons, pre-implantation HLA typing is only considered acceptable when it is combined with PGD. In the first PGD-HLA case, four clinical ART/

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