

Discussion on consent to donate UCB should address not only the donation, but also maternal and UCB unit testing for the mandatory infectious disease markers of blood-borne viruses (Table 15-2). The discussion should emphasize that the donation of UCB is for the benefit of any patient anywhere in the world who requires a transplant and that samples will be kept for future testing. UCB units can be kept for decades, and it may be that the mandatory markers pertinent at the time of donation will not be the same as those required when a unit is issued decades later. Donor mothers are advised that their physicians will be informed of any results that have relevance to the mother's or the child's health. Permission is given to share, on a confidential basis, relevant information about the donation with registries and transplant centers. Donor mothers are made aware that requests for additional information may be sent to relevant health-care professionals to ensure the safety of the donation for transplantation. The identities of donor and recipient are ensured by using unique alphanumeric identification codes.

B. Donor Selection

Donor information is required to ensure the safety and appropriateness of any single donation for a potential intended recipient. Risk factors in the donor's family medical history, travel history, and behavioral background may affect the safety of the donation for potential recipients. Hence, detailed questionnaires have been designed to capture this information from the newborn's parents to help reduce the risk of transmissible diseases and predispositions to disorders or genetic diseases not apparent at birth. The medical history interview includes review of the behavioral risk for human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV, HCV), including skin piercing and blood transfusion, as well as the presence of transmissible infections and diseases related to travel, such as malaria. Volunteer peripheral blood and marrow donors would probably manifest any genetic disease at the time they volunteer. This may not

Table 15-2. Consent for Unrelated Cord Blood Banking

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- Collection and storage of cord blood for transplantation to unrelated individuals worldwide
 - Possible risks and benefits to mother or infant, including medical and ethical concerns
 - Maintenance of linkage for the purpose of notifying infant family of communicable or genetic diseases
 - Examination of the mother's and infant's relevant medical notes and dialogue with relevant clinical professionals
 - Permission for infectious disease testing, including for human immunodeficiency virus, and for the mother's physician or mother to be notified in the event of abnormal test results relevant to the health of the mother or infant
 - Storage of samples for future testing
 - Storage of personal information
 - Right of the mother to refuse without prejudice
 - Research, quality control, or validation use if the donation is unsuitable for clinical use
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be the case for the infant donor of UCB, hence the need for specific screening for hematologic abnormalities including thalassemia and sickle cell disease.

Additional criteria for accepting donations are:

- Pregnancies must be at least 34 weeks of gestation because of the lower TNC counts associated with the smaller placenta and infant size of earlier gestational ages.
- Single gestation—multiple deliveries can lead to cross-contamination.
- There can be no known fetal abnormalities.
- The mother must have negative screening and testing for communicable diseases.

C. Collection of Cord Blood

The collection objective is to maximize the volume of blood harvested from the placenta while reducing risks of contamination from bacteria, fungi, or maternal blood and secretions, without influencing or interfering with the routine delivery procedures. Blood can be collected from the placenta following normal full-term vaginal delivery or caesarean section by one of two methods.

- **In-utero** collection performed by trained obstetricians once the infant has been delivered. The umbilical cord is clamped and cleaned, and the blood is aspirated from the placental vein while the placenta is still in utero. This method avoids the possibility of a failed collection resulting from damage of the placenta during delivery and reduces delay. Evidence shows this technique is associated with an increase in volume and reduced incidence of clotted collections.
- **Ex-utero** collections after the infant and placenta are delivered are handled by trained UCB bank staff in a dedicated area outside of the delivery room. Following delivery, the placenta is passed to the UCB bank staff to harvest the blood, following robust cleaning of the umbilical cord and aspiration of the blood from the placental vein. The use of a small number of dedicated UCB bank staff for ex-utero collection facilitates management of hospital staff training and reduces procedure variability.

Both methods require adherence to aseptic techniques to minimize contamination. The collection kit includes a large-bore needle attached to a closed, sterile collection bag containing an anticoagulant—usually citrate-phosphate-dextrose. The blood drains into the bag and the process takes only a few minutes to complete. To provide UCB units suitable for clinical use, the volume harvested needs to be maximized so collection should continue until the blood stops flowing. At this stage, identification of the placenta and UCB unit and their linkage to the mother is critical.

D. Processing of the Unit

A successful UCB bank requires long-term storage of a large number of units. Ensuring adequate space for UCB units has been addressed by processes to reduce the volume of the UCB unit before storage. Several different methods are in use: the automated Sepax Cell Separation System (Biosafe SA, Eysins,

Switzerland) and the AXP System (Thermogenesis Corp, Rancho Cordova, CA), the semi-automated top-and-bottom technique of the PrepaCyte-CB (BioE, St. Paul, MN), and the manual hydroxyethyl starch sedimentation method. These processes remove excess plasma and red cells in a closed system, leaving the UCB unit as a buffy coat of 20 to 30 mL, while maintaining both the quality and quantity of the nucleated cells and stem/progenitor cells. Use of the “waste” components from processing for testing and archiving leaves the stem cells for transplantation. Other techniques are used by some facilities and new technologies are being introduced that select more specific cell types, making inter-bank comparisons more difficult. Reducing the UCB unit to a standard volume allows the addition of a standard volume of cryoprotectant to the cells and permits uniform freezing of the units and more rapid thawing at the time of use.

UCB needs to be processed and frozen as quickly as possible following collection—typically within 48 hours. Systems for ensuring that the UCB units are stored and transported at validated temperatures are established by the individual banks to maintain the viability of the cells.

Standard cryopreservation protocols—freezing the cells in a final concentration of 10% dimethyl sulfoxide (DMSO), in controlled-rate freezers using validated freezing rates of between 1 and 4 C/minute and storage below -150 C —give an average of 80% recovery of nucleated cells and $>90\%$ recovery of progenitor cells, as measured by CD34 cell counts and colony-forming assays. Most storage bag systems allow for attached integral segments that can be removed for confirmatory HLA typing and testing at the time UCB units are selected as a possible match for a patient, but before the unit is thawed for transplantation.

E. Testing

- **Mandatory infectious disease screening** of the UCB unit is performed by testing the donor mother at the time of donation for HIV, HBV, HCV, human T-cell lymphotropic virus, cytomegalovirus, and syphilis. Additional testing may be required by applicable law prior to release of a unit for transplantation (eg, West Nile virus, toxoplasmosis, and Epstein-Barr virus). It is common practice to screen samples of the UCB unit for these mandatory markers at the time of selection.

Extra mandatory tests or improved testing technologies may have been introduced in the period between donation and selection, or the country of import may have additional testing requirements. For such purposes aliquots of both maternal and UCB unit samples are archived.

- **Microbial cultures** of the unit are performed at the end of processing to assess the product for bacterial and fungal contamination.
- **Total nucleated cell** content is assessed on the unit before and after processing to monitor the efficiency of the volume reduction system. The TNC content of the final product is a surrogate for engraftment potential and can be expressed as TNCs per recipient body weight.

- **Stem cell** content of the unit is assessed using CD34⁺ cell counts and a colony-forming assay on samples of the final product before cryopreservation.
- **Cell viability** of the final product is assessed and used as a determinant for banking the UCB unit.
- **HLA typing** of the unit for HLA-A, -B, and -DRB1 is performed using DNA-based techniques.

VI. REGISTRATION OF UNITS

On completion of donor selection, processing, and testing, a comprehensive review of clinical records, test results, and processing and freezing records is made to ensure the safety of the product for the potential recipient, eligibility of the donor, and compliance with regulations, standards, and specifications. All approved UCB units are made available for search through registration with national and international registries. The units are listed under a unique identifier with a minimum of the HLA type and TNC of the final product.

VII. CLINICAL RESULTS OF CORD BLOOD TRANSPLANTATION

Since the first successful sibling UCB transplant performed in 1988 to treat a patient with Fanconi anemia, UCB has increased significantly as a source of HSC support in patients with high-risk hematologic disorders receiving allogeneic HSCT for their disease. It has been estimated that >25,000 patients have undergone UCB transplantation worldwide. Early single-institution and registry studies showed a decreased relapse rate and an increased transplant-related mortality (TRM) rate with similar overall survival (OS) rates with UCB compared with other donor sources (Tables 15-3 and 15-4). The vast majority of the transplants involved one or two HLA-antigen mismatches between donor and recipient, with significant numbers of patients in advanced stages of disease. Neutrophil and platelet recovery after single-unit UCB transplantation are significantly delayed compared with marrow transplantation; the median time to neutrophil recovery ranges between 20 and 30 days, and cumulative rates of engraftment between 80% and 90%. Multiple studies demonstrate the devastating impact of low TNC dose on engraftment, TRM, and survival. The limiting cell dose particularly contributes to the inferior hematopoietic recovery and increased TRM in adults receiving a single-unit UCB transplant.

Increasing data demonstrate the critical importance of HLA-match level on transplant outcome. Increasing the cell dose overcomes the effect of HLA mismatches; conversely, improved HLA match can compensate for lower cell dose. In nonmalignant diseases, OS is affected by HLA mismatches; however, in malignant diseases HLA mismatches were found not to influence survival because of the need for a GVL effect.

Clinical studies in pediatrics (such as those by Rocha et al in 2001 and 2002) demonstrate slower, but complete, hematopoietic reconstitution in the majority of pediatric patients. Incidence of severe acute GVHD is lower, despite HLA mismatches. TRM, relapse rate, and OS are at least comparable with marrow transplantation.