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LEARNING OBJECTIVES

Upon completion of this exercise, the participant should be able to

• identify the landmark studies and observations made during the development of cord blood banking.
• explain the unique properties of umbilical cord blood.
• identify criteria for donor eligibility of umbilical cord blood stem cells.
• discuss the legal and ethical issues associated with cord blood banking.
• contrast public and private umbilical cord blood collection organizations.
A 25-year-old primigravida (G1P0) white woman received regular prenatal care for an uncomplicated pregnancy by her primary family care physician. She went to a large urban academic teaching hospital at 39 weeks’ gestation in stage 1 of labor. She was not taking any medications and had no underlying illnesses.

The patient’s contractions were occurring every 7 minutes, and her cervix was fully dilated at 6 cm. Her vital signs were stable and she was afebrile. She had not required any analgesia and stated that her level of pain was tolerable at 3 (pain scale 1-10). Her membranes ruptured 6 hours before presentation. Results of a screen for group B Streptococcus 5 days previously were negative. She had no history of sexually transmitted diseases, including syphilis, gonorrhea, and chlamydia. Likewise, testing performed in early pregnancy for hepatitis B (HbsAg, anti-HBc), hepatitis C (anti-HCV), and HIV 1 and 2 (nucleic acid test), as well as rapid plasma reagin, yielded negative results.

A member of the hospital cord blood banking team asked the patient if she was interested in donating umbilical cord blood (UCB) to the hospital’s public blood bank. The patient recalled seeing advertisements in pregnancy-related magazines, and had many questions, including concerns about the safety of the collection procedure for herself and the baby.

The UCB bank representative answered her questions and described the process of collection, the tests that were required and their implications, the differences between public and private banks, and the circumstances in which the unit of UCB would be used. The patient provided informed consent, underwent epidural anesthesia, and delivered a 3.5-kg (7.7 lb) healthy girl. After delivery of the placenta, UCB was collected in an adjacent room by specialized UCB bank staff.
UMBILICAL CORD BLOOD: A HEMATOPOIETIC STEM CELL GOLDMINE

A History of UCB-Derived Stem Cell Transplantation

The first known attempt at UCB stem cell transplant was performed by Ende and Ende in 1972 in a 16-year-old boy with acute lymphoblastic leukemia. The patient received fresh cord units from 8 different donors over a 17-day period, following a preparative regimen of 6-mercaptopurine and prednisone. One of these units engrafted, as evidenced by a change in the recipient’s ABO blood group; however, engraftment only lasted for 38 days. In 1974, Knudtzon reported the discovery of colony-forming units in human UCB and suggested that these hematopoietic stem cells could be useful in bone marrow replacement. In 1983, Koike reported that UCB cells could be cryopreserved, frozen, and recovered while maintaining cell viability and function. Finally, in 1988, the first successful UCB transplant was performed in Paris by Gluckman and colleagues. The recipient was a 6-year-old boy with Fanconi anemia who received HLA-matched UCB from his sister. The patient is reported to be well and disease-free >20 years later.

In 1992, John Wagner, Hal Broxmeyer, and Elaine Gluckman established the International Cord Blood Transplant Registry as a clinical outcome data repository to help determine the risks and benefits of UCB stem cell transplant. Their first report, published in 1995, summarized the findings in the first 44 UCB stem cell transplants performed in patients 0.8 to 16.3 years old. Of these patients, 10 had an HLA-matched unit, and the others received units with a 1 to 3 HLA antigen-mismatch. They reported a 91% probability of engraftment for a 0 to 1 HLA antigen-mismatch at a median of 22 days (range, 9-46 days) for neutrophils and 51 days (range, 15-117 days) for platelets. A correlation between cell dose and time to engraftment was not observed. Graft failure occurred in 9% of patients, all of whom had malignant disease. The probability of grade II to IV acute graft-vs-host disease (GVHD) was 3%, while the risk for chronic GVHD was 6%. Of patients who received a 0 to 1 HLA antigen-mismatched sibling-donor UCB stem cell product, 72% survived.

The first 2 Phase I trials of unrelated-donor UCB stem cell transplant were reported in 1996 by Wagner and colleagues and Kurtzberg and colleagues. In both of these trials, patients with hematopoietic malignancies or inborn errors of metabolism were transplanted with unrelated-donor UCB stem cells with a 4 to 6/6 match, with the exception of one UCB stem cell product with a 3/6 match. Kurtzberg reported a 100-day survival of 64% and 100-day event-free survival of 48%. Wagner reported a 6-month survival probability of 65%. Both also reported an approximate 10% incidence of grade III to IV GVHD.

In Europe, an Umbilical Cord Blood Transplant Registry (Eurocord) was established in 1993 as a data repository. In 1998, Gluckman and colleagues reported their initial experience between 1988 and 1995. Of the 143 UCB stem cell transplants at 45 member centers, 78 were from matched-related donors. They noted a significant difference in the 1-year survival between matched-related donors and matched-unrelated donor UCB stem cell transplants of 63% vs 29%. The incidence of acute grade II or higher GVHD with HLA-matched donors was 9%. In contrast, the
incidence among mismatched donors was 50% for HLA antigen-mismatched–related donors and 40% for unrelated donors. They also reported that neutrophil engraftment improved significantly when >3.7 x 10⁶ nucleated cells/kg were infused (94% vs 76%; P =.008).

The Cord Blood Transplantation Study (COBLT) was conceived by the National Heart Lung and Blood Institute and initiated in 1996 as a Phase II, multicenter study designed to determine the utility of unrelated UCB stem cell transplant in children and adults with malignant and nonmalignant disease. The initial goals of the study were to bank 15,000 UCB units from ethnically diverse donors, using standard operating procedures, with the long-term goal of studying UCB stem cell transplant. Three academic medical centers were awarded contracts to create unrelated donor blood banks. The donor recruitment phase ran from December 1997 to June 2001 and was targeted toward hospitals serving ethnically diverse populations. A total of 17,207 ethnically diverse units were collected, and 11,077 (64%) units were cryopreserved and quarantined. Of these, 79% met eligibility criteria and were subsequently HLA antigen-typed, and entered into the search registry. Despite increased representation of minority donors, UCB units collected from black donors had a lower rate of banking, owing to lower cell counts per unit volume compared with all other ethnicities.¹⁰

The results of unrelated-donor UCB transplants in pediatric patients from the COBLT study were published in 2008.¹¹ A total of 191 children with hematologic malignancy were enrolled between 1999 and 2003. This number of patients is further broken down into HLA antigen-matched categories, as follows: 6/6 = 17, 5/6 = 58, 4/6 = 111, and 3/6 = 5. The median infusion dose was 3 x 10⁷ total nucleated cells (TNC)/kg. The median time to neutrophil engraftment (>500/µL) was 27 days and platelet engraftment (>50 x 10⁶/mL) was 174 days. By day 42, 79.9% of patients had neutrophil engraftment. Acute grade III/IV GVHD occurred in 19.5%, and chronic GVHD at 2 years occurred in 20.8%. The rate of relapse by 2 years was 19.9%, and the probability of survival was 67.4% at 6 months and 49.5% at 2 years. The study also demonstrated that UCB units with a 1 to 2 HLA antigen-mismatch can be used to successfully treat children with acute leukemia.

In 2006, results from the COBLT study for children with lysosomal and peroxisomal storage diseases who received unrelated-donor UCB transplants were reported.¹² A total of 69 patients were enrolled between 1999 and 2004. The median age was 1.8 years (range, 0.1-17 years); 64% were male, and 81% were white. Patients received a median cell dose of 8.7 x 10⁷ TNC/kg, and the 1-year survival was 72%. By day 42, 78% of patients had engrafted neutrophils, with a median time to neutrophil engraftment of 25 days. Grade II to IV GVHD was observed in 36% of patients. The study did not assess the effects of UCB stem cell transplant on neurocognitive function, motor skills, or developmental delay, but the same group had previously reported that patients with Hurler syndrome and Krabbe disease had significantly improved neurocognitive outcomes and survival compared with patients who had never undergone stem cell transplant.

Analysis of data obtained from adults enrolled in the COBLT study, published in 2005,¹³ demonstrated worse outcomes when compared with the results reported in pediatric patients. A total of 34 patients were enrolled, with a median age of
34.5 years (range, 18.2-55 years). Of these patients, 1 was a 6/6 match, 10 a 5/6 match, and 23 a 4/6 match. The subjects received either total body irradiation/cyclophosphamide (n = 27), or busulphan/melphalan (n = 7) as preconditioning. Four subjects died before they could undergo transplant and were not included in the main analysis. Of the patients who received a transplant, 66% had neutrophil engraftment (absolute neutrophil count, >500/µL) by day 42 (median, 32 days) and 35% had platelet engraftment (platelets, >20 ×10^6/mL) by day 120 (median, 117 days), both of which were considerably lower than that seen in their pediatric counterparts. The cumulative incidence of acute GVHD was 34%. The primary endpoint of day 180 survival was met by 30% of the patients; however, only 2 patients remained alive at 36 months.

Results from the International Bone Marrow Transplant Registry and the National Cord Blood Program of the New York Blood Center for 682 adults with acute leukemia who received unrelated human progenitor cell (HPC) transplants were published in 2004. When compared with the 584 patients who received bone marrow, the 98 who received UCB had a lower risk for acute grade II to IV GVHD but had significantly delayed neutrophil recovery (median, 27 days vs 10 to 20 days) and platelet recovery (median, 60 days vs 29 days). However, there were no differences in transplant-related mortality, relapse rate, disease-free survival, or chronic GVHD.

One of the initial limitations in adult UCB transplant was the limited dose of TNC and CD34+ stem cells in a UCB unit. In 2000, the first trials of UCB stem cell transplant using double units in adults began. This method has been shown to provide an adequate cell dose, thus overcoming some of the previous barriers to adult UCB transplant. The outcomes for fully myeloablative and minimally myeloablative transplants, with similar cell doses, are comparable to single-unit UCB transplant in terms of neutrophil engraftment, platelet engraftment, transplant-related mortality, overall mortality, and disease-free survival. Sustained hematopoiesis after either transplant is usually derived from a single donor.

The first public UCB bank was established in 1991 with the support of the National Heart, Lung, and Blood Institute, as a research project, and the UCB bank at the New York Blood Center was established in 1993. Since the first unrelated UCB stem cell transplant, >14,000 unrelated UCB stem cell transplants have been performed worldwide, with >2500 in the United States. Between 1991 and 2006 the number of banked UCB units worldwide increased exponentially, from >1000 in 1995 to >10,000 in 1997, and from >100,000 in 2002 to 400,000 in 2009, at 100 different UCB banks in 21 different countries. As of 2009, >150 centers throughout the world have performed >20,000 UCB stem cell transplants, 14,000 of which were from unrelated donors. Currently >50% of unrelated-pediatric, and up to 20% of unrelated-adult HPC transplants are from UCB stem cells. In Japan, UCB stem cells are used in >50% of adult-unrelated HPC transplants.

UCB banking (ie, collection, processing, and storage) and transplant are regulated by the Food and Drug Administration. In addition, UCB banks and transplant centers can voluntarily become accredited by the Foundation for the Accreditation of Cellular Therapies (FACT) and the American Association of Blood Banks (AABB). Adherence
to guidelines is assessed through regular inspections every 2 years by the AABB and every 3 years by FACT.19,20,21

In 2005, the US federal government passed the C.W. “Bill” Young Stem Cell Therapeutic and Research Act, appropriated $80 million for the collection and maintenance of 150,000 UCB units, and established a National Cord Blood Bank Registry to be administered through the Health Resources Services Administration. Contracts were awarded to 9 blood banks, the National Marrow Donor Program, and the Center for International Blood and Marrow Transplant Research, respectively. This has allowed banking of larger numbers of units by public UCB banks and the creation of a single, consolidated database to facilitate inventory searches.5,22

Pediatric diseases successfully treated with UCB stem cell transplant now include hematologic malignancies, hemoglobinopathies (eg, thalassemia and sickle-cell disease), congenital immunodeficiency syndromes, including severe combined immunodeficiency disease, and inborn errors of metabolism, including Hurler syndrome and Krabbe disease.5

UCB has several unique properties that differ from those of hematopoietic progenitor cells. UCB contains a very high concentration of HPCs. These cells are usually in a slow or noncycling state, but with appropriate cytokine stimulation, can be induced to proliferate and differentiate along various hematopoietic and other cell lines. Also, because cord blood cells are immune-naive, they are more immunotolerant than adult T cells, allowing them to be used even if there is a 5/6 or 4/6 HLA antigen match with the recipient, something that cannot be done with peripheral blood–derived stem cells. They are also associated with a decreased incidence and severity of GVHD for corresponding levels of HLA matching when compared with bone marrow and peripheral blood–derived stem cells, respectively. Fortunately, there does not appear to be a decrease in the graft vs leukemia effect.23,24 The advantages and disadvantages of using UCB instead of other sources of human progenitor cells are shown in Table I.

The most important predictors of engraftment are the TNC and the degree of the HLA match between donor and recipient. Below the critical threshold of 2.5 $\times$ 10$^7$ TNC/kg and 1.7 $\times$ 10$^5$ CD34+/kg, there are very high rates of graft failure, transplant-related morbidity, and transplant-related mortality.25-27 Hence, double- or even triple-unit UCB stem cell transplant is performed in adults.27-30 In addition, the use of ex-vivo expansion is also under intense investigation.

Donor Eligibility and Informed Consent
Mothers who are at least 18 years old, have had an uncomplicated pregnancy, and are at 36 weeks’ gestation or later can be considered candidates for UCB donation. In addition, they must have negative results on required infectious disease tests, be at low risk of blood-borne diseases, have no known genetic diseases or chronic medical problems, have normal vital signs during labor, and may not be taking contraindicated medication.31-33 Based on these criteria, about 50% of potential donors are ineligible for collection. The most common causes for deferral are maternal fever, sexually transmitted disease(s), underlying maternal disease, use of unacceptable medications, and a complicated delivery.
Education about UCB banking ideally begins during pregnancy and is an integral part of the informed-consent process. Ideally, informed consent is obtained during pregnancy, ie, during routine antenatal care.32-35 Consent can also be obtained in the early stages of labor, or even after UCB collection; however, this is the least favored approach.

Intralabor consent involves approaching a woman in early labor to explain the procedure, answer questions, and obtain informed consent should she be willing to donate.34 The mother must have a cervical dilation of <7 cm and not have received narcotics or other medications that could interfere with her judgment in order to be approached for intralabor consent.

For consent to be informed, the mother must have been provided information about UCB banking, including that collection is entirely voluntary.36 With private UCB banking, this includes information that the donated UCB will be privately banked.

### Table I. Advantages and Disadvantages of Using UCB vs Other HPC Source.

<table>
<thead>
<tr>
<th>Advantages of UCB Stem Cells</th>
<th>Disadvantages of UCB Stem Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA mismatched units (4/6 or 5/6 match) can be successfully transplanted.</td>
<td>↑ Time until bone marrow recovery posttransplant:</td>
</tr>
<tr>
<td>↓ Time between search initiation and transplant (25-26 days earlier than with unmatched donor PBPC)</td>
<td>Mean time to neutrophil engraftment: PBSC = 8-10 d, UCB = 23 d with 6/6 match, 28 d with 1-2/6 mismatch</td>
</tr>
<tr>
<td>↓ Donor attrition compared with marrow collection</td>
<td>Mean time to platelet engraftment: PBSC = 10-12 d, UCB = 90 d</td>
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<tr>
<td>↓ Donor discomfort and collection-associated morbidity</td>
<td>↑ Duration of hospital stay</td>
</tr>
<tr>
<td>↑ In the potential pool of rare haplotypes, and ethnic minorities</td>
<td>↑ Transfusion support required</td>
</tr>
<tr>
<td>↓ Incidence of acute GVHD</td>
<td>↓ TNC and CD34+ cell dose (1 log less than PBSC or bone marrow) limits UCB transplants to children or small adults.</td>
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<tr>
<td>↓ Incidence of CMV, EBV, and other viral disease transmission (most infants have not had CMV or EBV exposure or infection)</td>
<td>↑ Incidence of graft failure (up to 35% in adults)</td>
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<tr>
<td>↓ Myeloablative preparative regimen or no preparative regimen still allows for transplant (Older patients, those with comorbidities, or with disease previously considered to be too advanced and who were not previously considered to be candidates for PBSC or bone marrow transplant, can undergo UCB transplant.)</td>
<td>Unable to provide a second stem cell dose or donor lymphocyte transfusion</td>
</tr>
<tr>
<td>↓ Incidence of posttransplant lymphoproliferative disease in children</td>
<td>↑ Risk for bacterial contamination</td>
</tr>
</tbody>
</table>

CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-vs-host disease; HPC, human progenitor cell; PBPC, peripheral blood progenitor cells; PBSC, peripheral blood stem cells; TNC, total nucleated cells; UCB, umbilical cord blood.
for the patient’s child’s or other family member’s use, information about the costs, including ongoing storage fees, and the consequences of nonpayment, which may include abandonment of the unit.

Public blood banks need to inform the mother that publicly banked UCB is for potential use by the general population and is not specifically available for her child or any siblings in the future. She is also told what tests will be performed and that tests for genetic diseases are included (Table II). Prospective donors are told that if any of these criteria are not met, the unit will not be banked. The mother will be informed of any positive test results but will not have access to any information about the final disposition of the unit.

UCB Collection

UCB stem cells can be collected either in utero or ex utero. There is no difference in product volume, TNC recovery, or CD34+ count between these 2 methods.34 With both methods, the umbilical vein is canulated in a sterile manner, and the blood is collected via gravity by sterile tubing connected to a collection bag containing citrate phosphate dextrose adenine anticoagulant. The procedure typically takes anywhere from 5 to 8 minutes.33 Collection generally poses no risk to the mother or the newborn, with the exception of the risk of neonatal anemia if the cord is clamped too early.

Ex utero collection is performed by dedicated collection staff employed by a UCB bank that typically serves several hospitals. The collection is usually performed in an adjacent room after the placenta is delivered (Image).31 By using this process, the collection can be performed in a more controlled environment to help ensure sterility and adherence to protocols, thus ensuring the highest quality. Logistical disadvantages

<p>| TABLE II. Tests To Determine if a UCB Unit Meets Criteria for Cryopreservation. |</p>
<table>
<thead>
<tr>
<th>Maternal Blood Sample*</th>
<th>UCB Sample</th>
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</thead>
<tbody>
<tr>
<td>Infectious disease testing:</td>
<td>UCB volume</td>
</tr>
<tr>
<td>HBV: HbsAg, anti-Hbc, or NAT</td>
<td>TNC</td>
</tr>
<tr>
<td>HCV: Anti-HCV, or NAT</td>
<td>ABO &amp; Rh typing</td>
</tr>
<tr>
<td>HIV: Anti-HIV-1, anti-HIV-2, or NAT</td>
<td>HLA class I &amp; II typing (molecular is now favored)</td>
</tr>
<tr>
<td>HTLV: Anti-HTLV-1, anti HTLV-2</td>
<td>Genetic disease testing</td>
</tr>
<tr>
<td>CMV: Anti-CMV</td>
<td>Bacterial cultures (aerobic, anaerobic)</td>
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<tr>
<td>WNV: NAT</td>
<td>Fungal culture</td>
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<tr>
<td></td>
<td>Hemoglobin electrophoresis</td>
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<tr>
<td></td>
<td>CD34+ count†</td>
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<td></td>
<td>CFU assay†</td>
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<tr>
<td></td>
<td>Cell viability†</td>
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<td></td>
<td>Genetic screening‡</td>
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</tbody>
</table>

CFU indicates colony-forming units; CMV cytomegalovirus; EBV, Epstein-Barr virus; GvHD, graft-vs-host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; NAT, nucleic acid amplification technology; PBPC, peripheral blood progenitor cells; PBSC, peripheral blood stem cells; TNC, total nucleated cells; UCB, umbilical cord blood; WNV, West Nile virus.

*Obtained within 7 days postdelivery.
†Postprocessing, before cryopreservation.
‡Performed by all public and some private UCB banks.
include the limited number of UCB bank staff available, the critical timing required
to coordinate collection with delivery, and the potentially reduced capture rates from
the available donor pool when demand for collection is high.

In utero collection is performed by the obstetrician or obstetrical staff during the third
stage of labor, before placental delivery. This is typically used for collections in private
UCB banking; however, some units for public banks are also collected this way. In
in utero collection has the advantage that, because the obstetrician or midwife performs
collections without dependence on auxiliary staff, all women potentially have access
to collection. Disadvantages include the increased risk for bacterial contamination,
increased incidence of labeling errors, UCB specimen clotting, and the decreased
ability to perform quality control for the collection procedure.

Factors Influencing UCB Stem Cell Yield
Factors that increase the overall yield include placental weight >500 g, increased
gestational age, higher birthweight, longer umbilical cord, greater UCB volume,
primigravida mother, younger maternal age, female newborn, and stress during
delivery (eg, prolonged labor, meconium in amniotic fluid, and lower umbilical cord
pH). It is postulated that the increased cytokine release during a stressful delivery
induces CD34+ mobilization from sites of hematopoiesis. Race also affects yield, with
whites having the highest cell counts per milliliter, and blacks the lowest.10,37-42

Transport, Processing, Storage, Thawing, and Infusion
Most UCB units are collected at hospitals and then transported or shipped to
the UCB bank. The units need to be transported or shipped in such a way as to
preserve the product and to pose no biologic hazard risk to others. Products must
be transported in validated containers that meet regulatory requirements. FACT
and AABB standards specify the required packaging, labeling, and the temperatures
that must be maintained in extreme environmental conditions.19-21,33 Studies have
demonstrated excellent cell viability at 24 hours after collection when the UCB is
stored at 4°C, or even at room temperature (15°C-25°C).33

When a unit is received it is checked for appropriate labeling and temperature, and
logged into inventory. A visual inspection of the unit is performed to look for leaks,
tears, clots, or discoloration. Test results then determine if the unit meets the criteria
required for storage.31 Tests performed on both maternal and UCB are listed in Table
II. Basic requirements before banking include a minimum volume of 50 mL, a TNC
count of 10 ×10⁸, and negative results on infectious disease workup.31 Only 50% of
units collected for public UCB banks meet criteria for cryopreservation; the most
common reason for rejection is insufficient UCB volume.19-21

To maximize the use of storage space, UCB units undergo volume reduction, as
well as red blood cell depletion before cryopreservation.17,33 Units are frozen, using
dimethyl sulfoxide (DMSO) and dextran 40, then stored at –80°C to –135°C in
either the liquid or vapor phase of liquid nitrogen.35,43 Good cell viability has been
reported after 15 years of storage.44 Test results are stored in a databank that may
be unique to the UCB bank, or part of a larger network consortium, such as the
National Marrow Donor Program or Eurocord.
The UCB unit is usually thawed immediately before infusing. This can be done in the transplant facility’s cell-processing laboratory (e.g., by placing the unit in a 37.5°C water bath) or at the bedside. In addition, some institutions may wash the thawed units to remove the DMSO or when there is a major ABO mismatch between donor and recipient. TNC, CD34+, and CD3+ cell counts, cell viability, and microbial cultures may also be performed. Cell viabilities of 80% and above are generally considered acceptable for UCB units.

UCB units are usually infused over 1 to 2 hours, and the patient is closely monitored during the infusion for signs of DMSO toxicity (e.g., headache, nausea and vomiting, abdominal pain, rash, bradycardia, hypotension) or other reactions.

**Differences Between Public and Private UCB Banks**

Public and private UCB banks are fundamentally different. Public UCB banks are not-for-profit organizations and are typically attached to either large academic medical centers or blood centers. They collect, process, and store UCB donated from mothers who consent to its use for unrelated-blood-donor UCB stem cell transplant. This is done at no cost to the mother, and she will not have specific access to the donated unit in the future. For the unit to be banked, the mother must agree to all required testing. These results are communicated to her, and she is asked to contact the UCB bank if she or the child develops certain illnesses. Neither the mother’s nor the newborn’s identity will be disclosed to any recipient, and she will not have access to any recipient information. When a publically banked unit is provided for transplant, the transplant recipient is charged $15,000 to $25,000. However, this fee is usually covered by health insurance.

Private UCB banking for transplant began in 1992. These UCB banks are usually for-profit and store UCB for the donor or other HLA antigen-matched siblings or family members. Usually the UCB is collected in utero by the obstetrician or midwife. The donor/family pays for these units to be collected and banked. Typical fees for initial collection and processing are $1500 to $2000, with ongoing yearly fees of $150/year to continue storage, with some offering lender financing. The number of units collected per year is now greater than those collected by public UCB banks, and as of 2008, >460,000 UCB units were privately banked in the United States. Estimates of the probability of the unit being infused range from 1:2500 to 1:250,000.

**Ethical and Legal Issues Associated With UCB Banking**

Before the advent of UCB banking and transplant, the umbilical cord and the placenta were considered, historically, to be medical waste, and as such were the property of the hospital. Newborn babies are considered the donors because the stem cells are derived from their bone marrow. However, they are not volunteer donors, and collection requires informed consent from the mother. Ideally, the father also provides consent; however, this is not legally necessary. As the legal guardian, the mother determines the disposition of this blood. It is postulated that when the child becomes of legal adult age, he or she would assume ownership; however, little to no UCB units have been stored long enough to establish this legal relationship. In cases where a privately banked unit has been “abandoned,” it is considered the property of the bank.
of the UCB bank to dispose of, sell, or use for research. Public cord banks dispose of units only if they do not meet storage criteria.

Several ethical concerns have arisen about the practice of UCB banking, particularly with private UCB banks. Public blood banks are inherently beneficent in that the donated UCB units are available for matched unrelated donors, with equitable access to all. Nonmalfeasance is achieved by collecting the UCB after the newborn is delivered, and the umbilical cord is clamped and cut, posing no risk to the mother or newborn. Because timing of cord clamping influences the TNC yield, there is a potential for those collecting UCB to clamp the umbilical cord too early, (ie, within 1-2 minutes) to increase the UCB stem cell yield and thus render the newborn anemic.

Genetic testing can cause unnecessary psychologic distress and harm to the family.46 This is particularly true if an adult-onset disease, for which there is no prevention or treatment, is detected and shared with family members. UCB banking is also potentially associated with risks to privacy and confidentiality.23 The need to obtain a maternal and family history and screen for infectious and genetic disease may uncover medical information that, if not closely guarded, could lead to discrimination against that person by society.

Access to private UCB banking is also not equitable.31,46,49 It is only available to those who have the socioeconomic means to afford it. Sensitive ethical concerns may also exist in cases when an infant is conceived solely to provide UCB stem cells for an existing sibling needing transplant or in cases where an embryo is selected and implanted based on HLA antigen compatibility with the potential recipient.

Concerns have been raised about issues of commercialism, truth in advertising, and exploitation of the mother’s vulnerability during pregnancy by private blood banks.31,46,49 The private blood banks advertise their services using terms such as “biologic insurance” that can lead mothers to conclude that there is a reasonable likelihood that her child may eventually require transplant of these cells, when the real probability of this approaches zero (ie, 1/20,000). Also, there is a risk that these banks have financial incentives to collect and store these products. In addition, the use of autologous UCB stem cell transplant to treat acute leukemia may not represent optimal treatment because of the potential for preexisting leukemogenetic mutations in the collected cells.48

Current and Future Areas of Research
With the recognition that engraftment time is inversely related to the number of stem cells administered and its impact on that success in adult transplant, research into using stem cells expanded in ex vivo culture systems is ongoing.33,34 In these studies, a portion of the UCB unit is cultured using various combinations of cytokines and growth factors, such as granulocyte-colony-stimulating factor, stem cell factor, and megakaryocyte growth and development factor. The expanded cells are then infused either at the same time as the unmanipulated UCB stem cells or at a later time, such as 12 or 14 days later. In other ex vivo expansion protocols, an entire UCB unit may be expanded and a second unmanipulated unit given as well. Other active areas of research are in the field of regenerative medicine using the plasticity of UCB stem...
cells with the ability to differentiate into nonhematologic cells to use for treatment of neurologic, cardiac, and neuromuscular disease.\(^\text{23,31}\)

**Case Conclusion**

The patient was an excellent candidate for UCB collection. She had an uncomplicated pregnancy and tested negative for infectious disease before labor. In addition, although in labor, she met the criteria for donation because she was in stage 1 of labor with a <7-cm cervical dilatation, was afebrile with normal vital signs, and had not received any narcotic or other sedative analgesia. Because she had heard about UCB donation before labor and could actively participate in the discussion with the collection personnel, she was able to provide informed consent.

**REFERENCES**


