Umbilical Cord Blood Banking: Implications for Perinatal Care Providers

This guideline has been reviewed by the Maternal/Fetal Medicine Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To evaluate the risks and benefits of umbilical cord blood banking for future stem cell transplantation and to provide guidelines for Canadian perinatal care providers regarding the counseling, procedural, and ethical implications of this potential therapeutic option.

Options: Selective or routine collection and storage of umbilical cord blood for future autologous (self) or allogeneic (related or unrelated) transplantation of hematopoietic stem cells to treat malignant and nonmalignant disorders in children and adults.

Outcomes: Maternal and perinatal morbidity, indications for umbilical cord blood transplantation, short- and long-term risks and benefits of umbilical cord blood transplantation, burden of umbilical cord blood collection on perinatal care providers, parental satisfaction, and health care costs.

Evidence: MEDLINE and PubMed searches were conducted from January 1970 to October 2003 for English-language articles related to umbilical cord blood collection, banking, and transplantation; the Cochrane library was searched; and committee opinions of the Royal College of Obstetricians and Gynaecologists, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists were obtained.

Values: The evidence collected was reviewed and evaluated by the Maternal/Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC), and recommendations were made using the evaluation of evidence guidelines developed by the Canadian Task Force on the Periodic Health Exam.

Benefits, Harms, and Costs: Umbilical cord blood is a readily available source of hematopoietic stem cells used with increasing frequency as an alternative to bone marrow or peripheral stem cells for transplantation in the treatment of malignant and nonmalignant conditions in children and adults. Umbilical cord blood transplantation provides a rich source of hematopoietic stem cells with several advantages, including prompt availability, decreased risk of transmissible viral infections and graft-versus-host disease (GVHD) in both human leukocyte antigen (HLA)-matched and HLA-mismatched stem cell transplants, and easier collection with little risk to mother or newborn. Potential limitations of umbilical cord blood transplantation include insufficient stem cell dose to reliably treat larger children and adult recipients, slower rate of engraftment, and the potential for transfer of genetically abnormal hematopoietic stem cells. The optimum method of cord blood collection is not yet clear, though available evidence would favor collection before delivery of the placenta.

The financial burden to the health care system for public cord blood banking and to families for private cord blood collection and storage is considerable.

Recommendations:

1. Perinatal care providers should be informed about the promising clinical potential of hematopoietic stem cells in umbilical cord blood and about current indications for its collection, storage, and use, based on sound scientific evidence (II-3B).

2. Umbilical cord blood collection should be considered for a sibling or parent in need of stem cell transplantation when an HLA-identical adult bone marrow cell or peripheral stem cell donation from a sibling or parent is unavailable for transplantation (II-2B).

3. Umbilical cord blood should be considered when allogeneic transplantation is the treatment of choice for a child who does not have an HLA-identical sibling or a well-matched, unrelated adult bone marrow donor (II-2B).

4. Umbilical cord blood should be considered for allogeneic transplantation in adolescents and young adults with hematologic malignancies who have no suitable bone marrow donor and who require urgent transplantation (II-3B).

5. Altruistic donation of cord blood for public banking and subsequent allogeneic transplantation should be encouraged when umbilical cord blood banking is being considered by childbearing women, prenatal care providers, and (or) obstetric facilities (II-2B).

Key Words: Umbilical cord blood, hematopoietic stem cells, blood banks, transplantation, donor, recipient

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INTRODUCTION

The transplantation of hematopoietic stem cells (HSC) is commonly used to treat malignant and nonmalignant disorders, such as acute and chronic leukemias, lymphomas, solid tumours, immune deficiencies, inborn errors of metabolism, and genetic diseases. Stem cells may be obtained from the patient (autologous) or from related or unrelated (allogeneic) donors. Although bone marrow or peripheral stem cell transplantation from a human leucocyte antigen (HLA)–matched sibling is preferred, only 25% of patients will have an HLA-matched sibling available. Alternative sources of stem cells include bone marrow and peripheral blood progenitor cells from unrelated donors and umbilical cord blood (UCB).

Umbilical cord blood is an excellent source of highly proliferative stem cells capable of completely reconstituting the hematopoietic system. Practical advantages of cord blood include a lower risk and severity of graft-versus-host disease (GVHD) in HLA-matched and -unmatched recipients, ease of collection without discomfort or risk to the donor, and prompt availability as a frozen graft. With growing experience and encouraging results over the past decade, cord blood banks have been established globally to supply hematopoietic stem cells from related and unrelated donors. The worldwide inventory of more than 145 000 cord blood donations has provided transplants to more than 3000 recipients, mainly in unrelated pediatric patients for hematologic conditions. In addition, an ever increasing number of private cord blood banks encourage women to store umbilical cord blood for potential future use by their children or themselves. Increasing public, media, and commercial interest in cord blood banking has resulted in an increased demand for information, counselling, and cord blood collection from Canadian childbearing women. A recent Canadian survey of pregnant women revealed that 70% of 443 women interviewed felt that their knowledge of cord blood banking was poor to very poor. Most respondents (68%) wanted to receive information about umbilical cord blood transplantation from their prenatal care provider or at prenatal classes. Given the growing demand for information and services related to cord blood banking, it is imperative that perinatal care providers keep abreast of the scientific, clinical, and ethical implications of UCB banking.

The quality of evidence and classification of recommendations have been adapted from the Report of the Canadian Task Force on the Periodic Health Exam (Table 1).

HISTORY OF CORD BLOOD TRANSPLANTATION

The first umbilical cord blood transplant was performed in 1970 in a 16-year-old boy with acute lymphoblastic leukaemia. The boy received cord blood units from 8 different unrelated donors, untested for any HLA compatibility, over 18 days. Only 1 unit engrafted, but the patient remained in complete remission with maintenance chemotherapy until...
his last follow-up appointment at 9 months. Subsequent laboratory experiments starting in 1982 confirmed that umbilical cord blood contained hematopoietic stem cells that might be suitable for transplantation. This research led to the collection and banking of cord blood at Indiana University, Indianapolis, from siblings of children who were in need of transplantation. In 1988 Gluckman and coworkers reported curing Fanconi anemia in a 5-year-old boy, using blood from his baby sister’s umbilical cord, in Paris, France. The New York Blood Centre established the Placental Blood Program in 1992 with publication of the outcomes of the first 562 cord blood transplants from unrelated donors in 1998. In 1993 the first 3 programs set up to establish large banks of cryopreserved cord blood collected from healthy newborns were established in New York, Milan, and Dusseldorf. The National Health Service of the UK established umbilical cord blood banking for stem cell transplantation in children and adults with a wide variety of hematologic malignancies. The National Blood Service of France established the Placental Blood Program, from healthy newborns in 1994, to establish large banks of cryopreserved cord blood. In the same year, the Alberta Cord Blood Bank became the first public umbilical cord blood bank in Canada. Currently there are 33 cord blood registries from 21 countries listed on the Bone Marrow Donors Worldwide Web site.

CLINICAL EVIDENCE

HLA-matched bone marrow transplantation from related and unrelated donors is an accepted treatment for conditions requiring bone marrow reconstitution. Only 25% of patients requiring hematopoietic stem cell transplantation have an HLA identical sibling. Although 76% of preliminary allogeneic searches yield a prospective donor, the time from initiating a search to transplantation is generally 4 months or more. Transplantation of HLA-mismatched bone marrow stem cells is associated with significantly reduced engraftment rates, severe graft-versus-host disease, increased infectious morbidity, and decreased survival. For patients without an HLA-identical sibling or matched unrelated donors, umbilical cord blood provides an attractive alternative.

Umbilical cord blood has been used clinically for transplantation therapy in children and adults with a wide variety of malignant and nonmalignant diseases (Table 2). Most of the published series are compilations of transplant results from numerous institutions where procedural methods, including preparative regimens and graft-versus-host disease prophylaxis schedules, were inconsistent. Although these reports have yielded important preliminary information, available evidence is retrospective, uncontrolled, and anecdotal.

Clinical Properties of Cord Blood Stem Cells

Preclinical in vitro studies demonstrated the proliferative superiority of primitive cord blood hematopoietic cells, compared with the bone marrow. The high proliferative capacity of bone marrow repopulating cells in umbilical cord blood has been confirmed in clinical transplants. A 100 mL unit of cord blood contains one-tenth the number of nucleated and progenitor cells present in 1000 mL of marrow, but because they proliferate rapidly, the stem cells in a single unit of umbilical cord blood can reconstitute the entire hematopoietic system. The likelihood of acute and chronic graft-versus-host disease with umbilical cord blood transplants is significantly reduced, compared with bone

Table 1. Criteria for quality of evidence assessment and classification of recommendations

<table>
<thead>
<tr>
<th>Level of evidence*</th>
<th>Classification of recommendations†</th>
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<tr>
<td>I: Evidence obtained from at least one properly designed randomized controlled trial.</td>
<td>A. There is good evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.</td>
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<td>II-1: Evidence from well-designed controlled trials without randomization.</td>
<td>B. There is fair evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.</td>
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<td>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</td>
<td>C. There is insufficient evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.</td>
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<td>II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</td>
<td>D. There is fair evidence not to support the recommendation for a diagnostic test, treatment, or intervention.</td>
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<td>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</td>
<td>E. There is good evidence not to support the recommendation for use of a diagnostic test, treatment, or intervention.</td>
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*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.
marrow transplants. This phenomenon is believed to be secondary to the decreased number and alloreactivity of umbilical blood lymphocytes, particularly T cells. As a result, there is increased likelihood of successful engraftment of cord blood transplants, despite HLA mismatches at 1 or more loci. For recipients with leukemia, the decreased immunoreactivity of umbilical cord blood stem cells may result in reduced graft-versus-leukemia effect, which may increase rates of disease relapse in UCB recipients. Factors which influence disease relapse in such patients include age of recipient, malignant risk group, and biology of disease.

The median time to neutrophil and platelet recovery after umbilical blood transplantation is longer than that expected after bone marrow or adult peripheral blood stem cell transplants. The delay in immune reconstitution following cord blood transplantation increases the risk of infection and transplant-related mortality and morbidity. Nevertheless, overall survival in pediatric cord blood transplant recipients is comparable with that observed following unrelated donor bone marrow transplants. The total nucleated cell count of the umbilical cord blood transplant relative to recipient size is the most important factor influencing successful engraftment and survival. Particularly poor results are seen with cord blood transplantation when the nucleated cell dose is less than $1.5 \times 10^8 /kg$. The effect of HLA incompatibility on the success of cord blood transplantation is less clear, but some investigators have observed an association between the degree of HLA mismatch and the probability of engraftment and GVHD.

### Related Donor Cord Blood Transplantation
There are 2 publications describing the results of 44 and 78 HLA-matched cord blood transplants from related donors. Transplant recipients were primarily children receiving treatment for malignant and nonmalignant diseases. Myeloid engraftment rates of 82% and 79% were reported with neutrophil recovery by 22 days and 30 days. Platelet engraftment rates were 67% to 90%. The probability of developing chronic GVHD was low, at 6% to 14%. Overall survival at 16 and 12 months post-transplant was approximately 60% in both groups.

### Unrelated Donor Cord Blood Transplantation
Several publications have reported results from unrelated donor cord blood transplants. The number of patients in these series varied from 18 to 562 with no control subjects, so the findings should be considered preliminary. Most recipients received cord blood grafts that were mismatched at 1 to 4 HLA loci with very few HLA-matched grafts. Myeloid engraftment rates of 81% to 100% with neutrophil recovery by 22 to 30 days were reported. Platelet engraftment rates were 67% to 90%.

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**Table 2. Diseases treated with cord blood transplantation**

<table>
<thead>
<tr>
<th>Malignant diseases</th>
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<tr>
<td>Acute lymphocytic leukemia</td>
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<tr>
<td>Juvenile myelomonocytic leukemia</td>
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<td>Acute myeloid leukemia</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Chronic lymphocytic leukemia</td>
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<td>Myelodysplastic syndrome</td>
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<td>Chronic myelogenous leukemia</td>
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<td>Neuroblastoma</td>
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<td>Common variable immunodeficiency-myelodysplastic syndrome</td>
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<table>
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<tr>
<th>Nonmalignant diseases</th>
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<td>Adrenoleukodystrophy</td>
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<td>Krabbe’s disease</td>
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<tr>
<td>Amegakaryocytic thrombocytopenia</td>
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<td>Langerhans cell histiocytosis</td>
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<td>Bare-leukocyte syndrome</td>
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<td>Lesch-Nyhan disease</td>
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<tr>
<td>Blackfan-Diamond anemia</td>
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<td>Leukocyte adhesion defect</td>
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<td>Dyskeratosis congenita</td>
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<tr>
<td>Neuronal ceroid lipofuscinosis</td>
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<tr>
<td>Familial erythrophagocytic lymphohistiocytosis</td>
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<tr>
<td>Osteopetrosis</td>
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<tr>
<td>Fanconi anemia</td>
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<tr>
<td>Severe aplastic anemia</td>
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<tr>
<td>Global cell leukodystrophy</td>
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<td>Severe combined immunodeficiency</td>
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<td>Gunter disease</td>
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<td>Sickle cell disease</td>
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<td>Hunter’s syndrome</td>
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<td>Thalassemia</td>
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<td>Hurler’s syndrome</td>
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<td>Wiskott-Aldrich syndrome</td>
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<td>Kostmann’s syndrome</td>
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<td>X-linked lymphoproliferative disorder</td>
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varied from 9% to 23%. The probability of chronic graft-versus-host disease was 0% to 25%. Survival at 6 to 12 months varied from 29% to 65%.

There have been no prospective randomized control trials (RCTs) of umbilical cord blood versus bone marrow transplantation comparing outcomes in similar patient populations. Three retrospective comparisons are available for review.9,10,13 Engraftment with umbilical cord blood transplantations was delayed, compared with bone marrow transplant, but overall engraftment rates at 45 days and 6 months were similar. The risk of graft-versus-host disease was decreased with cord blood transplantation, which is consistent with other reports. In patients treated for leukemia, the 3-year survival between groups was similar, and there was no evidence of a higher risk of leukemia relapse. There appeared to be a preserved graft-versus-leukemia effect after umbilical cord blood transplantation. Though there was an increase in early treatment-related mortality with umbilical cord blood transplants, the overall survival with limited (0 to 2) HLA-mismatched cord blood was similar to bone marrow transplantation, particularly in pediatric recipients.

**Adult Recipients**

Most umbilical cord blood transplants from unrelated donors have been performed in children, but the number in adults has grown steadily in recent years. There are 4 published reports of unrelated donor cord blood transplantation in adults, with the number of recipients ranging from 22 to 108.12–25 Most adult recipients received cord blood stem cells for treatment of hematologic malignancies. The rate of myeloid engraftment was between 81% and 90%, with neutrophil recovery at 22 to 32 days. Severe GVHD occurred in 3% to 40% of patients, and the probability of chronic GVHD varied from 16% to 40%. The probability of event-free survival varied from 21% to 53% at 1 year and 26% to 76% at 3 years. Factors that influenced outcome in adult recipients included the total nucleated cell dose infused per kg, the disease status at the time of transplantation, and the age of the recipient. Techniques to increase the nucleated cell numbers in cord blood transplants for adults including ex vivo expansion of hematopoietic stem cells and the use of multiple UCB units are being investigated.3 Available data support the use of cord blood transplantation from unrelated donors for young adults with hematologic malignancies and no appropriate bone marrow donor, especially those requiring urgent transplantation.

**Cord Blood Transplant Enhancement**

Despite optimal collection and processing procedures, only a small minority of umbilical cord blood donations contain sufficient cells for adults and children who weigh more than 50 kg. Using hematopoietic growth factors, it is possible to achieve up to a fiftyfold increase in hematopoietic stem cells contained in umbilical cord blood.26 Infusion of 80% of unmanipulated cord blood units with expansion of the remaining 20% has resulted in a five- to sevenfold increase in viable progenitor cells. The clinical use of expanded umbilical cord blood transplants has been well tolerated, but to date, there has been no definable improvements in clinical outcomes. However, because of the superior proliferative capacity and engraftment potential of UCB repopulation cells, cord blood remains an optimum target for further experimental evaluation of ex vivo expansion strategies.

Another approach to enhance early engraftment in larger recipients of umbilical cord blood transplants involves combining multiple unrelated cord blood units.27,28 Preliminary reports in which 4 to 12 HLA-unmatched donations were infused into pediatric and adult recipients have been promising, with satisfactory neutrophil recovery and evidence that multiple donations had engrafted. It is too early to determine whether this technique will facilitate or hinder recovery, since immune interactions between infused cord blood units and recipients could delay rather than augment donor cell engraftment. Since it is relatively easy to monitor engraftment of individual donations using HLA markers, it should be possible to evaluate multiple donations as a way of increasing hematopoietic cell dose after clinical transplants.

**Recommendations**

1. Perinatal care providers should be informed about the promising clinical potential of hematopoietic stem cells in umbilical cord blood and current indications for its collection, storage, and use, based on sound scientific evidence (II-3B).

2. Umbilical cord blood collection should be considered for a sibling or parent in need of stem cell transplantation when an HLA identical bone marrow or peripheral stem cell donation from a sibling or parent is unavailable for transplantation (II-2B).

3. Umbilical cord blood should be considered when allogeneic transplantation is the treatment of choice for a child who does not have an HLA-identical sibling or a well-matched, unrelated adult bone marrow donor (II-2B).

4. Umbilical cord blood should be considered for allogeneic transplantation in adolescents and young adults with hematologic malignancies who have no suitable bone marrow donor and who require urgent transplantation (II-3B).
INDICATIONS FOR CORD BLOOD DONATION

Philanthropic Donation
Public cord blood banks collect and store umbilical cord blood units for potential use by the population at large. Childbearing women are encouraged to donate their babies’ cord blood so that it may be cryopreserved and registered for potential recipients with no suitable related or unrelated HLA-matched donor. Umbilical cord blood is generally collected from a limited number of collection sites, with collection performed by either dedicated, trained blood bank personnel or perinatal care providers. For labour and delivery room staff collections, detailed instructions and collection kits are provided by the cord blood bank. The operating costs for public cord blood banking are generally provided by government agencies at no cost to donors or recipients. In Europe, NETCORD links cord blood banks to its Bone Marrow Donor Worldwide Registry, whereas public cord blood banks in the UK and US are linked through central registries. In Canada, the Alberta Cord Blood Bank (ACBB) is the only public umbilical cord blood bank with limited funding through the Tanya Smale Cord Blood Foundation. To date, the ACBB has received approximately 5000 cord blood donations, with 2700 processed and stored. More than 1000 units have been HLA-typed, and 4 units have been transplanted (personal conversation, with Dr. Akabutu, Medical Director, ACBB, October 2003). Searches of the ACBB database are conducted through the Canadian Cord Blood Registry, which is linked to the Caitlin Raymond International Registry.

Directed Donations in Families at Risk
Some transplant centres recommend cord blood collection and storage for potential use in a family member in need of stem cell transplantation. If the stem cells are HLA-matched, they may be used for the affected child or parent. If not, they may be used in the future for an HLA-matched sibling. If the newborn donor develops a disease, his or her own cord blood stem cells may be used in future for somatic gene therapy, pending development of these techniques. Directed cord blood units are commonly stored in private cord blood banks but may also be stored specifically for family member use by some public banks.

Autologous Cord Blood Donation
Commercial cord blood banks offer mothers the opportunity to store their babies’ umbilical cord blood stem cells indefinitely, in case the infant develops illness for which stem cell transportation may be indicated. At present, it is not certain how long frozen cord blood will remain viable. It is difficult to estimate the likelihood that an autologous cord blood donation will be used. It has been estimated that the risk of a child needing a bone marrow transplant before his or her 10th birthday is between 1:200 000 and 1:10 000. According to available figures, less than 5% of privately stored cord blood has been used clinically, and it has been estimated that the autologous use of umbilical cord blood occurs in 1:20 000 collections. The cost for commercial cord blood banking in North America is variable, with initial banking fees between $500 to $2000 and annual storage fees of $50 to $150 yearly. In Canada, there are now 6 private cord blood banks (5 in Toronto, Ontario, and surrounding metropolitan areas and 1 in Burnaby, British Columbia). Parents in Canada are charged between $600 and $900 for registration, cryopreservation, and storage, with annual storage fees between $100 and $150 yearly.

Attitudes of Pregnant Women
The attitudes of pregnant women toward umbilical cord blood banking has been addressed in 2 recent studies. In a survey of Canadian pregnant women, 86% of respondents indicated that they would store cord blood in a public bank, and 14% would choose private cord blood banking. Women who preferred public donation gave altruism and the expense of private banking as their rationale for this decision. Regarding other potential uses for umbilical cord blood donations, 67% of women would agree to store cord blood for research purposes, 39% for gene therapy, and 33% for drug manufacturing investigations. In Switzerland, an anonymous questionnaire was distributed to a small sample of women, 6 months after public cord blood donation, with questions concerning ethical and emotional attitudes following UCB donation, concerns about genetic testing and research, and willingness to donate umbilical cord blood in a subsequent pregnancy. Most (96.1%) indicated that they would donate umbilical cord blood again, and all respondents were certain that their decision to have done so was ethical. Regarding potential risks of genetic testing and experimentation of umbilical cord blood, there was a significant correlation between negative attitudes and the decision not to donate cord blood again.

Recommendations
5. Altruistic donation of cord blood for public banking and subsequent allogeneic transplantation should be encouraged when umbilical cord blood banking is being considered by childbearing women, prenatal care providers, and (or) obstetric facilities (II-2B).

6. Collection and long-term storage of umbilical cord blood for autologous donation is not recommended because of the limited indications and lack of scientific evidence to support the practice (III-D).
ADVANTAGES OF UMBILICAL CORD BLOOD TRANSPLANTATION

UCB offers several advantages over bone marrow and peripheral blood progenitor cells. It is a readily available, rich source of hematopoietic stem cells that can be harvested at no risk to mother or infant. Using appropriate methods of screening, the risk of infectious agents (bacteria, fungi, and viruses such as cytomegalovirus, Epstein-Barr virus, HIV, and hepatitis B) appears to be low in umbilical cord blood.30 There is convincing evidence that the frequency and severity of acute and chronic graft-versus-host disease may be lower with umbilical cord blood transplantation than with comparable matched stem cells from unrelated bone marrow or peripheral blood.9 Available evidence also suggests that umbilical cord blood transplantation may be performed with greater degrees of HLA mismatch than for unrelated donor bone marrow transplantation, which increases the pool of potential transplant donors.5 Ethnic balance in public cord blood banks can be maintained in heterogenous populations or controlled by targeting minority populations. Frozen cord blood can be easily shipped and thawed for use when needed, resulting in decreased time from initiation of a search to performing transplantation.

LIMITATIONS OF UMBILICAL CORD BLOOD TRANSPLANTATION

Despite the potential advantages, umbilical cord blood transplantation has a number of potential limitations. The quantity and quality of a single umbilical cord blood unit may not be sufficient to engraft larger children and adults reliably. The optimal volume required for safe and successful umbilical cord blood transplantation is unknown. This is a major limiting factor to more widespread use of cord blood, particularly in adults. The limited hematopoietic cell dose in individual cord blood donations has emerged as the most significant disadvantage of umbilical cord blood as a source of hematopoietic stem cells for clinical transplantation. There is also the potential for transfer of genetically abnormal cells. In addition, clinical results show that the frequency and rate of myeloid and platelet engraftment are slower than that observed with comparably matched bone marrow, leading to the possibility of increased rates of engraftment failure and transplant-related mortality.5–7 In contrast to bone marrow or peripheral blood progenitor cell transplantation, where it is possible to seek subsequent donations if needed, the unrelated cord blood donor cannot offer a second donation in the event of marrow failure or relapse of the disease. Finally, cord blood collection, storage, and transplantation raises numerous financial, ethical, and regulatory issues for health care providers and society.

UMBILICAL CORD BLOOD COLLECTION

There are 2 main techniques for collecting cord blood from the umbilical vein: before the placenta is delivered (in utero) or after (ex utero). *Ex utero* cord blood collection is performed as soon as possible after delivery of the placenta by dedicated trained personnel in a separate room, using a standard collection bag containing citrate–phosphate–dextrose anticoagulant plus or minus adenine.34 The placenta is generally suspended on a specifically designed frame or stand and blood is collected by gravity from the most distant possible venipuncture site. The umbilical cord is cleaned with antiseptic solution, and the collection bag needle is introduced into the umbilical vein. This method is commonly used by public cord blood banks, and only units of 40 ml are retained. Factors that have been associated with increased collected volume using *ex utero* collection techniques include Caesarean section, induced labour, prolonged labour (> 15 hours), cord length > 30 cm, singleton pregnancy, postterm pregnancy, birth weight 3500 g, and placental weight > 700 g.35 *Ex utero* cord blood collection by birth unit staff is inconvenient because of the additional time (25 minutes for set-up), space, and personnel required.

*In utero* cord blood collection is performed after the infant has been delivered but before delivery of the placenta.36
After the cord is clamped and the area of insertion is disinfected, cord blood is collected by venipuncture. A closed collection system is used to reduce the risk of bacterial and maternal fluid contamination (Figures 1a–1c). The umbilical cord blood unit is collected by gravity, which takes approximately 2 to 4 minutes. The total time required for in utero cord blood collection by perinatal care providers is less than 10 minutes, and there is no requirement for extra personnel. Factors which negatively affect the volume of cord blood collected include preterm delivery, multiple gestation, hypertension, intrauterine growth restriction, abnormal placentation, maternal transfer, emergency Caesarean section, and precipitous third stage.37 Factors associated with better collection volumes include absence of obstetrical complications and deferral of hospital cord blood screening tests. Private cord blood banks generally collect umbilical cord blood at the birth hospital using the in utero technique, with subsequent shipment of cord blood units to the private bank. Perinatal care providers with no previous experience or training in the procedure collect the cord blood. In Canada, perinatal care providers collect cord blood units for both public and private banking, using the in utero technique.

Several manoeuvres have been recommended to optimize the volume of cord blood collected. Clamping the umbilical cord within 30 seconds of delivery has been reported to improve recovery volume.38 Grisaru et al. found that the yield of cord blood volume was increased significantly simply by placing the newborn infant on the maternal abdomen after delivery.39 Using a technique in which as much blood as possible is withdrawn from the umbilical vein by syringe while the placenta is still in utero, followed by a second collection after infusion of the umbilical artery with sodium chloride solution, the mean volume collected was significantly increased (174 mL), compared with standard in utero collection by gravity (76 mL).40

Using either in utero or ex utero techniques for collection of umbilical cord blood, average cord blood unit volumes of 50 to 150 mL are commonly achieved. There have been several reports of retrospective comparisons of the 2 collection strategies following vaginal delivery and Caesarean section.41–43 Laskey et al. reported no advantage of either method regarding volume or nucleated cell count in a large retrospective series comparing in utero and ex utero collections. There was a higher rate of rejection of umbilical cord blood units secondary to labelling problems, bacterial contamination, and clotting with in utero versus ex utero collection (53% versus 40%).44 Sparrow et al. found no difference in volume, white blood concentration, or total nucleated cell number between in utero and ex utero cord blood collection. They reported increased cord blood volume at
Caesarean section and increased white blood cell concentration following vaginal delivery. More recently, Solves et al. reported higher volume, nucleated cell count, and CD34 cell count with in utero collection, compared with ex utero collection. However, cord blood collection following Caesarean section deliveries contained similar progenitor content to vaginal deliveries. Some blood banks, though, will not accept cord blood collected at Caesarean section because of concerns about possible increase in maternal infectious morbidity (personal conversation, Dr Akabutu, Medical Director, ACBB, October 2003).

Wong et al. reported collection of cord blood from the same cord before and after the placenta was delivered in a small sample of women. They observed that the concentration of nucleated cells and colony-forming units was higher when the cord blood was in utero than after it had been delivered and concluded that in utero collection was superior. In the only RCT of in utero versus ex utero cord blood collection method, Surbek et al. reported superior volume and nucleated cell counts associated with in utero collection, compared with ex utero collection. There have also been 2 small RCTs of umbilical cord blood unit collection during a Caesarean section, before and after placental delivery. In both studies, the volume of cord blood and total nucleated cell count for units collected before placental detachment was significantly increased, compared with ex utero collection.

In summary, while available evidence regarding the optimal method for cord blood collection is inconclusive, in utero collection may increase the yield of cord blood unit volume and nucleated cell count. From the perspective of perinatal care providers, cord blood collection before placental delivery appears to offer advantages in terms of time, space, and staffing requirements. The potential risks to mother and newborn, time demands on the obstetrical team, and possible requirements for modification of normal delivery routines associated with cord blood collection need to be clarified. In addition, the liability of care providers, should the cord blood unit be inadequate, contaminated, or mislabelled, should be assessed. In order to optimize cord blood retrieval without compromising perinatal care, standardized cord blood collection, labelling, and shipping instructions must be provided to obstetricians, family practitioners, midwives, and birth unit staff.

**Recommendations**

7. Birth unit staff should receive training in standardized cord blood collection procedures that optimize cord blood unit volume and reduce the rejection rate owing to labelling problems, bacterial contamination, and clotting (II-3B).

8. The safe management of obstetric delivery should never be compromised to facilitate cord blood collection. Maneuvers to optimize cord blood unit volume, such as early clamping of the umbilical cord, may be employed at the discretion of the perinatal care team, provided the safety of the mother and newborn remains the major priority (III-A).

9. Collection of cord blood should be performed after the delivery of the infant but before delivery of the placenta using a closed collection system and procedures that minimize risk of bacterial and maternal fluid contamination (see Figures 1a–1c) (I-B).

**BANKING ISSUES**

**Storage**

Considerable progress has been made in cryopreservation and thawing techniques to maintain viable hematopoietic stem cells in bone marrow, peripheral blood, and UCB. Cord blood is cryopreserved in the liquid phase of liquid nitrogen using the techniques described by Rubinstein et al. With current technology, it remains uncertain how long umbilical cord blood will remain viable after cryopreservation. Published data by Broxmeyer et al. suggest that cord blood can be stored frozen for 10 to 15 years with highly efficient recovery of viable and functional stem cells needed for successful transplantation. Most cord blood units that have been used clinically have been cryopreserved for 6 years or less. Final proof of the engrafting capability of cord blood stored for long periods of time must await clinical results demonstrating long-term successful engraftment.

**Safety Aspects of Cord Blood Banking**

Once collected, cord blood units are labelled and shipped to the bank, where they undergo safety testing, human leukocyte antigen typing, and cryopreservation. Public banks generally follow procedures in accordance with established standards. Procedures for transfer of cord blood units from birth hospital to private cord blood banks are less well controlled and defined. There is currently no requirement for registration or regulation of cord blood collection centres, banks, or transplant centres in Canada.

Testing cord blood and maternal blood for infectious agents (HIV, cytomegalovirus, human lymphotropic virus, hepatitis viruses, and syphilis) is required by public cord blood banks. Cord blood units are initially placed in quarantine until infectious testing is completed. If new units test negative for infectious disease, they are placed in long-term storage banks. Public banks also obtain detailed maternal and family history of genetic diseases, travel to countries with high rates of transmissible infections, and other high-risk behaviour regarding intravenous drug use and sexual behaviour. Cord blood unit screening is the same as that used by the Canadian Red Cross for blood donors.
Infectious disease testing procedures used by private cord blood banks are variable and poorly defined.

**Recommendations**

10. Public and private cord blood banks should strictly adhere to standardized policies and procedures for transplantation, safety testing, HLA typing, cryopreservation, and long-term storage of umbilical cord blood units to prevent harm to the recipient, to eliminate the risk of transmitting communicable diseases, and thus to maximize the effectiveness of umbilical cord blood stem cell transplantation (II-1A).

11. Canada should establish registration, regulation, and accreditation of cord blood collection centres and banks (III-B).

**ETHICAL ISSUES**

There are many unresolved ethical issues related to the clinical and experimental use of umbilical cord blood.52 These issues include determination of ethical procedures for donor recruitment and informed consent for cord blood donation to public banks, to private banks, and for research. Legal and ethical issues related to privacy, confidentiality, and ownership of cord blood units are complex and controversial. Whether cord blood donor information should be linked to individual cord blood units and whether donors should be notified of infection or genetic abnormalities remains controversial. Finally, there is considerable debate regarding the ethics of commercial cord blood banking, particularly related to the availability of this potentially valuable resource for clinical use and research.

**Donor Recruitment**

Expectant parents want to do what’s best for their child and are therefore susceptible to promotion and advertising regarding the potential benefits of umbilical cord blood banking. Private banks market cord blood collection as “biological insurance” and suggest benefits of cord blood collection and storage that lack scientific support.53 Commercial banks use various media, including the Internet, direct mailings, and videotapes, which include dramatic, impassioned language describing cord blood transplantation outcomes as “lifesaving” or “miraculous.” Public cord blood banks encourage pregnant women to consider cord blood donation for altruistic motives. To ensure equitable recruitment, families and care providers must be provided with accurate, unbiased information about the potential benefits and risks of cord blood banking. Messages that provoke parental guilt for not choosing to bank cord blood should be discouraged, so that parents have autonomy in their decision making about cord blood banking. In addition, coercive strategies should not be employed to recruit cord blood donors from ethnic minorities.

**Informed Consent**

Since newborn infants cannot consent to the collection, testing, donation, and long-term storage of their cord blood, parents must make these decisions on their behalf. It is generally agreed that cord blood collected for transplantation is not waste material and that informed consent is required because of the sensitivity of medical information that must be obtained to ensure the safety of potential recipients.52–54 Prenatal, intrapartum, and after-collection consent policies and practices have been developed and implemented by cord blood banks and professional organizations to accommodate the diverse procedural, logistic, and financial priorities of public and private cord blood banks.53 For mothers to give informed consent, they must be provided with information about the procedures that are followed for collection, processing, testing, storing, and use of the umbilical cord blood. They should know what measures will be taken to ensure that personal and medical information will be kept confidential. They must also be counselled about disclosure of abnormal test results and the importance of contacting the storage facility in the event their child develops a serious illness. If the cord blood is to be stored by a private bank, issues of ownership, dispositional authority, and cost should be clearly defined.

The consent process is difficult, if not impossible, to achieve during labour, when women are distracted by the physical and emotional stress of the intrapartum experience. Postponing the consent procedure until after cord blood collection improves efficiency and reduces recruitment costs, with no additional burden on perinatal care providers; however, umbilical cord blood is collected without the parents’ knowledge or explicit consent. The Working Group on Ethical Issues in Umbilical Cord Blood Banking and the American Academy of Pediatrics consider intrapartum and after-collection consent unethical and recommend that written informed consent be obtained during prenatal care, before the onset of labour, followed by confirmation of consent after delivery.52,56

**Privacy and Confidentiality**

There is considerable debate as to whether public cord blood units should remain traceable to the donor.52,57,58 Advocates of maintaining linkage between cord blood units and infant donors point out that such linkage allows donors and recipients to be informed of positive test results and receive appropriate referral and treatment. It also allows donors and recipients to be informed of the results of new screening tests conducted at a later date. Linked donors may
also provide informed consent for cord blood testing, which was not anticipated at the time of collection.

Unfortunately, the autonomy of linked donors may be compromised if personal and (or) medical information is disclosed to insurance companies, schools, or employers. There may also be serious repercussions related to identification of severe congenital diseases for which there is no cure, such as HIV infection. The donor’s identity should be protected from the recipient, since the recipient may wish to contact the donor for additional stem cells in the future. To avoid adverse consequences of linkage, donor privacy and the confidentiality of test results must be carefully protected.

Commercial Cord Blood Banking

Private companies view umbilical cord blood as a potential source of profit through storage fees and development of future therapies. Despite the lack of scientific evidence to support cord blood storage for autologous use, the number of private cord blood banks in Canada continues to grow, particularly in metropolitan Toronto and Vancouver, where new parents are susceptible to the marketing strategies of commercial banks. Directed cord blood donations for autologous or family member use are unavailable for public donation or research; this limits the supply of cord blood donations in Canada to the ACBB, which is inadequately funded to meet the cord blood transplantation needs of the population. Since hematopoietic stem cells from umbilical cord blood have greater potential as a collective asset than as an individual asset, eligible pregnant women should be encouraged to consider public cord blood donation by their prenatal care providers.

Recommendations

12. Recruitment of cord blood donors should be fair and noncoercive. Criteria to ensure an equitable recruitment process include the following: (a) adequate supply to meet population transplantation needs; (b) fair distribution of the burdens and benefits of cord blood collection; (c) optimal timing of recruitment; (d) appropriately trained personnel; and (e) accurate recruitment message (III-A).

13. Informed consent for umbilical cord blood collection and banking should be obtained during prenatal care, before the onset of labour, with confirmation of consent after delivery (III-B).

14. Linkage of cord blood units and donors is recommended for product safety. Policies regarding the disclosure of abnormal test results to donor parents should be developed. Donor privacy and confidentiality of test results must be respected (III-C).

15. Commercial cord blood banks should be carefully regulated to ensure that promotion and pricing practices are fair, financial relationships are transparent, banked cord blood is stored and used according to approved standards, and parents and care providers understand the differences between autologous versus allogeneic donations and private versus public banks (III-B).

16. Policies and procedures need to be developed by perinatal facilities and national health authorities to respond to prenatal requests for public and private cord blood banking (III-C).

REFERENCES


