

Umbilical Cord Blood: Counselling, Collection, and Banking

This clinical practice guideline has been prepared by the Cord Blood Banking Working Group, reviewed by the Clinical Practice – Obstetrics, Maternal Fetal Medicine, Family Physician Advisory, and Aboriginal Health Initiative Committees, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all contributors.

Abstract

Objective: To review current evidence regarding umbilical cord blood counselling, collection, and banking and to provide guidelines for Canadian health care professionals regarding patient education, informed consent, procedural aspects, and options for cord blood banking in Canada.

Options: Selective or routine collection and banking of umbilical cord blood for future stem cell transplantation for autologous (self) or allogeneic (related or unrelated) treatment of malignant and non-malignant disorders in children and adults. Cord blood can be collected using in utero or ex utero techniques.

Outcomes: Umbilical cord blood counselling, collection, and banking, education of health care professionals, indications for cord blood collection, short- and long-term risk and benefits, maternal and perinatal morbidity, parental satisfaction, and health care costs.

Key Words: pregnancy, umbilical cord blood, informed consent, counselling, collection, storage, banking, stem cell transplantation, ethics, public, private, Canada.

J Obstet Gynaecol Can 2015;37(9):832–844

Evidence: Published literature was retrieved through searches of Medline and PubMed beginning in September 2013 using appropriate controlled MeSH vocabulary (fetal blood, pregnancy, transplantation, ethics) and key words (umbilical cord blood, banking, collection, pregnancy, transplantation, ethics, public, private). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date limits, but results were limited to English or French language materials. Searches were updated on a regular basis and incorporated in the guideline to September 2014. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

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 cell transplantation to treat malignant and non-malignant conditions in children and adults. There is minimal harm to the mother or newborn provided that priority is given to maternal/newborn safety during childbirth management. Recipients of umbilical cord stem cells may experience graft-versus-host disease, transfer of infection or genetic abnormalities, or therapeutic failure. The financial burden on the health system for public cord blood banking and on families for private cord blood banking is considerable.

Recommendations

1. Health care professionals should be well-informed about cord blood collection and storage and about factors that influence the volume, quality, and ability to collect a cord blood unit. (III-A)
2. Health care professionals caring for women and families who choose private umbilical cord blood banking must disclose any financial interests or potential conflicts of interest. (III-A)
3. Pregnant women should be provided with unbiased information about umbilical cord blood banking options, including the benefits and limitations of public and private banks. (III-A)
4. Health care professionals should obtain consent from mothers for the collection of umbilical cord blood prior to the onset of active labour, ideally during the third trimester, with ample time to address any questions. (III-A)

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁷⁸

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.⁷⁸

5. Health care professionals must be trained in standardized procedures (ex utero and in utero techniques) for cord blood collection to ensure the sterility and quality of the collected unit. (II-2A)
6. Umbilical cord blood should be collected with the goal of maximizing the content of hematopoietic progenitors through the volume collected. The decision to bank the unit will depend upon specific measures of graft potency. (II-2A)
7. Umbilical cord blood collection must not adversely affect the health of the mother or newborn. Cord blood collection should not interfere with delayed cord clamping. (III-E)
8. Health care professionals should inform pregnant women and their partners of the benefits of delayed cord clamping and of its impact on cord blood collection and banking. (II-2A)
9. Cord blood units collected for public or private banking can be used for biomedical research, provided consent is obtained, when units cannot be banked or when consent for banking is withdrawn. (II-3B)
10. Mothers may be approached to donate cells for biomedical research. Informed consent for research using cord blood should ideally be obtained prior to the onset of active labour or elective Caesarean section following established research ethics guidelines. (II-2A)

or premalignant cells. The establishment of cord blood banks has allowed rapid access to well-characterized CBU by transplant centres around the world, and to date, cord blood has been used in over 30 000 transplants.²

Hematopoietic Stem Cell Transplantation

Transplantation of blood-forming stem cells to regenerate the blood and immune system following dose-intensive radiation treatment remains a potentially life-saving procedure for patients with malignant and non-malignant blood and immune disorders such as leukemia, lymphoma, aplastic anemia, and inherited metabolic diseases.³ Blood-forming progenitors can be harvested from patients (autologous) or from healthy HLA-compatible (allogeneic) donors who are related or unrelated. Blood stem cells can be procured from bone marrow harvests, via apheresis of peripheral blood following cytokine stimulation or from umbilical cord blood.⁴⁻⁶ Health care professionals should understand that UCB contains blood-forming stem cells that can be used in HSC transplantation and also contains other progenitor cells that are involved in tissue repair and in the modulation of immune responses.

Immune compatibility is determined by the HLA genes and is a dominant factor in the selection of an allogeneic donor or CBU. HLA-matched sibling donors are typically preferred but are available for only a minority of patients. With declining fertility rates in Canada over the past 50 years, patients will have diminishing odds of having an HLA-matched sibling donor⁷ and transplant recipients will rely more heavily on unrelated donors and umbilical cord

INTRODUCTION

Since the first umbilical cord blood transplant in 1988, cord blood has been established as an alternative source of HSC for bone marrow reconstitution.¹ Cord blood has several advantages over bone marrow and mobilized peripheral blood HSC for transplantation, including its availability, negligible risk to the donor, less stringent HLA matching requirements, and less chance of GVHD. Limitations of UCB include insufficient quantity and quality of a single CBU to engraft adults, slow engraftment rates, and the potential for transfer of genetically abnormal

blood donors. More than 23 million volunteer donors on 73 worldwide registries from 53 countries may be searched on a website facilitated by BMDW² in accordance with standards established by the WMDA,⁸ which permits the identification of potential unrelated donors who are willing to donate bone marrow or peripheral blood stem cells, including donors listed in the Canadian Blood Services One Match Marrow and Stem Cell Network⁹ and the Stem Cell Donor Registry at Héma-Québec.¹⁰ The BMDW-affiliated registries include banked umbilical cord blood from more than 611 000 donors from 48 public cord blood banks in 33 countries, which expands the options even further, especially for patients with more unusual HLA haplotypes.²

Role of Umbilical Cord Blood

Umbilical cord blood is highly enriched for blood-forming stem cells and offers some advantages in the setting of allogeneic transplantation. Cord blood inventories can be searched rapidly using sophisticated and coordinated global computerized search algorithms in accordance with guidelines established by the WMDA and units are readily available from a network of accredited banks worldwide.⁸ Another advantage of using cord blood is its greater flexibility in HLA matching. Although fully matched CBUs are associated with optimal outcomes in cord blood transplantation,^{11,12} disparities in HLA between donor and recipient are better tolerated than with unrelated donor transplantation because HLA matching requirements are less stringent and the risks of GVHD and graft failure are lower.¹³ Unrelated donor workups require confirmatory HLA typing and other testing for transmissible diseases and the general health status of the donor, and there may be logistical challenges that delay the collection of cells from unrelated donors; however, unrelated donors offer the prospect of future donor leukocyte infusions or additional cells for boosting the graft function, which is not possible with CBUs.

ABBREVIATIONS

AABB	American Association of Blood Banks
BMDW	Bone Marrow Donors Worldwide
CBU	cord blood unit
CIBMTR	Center for International Blood and Marrow Transplant Research
FACT	Foundation for the Accreditation of Cellular Therapy
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
UCB	umbilical cord blood
WMDA	World Marrow Donor Association

The major disadvantage of cord blood transplantation is the limited dose of stem cells available in CBUs. UCB volume limits the utility of cord blood transplantation for larger recipients, including most adults, but it remains an issue even in pediatric transplantation. Despite being highly enriched for HSCs, the limited volume that can be collected (100 to 200 mL) means the total dose of stem cells may contribute to delayed engraftment following transplantation and increased risk of bleeding or infection in recipients.^{14,15} Several strategies to augment the speed of engraftment following UCB transplantation have been investigated, including methods to expand to HSCs *ex vivo* before transplantation, co-transplantation of mesenchymal stromal cells to accelerate homing and engraftment, and double cord blood transplantation^{16,17} These strategies, however, will likely introduce significant additional costs, and their role in transplantation remains under development.

The cost of CBUs poses another significant barrier to more widespread use of cord blood as an alternative source of stem cells, especially with the high cost of obtaining CBUs from international public banks. It may be possible to acquire domestic CBUs at lower prices than typical international fees of US\$25 000 to \$40 000 per cord.¹⁸ During an era of cost containment, banks and transplant centres will need to address economic factors for banking establishments to remain viable and to allow transplant centres to embrace greater utilization of cord blood.^{19,20}

Indications for Use of Cord Blood from a Family Member

A recent analysis of data from the CIBMTR reviewed the use of related allogeneic transplantation using umbilical cord blood stored in private family banks or through a directed donation program with a public bank. This approach may be useful when bone marrow or peripheral blood stem cells cannot be collected readily from a sibling, such as when siblings are infants. A total of 244 patients from 73 centres were reported to the CIBMTR between 2000 and 2012. Transplants were performed most commonly for acute leukemia (37%), thalassemia or sickle cell disease (29%), Fanconi anemia (7%), and inherited red cell, immune, or metabolic disorders (18%). The Eurocord registry has identified more than 500 patients transplanted with related cord blood from 1988 to 2010.²¹ Most recipients were children, and all but 29 were HLA-matched. Patients and their families who travel abroad to undergo related cord blood transplantation may be exposed to increased risks of complications that may jeopardize their safety and also be associated with significant personal expense.²² The regulatory oversight concerning transplantation is

dramatically different from Canada in some jurisdictions and for the safety of patients this form of medical tourism is highly discouraged.

Recommendation

1. Health care professionals should be well-informed about cord blood collection and storage and about factors that influence volume, quality, and ability to collect a cord blood unit. (III-A)

PUBLIC CORD BLOOD BANKING

Public cord blood banks are sponsored and funded nationally or locally to process and store donated umbilical CBUs. The donated CBUs are HLA-typed and entered into a national or international registry that allows them to be searched, in a manner similar to bone marrow registries, by transplant centres around the world in need of a donor. A CBU stored in a public bank is made available to any patient in need of a transplant for which it is a suitable match and is not reserved for the donating family. With public banks, there is no guarantee that donors or their family members will necessarily have access to their specific donor unit in the future.

Public banks do not directly charge the family for the processing and storage of the donated CBU, but a CBU obtained from a public bank outside of Canada can be extremely costly.¹⁸ The high cost of obtaining international CBUs has been the subject of much discussion, and prices for these units are beginning to decline. The cost of establishing and running a national public bank, however, is formidable and is borne by the general public. It may be possible to recover some costs of the public banking efforts through fees to international transplant centres, but reciprocity in reducing costs would allow transplant centres greater access to CBUs.

Considerations Regarding Public Banking

Both public and family cord blood banking establishments in Canada must meet Health Canada regulatory requirements for cells, tissues, and organs.²³ These regulations include all aspects of recruitment, collection, transportation, storage, testing, and documentation, and ultimately, the release of the units to transplant centres. Moreover, public banks should seek accreditation from international bodies such as AABB²⁴ and FACT²⁵ to remain relevant on the international stage. This is essential to their economic viability and the assurance of optimal quality and safety of the products. Public cord blood banking is ideally suited to addressing the needs of patients from ethnic minorities and patients with uncommon HLA haplotypes who remain underrepresented on worldwide registries of unrelated donors. The selection of partner hospitals,

therefore, should include a careful assessment of how well the bank can address issues such as ethnic diversity within the population of expectant mothers and issues that may impact access to mothers and the collection of large volume CBUs.

The goal of public cord blood banks is to create an inventory of assessable CBUs suitable for hematopoietic stem cell transplantation. Public banks set very strict criteria for collection volume and total nucleated cell doses to create an inventory of high quality units that will be associated with more rapid engraftment and with acceptable rates of transplant-related complications. As a consequence, a significant number of CBUs donated to public banks are discarded or donated to research.

Public cord blood banks are designed to serve the needs of patients and cannot reasonably accommodate every mother's desire to donate cells. The practices of banking establishments and partner hospitals must adhere to the regulations outlined by Health Canada,²³ and this imposes a level of standardization and reliance on protocols for health care professionals that often exceeds normal health care practices. Managing the impact of public cord blood banking on the perinatal routines and practices of the health care team and mothers is an important consideration. Mothers need to learn about public cord blood banking options well before delivery and should ideally provide permission to collect before the onset of active labour or early in labour while consent can reasonably be given. Working closely with health care professionals in the community, many public banking establishments obtain consent to collect first and then determine whether the unit is bankable based on the volume and total nucleated cell count at the time of collection. These parameters are meant to identify units with the greatest utility in the setting of transplantation. More than 80% of units selected for transplantation from the inventory of cord blood banks contain more than 1.2×10^9 nucleated cells,¹⁸ and more established banks replenish their inventories exclusively with units of more than 1.5×10^9 cells. If a collected unit meets initial screening criteria for eligibility, a more complete acquisition of maternal history, clinical findings, and lab testing for transmissible infectious diseases is performed. This 2-stage approach focuses time and resources on the units with the greatest likelihood of being requested by transplant centres. The extensive time and resources required to administer the maternal health questionnaire and arrange for the testing of infectious disease markers necessitates the involvement of personnel dedicated to the banking effort. These personnel need to work cooperatively with health care professionals to ensure that banking efforts are fruitful and that the needs of the

mothers and babies are not compromised. When units are collected but do not meet the threshold for volume or total nucleated cell count needed for the unit to be banked, the cord blood can be made available for biomedical research through programs such as the Cord Blood for Research Program at Canadian Blood Services. Public cord blood banking is resource-intensive and banking facilities need to partner with birth units to meet the demands and expectations of transplant centres and their patients. Public banks and collecting hospitals should work collaboratively to identify compatible donors from underrepresented ethnic groups, particularly First Nations, Inuit, and Metis.

PRIVATE CORD BLOOD BANKING

Private (also known as family) cord blood banks store processed umbilical CBUs for the private use of the family. The family of the newborn child pays a fee to process and store the CBU and the mother is typically named the legal custodian of the banked CBU. Thus the banked CBU is accessible only to the family who banked it and will be available to them if and when required. Some Canadian private UCB banks also fund “medical needs” programs whereby the cost to process and store the UCB is waived for families whose expected child has a sibling in need of a bone marrow transplant.

Private banks charge the family for processing and storing the CBU for their exclusive use by the family. The average cost in Canada is about \$1200 for processing and first year of cryopreservation. Subsequent yearly storage fees generally run between \$100 and \$130. Alternative payment plans are often offered, including an 18-year single-cost plan in some cases. Eighteen years is a logical term for such a plan, since the child from which the cord blood was collected will have reached the age of majority at the end of the term and can then decide whether or not to continue to bank the CBU.

Considerations Regarding Private Banking

Because of the inheritance of HLA, the chance of any sibling being a full HLA match to another sibling is essentially 25%, and this chance increases with the number of siblings. The use of HLA-matched related CBUs may reduce the risk of GVHD and improve transplant outcomes over the use of unrelated cord blood transplantation if the number of cells in the stored unit is sufficient and if tests for transmissible disease are satisfactory.

Although GVHD occurs less commonly following HLA-matched marrow and peripheral blood stem cell transplant in an era of high resolution HLA typing, studies of cord blood transplants show a significant reduction in GVHD.

Indeed, early Eurocord studies in patients with leukemia suggest that rates of GVHD following related cord blood transplants²⁶ may be less than rates following unrelated cord blood transplantation.²⁷ Similarly, in non-malignant diseases treated by related or unrelated cord blood transplants, Bizzetto found that the risk of acute GVHD was lower with related cord blood transplants compared to unrelated cord blood and the 3-year survival rate was better.²⁸

Since CBUs are already paid for and stored in private banks, there is no cost to the medical system when the units are used except for specific hospital costs. The cost of obtaining public units, however, can be prohibitive, although they may be discounted or waived for domestic use and continue to decrease as worldwide inventories increase.

The goal of private cord blood banks is to cryopreserve quality CBUs that may be used for hematopoietic stem cell transplantation or future regenerative medicine therapies. Thus private banks typically do not use the same banking criteria as public banks in terms of collection volume and total nucleated cell doses. Private banks appeal to families whose intended recipient for a hematopoietic stem cell transplant may be much smaller than the 60 kg recipient targeted by public banks. Several new technologies in development are intended to either expand the number of HSCs in a given CBU or improve the homing of the HSCs to the bone marrow with the aim of improving the speed of engraftment. These developing technologies are not routinely available at this time. Success in these technologies, however, would allow “small” units banked today to be useful for larger recipients in the future.

Regenerative medicine refers to the process of replacing or repairing human cells, tissues or organs to return or establish normal functioning. Cord blood stem cells are presently being examined for use in regenerative medicine or for treating non-blood diseases including type 1 diabetes, cardiovascular repair, traumatic brain injury, cerebral palsy, autism, and hearing loss. Some of these trials are restricted to patients having access to their own (autologous) cord blood, whereas many of these research protocols have reported the use of allogeneic CBUs.²⁹ Therapeutic cell doses have yet to be established. Private cord blood banks set their own acceptance criteria for banking CBUs, which results in a much higher percentage of their collected units being banked than those of public banks.

A banked CBU from a person with no family history of disease treatable by bone marrow transplantation arguably has a very low chance of being used. The chance that a person will contract a disease treatable by their

stored cord blood by age 21 has been estimated to be approximately 0.005% to 0.04%.¹⁷ A more recent analysis of the likelihood of requiring a bone marrow transplant has taken into account treatable diseases up to the age of 70 years, the upper limit for bone marrow or peripheral blood stem cell transplants at some centres. This is a model more representative of the concept of family banking, although it remains unclear how long autologous units can be stored with current cryopreservation methods. In that calculation, the probability of the need for hematopoietic transplantation for a family member is about 1/400 and may be as high as 1/200.³⁰

With future advances in medical technology such as gene therapy, tissue therapeutics for treatment of non-blood diseases, and ex vivo cell expansion, the probability of a banked CBU, especially an autologous CBU, may increase, and this provides a compelling rationale for some families to privately bank their children's cord blood. On the other hand, improvement in medical treatment of serious disease may make the need for stem cell transplantation less necessary in the future and result in a reduced probability of using a banked CBU. As a result, it is now impossible to predict the future value of family UCB banking. Private cord blood banks must provide accurate and transparent information regarding fees, likelihood of using the CBU, methods of opting out and other costs to patients and families.

Recommendation

2. Health care professionals caring for women and families who choose private umbilical cord blood banking must disclose any financial interests or potential conflicts of interest. (III-B)

COORDINATION OF PRIVATE AND PUBLIC BANKS

CBUs that are stored in private banks cannot be searched by transplant centres for unrelated patients but may be used for autologous hematopoietic transplantation or allogeneic transplantation for another family member. Although uncommon at present, the use of autologous or related UCB transplantation may change in the future in response to ongoing studies of novel applications in areas such as regenerative therapy. Guidelines and transparency with respect to fees, chances of using the unit, methods of opting out and other costs should be available to patients and families. Transferring banked units from private banks to public banks is challenging and guiding principles have been established by the WMDA that highlight issues such as the requirement for donor consent for public banking at the time of collection, the need to meet regulatory and

accreditation standards applicable for publicly banked units, and the requirement for separate storage away from units that do not meet public banking criteria.⁸ In addition, the safety of infusing autologous banked units has been demonstrated in numerous settings although significant differences in indicators of CBU quality were reported in a recent study compared with publicly banked units.³¹ Increased collaboration between private and public banks may help to improve the quality of all CBUs collected.

EDUCATION OF PARENTS AND HEALTH CARE PROFESSIONALS

Despite growing evidence of the therapeutic benefits of umbilical cord derived stem cells and promotion of umbilical cord blood collection for allogeneic, family-directed, or autologous use in the media, surveys reveal that the majority of pregnant women (70 to 80%) lack knowledge about stem cells and cord blood banking and want more information.^{32–36} While most women (80% to 90%) would prefer to receive information about cord blood banking from their health care professionals, prenatal education and counselling is only provided to a minority (15 to 30%).^{33,36,37} Consequently, many pregnant women receive information through printed material, the internet, or the media.^{36,37} Surveys from Canada, Europe, and the United States suggest that once informed, the majority of women would consider donating cord blood for therapeutic use.^{32,36,37} Overall, women appear to be more inclined to donate to public banks than to private or mixed banks.^{32,36,37} Approximately 80% of practicing obstetricians in the United States feel confident in discussing cord blood options with their patients, but less than 50% indicate that they have sufficient knowledge of cord blood donation to effectively answer patients' questions about donation.³⁸

Not surprisingly, women are often misinformed and confused about the risks and benefits of umbilical cord blood donation and the advantages and limitations of cord blood banking options. In evaluating their choices, women may be motivated to donate their baby's umbilical cord blood to a public cord blood bank as an altruistic act of civic responsibility or to a private bank for the potential future benefit of their child or immediate family.³⁹ Physicians and other health care professionals are recognized as the primary source of information and guidance for pregnant women and should be well-informed about the practical implications of umbilical cord blood collection and storage and the benefits and limitations of public and private cord banks. Health care professionals in perinatal facilities should become actively involved in the provision of education about cord blood

banking and policies regarding cord blood collection and in the development of collection protocols to improve cord blood volume and quality.^{33,40,41} Though storage of cord blood for autologous use remains controversial, therapeutic indications for umbilical cord blood stem cells and the use of autologous and family-directed CBUs for transplantation is growing.^{42–46} Information about cord blood collection and banking provided by health care professionals must be balanced and accurate about its advantages and disadvantages.⁴⁷ Prospective parents should understand that infants with an underlying genetic disease are very unlikely to be transplanted with autologous cord blood that generally harbours the same gene abnormality and that many diseases may not be amenable to therapy until new treatments are developed.⁴² Parents also should be informed about maternal infectious disease and genetic testing and the process for disclosure of abnormal findings. Physicians and health care professionals should provide unbiased information about both public and private cord blood banking and should encourage directed donation for immediate family members with specific treatable diseases.⁴⁸ Health care professionals are discouraged from endorsing specific cord blood banks and are obliged to disclose any financial or other conflicts of interest.⁴²

Obstetricians should be knowledgeable enough about the present uses of umbilical cord blood to be able to have a discussion with patients and answer most questions. It is important to be able to discuss the differences between public and family banking and to know which options are available.

Recommendation

3. Pregnant women should be provided with unbiased information about umbilical cord blood banking options, including the benefits and limitations of public and private banks. (III-A)

INFORMED CONSENT

Because newborn infants are unable to consent to the collection, testing, donation, and storage of their cord blood, informed consent must be obtained and documented from the mother or father. Cord blood collected for therapeutic use or research is not considered waste material and it is generally agreed that informed consent for collection is required.⁴⁹ Prenatal, pre-labour, and post-collection consent policies have been developed by cord blood banks and professional organizations to address the procedural and financial priorities of public and private blood banks,^{43,44} and so could be obtained at presentation in early labour. It is generally agreed that consent should be obtained prior

to the onset of active labour and ideally during the third trimester of the prenatal period.⁵⁰ A phased consent policy for cord blood donation has been proposed and endorsed by the American Academy of Pediatrics.⁵¹ In phase one, information about cord blood banking including risks, benefits, advantages, and limitations is provided to parents as part of prenatal care. Donor registration with the cord blood bank and perinatal institution is also recommended. The second phase of the consent policy occurs when a woman is admitted to the birth unit for labour and delivery. Eligibility criteria for cord blood collection include the absence of active labour, intact membranes, term singleton pregnancy, no history of viral, congenital, or genetic diseases and the ability of the mother to understand the implications of cord blood collection.

The procedure for obtaining consent is limited to an explanation of the need to collect blood immediately following delivery, a description of the collection technique, and information about the possible risks of the procedure. The post-collection consent procedure addresses maternal infectious and genetic disease testing, access to health record information and newborn screening tests, maternal medical history, cord blood processing and storage, and the potential use of cord blood for therapeutic and research purposes. The mother's right to refuse collection, processing, or storage of the cord blood at any time without prejudice must be inherent in the consent process. It is also important for parents to be assured that information related to the infant donor and the donor's family will remain confidential and maintained by the cord blood bank so that parents or physicians can be notified of infectious or genetic diseases.⁴⁹

Consent policies and procedures vary widely across regional and national jurisdictions, public and private cord blood banks, and perinatal care facilities. Standardization of informed consent for umbilical cord blood donation following AABB²⁴ and FACT²⁵ guidelines is recommended. Institutional review and approval of cord blood donation consent policies are also encouraged.⁴⁹ If cord blood does not meet criteria for clinical use or when donors decide to terminate storage of a CBU, cord blood banks are encouraged to offer donors the opportunity to donate the cord blood to research, subject to donor consent.⁵²

Recommendation

4. Health care professionals should obtain consent from mothers for the collection of umbilical cord blood prior to the onset of active labour, ideally during the third trimester, with ample time to address any questions. (III-A)

UMBILICAL CORD BLOOD COLLECTION

Umbilical cord blood is collected from the umbilical vein either before the placenta is delivered (in utero) or following placental delivery (ex utero). Both methods have advantages and disadvantages.⁵³ Both techniques are in use at Canadian public cord blood banks, although the in utero technique is preferred by most public banks in the United States and many European countries because it can be performed in the delivery room by birth unit staff, is easy to learn, and does not usually require additional personnel or resources.^{53,54} All private banks use in utero collection methods. Evidence from comparative studies suggest that the in utero technique yields slightly higher volumes of cord blood and higher yields of total nucleated cells compared to the ex utero technique.⁵⁵⁻⁵⁷

The standard in utero method for cord blood collection uses a closed collection system to reduce the risk of infection and maternal fetal fluid contamination. The umbilical cord is double-clamped approximately 3 to 5 cm from the umbilicus and transected between the clamps. After the infant has been removed from the field, the cord is prepared for venipuncture using a povidone iodine applicator. The needle of the cord collection kit is then inserted into the umbilical vein and the CBU is collected by gravity. The time required to perform the cord collection procedure is approximately 5 to 10 minutes and additional personnel are not required.^{54,58,59} Factors known to reduce cord blood volume include maternal hypertension, smoking, multiple gestation, preterm delivery, intrauterine growth restriction, abnormal placentation, emergency CS, precipitous delivery, and maternal transfer.^{17,59} Factors associated with higher cord blood volumes and greater yield of nucleated cells include birth weight, placental weight, gestational age, induction of labour, prolonged labour, CS, early cord clamping, first born infants, Caucasian ethnicity, and female infant gender.⁶⁰ Umbilical cord blood obtained after CS for acute fetal distress also appears to significantly increase total nucleated cells, CD34+ cells, and white blood cells without compromising cord volumes and should not preclude cord blood collection unless maternal and newborn safety may be compromised.^{61,62}

A number of manoeuvres have been proposed to optimize cord blood volume. Using large syringes (50 to 60 cc) and a syringe withdrawal-saline flush-syringe withdrawal technique as part of the closed collection system have yielded significantly higher mean volume collected (150 to 175 mL), compared with standard in utero collection by gravity (75 to 100 mL). Clamping the umbilical cord within 30 seconds of delivery and placing the newborn

infant on the maternal abdomen after delivery have also been reported to improve recovery volume and CD34+ cell content,^{63,64} however, this early clamping defeats the benefits of delayed clamping.

Ex utero cord blood collection is performed by dedicated, trained personnel in a separate room and standard collection bag as soon as possible after delivery of the placenta. The cord blood is collected by gravity with the placenta suspended on a specifically designed stand.^{54,65} Although this method allows birth unit staff to focus on maternal and infant health, the procedure requires additional trained personnel, resources, and cost but reduces the frequency of non-conformances associated with collection of units from staff that are not affiliated with the bank. Disadvantages of this method are the possibility of lower cord blood volume and total nucleated cell counts. As with in utero collection, factors associated with increased collected volume using the ex utero technique include: singleton pregnancy, post-term pregnancy, induced labour, prolonged labour, CS, cord length greater than 30 cm, birth weight \geq 3500 g, and placental weight $>$ 700 g.^{48,54,66}

Umbilical cord collection poses a number of logistical issues that may increase the burden for busy birth units. The consent procedure and associated paperwork adds time and inconvenience to the work of health care professionals. Collection procedures performed during the third stage of labour at a time when both mother and baby require attentive care and risk of postpartum hemorrhage must not jeopardize maternal newborn health. Birth unit personnel feel under pressure to obtain adequate volume of cord blood and to avoid bacterial contamination. Attention to the cord blood collection may also impact on the care of other mothers and infants. Consequently, umbilical cord blood collection should not interfere with the normal management of the third stage or compromise the safety of mother and baby.^{59,67} Contraindications to cord blood collection include preterm birth, serious maternal medical or obstetric complications, such as cardiac arrest, stroke, eclampsia or massive hemorrhage, and perinatal asphyxia.

Regulatory Issues and Practice Standards for Collecting and Processing Umbilical Cord Blood

Cord blood banks must adhere to strict regulatory requirements and focus on additional factors to ensure that UCB units stored in the bank are of the highest quality and thus remain beneficial to transplant centres and their patients. Accreditation and compliance with nationally and internationally recognized regulatory bodies ensure that all aspects of recruitment, donor screening, collection

and transport, processing, testing, freezing, storage, and distribution are standardized and meet international thresholds of quality. The use of current measures of graft potency is also critical so transplant centres and patients have confidence regarding the assurance of timely engraftment following transplantation. The collection and storage of UCB must adhere to Health Canada regulations under the cells, tissues, and organs guidelines²³ to ensure the quality of CBUs in terms of HSC content, absence of infectious agents, and risk of transmitting genetic disease. In addition, international guidelines are provided by FACT and AABB. These shape operational issues related to cord blood banking in Canada and around the world through the International NetCord Foundation).

Recommendations

5. Health care professionals must be trained in standardized procedures (ex utero and in utero techniques) for cord blood collection to ensure the sterility and quality of the collected unit. (II-2A)
6. Umbilical cord blood should be collected with the goal of maximizing the content of hematopoietic progenitors through the volume collected. The decision to bank the unit will depend upon specific measures of graft potency. (II-2A)
7. Umbilical cord blood collection must not adversely affect the health of the mother or newborn. Cord blood collection should not interfere with delayed cord clamping. (III-A)
8. Health care professionals should inform pregnant women and their partners of the benefits of delayed cord clamping and of its impact on cord blood collection and banking. (II-2A)

Timing of Umbilical Cord Clamping

There is growing evidence of the benefit of delayed cord clamping for 1 to 3 minutes in preterm infants (< 37 weeks).⁶⁸⁻⁷¹ Systematic reviews have demonstrated that delayed cord clamping in preterm infants results in reduced need for transfusions, better circulatory stability, improved blood pressure and decreased risk of intraventricular hemorrhage and necrotizing colitis.^{68,71} Recent evidence suggests that delayed cord clamping in very preterm and very low birth infants protects against motor disability at 7 months of age.⁷⁰ In light of this evidence, several professional organizations have recommended implementation of delayed cord clamping for preterm infants despite health care professionals' concerns about the need for immediate resuscitation and risk of hypothermia.⁷² Since umbilical cord banking is generally contraindicated in preterm infants, delayed cord clamping in this population should have no impact on cord blood banking.

Delayed cord clamping in term infants has been consistently shown to enhance placental transfusion at birth and increase hemoglobin, hematocrit, ferritin levels, and iron stored up to 6 months of age.^{70,73,74} Though prevailing evidence also suggests that delayed cord clamping promotes higher iron stores in the longer term,⁷⁰ delayed cord clamping did not affect iron status or neurodevelopment at age 12 months in a recent randomized controlled trial of healthy term-born infants in Sweden.⁷⁵ Concerns have been raised regarding the increased risk of phototherapy for postnatal jaundice and polycythemia associated with delayed cord clamping.⁷⁴ WHO recommends a 1 to 3 minute delayed cord clamping in term infants, particularly in populations where iron deficiency anemia is endemic and provided there is provision for screening and treatment of neonatal jaundice.⁷⁶ SOGC recommends weighing the risk of neonatal jaundice against the physiological benefit of increased hemoglobin and iron levels,⁷¹ whereas ACOG concludes that there is insufficient evidence to support or refute delayed cord clamping in term infants.⁷² Based on the available evidence, delayed cord clamping in health term infants appears to be beneficial provided that treatment for jaundice requiring phototherapy is available.⁷⁰

Umbilical cord collection in preterm infants (< 37 weeks gestation) is generally contraindicated. Early cord clamping within 30 seconds of delivery is associated with optimal volume and progenitor cells for cord blood collection while delayed cord clamping for 1 to 3 minutes decreases the volume of cord blood available for collection. While cord blood collection following delayed cord clamping is not contraindicated, parents should be aware that the practice may preclude collection of sufficient cord blood for banking.

RESEARCH AND POTENTIAL FUTURE USE OF UMBILICAL CORD BLOOD

There is increasing interest in the use of cord blood for novel indications in regenerative therapy or as a means of immune modulation. A recent systematic review identified a small number of published studies involving approximately 300 patients.²⁹ The most common emerging area described in these studies addressed the repair of neurological conditions, including cerebral palsy. A large study using umbilical cord blood in the treatment of cerebral palsy is ongoing.⁷⁷ Other diseases that may be amenable to cord blood transplantation include type I diabetes and liver disease. Some studies have investigated the use of mesenchymal stromal cells expanded from umbilical cord blood. It is not yet clear how effective cord blood-derived cells are in these novel

indications as most studies are uncontrolled and involve few subjects and are proof-of-principle in nature only. Moreover, strategies to culture cells from cord blood may complicate banking efforts and introduce new regulatory challenges. It remains to be seen whether public banks will develop methods to screen for umbilical CBUs that are better suited to applications in regenerative therapy or immune modulation or whether increasing numbers of public banks will develop methods to store HSCs or other cell types expanded from cord blood. UCB represents a rich source of progenitor cells with a broad range of biological functions and tremendous potential for the development of novel cell-based therapies.

Recommendations

9. Cord blood units collected for public or private banking can be used for biomedical research, provided consent is obtained, when units cannot be banked or when consent for banking is withdrawn. (II-3B)
10. Mothers may be approached to donate cells for biomedical research. Informed consent for research using cord blood should ideally be obtained prior to the onset of active labour or elective Caesarean section following established research ethics guidelines. (II-2A)

CORD BLOOD BANKING IN CANADA

Current banking efforts reflect state of the art practices which will make the Canadian contribution important. Public banking activity has occurred in some regions of the country for several years (Alberta Cord Blood Bank, Héma-Québec Cord Blood Bank, and the Victoria Angel Registry of Hope), and the launch of the National Public Cord Blood Bank at Canadian Blood Services began in 2013. The establishment of a public bank with the capacity to store many high quality HLA-typed CBUs from a diverse cross-section of ethnicities should benefit both Canadian and international patients. Such a bank would increase the odds of finding a suitably matched CBU for patients in need of a hematopoietic cell transplant who do not have a matched sibling or unrelated donor. Recently, some public banks such as Héma-Québec have instituted a medical needs program to store, for up to 2 years, a CBU from a sibling of a child requiring a bone marrow transplant for the express use of that family member in need of the transplant. Private banks existed in Canada prior to public banking efforts and offer the possibility of a related cord blood transplant for patients and the option of possible autologous transplantation. Indications for autologous use, however, remain under debate and are not performed routinely.

Public Cord Blood Collection in Canada as of 2015

The National Public Cord Blood Bank at Canadian Blood Services has been collecting and storing units since September 30, 2013, building on the recognized need for a national effort in public cord blood banking in Canada. The initial collection and manufacturing site is in Ottawa. A second manufacturing site and collection site in Edmonton became operational in July 2014, and additional collection sites in Vancouver and Brampton began contributing to the bank in January 2015. The bank intends to store more than 10 000 high quality units by 2018 and the units will have high cell content and engraftment potency, be searchable internationally through the BMDW, and reflect the ethnic diversity of Canada, including First Nations, Inuit, and Metis who have low UCB representation. Héma-Québec has a public cord blood bank that is FACT-accredited and has more than 9000 units stored since they first started collecting in 2004. The units are searchable through the BMDW and they have supplied cord blood for more than 100 Canadian and international patients. The collection hospitals are in Montreal and Laval. The Victoria Angel of Hope Registry is a third Canadian public cord blood bank affiliated with the Cells for Life family bank in Toronto that continues to recruit expectant mothers. It has recently registered with BMDW and offers international searching of its inventory of several hundred CBUs.

SUMMARY

The National Public Cord Blood Bank was established by the Canadian Blood Services in 2013 and public cord blood banking will be available in selected Canadian sites focussed on the storage of a diverse ethnic cross-section of HLA-typed CBUs. Public cord blood banking at Héma-Québec and the Victoria Angel of Hope Registry continues to grow. Private cord blood banking facilities are located in major urban centres in Canada and provide the opportunity for family cord blood collection and storage from coast to coast.

Health care professionals should be aware of current recommendations for education, counselling, obtaining informed consent, collection, and storage of umbilical cord blood. Information regarding cord blood banking options in Canada should be presented in a comprehensive and unbiased manner.

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