

Umbilical Cord Blood Banking: Consensus Statement of the Indian Academy of Pediatrics

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FOR THE 'GUIDELINES ON UMBILICAL CORD BLOOD BANKING' COMMITTEE OF INDIAN ACADEMY OF PEDIATRICS*

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Justification: Practitioners and people need information about the therapeutic potential of umbilical cord blood stem cells and pros and cons of storing cord blood in public versus private banks.

Process: Indian Academy of Pediatrics conducted a consultative meeting on umbilical cord blood banking on 25th June 2016 in Pune, attended by experts in the field of hematopoietic stem cell transplantation working across India. Review of scientific literature was also performed. All expert committee members reviewed the final manuscript.

Objective: To bring out consensus guidelines for umbilical cord banking in India.

Recommendations: Umbilical cord blood stem cell transplantation has been used to cure many malignant disorders, hematological conditions, immune deficiency disorders and inherited metabolic disorders, even when it's partially HLA mismatched. Collection procedure is safe for mother and baby in an otherwise uncomplicated delivery. Public cord blood banking should be promoted over private banking. Private cord blood banking is highly recommended when an existing family member (sibling or biological parent) is suffering from diseases approved to be cured by allogeneic stem cell transplantation. Otherwise, private cord blood banking is not a 'biological insurance', and should be discouraged. At present, autologous cord stem cells cannot be used for treating diseases of genetic origin, metabolic disorders and hematological cancers. Advertisements for private banking are often misleading. Legislative measures are required to regularize the marketing strategies of cord blood banking.

Keywords: *Hematopoietic stem cell transplantation; Hybrid mode; Guidelines; Umbilical cord.*

Umbilical cord blood (UCB) was once considered a waste product and was discarded with the placenta after delivery. With advances in medicine, it has been found to be a rich source of life-saving hematopoietic stem cells and has saved many lives in the recent decades. Human Leucocyte Antigen (HLA) matching is required to prevent rejection and other transplant related complications. HLA-matched donors can potentially save patients from serious illnesses like malignancies, storage diseases and hematological disorders, but may not be available for the majority of suffering patients. With advances in cord blood transplantation, many such patients are now able to find a fully or partially HLA-matched cord blood donor. Various centers across the world are performing cord blood stem cell transplantation for a variety of genetic, hematologic, immunologic, metabolic, and oncologic disorders. On the other hand, a number of private cord blood banks have been established in the recent years that encourage parents to

bank their children's UCB for autologous use or for directed donor allogeneic use for a family member. This article discusses the consensus of the Indian Academy of Pediatrics (IAP) regarding the indications and benefits for storing the UCB in public or private banks based on the expert panel recommendations and the review of the scientific literature.

We aimed to provide recommendations regarding the therapeutic indications of umbilical cord stem cells and the difference between storing cord blood in public versus private banks. Experts in the field of Hematopoietic Stem Cell Transplantation (HSCT) were invited from across India, and a one-day consultative meeting was convened under the aegis of Indian Academy of Pediatrics on 25th June 2016 in Pune. Based on the discussion of the experts and the review of scientific literature, a manuscript was drafted and was circulated to all the authors. Their suggestions were reviewed and incorporated in the final consensus guidelines.

Characteristics of Umbilical Cord Stem Cells

Umbilical cord blood (UCB) collected from the umbilical cord differs from the peripheral blood in its properties [1]. It is a rich source of hematopoietic stem cells, which have the properties of self-renewal as well as the ability to differentiate into myeloid and lymphoid cell lineages. DNA in these cells has a longer telomere length, which helps in long time hematopoiesis. The cord blood is also a rich source of mesenchymal cells, which are known to suppress the response of Graft-versus-host disease (GVHD) and has naïve T cells with minimal recognition of foreign antigen [1]. These properties of cord blood cells have been successfully exploited in the treatment of various malignant, hematological and storage disorders by using UCB as a source of stem cells in HSCT. UCB can be cryopreserved and stored for >15 years with efficient recovery of stem cells on thawing [2].

CORD BLOOD BANKING

UCB can be collected from the placenta during the third stage of labor (after delivery of baby) or after the delivery of placenta. This process does not pose any risk to the baby or mother. UCB is collected from the umbilical vein into a sterile closed system collection bag containing an anticoagulant solution. Blood from placenta flows through the cord by gravity into the collection bag which is placed lower [1]. Then the bag is transported to the cord blood bank, where it is tested, processed and cryopreserved. There is a loss of blood volume and cell count during these processes. The entire procedure must be performed by properly trained and qualified personnel in a well-equipped laboratory to minimize microbial contamination of the unit and loss of viability of the stem cells. After thawing, this product can be transplanted into a host after they have received conditioning/ preparative regimen for transplant. As the stem cell count of the product is correlated with the outcome of future transplantation, it might be tempting for the bankers to increase the product volume by early cord clamping to collect more cord blood. However, this is an unethical practice as delayed cord clamping has a positive effect on the hematological status of the infant [3]. Hence, cord blood collection should not change the routine practice of umbilical cord clamping. Also, cord blood collection is not advisable in complicated deliveries like twin gestation and prematurity. All UCB units may not meet the established criteria for storage due to insufficient volume, delayed processing and/ or low stem cell count. There are no documented benefits of banking the placental tissue or Wharton's jelly.

Umbilical Cord Blood Transplantation (UCBT): Only 25-30% of patients who require allogenic HSCT can find an HLA-matched sibling donor. UCB serves as an

alternative stem cell source. In October 1988, Gluckman performed the first UCBT in a 5-year-old child with Fanconi anemia, who remains in complete hematological and immunological reconstitution for more than 25 years [2]. Initially, UCBT was performed only in children weighing up to 10-15 kg, as the low number of stem cells in a single unit was thought to be insufficient for older children and adults. Nowadays, it is used increasingly even in adults, using double umbilical cord blood units [2]. The advantages of using UCB are that it is readily available and it can be transplanted across HLA barriers. As compared to bone marrow and peripheral blood HSCT, UCBT is associated with a lower risk of GVHD, which is a complication seen after allogenic HSCT. However, UCBT is associated with delayed engraftment of donor cells, has a fixed stem cell dose (with no chance for a repeat procedure) and poor immune reconstitution.

Public versus private cord blood banking

The first publicly funded cord blood bank was established in New York in 1993 [4]. Cord blood units stored in public banks are available for the patients in need worldwide. A patient from any corner of the world can access the cord blood units in a public bank through search performed by various registries worldwide, if they get HLA-matched. The donors are not charged for the storage process. The recipients who will be using the cord blood units for their treatment will be charged. The list of public cord blood banks in India is provided as **Annexure II** [5].

In a private bank, UCB is stored privately for a particular family which opts for cord blood storage, and can be utilized by the family as the need arise. The likelihood that they will ever be used is remote (range of available estimates is from 1:1000 to 1:200 000) [3]. The family will be charged for the storage process. The number of cord blood units stored in private banks far exceeds that stored in international stem cell registries for public use [4], and is three times more than that in public banks [6]. This deprives a patient in need of an HSCT from a potentially life-saving UCB unit, as cord blood units stored in private banks are not available for the general population. In one study, quality parameters of privately banked cord blood units are found to be inferior to those stored in public banks [7].

Facts and myths of private cord blood banking

The young and expecting parents, who are anxious, are vulnerable to the emotional marketing of the private cord blood banks [3]. Parents' sense of obligation towards their own children is exploited in this field. Private cord blood banking has been projected as a panacea for a long

list of medical conditions in future. The fact is that these autologous cord stem cells (one's own stem cells) cannot be used to cure genetic disorders (including hemoglobinopathies, storage disorders, *etc.*) as these cord stem cells harbor the same genetic mutation, resulting in disease. Also, in hematological malignancies, allogenic stem cells are preferred over autologous stem cells due to the proven therapeutic effect of graft-versus-leukemia reaction, which occurs only in allogenic transplantation. Autologous stem cells are used in high-risk solid tumors. However, even if such indication arises, stem cells can readily be harvested from the peripheral blood or bone marrow of the patient, which provide similar results to that using UCB.

Private banking is highly recommended when there is an existing family member (sibling or biological parents only) suffering from a condition approved to be cured by allogenic stem cell transplantation like leukemia, hemoglobinopathy, bone marrow failure, *etc.* (directed donor cord blood collection). Thalassemia is a common non-malignant indication for HSCT in India. An unaffected HLA-matched sibling donor (MSD) is the ideal donor for thalassemia transplants. UCB from unaffected MSD can be used for thalassemia transplants. Hence, directed donor cord blood collection is advisable in this scenario. However, even if it is not stored for some reasons, HSCT can still be accomplished in future using bone marrow or peripheral blood stem cells from an unaffected MSD. UCB stored from a healthy sibling cannot be used, if it is not HLA-matched with the recipient. Storing for family members other than siblings or biological parents are unlikely to be useful. A single UCB unit may not be sufficient in an adult as the cell dose per kg body weight may be insufficient [9]. The chance of a cord blood being utilized is at least 100 times greater in a public bank as compared to private bank [6]. The myths spread favoring private banking appear to be a propaganda – exploiting people purely for a profitable business. Promotional advertisements by private cord blood banks are often misleading for the public. In countries like France and Italy, private cord blood banking and any form of advertisement regarding this is illegal.

The difference between public and private cord blood banking is briefly summarized in **Table I**.

Indian Perspective

India, being the second most populous country, possesses a great potential in the field of cord blood banking. Unfortunately, private cord blood banking has been projected as a form of 'biological insurance' and panacea for a long list of genetic and acquired illness. In India, there are four public blood banks and more than five private cord

blood banks that are functional at present. Public cord banking is the need of the hour, yet has not flourished in our country. Another fact is the lack of awareness regarding the utility of cord stem cells and its uses among the general population as well as the medical personnel including the pediatricians and obstetricians, who will be approached by parents opting for cord blood storage in private or public banks. A study conducted in the year 2013 among 100 individuals from general population attending medical genetics out-patient department and 100 clinicians working in a tertiary care hospital in Lucknow revealed an alarming information that 58% doctors and 82% of lay persons were unaware of the indications of umbilical cord blood transplantation [9]. Around 37% doctors and 42% laypersons erroneously felt that cord blood could be used to treat any genetic disorder including Duchenne muscular dystrophy and intellectual disability. More alarming result of the study was that 90% doctors felt that umbilical cord blood from a child can be used to treat thalassemia in the same child, which is also incorrect [9]. This study highlights the need for awareness among the doctors regarding the established and approved indications of cord blood in autologous and allogenic stem cell transplantation.

Stem Cell Therapy – A Speculative Field

The role of cord stem cells in regenerative medicine is still under research and the benefits in this aspect are largely speculative. Regenerative medicine is a field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type to repair damaged or destroyed cells or tissue [10]. This 'Stem cell therapy' is different from HSCT and is experimental and not standard of care. The role of stem cell therapy in conditions including diabetes mellitus, neurological conditions (like cerebral palsy, birth asphyxia, spinal cord injury) and myocardial infarction are still at the level of preclinical studies (in animals) or in phase I/II clinical studies [11-14]. Hence, stem cell therapy is not an approved therapeutic modality in such conditions till date. The Indian Council of Medical Research guidelines recommend that there are no approved indications for stem cell therapy other than HSCT in selective conditions. Therapeutic use of stem cells in other conditions shall be treated as investigational and conducted only in the form of a clinical trial after obtaining necessary regulatory approvals. Use of stem cells for any such purposes outside the domain of a clinical trial will be considered unethical and is not permissible [10].

Future Prospects – Hybrid Model

The emerging aspect in the field of cord blood banking, which has blurred the divide of public and private

TABLE I PRIVATE *VERSUS* PUBLIC CORD BLOOD BANKING

	<i>Private bank</i>	<i>Public bank</i>
Funding	Family opting to store cord blood pays,	Public funding: Not-for-profit. Fee is charged when a unit is used.
Aim	Profit, aggressive marketing.	Creation of an inventory of cord units for unrelated use.
Beneficiary	Available only to donor of the cord, or a family member.	Available to matched recipients nationally or internationally.

banking, is the 'hybrid model'. Certain private cord blood banks in the United States, Belgium, Canada, *etc.* have adopted this strategy [4]. These adopt various policies in which both public and private banking can be

incorporated. A bank might offer both public and private banking and the family are allowed to make an informed decision. Certain banks store privately but the parents are either obliged or provided an option to donate the cord once a patient in need finds it matched (the storage fee gets reimbursed) [4]. Legislative measures have brought a proportion of cords in private banks for public access in some places [4]. Commitment from Indian government in bringing legislative measures to ensure at least a proportion of cord bloods stored in vast numbers from this diverse and populous country are available for the patients in need of HSCT who do not have a matched sibling donor or matched unrelated donor available. Cord bloods stored in private banks would have an extremely low utility rate as the regenerative medicine with potential uses in conditions like diabetes mellitus, *etc.* are still only hypothetical.

Box 1. IAP CONSENSUS FOR CORD BLOOD BANKING IN INDIA

- Umbilical cord blood is a rich source of hematopoietic stem cells, which have been successfully used for curing various conditions including malignancies, hematological conditions, primary immunodeficiency and few selected inherited metabolic disorders.
- Umbilical cord blood can be safely collected from the placenta without any risks to the baby and the mother in an otherwise uncomplicated delivery.
- Cord blood collection is not advisable in complicated deliveries.
- Public cord blood banking serves the actual purpose of preservation, which provides cord blood stem cells for the patients lacking matched sibling donor or matched unrelated donors, in need of hematopoietic stem cell transplant.
- Autologous cord blood stored privately cannot be used for treating one's own genetic conditions in future (including hemoglobinopathies, storage disorders, hemophagocytic lymphohistiocytosis, immunodeficiencies, *etc.*) as the cord stem cells harbor the genetic abnormality leading to the disease.
- Autologous cord blood is not preferred in treating various hematological malignancies, due to proven therapeutic effect of graft-versus-leukemia reaction seen only in allogenic stem cell transplantation.
- Cord blood storage is not indicated for autologous stem cell transplantation.
- Public cord blood banking should be promoted, which expands treatment options for patients suffering from certain serious illnesses.
- India, with high birth rate and diverse genetic pool, has a bright prospect in public cord blood banking to increase the chances of finding HLA-matched hematopoietic stem cells for transplant.
- Private cord blood banking is not a 'biological insurance' and its role in regenerative medicine is still hypothetical.
- Private cord blood banking is recommended only if there is an existing family member (siblings or biological parents only), who is currently suffering from diseases approved to be benefitted by allogenic stem cell transplantation.
- It is imperative to spread awareness about myths and facts about cord blood banking (public and private) among the public (by mass campaigning) and among the health workers (by including this subject in under graduate academic curriculum).
- Advertisements for private cord blood banking by companies (*e.g.*, by using celebrities) are often misleading and exploit parents' emotions for profit, at the vulnerable period of pregnancy.

CONSENSUS STATEMENT OF IAP

IAP recommends the information provided in **Box 1** to be provided to the treating obstetrician and the pediatrician who are considering giving option of cord blood banking to a family.

Recommendations of International Societies

American Academy of Pediatrics recommends preferring public UCB banks [15]. Role of private banking is limited and are not subjected to strict regulatory oversight and may be of lesser quality. Parents should be informed about the potential benefits and limitations of autologous cord cells and the lack of scientific data in its use in regenerative medicine. Regulatory agencies have to ensure that the cord blood banking programs comply with accreditation standards [15]. American Society for Blood and Marrow Transplantation encourages public UCB banking, as the probability for using one's own cord blood is very small (0.04 to 0.0005%) [6]. Society of Obstetricians and Gynaecologists of Canada suggests that there is minimal harm to the mother or newborn with UCB banking if priority is given to maternal/newborn safety during childbirth and collection should not interfere with delayed cord clamping [16]. Unbiased information about UCB banking options should be provided to pregnant women prior to the onset of active labor, ideally during the third trimester, with ample time to address any questions [16].

CONCLUSION

Policymakers should promote public cord blood banking. The myths and lack of awareness regarding cord blood banking among health care professionals and the public is a big threat leading to exploitation by private banking. The narrow indications of the possible utility of the baby's cord blood stored privately should be highlighted to the family opting for cord blood banking.

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Contributors: VG, PM: designed the manuscript; AS, DB, SPY, NR, MK, SB, RM, PJ: analyzed and critically reviewed the manuscript. All authors approved the manuscript.

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ANNEXURE I: PARTICIPANTS OF THE CONSULTATIVE MEETING

Chairperson: Pramod Jog; **Convener:** Anupam Sachdeva.

Experts (In alphabetical order): M Deenadayalan (Chennai), Dinesh Bhurani (Delhi), Mamta V Manglani (Mumbai), Manas Kalra (Delhi), Nita Radhakrishnan (Delhi), Ruchira Misra (Delhi), Sandip Bartakke (Pune), Santanu Sen (Mumbai), Satya Prakash Yadav (Delhi), Shailesh Kanvinde (Pune), S Sirisha Rani (Hyderabad), Sunil Bhat (Bengaluru), Vikas Dua (Delhi), Vinod Gunasekaran (Delhi).

ANNEXURE II: LIST* OF PUBLIC CORD BLOOD BANKS IN INDIA

<i>Cord blood bank</i>	<i>Contact details</i>	<i>Email ID</i>	<i>URL</i>
Jeevan	22, Wheatcrofts Rd, Seetha Nagar, Nungambakkam, Tamil Nadu. +91 44 4352 4242 +91 44 2835 1200	stemcell@jeevan.org	http://www.jeevan.org/stem-cell-bank/
Reliance	Dhirubhai Ambani Life Sciences Center. Thane-Belapur Road, Navi Mumbai. Phone Numbers:+ 91 (22) 6767 8000 + 91 (22) 6767 8000	info@relbio.com	http://www.rellife.com/cord_blood.html
School of Tropical Medicine	108, Chittaranjan Avenue, Kolkata, West Bengal. Phone Number: +91 33 2212 3697	—	http://www.stmkolkata.org/rmts/cordbloodbank.html
StemCyte India	Apollo Hospital Campus, Bhat GIDC Estate, Ahmedabad Rd, Gandhinagar, Gujarat. Phone Number: +91 79 2687 0634	info@stemcyteindia.com	http://www.stemcyteindia.com/

*in alphabetical order.