JAHR | Vol. 6/1 | No. 11 | 2015

UDK: 614.253:618.38:608.1(045)

Review article

Received: 20.03.2015.

Barbara Corsano, Dario Sacchini, Mária Šuleková[+], Roberta Minacori, Pietro Refolo, Antonio G. Spagnolo,

Institute of Bioethics (Director: A.G. Spagnolo), "A. Gemelli" School of Medicine, Università Cattolica del Sacro Cuore, Rome (Italy); [+]Faculty of Education, Trnava University in Trnava (Slovakia)[*]

Allogeneic versus Autologous: ethical issues in umbilical cord blood use

ABSTRACT

OBJECTIVE. To analyse some ethical issues involved in umbilical cord blood (UCB) collection, storage and use.

MATERIALS AND METHODS. Ethical issues were addressed in the light of the well-known fundamental ethical principles for biomedicine: beneficence/non maleficence, respect for autonomy and justice. Specific issues that have been debated concerning the clinical utility of autologous use compared with allogeneic use for transplantation, the validity of informed consent, especially in private UCB banking, and finally the controversial question of private UCB banking for-profit compared to public UCB banking non-profit.

RESULTS. Our ethical analysis has highlighted that the allogeneic UCB use for transplantation, compared to autologous UCB use, seems to fulfil the principle of beneficence/non maleficence as it provides "logistic" and clinical benefits and it decreases risks; the acquisition of informed consent requires some counselling, particularly for autologous collection; finally, public UCB banking seems to fulfil the criteria for justice more than private ones.

CONCLUSION. Present and future therapeutic UCB possibilities for treating a wide variety of diseases need to increase the number of UCB units available. For this purpose, a "gift" culture and a "solidarity chain" between donors and recipients are requested. Moreover, in recent years, a further and emerging model of bank seems usable, i.e. "hybrid" banking.

Keywords: autologous, allogeneic, stem cells, cord blood, banking

[*] Contact address: Dario Sacchini. Institute of Bioethics (Director: A.G. Spagnolo), "A. Gemelli" School of Medicine, Università Cattolica del Sacro Cuore; 1, Largo F. Vito, 00168 Rome (Italy); e-mail: dsacchini@rm.unicatt.it

Introduction

Umbilical cord blood (UCB) is a rich source of multipotent stem cells with high regeneration capacities and potential differentiation into various tissue specific cells. So UCB stem cells are candidates for future use in treating a wide variety of diseases thanks to their potential in restoring hematopoietic, epithelial, endothelial and neural tissues both "in vitro" and "in vivo"[1].

At the moment, UCB cells are successfully used to treat different hematologic malignancies, but their future applications in regenerative medicine are potentially greater and also include a large number of non-hematopoietic diseases, which are currently incurable.

In recent years, actual and potential successes in UCB transplantation and in regenerative medicine have generated popular/scientific expectations and an increasing interest in establishing and developing UCB banks worldwide, both public and private, for the storage of UCB units.

To 2014, more than 600.000 UCB units (data available on www.bmdw.org , www.nmdp.org) have been donated and stored in about 120 public banks for allogeneic use and they were included in a global network[2,3]. Furthermore, over 1.000.000[4] UCB units have been stored in many private banks for autologous (personal) use, and this number is rapidly growing.

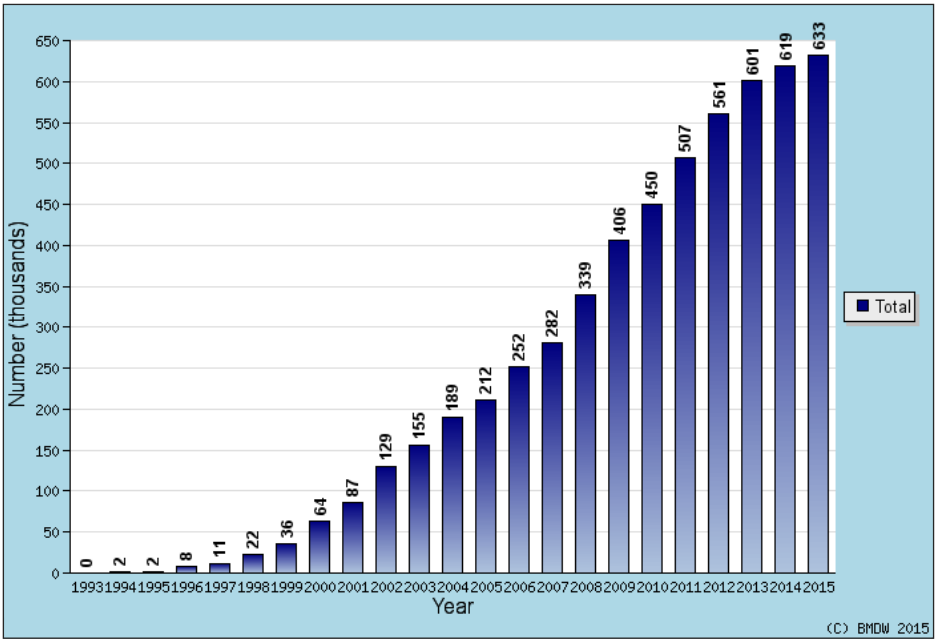
[1] Rosenthal J, Woolfrey AE, Pawlowska, A et al, »Hematopoietic Cell Transplantation With Autologous Cord Blood in Patients With Severe Aplastic Anemia: An Opportunity to Revisit the Controversy Regarding Cord Blood Banking for Private Use«, *Pediatr Blood Cancer,* 2011, 56: 1009–12.

[2] Gluckman E, Ruggeri A, Volt F et al, »Milestones in umbilical cord blood transplantation«, *Br J Haematol.* 2011, 154 (4):441-7.

[3] http://www.bmdw.org (19 March 2015).

[4] Wagner AM, Krenger W, Suter E et al, »High acceptance rate of hybrid allogeneic-autologous umbilical cord blood banking among actual and potential Swiss donors«, *Transfusion*. 2013, 53(7):1510-9.

Table I - Total number of cord blood units (available on http://www.bmdw.org/index.php?id=statistics_cordblood)



Compared to the number of related (sibling) and unrelated allogeneic UCB transplants (over 20.000), autologous transplants (about 100) still play a very limited role in the treatment of some specific diseases, as documented by the small number of clinical cases mostly with unknown outcomes[5] (cf. Table II for the concepts of autologous and allogeneic).

[5] Thornley I, Eapen M, Sung L et al, »Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians«. *Pediatrics,* 2009, 123(3):1011-7. Ballen K, »Challenges in umbilical cord blood stem cell banking for stem cell reviews and reports«*, Stem Cell Rev,* 2010, 6: 8–14. Forraz N, McGuckin CP, »The umbilical cord: a rich and ethical stem cell source to advance regenerative medicine«, *Cell Prolif.,* 2011, 44 (Suppl. 1): 60–9. Ferreira E, Pasternak J, Bacal N, et al, »Autologous cord blood transplantation«. *Bone Marrow Transplant*, 1999, 24:1041. Hayani A, Lampeter E, Viswanatha D, et al, »First report of autologous cord blood transplantation in the treatment of a child with leukaemia«. *Pediatrics,* 2007, 119: e296–e300.

Table II - Glossary

ALLOGENEIC	AUTOLOGOUS
Donor and recipient are different: UCB stem cells are obtained from a donor and suitable for the infusion in another person (related or not related)	Donor and recipient are identical: UCB stem cells are taken and applied in the same person
Legenda UCB = umbilical cord blood	

The use of UCB cells (particularly their collection and storage) raise some ethical issues[6]. They were methodologically addressed in the light of the well-known fundamental ethical principles of biomedicine: the principles of beneficence/non maleficence, the principle of autonomy and the principle of justice.

Particularly, the following issues will be debated: a) clinical appropriateness and beneficence/non maleficence of UCB allogeneic donation or autologous storage for transplantation; b) validity of informed consent (IC) to UCB donation/storage; c) the economic issue in private UCB banking.

1. Clinical appropriateness and beneficence/non maleficence of UCB allogeneic donation or autologous storage for transplantation

The first requirement for assessing the ethical acceptability of any treatment is to assess the balance between benefits for patients and for society, and the risks of adverse effects (principle of beneficence/non maleficence).

According to Rocha and Locatelli in 2008[7], there are substantial "logistic" and clinical benefits in UCB allogeneic use, compared to other stem cell sources for allogeneic hematologic stem cells transplantation (HSCT)[8]:

[6] Skene L, »Development of stem cells from umbilical cord blood and blood banking: "non-controversial" and "free of political and ethical debate"?«, *J Law Med*, 2012, 19: 490-6.

[7] Rocha V, Locatelli F, »Searching for alternative hematopoietic stem cell donors for pediatric patients«, *Bone Marrow Transplant*, 2008, 41: 207–14.

[8] Rocha V, Gluckman E, »Improving outcomes of cord blood transplantation: HLA matching, cell dose and other graft- and transplantation-related factors«, *British Journal of Haematology*, 2009, 147: 262–74.

(i) significantly faster availability of banked cryo-preserved UCB units, with patients receiving UCBT a median of 25–36 days earlier than those receiving an unrelated bone marrow graft;

(ii) extension of the donor pool due to tolerance of 1–2 Human Leucocyte Antigen (HLA) mismatches out of six;

(iii) lower incidence and severity of acute graft-versus-host disease (GVHD);

(iv) lower risk of transmitting infections by latent viruses, such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV);

(v) lack of risk to the donor;

(vi) higher frequency of rare haplotypes compared to bone marrow registries, because it is easier to target ethnic minorities.

Nevertheless, there are some possible disadvantages in UCB use. As discussed by Samuel et al.[9], UCB contains a limited cell dose; it presents higher graft failure rates and a lower speed of hematopoietic stem cell recovery as well as a higher rate of infection. Advantages and disadvantages are highlighted in Table III.

Table III - UCB stem cells use: advantages vs disadvatages (in comparison to other sources of allogeneic HSCT)

ADVANTAGES (by Rocha and Gluckman*)	**DISADVANTAGES** (by Samuel et al.**)
Significantly faster availability of banked cryo-preserved UCB units, with patients receiving UCBT a median of 25–36 days earlier than those receiving an unrelated bone marrow graft; Extension of the donor pool due to tolerance of 1–2 HLA mismatches out of six; Lower incidence and severity of acute GVHD; Lower risk of transmitting infections by latent viruses, such as CMV and EBV; Lack of risk to the donor; Higher frequency of rare haplotypes compared to bone marrow registries, because it is easier to target ethnic minorities.	Limited cell dose Higher graft failure rates Inferior speed of hematopoietic stem cell recovery A higher rate of infection
Legenda: UCB = Umbilical Cord Blood UCBT = Umbilical Cord Blood transplant HSCT = Haematopoietic Stem Cell Transplantation HLA = Human Leucocyte Antigen	GVHD = Graft-Versus-Host Disease CMV = Cytomegalovirus RBV = Epstein–Barr virus
*Rocha V, Gluckman E. Improving outcomes of cord blood transplantation: HLA matching, cell dose and other graft- and transplantation-related factors. British Journal of Haematology, 2009; **147**: 262–74.	**Samuel GN, Kerridge IH, O'Brien TA. Umbilical cord blood banking. MJA 2008; **188**: 533-5.

[9] Samuel GN, Kerridge IH, O'Brien TA, »Umbilical cord blood banking«, *MJA,* 2008, 188:533-5.

Recent evidences suggest that these disadvantages will be improved through the co-transplantation of two UCB units from different donors ("double cord" transplant) and the expansion of the volume of cord blood protocols (increasing the number of stem cells).

Moreover, recent findings on graft engineering and underway studies are currently evaluating the feasibility of "ex vivo" expansion of the units.[10]

Certainly, the growing and recognized value of UCB transplantation is supported by existing clinical practice and a range of studies. The clinical use of UCB may also become the front-line treatment for children suffering from leukaemia[11].

Finally, recent clinical studies extend the potential of neonatal stem cells for clinical applications beyond haematotherapies to autoimmune disorders, cerebral palsy and type I diabetes[12].

Therefore, on the basis of these considerations, the allogeneic use of UCB stem cells seems fulfil the principle of beneficence. In fact, as also pointed by Di Sciascio et al. "they have the stated goal of curing or effectively controlling diseases that cannot be managed with current treatment protocols. Therefore, the intentions of those who intend to use the stem cells qualify in principle as positive, reflecting also a classic aspect of medical ethics: the protection of life and health of the patient"[13].

The absence of a clear and effective therapeutic indication to autologous UCB use that negates the purpose of the beneficence, which is intrinsic to allogeneic UCB donation and that would give a first indication of the autologous storage. Physical life is the first fundamental value of the person. So, it follows that we should prioritize respect for life in the ethical evaluation of the current or future use of any treatment, or even its storage.

Here the complex and multidimensional concept of "appropriateness"[14] comes in.

---

[10] Escalo´n MP, Komanduri K, »Cord blood transplantation: evolving strategies to improve engraftment and immune reconstitution«, *Curr Opin Oncol*, 2010, 22: 122–9. Delaney C, Heimfeld S, Brashem-Stein C, et al, »Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution«, *Nat Med*, 2010, 16: 232–6.

[11] Stanevsky A, Goldstein G, Nagler A, »Umbilical cord blood transplantation: pros, cons and beyond«, *Blood Rev*. 2009, 23: 199-204. Holland P, Mc Cauley C, »Private Cord Blood Banking-current use and clinical future«, *Stem Cell Rev and Rep,* 2009, 5:195-203.

[12] Forraz N, McGuckin CP, »The umbilical cord: a rich and ethical stem cell source to advance regenerative medicine«, *Cell Prolif*, 2011, 44 (Suppl. 1): 60–9.

[13] Di Sciascio G, Tambone V, Sacchini D, »Sull'utilizzo delle cellule staminali a fini terapeutici e le fonti della moralità«, *Clin Ter,* 2007, 158: 21-5.

[14] Art 3 of *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. (Oviedo 1997). http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm (19 March 2015); Dipartimento della Programmazione e dell'ordinamento del Servizio Sanitario Nazionale. Direzione Generale della Programmazione Sanitaria, Ufficio

A cure can be considered "appropriate" when it is associated with a net benefit or when it maximizes the benefit and minimizes the risk to the patient. Therefore, a treatment is "appropriate" when it fulfils the effective clinical indications, at the right time, in an adequate manner, for the patient's benefit.

Without these essential elements of proven effectiveness and net benefit to the patient a treatment is "inappropriate"., Autologous UCB use would be considered "inappropriate" for the following reasons: its limited clinical applications to particular types of diseases and in particular stages of disease; the very low probability of using UCB stem cells - between 0,04% (1: 2.500) to 0,0005% (1: 200.000) - during the first 20 years[15]; the fact that autologous transplants are not recommended for hereditary or oncohaematological diseases[16], because cord blood cells might be already be bearers of the disease markers without benefit, but with harm to the patient; little available information whether the internationally accepted quality criteria for stored samples are met[17]; the uncertain shelf life of stored UCB samples; the regenerative medicine perspectives are still widely hypothetical or in initial trials.

Moral obligation also requires respecting the principle of non-maleficence, i.e. the Hippocratic *primum non nocere* (first do not harm).

Concerning the recipient, it has not been proved that UCB transplantation implies a greater risk than transplantation using bone marrow-derived hematopoietic stem cells or peripheral blood stem cells.

In the same way, the literature shows that no risk is associated with the donation, neither for the mother nor for the child, since the umbilical cord cut and blood collection is fully compatible with proper care for the newborn.

However, a point that is still debated is the timing of umbilical cord clamping, especially for what concerns the assessment of the optimal time to clamp the

III Ex D.G.Progs. *Manuale di formazione per il governo clinico: Appropriatezza.* (July 2012). http://www.salute.gov.it/imgs/C_17_pubblicazioni_1826_allegato.pdf (19 March 2015). Consiglio d'Europa, Comitato Dei Ministri, Raccomandazione N.° R (97) 17 del Comitato dei Ministri agli Stati Membri: *Sullo Sviluppo e l'Attivazione di Sistemi di Miglioramento della Qualità (Smq) dell'Assistenza Sanitaria*. http://www.salute.gov.it/imgs/C_17_pubblicazioni_28_allegato.pdf (19 March 2015); Ministero Del Lavoro, Della Salute E Delle Politiche Sociali. *Uso appropriato delle cellule staminali del sangue del cordone ombelicale – Elementi informativi essenziali*. (18 March 2009). http://www.trapianti.salute.gov.it/imgs/C_17_pubblicazioni_941_allegato.pdf (19 March 2015).

15 Ballen KK, Barker JN, Stewart SK et al, »American Society for Blood and marrow Transplantation (Asbmt) Committee Report - Collection and Preservation of Cord Blood for Personal Use«, *Biol Blood Marrow Transplant,* 2008, 14:356-363; Nietfeld FF, Pasquini MC, Logan BR, et al, »Lifetime Probabilities of Hematopoietic Stem Cell Transplantation in the U.S.« *Biol Blood Marrow Transplant,* 2008, 14:316-322.

16 McKenna D, Sheth J, »Umbilical cord blood: current status & promise for the future«. *Indian J Med Res*, 2011, 134:261-9.

17 Spurr EE et al, »Cryopreserved human haematopoietic stem cells retain engraftment potential after ex- tended (5-14 years) cryostorage«, *Cryobiology*, 2002, 44 (3):210, 2002.

umbilical cord in preterm and full-term newborns without causing any harm to the child, which could be deprived of a significant quantity of blood, iron, and other benefits in the case of early procedure.

Some reviews of randomized controlled trials (RCTs)[18], comparing the effects of early and late cord clamping on maternal and infant outcomes, have showed that delayed cord clamping (at least 2 minutes after birth) appears beneficial for preterm[19] and full-term newborns: it improves both the short- and long-term hematologic and iron status of full-term infants.

On the other hand, some observational studies suggest that delayed umbilical cord clamping puts newborns at a higher risk of suffering from polycythemia, respiratory distress, hyperbilirubinemia, and other neonatal disorders[20].

A RCT conducted by Andersson et al. (2011)[21] has compared early clamping (within 10 seconds after birth) and late clamping (to 180 seconds after birth) in 400 term newborns. At 2 days after birth the study showed a prevalence of a significantly lower anaemia in the second than the first group. After 4 months haemoglobin values were equal in the 2 groups, even if ferritin levels were lower in babies with early clamping.

So, timing of cord clamping is an open question for obtaining a high concentration of stem cells needed for altruistic donation or private conservation.

No doubt the late clamping of the umbilical cord is necessary and recommended in premature newborns and in developing countries to allow a protracted placental perfusion before clamping and obtain a physiological normovolemia and a considerable iron transfer (about 30 mg) at birth[22].

Moreover, according to data reported by Navarrete at the "*World Cord Blood Congress III: Cord Blood Transplantation and Immunology of Haematopoietic Stem Cell Transplantation*" (Rome, 27 - 29 October 2011) related to about 600.000 collected samples in public banks, no serious diseases have been recorded or

[18] Hutton EK, Hassan ES, »Late vs Early Clamping of the Umbilical Cord in Full-term Neonates: systematic review and meta-analysis of controlled trials«, *JAMA,* 2007, 297: 1241-52; Chaparro CM, Neufeld LM, Tena Alavez G, et al, »Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial«, *Lancet*, 2006, 367: 1997-2004.

[19] Baenziger O, Stolkin F, Keel M et al, »The Influence of the Timing of Cord Clamping on Postnatal Cerebral Oxygenation in Preterm Neonates: A randomized, Controlled Trial«, *Pediatrics*, 2007, 119: 455-9.

[20] Hutton EK, Hassan ES, »Late vs Early Clamping of the Umbilical Cord in Full-term Neonates: systematic review and meta-analysis of controlled trials«, *JAMA,* 2007, 297: 1241-52.

[21] Andersson O, Hellstrom-Westas L, Andersson D et al, »Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomized controlled trial«, *BMJ,* 2011, 343: 7157.

[22] Kinmond S, Aitkison TC, Holland BM et al, »Umbilical cord clamping and preterm infants: a randomized trial«, *BMJ,* 1993, 306(Jan): 172-5.

described in newborns after cord clamping, which probably occurred about 60 seconds after childbirth [23].

Thus, a time of clamping not less than 60 seconds after childbirth appears to be the recommended time to protect the newborn's health, even if this could go to the detriment of a collection of an adequate amount of cord blood.

2. Validity of informed consent

A second ethical requirement for the use of any treatment is an autonomous choice (principle of respect for autonomy). This argument is clearly connected to topic of informed consent (IC), i.e the act of an individual exercising a free and aware choice about whether or not to participate in research or to undergo medical treatment.

In the context of the UCB use, some key aspects of IC are: *what* information; *who* is the owner of the umbilical cord and thus the "donor" (mother or baby), and who is empowered to give consent on behalf of him (including competence for understanding and decision); *for which* purpose collecting UCB stem cells, whether for an altruistic intention (allogeneic and/or research) or for any personal autologous use in the future.[24.]

A consent to be valid should be "informed, free, express, specific and documented"[25] and it should be fundamentally characterized by four elements: the provision of information, understanding of information, freedom of decision, the decision-making capacity[26].

The information is critical to the decision-making of the patient and it should be as truthful and complete, to ensure to the person to choose freely and consciously. The principle of respect for autonomy implies, in fact, the right to give consent, based on full and transparent information.

This is the crux of the ethical controversies: if IC is defined as "a process by which a subject voluntarily confirms its willingness to participate in a particular trial, after having been informed of all aspects of the process that are relevant to the individual's decision to participate"[26], how could a choice be "free" and the consent really

[23] Navarrete C, »Review of International Fees for the provision of cord blood units«, *World Cord Blood Congress III*, October 27-29, 2011, ABS: 28.

[24] Petrini C, »Umbilical cord blood collection, storage and use: ethical issues« *Blood Transfus,* 2010, 8: 139-48. Sacchini D, Pennacchini M, »Informed consent«, *Clin Ter,* 2010, 161: 397-9.

[25] Art. 14, comma 1 of *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,* http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm (19 March 2015).

[26] Russo G, »Consenso informato. Dimensioni generali« in: Russo G (ed). *Enciclopedia di Bioetica e Sessuologia*. Leumann (TO): Elledici; 2004, pp. 524-526

"informed" in such situations of misleading and incorrect information? What would be an adequate information?

With reference to the autologous collection, the *American Academy of Pediatrics*[27] and the *American College of Obstetricians and Gynaecologists*[28] doubts the validity of IC obtained by private banks, whose marketing strategy sometimes uses a particularly aggressive advertising approach. Websites, representatives, brochures/ flyers using messages, advertisements and images (eg: happy moments of a family, beautiful and smiling children, etc ...), which aim to arouse emotions in the subject who sees or hears them, in an attempt to involve the expectant parents in a choice that would be especially emotional.

These private banks mention frequently as their "rationale" the hypothesis that future treatment programs for tissue repair/replacement will be developed (including heart, nervous system, liver, etc.).

Advertising declarations like *"a once in a lifetime opportunity", "storing your baby's umbilical cord blood could save their life",* and *"don't let a precious resource go to waste*"[29] are misleading, because they promise to "close in the safe" the umbilical cord as a kind of biological insurance, creating in parents the illusion that the cord blood can represent a kind of therapeutic panacea for every disease and, at the same time, generate guilt, especially for those mothers who cannot buy a "hope for life" for their child[30].

This creates a real "business of hope", which preys on the desire of parents to give their child every advantage, and their concern about the real and hypothetical risks of future diseases for the child, on the particular emotional state of psychological vulnerability that characterizes the period of pregnancy.

Actually, the scientific evidence affirms a greater "biological life insurance" in UCB donation for allogeneic use – that is accessible to anyone who needs it and actually used for several thousands of patients each year, with a good chance to find one's own donated UCB unit in case of need - rather than save it for future personal therapeutic applications, today still hypothetical and not well-defined.

---

[27] American Academy of Pediatrics, *Pediatrics Group Recommends Public Cord Blood Banking*, *JAMA,* 2007, 297: 576.

[28] ACOG committee opinion number 399, February 2008, »Umbilical cord blood banking«, *Obstet Gynecol*, 2008,111:475–7.

[29] Sullivan MJ, »Banking on cord blood stem cells«, *Nat Rev Cancer*, Jul 2008, 8(7):555-563.

[30] Klingebiel T, »The Price of Hope«, *Dtsch Arztebl Int*, 2009, 106(50): 829–30.

The *American Society for Blood and Marrow Transplantation* (2008)[31] agrees with it: in fact, it criticized UCB collection and preservation for personal use, pointing out the remote chance of using one's own UCB collected at the birth (probably between 0,04% and 0,0005% in the first 20 years of life).

Two studies – Capone et al (2010)[32] and Rebulla and Lecchi (2011)[33] - have analysed the contents of different private cord blood banks websites, , finding sometimes misleading, deceptive, and unclear information. Several national and international documents emphasize the need for an accurate and adequate information.

Recommendation Rec(2004)8 of the Council of Europe[34] emphasizes this aspect: «Accurate information should be provided to the population about the advantages and disadvantages of cord blood banks. Where autologous cord blood banks are being established, the promotional material or information provided to families must be accurate, and fully informed consent to cord blood storage must be obtained».

The *European Group on Ethics in Science and New Technologies*[35] (EGE), regarding the need to provide accurate and truthful information, reports: "If commercial banks are allowed (in any EU member state), appropriate information should be given to consumers willing to use their services, including the fact that the likelihood that samples may be used to treat one's child is currently negligible, that future therapeutic possibilities are of a very hypothetical nature, and that up until now there is no indication that the present research will lead to s,pecific therapeutic applications on one's own cord blood cells."; and also "...information should be particularly explicit, that the auto conservation has little value in the current state of scientific knowledge. This information should be made clear on all media, including Internet, and in any contracts linking commercial banks to their customers".

IC also raises the question on who is the owner of the UCB, and therefore, who should give the consent (only the mother, or the father as well). On this matter, Petrini has showed two opposing positions: some suggest that the cord blood sample

31 Ballen KK, »ASBMT Committee Report - Collection and Preservation of Cord Blood for Personal Use«, *Biol Blood Marrow Transplant,* 2008, 14:356-363.

32 Capone F, Lombardini L, Pupella S et al, »Cord blood stem cell banking: a snapshot of the Italian situation«, *Transfusion,* 2011, Sep;51(9):1985-94.

33 Rebulla P, Lecchi L, »Towards responsible cord blood banking models«, *Cell Prolif*, 2011, 44 (Suppl. 1): 30–4.

34 Council Of Europe: Committee of Ministers, *Recommendation Rec(2004)8 of the Committee of Ministers to member States on autologous cord blood banks*, (2004), https://wcd.coe.int/ViewDoc.jsp?id=744641&Lang=en (19 March 2015).

35 European Group on Ethics in Science and New Technologies, Opinion 19, *Ethical aspects of umbilical cord blood banking*. (16 March 2004). http://ec.europa.eu/bepa/european-group-ethics/docs/avis19_en.pdf. (19 March 2015).

is the property of the child since it is developmentally, biologically and genetically part of the child; others affirm that it is the mother's property once the cord is cut.

In any case, the expression of autonomy becomes problematic if establishing who is the "autonomous agent" is controversial[36]. The mother is usually required to give consent, but - if it is accepted that the cord blood belongs to the baby - it should be considered that the mother does not consent for herself, but on behalf of the baby. Moreover, she shares parental authority with the father. Therefore, the father's involvement in the consent process is highly recommendable.

On this matter, Salvaterra's approach to the question is appreciable: she affirms that a "participatory approach" could be the key to understand the process of donation implying a plurality of actors (pregnant women, future parents, donors, health professionals and institutions), that have different experiences and values. In this complex situation, implementing an intimate relationship between knowledge and choice guarantees conditions for a good service to the "person"[37].

It clearly shows how both the knowledge of decision-making processes applied to cord blood donation and the comprehension of underlying motivations might orient institutions, health professionals and public organisations to develop guidelines, that recommend for providing an accurate information on cord blood donation.

A suggestion could be to start the process of IC long before the birth, so that parents have more time to make a free and responsible decision. In any case, it should not be requested just before childbirth.

Moreover, IC should be presented in a standardized form (i.e., a signed written statement, with no technical or confusing language, and not accepted in haste, etc.)[38] and obtained by trained healthcare workers and not from parties with any conflicts of interest, especially economic ones, which, for example, may recommend the UCB collection for autologous use because they are employees of private banks.

---

[36] Stewart CL, Aparicio LC and Kerridge IH, »Ethical and legal issues raised by cord blood banking — the challenges of the new bioeconomy«, *Med J Aust,* 2013, 199 (4): 290-292.

[37] Salvaterra E, Casati S, Bottardi S et al, »An analysis of decision making in cord blood donation through a participatory approach«, *Transfus Apher Sci*, 2010, 42: 299–305.

[38] Petrini C, »Umbilical cord blood collection, storage and use: ethical issues«, *Blood Transfus,* 2010, 8: 139-48.

3. Economic issue in private UCB banking

A further requirement for ascertaining whether the use of any treatment is ethically acceptable is to assess if it is compatible with the principle of justice. Within the context of UCB use, this argument is connected to the economic issue in UCB banking, especially in private banking.

The economic factor present in the UCB private banking will be analysed not only in terms of the profits, but also in terms of the storage costs in charge of the parents.

Public and private UCB banking is widely debated from a scientific and ethical point of view. In a paper[39], Rebulla and Lecchi have analysed and discussed their differences (cf. Table IV), also considering several ethical issues closely related to technical aspects: minimum cell dose per unit in inventory, techniques for UCB unit volume reduction, number of aliquots per banked unit, liquid versus vapour nitrogen storage, UCB unit overwrapping, proportion of ethnic minorities in inventory, reimbursement fee per transplanted patient versus per distributed UCB unit.

Table IV - Main differences between public and private banking

PUBLIC BANKING	PRIVATE BANKING
The UCB is given to be made available to the public Public donation goes in an international network Donor selection, sample acquisition, storage, transport and cellular viability are strictly accordant with International Quality Controls Public banks have to meet very strict, defined and international quality standards (as Netcord-FACT) to ensure the use of the cells for therapy Increase of the donation represents a guarantee for the same donor who can found in case of need a reliable source of stem cells Public donation promotes a culture of gift and solidarity All costs are paid by State; no cost to the parents who donate Partial HLA compatibility is admitted and verified in specific international registries	The UCB is reserved for the newborn donor or his/her family All samples are stored, disregarding quantitative criteria in terms of collected cord blood volume; so the sample might not be sufficient for the purposes of its clinical use There is no clear evidence of certified quality control, often related to the high costs and to the policies of individual banks Autologous storage could be subject of economic speculation and it is experienced as a "life insurance", but it likely remains unused in the majority of cases Private banks are characterized by an aggressive commercial business All storage costs are paid by the parents for 15-20 years Full HLA compatibility in all the cases

[39] Rebulla P, Lecchi L, »Towards responsible cord blood banking models«, *Cell Prolif*, 2011, 44 (Suppl. 1): 30–4.

Regarding to the issue "for profit", Article 21 of *Convention of Oviedo* states "The human body and its parts shall not, as such, give rise to financial gain."[40] Additionally, Article 2 of *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin*[41] says "The provisions of this Protocol applicable to tissues shall apply also to cells, including haematopoietic stem cells". This is stated by Article 3 of *Charter Of Fundamental Rights Of The European Union*[42] "The prohibition on making the human body and its parts as such a source of financial gain" and by Article 7 of *Recommendation Rec(2006)4*[43] *of The Committee of Ministers to Member States on Research on Biological Materials of Human Origin* "Biological materials should not, as such, give rise to financial gain".

Within the national and European legal framework, the prohibition of human body marketing is established. Under this rule, the tissues – and also stem cells - are considered *extra commercium* goods and, therefore, cannot be a source of profit. Subjecting the body to commercialization would be detrimental to human dignity, as a result the private UCB banks led explicitly by a for profit logic, are an undeniable ethical critical issues. Just as you cannot buy or sell blood or organs, you should not take undue profit from UCB stem cell storage.

On the contrary, private banks are now all over the world and have increased in number in recent years, becoming a real "industry" and transforming cord blood from a biological resource into an important bio-economic resource. This is reported in Capitalizing on Opportunities in Cord Blood Industry Growth[44], an industry-report that highlights how the UCB banks represent an opportunity for profit and competition and provides tools to learn and study not only the market and future perspectives, but also the "expectations of potential customers" (i.e. expectant parents) to better define market strategies and monitor competitiveness.

---

[40] *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. Oviedo 1997). http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm (19 March 2015).

[41] *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin*. Strasbourg, 2002. http://conventions.coe.int/treaty/en/treaties/html/186.htm (19 March 2015).

[42] *Charter Of Fundamental Rights Of The European Union*. 2010. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:083:0389:0403:en:PDF (19 March 2015).

[43] Council of Europe: Committee of Ministers. *Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin*. https://wcd.coe.int/ViewDoc.jsp?id=977859 (19 March 2015).

[44] http://www.marketresearch.com/BioInformant-Worldwide-L-C-v3663/Capitalizing-Opportunities-Cord-Blood-Growth-7863251/ (19 March 2015); http://www.bioinformant.com/category/cord-blood/ (19 March 2015).

It is clear that public and private UCB banks are the expression of two different approaches: the model of social justice, which postulates the right to health as a fundamental human right and promotes solidarity between citizens through the philosophy of voluntary and free donation[45], and the model of supply and demand, pointing instead to a liberal interpretation of the parents' autonomy.

So, the bioethical debate is between the principle of social solidarity and the rights of individual freedom. Private banking, based on individualism and the principle of respect for individual autonomy, could introduce, therefore, more than one variable of social discrimination and go against the realization of the "common good".

A first discrimination is linked to the costs paid by the parents for the private storage of UCB samples. This could be also source of possible inequality between the rich and the poor and so private banking could become a prerogative only for wealthier households. This could represent a violation of the individual's right to a fair access to health care.

Moreover, choosing private banking - in view of hypothetical future therapeutic autologous use - could deprive patients, both children and adults, of access to a considerable amount of blood units, and consequently, of higher chances of cure.

We must not forget that not all can find suitable donors within existing international registries. In particular, the likelihood of finding a donor varies across racial/ethnic groups and this variation is due to under-representation of some ethnic groups within donor registries and to increased HLA diversity within some ethnic groups.

Another important limitation of private UCB banking is the variability in quality standards unlike public UCB banking that use specific standard operating protocols and must meet international criteria and requirements, including adequate cell count and volume. In fact, rigorous donor screening and infectious disease testing might not be required in private UCB banking as in public banks[46].

---

[45] Sykora P, »Altruism in Medical Donations Reconsidered: the Reciprocity Approach« in: Steinmann M, Sykora P, Wiesing U (eds),.*Altruism Reconsidered. Exploring New Approaches to Property in Human Tissue.* Ashgate: Farnham-Burlington, 2009, pp 13-49; Hoppe N, »A Sense of Entitlement: Individual vs. Public Interest in Human Tissue« in: Lenk C, Sándor J, Gordijn B (eds). *Biobanks and Tissue Research. The Public, the Patient and the Regulation*. Heidelberg London New York: Springer Dordrecht, 2011, pp. 53-64. Titmuss RM. *The Gift Relationship: From Human Blood to Social Policy*. London: George Allen & Unwin Ltd, 1970.

[46] Sun J, McLaughlin C, Sledge L et al, »Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired neurologic disorders«, *Transfusion,* 2010, 50:1980–7; ACOG Committee Opinion n 399, »Umbilical cord blood banking«,. *Obstet Gynecol,* 2008,111:475–7; Cord Blood Working Group, »Combined private and public banking of cord blood and other related products«, Leiden, NL: *World Marrow Donor Association*, 2012. http://www.worldmarrow.org/fileadmin/Committees/Cord_Blood_Working_Group/20120328-CBWG-PPR-Hybrid.pdf (19 March 2015).

Under the pressure of financial incentives, private UCB banks typically store the UCB regardless of its quality and do not provide quality reports on the UCB unit (including such metrics as the cell dose collected and the viability of the cells) to the client. So, there is a reasonable possibility that UCB units stored in private banks could be considered substandard and not be able to assure an adequate quality and, therefore, could be therapeutically ineffective when donors seek to use their UCB[47].

Another critical point is the collection of the sample that in private UCB collections may be performed by medical or nursing personnel with limited experience in UCB[48].

On the contrary, public UCB banking considers cord blood as a "common good" just like blood and organs and through it the access to benefits related to "life saving" availability (such as blood transfusion, cell therapy and organ transplantation) could be ensured for all individuals in need[49].

The "common good" can be defined as "the good of all and of each"[50] and in this perspective it should ensure equal treatment respecting the equal dignity of all human beings and the different needs of each person relating to their state of health or disease. Promoting the common good is promoting the good of each[51].

In light of the fact that today only a small amount of donations collected in public banks are used for transplantation, this means that in the case where an altruistic donor needs an autologous transplant, he/she may find their own cord blood unit still available[52].

As already mentioned, to 2015 more than 600.000 UCB units were banked in about 120 public banks worldwide for "public" use, but these impressive numbers are insufficient to satisfy all the medical needs for UCB, so additional efforts are required to ensure that all patients, including ethnic minorities, can promptly find a suitable donor[53].

---

47 Moises Serrano-Delgado V, Novello-Garza B, Valdez-Martinez E, »Ethical issues relating to the banking of umbilical cord blood in Mexico«, *BMC Medical Ethics,* 2009, 10:12; Sun J, Allison J, Mc Laughlin C et al. »Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired autologous disorders«, *Transfusion,* 2010,50:1980-7.

48 Butler MG, Menitove JE, »Umbilical cord blood banking: an update«, *J Assist Reprod Genet*, 2011, 28:669–76.

49 Sacchini D, Liumbruno GM, Bruno G et al, »Ethical and deontological issues in Transfusion Medicine«, *Blood Transfus,* 2013,11:14-25.

50 S. Vanni Rovighi, *Istituzioni di filosofia*, Brescia: La Scuola, 1982, p. 150.

51 Sgreccia E, *Manuale di bioetica. I. Fondamenti ed etica biomedica*, Milano: Vita e Pensiero, 2007: 227-228.

52 Fox NS, Chervenak FA, McCullough LB, »Ethical considerations in umbilical cord blood banking«, *Obstet Gynecol*, 2008, 111:178–82.

53 Gluckman E, Ruggeri A, Volt F et al, »Milestones in umbilical cord blood transplantation«, *Br J Haematol,* 2011, 154 (4):441-7; http://www.bmdw.org (19 March 2015); Rebulla P, Lecchi L. »Towards responsible cord

As highlighted by Rebulla e Lecchi[54], the first responsibility of all stakeholders (governments, clinicians, scientists, patients, and industry) should be the promotion of altruistic UCB donation and development of UCB banking models able to fully meet all patients' needs.

Regarding private banking for an autologous use, at present indications for autologous UCB transplantation are restricted to few specific diagnoses (for example childhood cancer)[55].

Eventual additional indications for autologous UCB transplantation and the promising development of new therapies in regenerative medicine, together with the data concerning the limited funding available for public UCB banks, could lead to re-assessing private UCB banking.

4. Hybrid banking: solution or compromise?

On this matter, it should be noted that recently combined (or "hybrid") public/private UCB banking is emerging in some countries and also this solution could be taken into account.

To date, two models of hybrid bank begin to appear: the "sequential" model and the "splitting" model[56].

The "sequential" model is characterized by two subsequent steps: at first the UCB unit is privately stored, HLA typed and anonymously registered in the international stem cell registry; later, only if the UCB unit is requested for the allogeneic transplantation for an unrelated, parents are asked again to release their consent. If parents decide to consent to donate their UCB unit, they would be reimbursed the costs incurred for the private banking. One of the limitations of this model is that it could frustrate the parents' desire to keep UCB for their child.

blood banking models«, *Cell Prolif,* 2011, 44 (Suppl. 1): 30–4.

54 Rebulla P, Lecchi L, »Towards responsible cord blood banking models«,*Cell Prolif*, 2011, 44 (Suppl. 1): 30–4.

55 Rosenthal J, Woolfrey AE, Pawlowska, A et al, »Hematopoietic Cell Transplantation With Autologous Cord Blood in Patients With Severe Aplastic Anemia: An Opportunity to Revisit the Controversy Regarding Cord Blood Banking for Private Use«, *Pediatr Blood Cancer,* 2011, 56: 1009–12.

56 Wagner AM, Krenger W, Suter E et al, »High acceptance rate of hybrid allogeneic-autologous umbilical cord blood banking among actual and potential Swiss donors«, *Transfusion*, 2013, 53(7):1510-9; O'Connor MA, Samuel G, Jordens CF et al, »Umbilical cord blood banking: beyond the public-private divide«, *Transfusion*, 2013, 53(7):1510-9; Manegold G, Meyer-Monard S, Tichelli A et al, »Controversies in hybrid banking: attitudes of Swiss public umbilical cord blood donors toward private and public banking«, *Arch Gynecol Obstet*, 2011, 284: 99–104; Petrini C, »Ethical issues in umbilical cord blood banking: a comparative analysis of documents from national and international institutions«, *Transfusion,* 2013, 53: 902-10; Parco S, Vascotto F, Visconti P, »Public banking of umbilical cord blood or storage in a private bank: testing social and ethical policy in northeastern Italy«, *J Blood Med,* 2013, 4:23–9.

In "splitting" model, adopted by the Virgin Health Bank[57] in the UK, 80% of the initial UCB unit is stored in the public inventory and 20% for private use. One of the limitations of this model is related to the possibility of a low cellularity following the separation of the sample into two portions that could make samples unsuitable for transplantation[58].

In a recent prospective survey, Wagner et al.[59] have investigated the acceptance of hybrid UCB banking among actual and potential UCB donors by comparing a group of parents and pregnant women (with or without children) with a group of women at reproductive ages.

One of the most interesting emerged data is that the majority (49% overall) would prefer the hybrid model if such an option was available[60].

Nevertheless, ethical issues are also present in hybrid banking: the need to ensure sample quality by adopting international quality standards; to determine the sample ownership (bank or parents?); to provide adequate and impartial information, and to obtain a true IC from parents.

Conclusion: Towards a culture of "donation"

UCB stem cells offer the possibility to treat a wide range of diseases. However, their use raises some ethical issues. Following the well-known basic ethical principles for biomedicine (i.e. beneficence/non maleficence, autonomy and justice) as methodological reference, it is possible to highlight that: 1) allogeneic UCB use, compared to the autologous UCB use, seems fulfil better the principle of beneficence/non maleficence as it provides logistical and clinical benefits and it decreases risks; 2) acquisition of IC requires an adequate counselling, particularly for what concerns autologous collection; 3) public UCB banking seems to fulfil the criteria for justice more than private banking.

Beyond these considerations, the implementation of this new therapeutic possibility for treating a wide variety of diseases needs a culture of "donation" and a "solidarity chain"[61] between donors and recipients as background. Donation is an exercise of

[57] Branson R, »World's first public-private cord blood bank launched in UK«, *BMJ*, 2007, 334(7587): 229.

[58] Guilcher GM, Fernandez CV, Joffe S, »Are hybrid umbilical cord blood banks really the best of both worlds?«, *J Med Ethics*, 2015, 41(3):272-5.

[59] Wagner AM, Krenger W, Suter E et al, »High acceptance rate of hybrid allogeneic-autologous umbilical cord blood banking among actual and potential Swiss donors«, *Transfusion*, 2013, 53(7):1510-9.

[60] Ibid, pp. 1510-9.

[61] Rebulla P, Lecchi L, »Towards responsible cord blood banking models«, *Cell Prolif*, 2011, 44 (Suppl. 1): 30–4.

freedom and of responsibility, and an investment in the other, in the world, in human possibilities.

For this reason, policies that provide opportunities for all women to donate UCB should be implemented, increasing the culture of "donation" through educational outreach: this is the main ethically feasible way to guarantee respect for each person's responsible choices in society and to effectively promote donation as a noble act of human solidarity[62].

An alternative that should be explored is "hybrid" banking, because it could combine together the respect for individual autonomy, that would respect his/her right to choose autologous UCB storage, with solidarity towards those in need that is at the base of allogeneic donation. Further reflection is needed, as this new model of banking raises further ethical issues, that are closely related to private/public UCB banking ones. Additionally, this new "combined" public-private model would increase the number of available UCB units for addressing the ever-increasing number of patients requiring UCB transplantation and could lighten the economic difficulties of many countries.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to.

ACKNOWLEDGMENTS

The authors thank Dr. Joseph Meaney for critically reviewing the first draft of the manuscript.

[62] Nanni Costa AN, Simón i Castellvì JM, Spagnolo AG, et al, »A colloquium on the congress "A gift for life. Considerations on organ donation«, *Transplantation,* 2009, Oct 15; 88(7 Suppl): S108-58.

Barbara Corsano, Dario Sacchini, Mária Šuleková,
Roberta Minacori, Pietro Refolo, Antonio G. Spagnolo

Alogeno naspram autolognog: etička pitanja pri uporabi krvi iz pupčane vrpce

SAŽETAK

Cilj: Analizirati etička pitanja vezana uz prikupljanje, skladištenje i upotrebu krvi prikupljene iz pupčane vrpce.

Materijali i metode: Etička pitanja postavljena su u odnosu na temeljna etička načela u biomedicini: dobročinstva/neškodljivosti, poštovanja autonomije i pravde. Specifična pitanja o kojima se raspravlja tiču se kliničke korisnosti autologne uporabe krvi iz pupčane vrpce u usporedbi s korištenjem alogena za transplantaciju, valjanost informiranog pristanka, posebno kod privatnog pohranjivanja krvi iz pupčane vrpce, te kontroverzno pitanje pohrane krvi iz pupčane vrpce u svrhu profita u usporedbi s neprofitnim pohranjivanjem.

Rezultati: Naša etička analiza pokazala je kako je alogena upotreba krvi iz pupčane vrpce u transplantaciji, za razliku od autologne uporabe, ispunila principe dobročinstva/neškodljivosti jer pruža logističke i kliničke prednosti te smanjuje rizik. Pri dobivanju informiranog pristanka potrebna su dodatna savjetovanja, osobito za autologne materijale. Konačno, javno skladištenje krvi iz pupčane vrpce ispunjava kriterije pravednosti više nego privatno skladištenje.

Zaključak: Trenutne i buduće terapeutske mogućnosti koje nudi krv iz pupčane vrpce u liječenju bolesti pokazatelj su veće potrebe za krvlju iz pupčane vrpce, stoga je potrebno razvijati kulturu poklanjanja i solidarnosti između darivatelja i primatelja. Unazad nekoliko godina pojavio se koristan model skladištenja krvi, tzv. „hibridno" skladištenje.

Ključne riječi: etika, alogeno, autologno