Med Law (2006) 25:553-561

Medicine and Law

Stem Cells

COLLECTION OF FETAL BLOOD FOR STEM CELL RESEARCH AND THERAPY

L. Iffy, * V. Varadi, ** N. Portuondo, * N. Ende ****

Abstract: Stem cell research has generated novel therapeutic opportunities at the expense of new ethical and legal problems. Its promoters recommended early clamping of the umbilical cord to maximize the amount of acquired fetal blood. Fear has been expressed, therefore, that the donor could be compromised by this approach. Actually, the problem is more complex than generally assumed. In certain clinical situations the neonate may benefit from or become harmed by additional blood volume. Gravity influences the direction of umbilical blood flow and, thus the consequences of early or delayed cord clamping. Therefore, vaginal birth promotes blood flow from the placenta to the fetus, whereas delivery by cesarean section usually has the opposite effect. Largely ignored in the course of the relevant debates, the above facts require consideration. The controversy may be beneficial in the long run by drawing attention to this relatively neglected aspect of perinatal medicine.

Keywords: Stem cells; umbilical circulation; cord clamping; neonatal blood volume.

* Professor of Obstetrics & Gynecology, UMDNJ – University Hospital, Newark, New Jersey, USA

** Clinical Professor, Division of Neonatology, St. Margit Hospital, Budapest, Hungary

*** Attorney at Law, Law Firm of Schwartz, Simon, Edelstein, Celso & Kessler, Florham Park, New Jersey, USA

**** Professor of Pathology, UMDNJ –University Hospital, Newark, New Jersey, USA

The discovery that stem cells, obtainable from the placenta following childbirth, can be used in clinical practice for a variety of therapeutic purposes generated great interest among scientists[1-8]. In the same process, it became clear that large scale clinical utilization of fetal cells would open attractive commercial opportunities. Both for research and therapy, the quantity of the available fetal blood became a critical issue. A leader in stem cell research, Biocyte Corporation, circulated instructions for investigators, recommending early clamping of the umbilical cord, in order to increase the amount of blood retained in the placenta and thus the quantity of stem cells available for harvesting. The patent of the company even included a stipulation that the cord should be clamped before the end of its pulsation, in order to prevent the continued flow of blood into the circulation of the neonate. Early clamping was also recommended for premature infants in the original patent.

Criticism from a variety of sources soon followed. Concern was expressed with regard to the use, whether intentional or incidental, of premature babies as blood donors, noting their decreased tolerance to hypovolemia. Neonates born in Third World countries, where maternal anemia is rampant, were considered particularly at risk, if used as stem cell donors by unduly aggressive blood collectors.

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1. Ende M & Ende N Hemopoetic transplantation by means of fetal (cord) blood. 1972 *Virginia Med Monthly* 99: 276-280.

2. Ende N Rameshwar P & Ende M Fetal cord blood potential for bone marrow transplantation. 1989 *Life Sci* 44: 1987-1990.

3. Broxmeyer HE Questions to be answered regarding umbilical cord blood hemopoetic stem and progenitor cells and their use in transplantation. 1995 *Transfusion* 35: 694-702.

4. Wagner JA Umbilical cord blood transplantation. 1995 *Transfusion* 35: 619-621.

5. Ende N Chen R & Reddi AS Transplantation of human umbilical cord cells improves glycemia and glomerular hypertrophy in type 2 mice. 2000 *B B R C* 321: 167-168.

6. Ende N Chen R & Reddi AS Effect of human umbilical cord blood cells on glycemia and insulitis in type 1 diabetic mice. 2004 *B B R C* 325: 665-669.

7. Ende N Chen R & Reddi AS Transplantation of human umbilical cord blood cells improves glomerular hypertrophy in type 2 diabetic mice. 2004 B B R C 321: 168-171.

8. Ende N & Reddi AS Administration of human umbilical cord blood to low birth weight infants may prevent the subsequent development of type 2 diabetes. *Med Hypotheses.* (In Press.)

The appropriate time for the clamping of the umbilical cord has been and remains a controversial subject. Because the placenta offers the lowest resistance in the fetal circulatory system, close to one-half of the total cardiac output flows through it[9].

The exchange of arguments in favor of and against intensive fetal blood collection induced the American Medical Association to address the controversy with guidelines, issued in 1994[10] and upgraded in 1996. This authority concluded that blood collection should be conducted within the boundaries of "normal clamping protocols" and in such a manner that it would not "endanger the infant". Wisely, the directive made no attempt to explain what protocol might endanger the newborn child, since there was little consensus in this regard in the medical literature.

Working in the absence of regulatory control, traditionally, blood banks in the United States followed the general standards created by the American Association of Blood Banks (AABB). They also applied the latter to cord blood donations, due to the absence of relevant legislation in the states other than Florida, Illinois, Maryland and Texas. Because the legislators set no specific standards and because the relevant laws of the quoted states lacked uniformity, the activities of cord blood banks drew the attention of Federal regulatory agencies as well as that of legislators. The interest of the US Government in the clinical utilization of stem cells may have been triggered by the fact that it offered a credible alternative to the use of embryonic stem cells; an approach which had generated many religious and ethical objections. As a result, at a time of this writing, there is a proposed law before the US Congress which intends to bring the use of stem cells under the authority of a National Cord Blood Stem Cell Bank. The "Cord Blood Stem Cell Act", introduced in 2005, has strong support by both parties both in the House of Representatives (H.R. 596) and in the Senate (S. 981). This proposal is also supported by the Cord Blood Study Committee of the Institution of Medicine (IUR), even if not without reservation. This institution, while in favor of "uniform standards", objected to the establishment of a single all powerful regulatory agency. Despite the controversy, a National Blood Bank has already been legislated and approved by the President. Nonetheless, since this high

9. Philippe E Pathologie Feto-Placentaire. 2nd ed. 1986 Paris, Masson, p.7.

10. American Medical Association. Code of medical ethics: Current opinions with annotations. *Fetal umbilical cord.* 2nd ed. 1994; 165, p. 30.

level dialogue has only started, there is reason to anticipate much further dispute before the formulation of a final national legislation.

Predictably, additional political controversies will emerge about the fate of the National Marrow Donor Program. In effect, this is a large computerized data base which lists thousands of potential major human histocompatibility gene complex (HLA) tissue typed donors. It seems likely that this complex system will lose its importance, once adequate fetal cord blood supply becomes available, since the latter does not need to be fully matched with the blood types of recipients.

Medical Considerations

Although the mode and time of severing the umbilical cord have age-old old religious, social and superstition driven overtones, they received relatively little attention from midwives and physicians throughout the past centuries. Based on "the more the better" principle, physicians traditionally assumed that the newborn child would benefit from receiving the maximum amount of blood from the placenta. However, investigators who addressed this subject objectively came to realize that the issue was not as simple.

A variety, clinical considerations influence the effect of early (<30 seconds) versus late (>30 seconds) clamping of the umbilical cord. Early severing permits prompt resuscitation of the neonate. Delayed disruption of the circulation, under circumstances of vaginal delivery, facilitates the infusion of blood from the placenta to the newborn child. The available data do not show a difference in terms of Apgar score or neonatal tachycardia. On the one hand, late clamping can decrease the number of infants with low iron reserve at the age of 3 months. Nonetheless, there is no clear evidence to indicate that the time of cutting the cord has significant effect upon the welfare of babies born at term gestation. On the other hand, some recent data suggest that early clamping may be detrimental for low birth weight babies[6-8].

In preterm infants, there may be advantages deriving from the infusion of additional blood volume from the placenta after delivery[11]. These include

11. Mercer JS McGrath MM Hensman A Silver H & Oh W Immediate and delayed cord clamping in infants born between 24 and 32 weeks; a pilot randomized controlled trial. 2003 *J Perinatol* 23: 466-472.

higher initial blood pressure[12] and increased hematocrit level 4 hours after birth, leading to a reduced need for red blood cell transfusion[12,13]. Increased blood volume may improve arterial-alveolar oxygen tension ratio and reduce the dependency on supplemental oxygen during the first day postpartum. However, on the other hand, it may cause polycythemia, volume overload and hyperbilirubinemia[14]. Whether it also reduces the risk of intraventricular hemorrhage remains a disputed issue[11,14,15].

There are clinical situations where reduction of the blood volume received at delivery benefits the infant[16]. A case in point is fetal sensitization against some of the maternal blood groups[11-14]. Besides, premature infants suffering from inadequate liver and/or kidney functions, as well as those born with congenital heart defect, may be harmed by an unduly large blood volume[17,18]. In general, whereas full term neonates derive no proven advantage from the infusion of extra blood volume at birth[19], preterm newborns may occasionally benefit from it either immediately or later in the neonatal period[11-14].

An important and far too often ignored confounding factor is the role of gravity. The newborn child, held under the level of the placenta, attached to the uterine

12. Hofmeyer GJ Gobetz L Bex PJ *et al.* Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. 1993 Dec 29. *Online J Curr Clin Trials*., Doc No 110.

13. Rabe H Reynolds G & Diaz-Rossello J Early versus delayed umbilical cord clamping in preterm infants. 2004 Oct 18. Cochrane Database Syst Rev.

14. Kinmond S Aitchison TC Holland BM Jones JG Turner TL & Wardrop CA Umbilical cord clamping and preterm infants: A randomized trial. 1993 *BMJ* 306: 172-175.

15. Ibrahim HM Krouskop RW Lewis DF & Dhanireddy R Placental transfusion: Umbilical cord and preterm infants. 2002 *J Perinatol* 20: 351-354.

16. Capasso L Raimondi F Capasso A Crivaro V Capasso R & Paludatto R Early cord clamping protects at risk neonates from polycythemia. 2003 *Biol Neonate* 83: 197-200.

17. Rabe H Wacker A Hulskamp G *et al.* A randomized clinical trial of delayed cord clamping in very low birth weight preterm infants. 2000 *Eur J Pediatr* 159: 775-777.

18. Kovacs L Elettani vajudas es szules. In: Papp Z (ed.) Szuleszet-Nogyogyaszat Tankonyve, Budapest, *Semmelweis Publ.* 1999, pp. 362-388.

19. Ende N Portuondo N & Iffy L The time of clamping the umbilical cord. 2006 *Magy Noorv Lap (Budapest)* 69: 5-8.

wall, receives blood through the umbilical cord after the delivery[20]. In contrast, babies held above the level of the uterus may lose as much as 50 ml of blood within a few minutes, comparable in magnitude to a sudden blood loss of 1 liter in an adult individual.

Normal vaginal delivery favors the direction of the blood flow towards the neonate. The opposite is true when the delivery is abdominal and, for some length of time, the baby is held above the mother's abdomen. It follows, therefore, that whereas delayed cord clamping may increase the amount of obtainable blood in most cases of vaginal birth, delivery by cesarean section invites the opposite result.

Interestingly, the effect of gravity upon early or late cord clamping received little, if any, attention while a heated controversy surrounded the subject. Meanwhile, the escalating rates of abdominal deliveries the world over have fast increased, year after year, the number of newborns for whom early interruption of the umbilical circulation was conducive to an increase, rather than reduction, of their blood volume. Since the rate of cesarean deliveries reached 27% in the United States recently, about one out of four neonates became ideal blood donors in the absence of early cord clamping.

The collection of cord blood should be performed before the delivery of the placenta, using a closed system and procedures that minimize contamination by microorganisms and maternal body fluids[21]. Naturally, in the case of premature infants, the amount of blood obtained must be minimized.

In the light of the currently available data, it appears likely that the risks and benefits of early or late clamping of the cord only rarely become clinically obvious. Thus, the controversy that has surrounded this issue may have been exaggerated. On the other hand, it may prove beneficial in the long run by spreading light on a subject which received little attention in the past.

It seems that the time and mode of cord clamping have been governed more by habits and traditions than by scientific facts. This trend is well illustrated by

20. Duckman S Merk R Lehman WX *et al.* The importance of gravity in delayed ligation of the umbilical cord. 1953 *Am J Obstet Gynecol* 66: 1214-1223.

21. Armson BA Umbilical cord blood banking: Implications for perinatal care providers. 2005 *J Obstet Gynecol Can* 27: 263-290.

the misconception, quoted even in some contemporary textbooks[22], namely that the umbilical cord, wrapped around the neck or the body of the half born fetus, should be clamped and cut before the delivery of the body. Some of the authors have reported several cases where this ill conceived practice had resulted in neonatal death or permanent hypoxic brain damage, after shoulder dystocia had prevented timely extraction of the fetal body[23,24]. Fortunately, early or late clamping of the cord of an already born child is unlikely to entail comparable disasters. Nonetheless, clear understanding of the effects of severing the cord in relation to the method and circumstances of the delivery probably could still provide benefits in terms of reduced neonatal morbidity.

Legal issues

Several legal confrontations developed in the intellectual property field among the various industrial companies involved in cord blood banking. PharmaStem Therapeutics, Inc. (previously known as Biocyte Corp.) was successful in obtaining two American patents (US patents No. 5004681 and 519253) in the early 1990's. The company was not equally successful in Europe. Their originally acquired patent concerning the cryopreservation of stem cells (EPO343217) was revoked in 2003 after legal confrontation with competitors. Following years of litigations, involving reversal of a jury decision by a lower court, a higher court confirmed the US patents of the company. (*PharmaStem Therapeutic, Inc. v. ViaCell, Inc.* 2004 WL 2898061.) However, some other court actions are still in progress and may continue for some length of time. Meanwhile, American Cord Banks and hospitals utilize PharmaStem technology on the basis of a mutually acceptable licensing agreement.

The emergence of new legal controversies about the acquisition and use of fetal stem cells is highly likely. There is little doubt that in the United States as well as elsewhere the courts will have to formulate answers to a variety of vexing questions:

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22. Cunningham FG Gant FN Leveno KJ Gilstrap LC III Hauth GC & Wenstrom KD. *Williams Obstetrics*, 21st ed. New York, McGraw-Hill, 2001, pp. 319-320.

23. Iffy L & Varadi V Cerebral palsy following cutting of the nuchal cord before delivery. 1994 *Med Law* 13: 323-330.

24. Iffy L Varadi V & Papp E Untoward neonatal sequelae deriving from cutting the umbilical cord before delivery. 2001 *Med Law* 20: 627-634.

A. Who is the owner of the preserved cord blood and the stem cells contained in it: the blood bank, the parents or the child?

B. Who has legitimate access to the laboratory results when the cord blood to be used for stem cell donation is tested?

C. Who will be legally responsible if a disease is inadvertently transmitted from the blood donor to a recipient?

D. Whether and how the privacy of the cord blood donor and his/her family should be protected?

E. Could low birth weight infants be injured if used as blood donors?

F. How to ensure equal access to stem cells, free of ethnic, social, economic, religious or other discrimination?

The legal system often struggles to balance the issue of equal access to discoveries and new technologies against the protection of intellectual property rights. It appears that under the current legal framework, U.S. courts will tend to be flexible in applying standards to protect a patented procedure, as long as regulatory means exist to facilitate the use of the technology and, at the same time, protect the financial investment that promotes scientific research. As an example, in a dispute over the use of a system for the identification and isolation of stem cells in blood samples, one federal court deferred to the FDA's expertise in deciding whether certain activities should be exempted from patent protection[25]. It appears likely that future disputes in the area of cord blood patent infringement will be similarly referred to the regulatory agency.

With regard to proprietary rights, there are two competing and sometimes conflicting lines of precedents that make it difficult to predict how this issue will evolve in the courts. The first line of cases involves decisions over the property rights to cryopreserved human embryos. These cases are often presented in terms of the material being considered "property", such that it belongs to one parent or the other[26,27] or to one party or another[28]. The second

25. *Nexell Therapeutics, Inc. v. Amcell Corporation,* 142F. Supp. 2d 407 (D. Delaware 2001).

26. *Davis v. Davis*, 842 S.W. 2d 588 (Tenn. 1992).

27. *Hecht v. Superior Court,* 16 Cal. App. 4th 836, 20 Cal. Rptr. 2d 275 (Cal. App. 2 Dist. 1993).

28. *York v. Jones*, 717 F. Supp. 421 (E.D. Virginia 1989).

line of cases involves decisions over medical consent which, by implication, underscores the rights, if any, of the newborn. For example, in the seminal case involving a patient's right to cellular material, later used for medical research, the Supreme Court of California refused to apply the "property" rights theory[29]. Instead, the Court decided the issue in terms of medical consent. By restricting this debate to "consent" rather than "property" rights, the Court limited liability for third parties that became involved in the research at a later stage. In addition, the Court put the inquiry squarely in the hands of the parties that participated in the exchange of the cellular material. On the other hand, in the context of cord blood, the inquiry cannot focus only on consent, because the material, arguably, belongs to the newborn who cannot give one. Hopefully, when this issue becomes the subject of legal battle, the courts will recognize certain property interests concerning the newborn's cord blood, while restricting the liability inquiry to issues of "consent".

With regard to the issue of confidentiality and equal access, the implementation of research protocols that incorporate confidentiality agreements and protection against discrimination can be predicted. Very likely these will ensure that the information collected remains available for future use, while protecting privacy and other constitutional rights. Nonetheless, these protocols are likely to be challenged in court if their enforcement is seen as piecemeal. It is likely that some federal regulation will eventually be required to guarantee uniformity in the application of these protocols.

Inevitably, as the cord blood industry develops and expands, and in the same process novel technical approaches are discovered, further legal problems will also emerge concomitantly. Some of these have already materialized, such as the already mentioned intellectual property rights and the increasing need for government regulations. Beyond doubt, others will evolve as time goes by. It appears probable that the timing of intrapartum cord clamping will be one of the relevant controversies to be resolved[30].

29. *Moore v. Regents of the University of California,* 51 Cal. 3d 120 (Cal. Sup. Ct. 1990).

30. Ende N Questions to be answered about the umbilical cord. 1996 36: 288-289.