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The time of clamping the umbilical cord. (A Controversial Aspect of Stem Cell Research)*

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Summary: Progress in the field of stem cell research has generated a variety of new ethical and legal problems in the United States. Some hotly debated issues relate to the opportunity of harvesting stem cells from the placental blood immediately after delivery. The optimum time for cutting the umbilical cord is widely assumed to be different from the point of view of the child and from that of the cord bank seeking the maximum obtainable blood volume. The article draws attention to the fact that relatively little is known about the circumstances where the neonate benefits from increased or reduced blood volume. Besides, the direction of the feto-placental blood transfer is subject to the forces of gravity. The effect of the latter is generally different in vaginal and abdominal deliveries. Consequently, the often emotionally charged dispute with regard to the optimum time of cord clamping for the purpose of fetal blood banking rests upon relatively limited scientific basis. The appropriate timing of omphalotomy requires, therefore, further investigation.

Keywords: Stem cells, umbilical cord blood, cord clamping, blood banks.

The subject of cord clamping raised medical, ethical and legal concerns when stem cell research revealed the usefulness of placental blood for various therapeutic purposes [1–10]. Interest in potential commercialization of stem cells has fueled the development of an industry for the collection of umbilical cord blood. Erroneously assuming that it provides an increased amount of blood invariably, early cord clamping was recommended by the manufacturers. This policy was promoted emphatically by Biocyte Corporation during the initial phases of the relevant research. The company's patent even incorporated instruction to blood collectors with regard to the desirability of cutting the umbilical cord before the cessation of its pulsation. Among the critics of this policy, there was particular concern about babies born in Third World countries, where severe maternal anaemia is common. Similar reservations were expressed about premature neonates, because of their vulnerability both to hypovolemia and hypervolemia. The above quoted policy generated, the-

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refore, opposition on ethical grounds by those who felt, probably correctly, that its implementation could be detrimental for some newborns. The American Medical Association, in a directive issued in 1994 and updated in 1996, addressed the controversy in a Solomonic manner, stating the "normal clamping protocols should be followed and not altered in such a was that might endanger the infant". This advice bypassed, however, the fact that there was little consensus about the circumstances where early or late clamping of the cord influenced the neonatal outcome.

Historically, cord blood banks have followed the general practice standards developed by the American Association of Blood Banks (AABB). However, they operated in the United States free of regulatory control. Only a few states have laws pertaining to to cord blood donations. These include Florida, Illinois, Texas and Maryland. Regretfully, these regulations lack unformity and specific standards. Cord blood banks have attracted the attention of regulatory agencies, perhaps because the use of umbilical stem cells emerged as an alternative to the ethically compromised embryonic stem cell research. The U.S. Congress is considering a legislation currently which, if approved, will create a National Cord Blood Stem Cell Bank. The so called Cord Blood Stem Cell Act of 2005 has now been introduced with strong bipartisan support both in the House of Representatives (H.R. 596) and in the Senate (S. 981). In support of the proposed legislation, the Institute of Medicine (IUM) Cord Blood Study Committee issued a statement supporting a "uniform standard of care for all patients requiring cord blood transplantation" but objecting against the establishment of a single cord blood accrediting agency. It appears likely that a long dialogue among the interested parties will precede the passage of these bills.

A predictable subject of future political controversy is the National Marrow Donor Program. This is an extensive computer data base where thousands of tissue typed (major human histocompatibility gene complex – HLA) donors are listed. The authors consider this system obsolete since cord blood does not require to be fully matched. The only real obstacle to its more extensive use is its inadequate available volumen.

The cord blood bank industry has been active in courts fighting legal battles in the intellectual property field. Biocyte Corporation (now known as PharmaStem Therapeutics, Inc.) obtained two separate patents in the United States (U.S. Patent No 5004681 and US Patent No 519253 issued in 1991 and 1993 respectively). This firm also acquired a patent in Europe (EPO 343217) with regard to the cryopreservation of stem cells obtained from umbilical and placental blood. The European patent was revoked in 2003, following successful legal confrontations were equally intensive. The argument against Biocytes's patent included their failure of giving credit to the first published data [1], an omission which the firm corrected subsequently. Eventually, after protracted court actions, involving claims of patent infringement against various cord blood banks, the courts reversed the findings of a jury and ruled, as a matter of law, that there was no infringement of the U.S. patents. (PharmaStem Therapeutics, Inc. v. ViaCell, Inc. 2004 WL 2898061). PharmaStem has obtained additional related patents (US Patents No. 6462645 and 6605275, issued in the years of 2002 and 2003 respectively) and continues to fight other cord blood banks in court. However, most active cord banks in America, as well as certain hospitals and research institutions, new utilize the PharmaStem technology under appropriate licensing agreements.

New legal issues are likely to arise in the future in the context of umbilical blood collection, preservation and use. For example, future court cases may decide who among the parents and child owns the preserved cord blood or the cells derived therefrom; if and when the cord blood is tested, who should have access to the medical information deriving from such tests, who will be liable for diseases transmitted through cord blood donation; how to protect confidentiality of donors and users; and how to ensure equal access to cord blood by avoiding ethnic, social, economic and other forms of discrimination. As the cord blood industry develops and novel technologies emerge, there will be relevant legal implications. Some of these have already materialized, such as intellectual property challanges and increased government regulation, others are bound to evolve

with the passage of time. There is little doubt that issues relating to the time of cord clamping will be among them.

Relevance to Obstetric Practice

The appropriate time for clamping the umbilical cord has been and remains a controversial subject. Traditionally, physicians have instinctively felt that the infusion of a maximum amount of blood into the circulation of the newborn child is beneficial. However, objective analysis of the subject does not support this assumption. An anaemic neonate is bound to benefit from additional blood. In contrast, others, including those with blood group sensitization, premature babies with inadequate liver function and those suffering from congenital heart defect may be harmed by a large blood volume [12–15]. One confounding factor is that only neonates held under the level of the uterus receive blood from the placenta after delivery [16]. Those held above the level of the uterus may lose 50 ml or more blood in a few minutes. Generally, the latter situation prevails when delivery is effected by cesarean section. Thus, early versus delayed cord clamping is likely to have oppostie effects in cases of abdominal versus vaginal deliveries respectively.

Throught the years of stem cell research, little, if any, attention was paid to the question of how the ever increasing rate of cesarean births [17] may affect the consequences of early and delayed cord clampings. Actually, since early clamping is often inevitable following abdominal delivery neonates born by cesarean section; 27 percent of all newborns in the United States currently, are ideal blood donors.

Because the risk and benefits of early versus delayed cord clmping are only obvious in a minority of clinical situations, it appears that the controversy that surrounds this subjects is eaggerated. Nonetheless, the growth of an industry, the existence of which hinges upon the collection of a sufficient amount of placental blood, is bound to arise ethical and legal concerns. Undoubtedly, the circumstances and time of cord clamping will generate further discussions and disputes. The ensuing dialogue may have a beneficial side effect, however, by drawing attention to a long ignored aspect of perinatology, namely the significance of the time of cord clamping in various clinical situations.

An extreme example of the misconceptions about the optimum time for cord clamping is the traditional recommendation, repeated even in contemporary obstetric textbooks, that the cord wrapped around the neck or body of the fetus should be clamped and cut before the delivery of the body [12]. Our group has reported several cases of neonatal death and catastrophic neurological damage deriving from this ill-advised policy, when arrest of the shoulders at birth prevented immediate extraction of the body after the severance of the halfborn baby's lifeline [18, 19]. Although the adverse sequelae of capricious cord clamping are less dramatic, it appears likely that practitioner engaged in obstetrics could benefit from better understanding of those circumstances that "might endanger the infant". It is fair to conclude that our current knowledge in this area is woefully limited.

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A foetus véréből származó úgynevezett őssejtekkel foglalkozó kutatás számos etikai és jogi problémát vetett fel az Egyesült Államokban. Heves vitákhoz vezetett az a körülmény, hogy az őssejtek terápiás célokra való optimális felhasználása érdekében a köldökzsinór korai elvágására buzdították a szülészeket a tárgykörrel foglalkozó kutatók és a klinikai felhasználásban financiálisan érdekelt vérellátó intézmények. Ez a széles körben vitatott javaslat azon a meggondoláson alapult, hogy a köldökzsinór korai elzárása megakadályozza a véráramlást az újszülött felé, és így maximális mennyiségű magzati vért hagy hátra a placentában az őssejtgyűjtés céljára. A szerzők felhívják a figyelmet arra, hogy valójában kevés megbízható adat van az irodalomban arról, hogy mikor és milyen körülmények között optimális a nagyobb mennyiségű vérátjutás az újszülött számára. A tárgykör etikai és jogi vonatkozásaival foglalkozó szakértők ugyancsak figyelmen kívül hagyták azt a körülményt, hogy a vér áramlási irányát a köldökzsinórban a gravitáció törvényei szabályozzák. A természetes szülés körülményei a vérnek a placentából a foetusba való infusiójának kedveznek. Ezzel szemben császármetszés esetén az áramlás általában ellenkező irányú. Mindebből az következik, hogy az őssejtek felhasználásával foglalkozó jogi, etikai és orvosszakértők valójában tudományos alapokon álló információk nélkül vitatkoznak a köldökzsinór elvágásának optimális idejéről a rendkívüli terápiás fontosságú őssejtek gyűjtésének a hátterében. Lehet, hogy ez a meddő vita fel fogja hívni a figyelmet arra, hogy a köldökzsinór elvágásának optimális ideje a szülészet viszonylag elhanyagolt területe, amely az eddiginél több figyelmet érdemel.

Kulcsszavak: őssejtek, köldökzsinórvér, omphalotomia, vérellátó szolgálat

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