Saving umbilical blood from newborn infants: the clinical potential, economics and ethics
Abstract:

Umbilical cord blood is the blood remaining in the placenta and umbilical cord after childbirth. It had previously been considered a waste by-product from the birth process. However, since the first umbilical cord blood transplant in the 1970s, research to understand and discover the full potentials of umbilical cord blood for clinical use has changed this view. This research suggests that umbilical cord blood is a source of a range of different stem cells from hematopoietic stem cells used to treat blood disorders to mesenchymal stem cells and unrestricted somatic stem cells which have a wider differentiation potential but their existence is controversial. The discovery of these cells offer a valuable and ethically acceptable alternative to embryonic stem cells, but more research is needed to determine the full extent and volume to which these cells can be found in umbilical cord blood. As the use of umbilical cord blood has become more popular in recent years, public and private cord blood storage banks have emerged. Debate still rages about the relative merits of public versus private banks in terms of personal and national economic costs as well as accessibility and legal issues. The future is likely to see a greater investment in public banks due to the wider economical and long-term health benefits. There are now no major objections to the use of umbilical cord blood for clinical applications and with continued research it is likely to prove to be a valuable source of stem cells.

Introduction:

Umbilical cord blood (UCB) is the blood that remains in the placenta and attached umbilical cord after childbirth. Historically it has been considered as a waste by-product from the birth process and was routinely discarded. However, this blood is now known to contain various types of stem cells, leading to a substantial increase in the clinical use and research investigation of UCB in hematopoietic transplantation and regenerative medicine (Moise Jr, 2005). This has led to the UCB of many newborn infants being collected and saved after birth rather than discarded.

Stem cells are undifferentiated cells that can renew themselves and differentiate into a range of specialised cell types (Zhong et al., 2010). The main sources of stem cells are embryonic stem cells and adult stem cells. Embryonic stem cells are found in the early stages of the developing embryo. They are pluripotent which means they have the ability to form cells of
all tissues of the adult organism (de Wert and Mummery, 2003). This makes them a potential source of cells for regenerative therapies but there are many ethical, political and clinical objections to their use. Adult stem cells can be isolated from a variety of adult tissues making their use more widely acceptable. They are multipotent, meaning they can differentiate into a smaller range of cells than embryonic stem cells, making them more specialized and giving them an important function in tissue replacement and repair (de Wert and Mummery, 2003). UCB may be seen as a form of adult stem cell, since the blood is taken after the birth of a child. However, unique characteristics of UCB may lead to its recognition as an alternative source of stem cells. Recent studies suggest UCB is a source of a range of different stem cell types (Harris and Rogers 2007), bringing it closer to the clinical potentials of embryonic stem cells than typical adult stem cells.

The concept of using UCB in medicine was introduced in the 1970s by Ende and Ende who used a series of fresh UCB units to treat a patient with leukaemia after conventional chemotherapy (Ende and Ende, 1972). However, it was the work of Broxmeyer and Boyse in 1982 that developed the concept and moved it to serious clinical trials; they evaluated the hematopoietic potential of UCB in vitro and developed efficient methods of collecting and storing large volumes of the blood (Gluckman, 2011). In 1988 the first UCB transplant was enabled by collaborative research from three groups. Auerbach et al. (1990) described a method for prenatal diagnosis of foetuses at risk for Fanconi anaemia, to identify those that were unaffected with the syndrome and were human leukocyte antigen (HLA)-identical to affected siblings. Human leukocyte antigens play a major role in the immune recognition of foreign proteins (Moise Jr, 2005), and being HLA-matched means that the donor and recipient’s tissues are immunocompatible. Research done by Broxmeyer et al. (1989) suggested that umbilical cord blood from a single newborn could serve as a source of autologous (patient’s own stem cells) or major histocompatibility complex-matched allogeneic (stem cells from a donor) transplantable hematopoietic repopulating cells. Informed by these studies, Gluckman and her team pioneered a UCB transplant from an unaffected sibling to promote hematopoietic reconstitution in a patient with Fanconi anaemia (Gluckman et al., 1989).

This transplant by Gluckman et al. (1989) was an allogeneic transplant from a related donor: a sibling. The first UCB transplant from an unrelated donor was performed by Kurtzberg et al. in 1996. They demonstrated that partially mismatched UCB from unrelated donors can
provide an alternative source of stem cells for hematopoietic reconstitution (Kurtzberg et al., 1996). Shortly after this, the first successful unrelated UCB transplant in an adult was carried out (Laporte et al., 1996). Before this, all successful patients had been children due to relatively low numbers of hematopoietic precursor cells in units of cord blood; but this study indicated that transplantation of UCB stem cells is feasible in adults.

In recent years, collection of cord blood after the birth of a child has become a common practice in many hospitals. This blood is then donated to a public UCB bank or can be stored privately in commercial blood banks. Recent estimates suggest that, globally, about 400,000 cord blood units are stored for public use and 900,000 units for private use (Ballen, 2010). There have been more than 20,000 UCB transplants reported around the world, mostly to treat patients with haematological and immunological conditions needing to restore haematopoiesis or their immune systems (Forraz and McGuckin, 2011), with the majority of these transplants being from unrelated donors. In this review, the clinical potentials of saving UCB from a newborn infant will be presented, as well as associated economic and ethical concerns.

Clinical Potentials:

Since the first UCB transplant in 1988, research effort has increased to investigate the full potentials of UCB for clinical use and to discover different types of stem cells it may contain. UCB has many advantages due to the immaturity of cells from newborn individuals (Gluckman and Rocha, 2009). It is easy and safe to obtain without harm to mother or child. UCB is primarily composed of monocytes and lymphocytes which are types of white blood cells. The lymphocyte population of UCB is immunologically immature. Willert et al. (2008) state that it is these immunologically immature characteristics, as well as anti-inflammatory properties of UCB, that are responsible for low frequency and reduced severity of graft-versus-host disease (GVHD) in allogeneic transplants, while Rocha et al. (2000) claim the immunological properties of T-cells in the blood reduce their capacity to induce GVHD in the first place. GVHD is a common and potentially fatal immune reaction between donor blood immune cells and the recipient’s body (Smith and Thomson, 2000). The largest stem cell population in UCB is hematopoietic stem cells. In addition, recent studies have reported that
UCB may also contain mesenchymal and embryonic-like stem cells which have a wider potential to differentiate into other cell types.

Hematopoietic stem cells (HSCs) can give rise to all cell types of blood, but their multipotent plasticity limits them to producing blood cells only. They are a type of adult stem cell as they are found in tissues after birth and large volumes are found in the placenta and umbilical cord. They migrate to the bone marrow within hours after delivery, where they provide a life-long supply of stem cells and all blood-forming elements (Rogers and Casper, 2004). It is known that a small number of HSCs can expand to generate a very large number of daughter HSCs. This knowledge is used in transplantations when a small number of HSCs can reconstitute the entire hematopoietic system of patients with some malignant and non-malignant diseases. Previously, bone marrow and adult peripheral blood were thought to be the only sources of HSCs for transplantation but the work of Broxmeyer et al. in 1989 showed that HSCs also exist in human UCB. Since this finding, UCB has been considered as an alternative source of HSCs for allogeneic stem cell transplantation (Zhong et al., 2010). UCB has a higher concentration of HSCs, having more HSCs per volume than peripheral blood or bone marrow (Rogers and Casper, 2004) but the small volume of blood collected had limited cord blood HSC transplantations to paediatric patients or small adults in the past. However, recent research has developed ways of expanding the cells ex vivo for use in adult transplantations. In addition, research by Barker et al. (2005) suggests that transplantation of more than one cord blood unit may compensate for the low cell count that limits transplantations in adults. They successfully transplanted two partially HLA-matched cord blood units in adults, which demonstrated the feasibility and safety of double-unit UCB transplantations. This result enables HSC transplantation for many patients previously denied access to this treatment due to the low cell dose in a single unit.

HSC transplantations from UCB are becoming increasingly common. In the USA (Hollands and McCauley, 2009) and in Japan (Gluckman, 2011) approximately 50% of all HSC transplants now use UCB. HSC transplantation is used as the treatment of choice in selected high-risk or recurrent hematologic malignancies and non-malignancies, marrow failure syndromes, severe congenital immunodeficiency states, and selected metabolic disorders (Cairo and Wagner, 1997). Diseases such as Fanconi anaemia, Hunter syndrome, Thalassemia and several forms of leukaemia and lymphomas have all been successfully treated using UCB. The main restriction of using cord blood transplants as a source of HSCs has been
delayed hematopoietic reconstruction or failed engraftment due to low cell dose (Zhong et al., 2010) but a low risk of GVHD and ability to use partial HLA-mismatched units without harm to the recipient make cord blood an attractive source of HSCs.

Although the presence of HSCs is well known, there is controversy as to whether UCB also contains mesenchymal stem cells (MSCs). MSCs are stem cells with a wider potential to differentiate than HSCs. They are rare, multipotent stem cells that can differentiate into a range of cells of different lineages such as bone, cartilage and fat. It is thought that differentiation abilities of MSCs decrease with age. Cells in UCB are considered “young” and therefore may be an excellent source of MSCs. This topic is still under debate with some research confirming the presence of MSCs in UCB while others report the absence of such stem cells. Erices et al. (2000) used preterm cord blood in their study and found that UCB cells, when set in culture, gave rise to cells which exhibited a mesenchymal-like phenotype. They suggested the presence of MSCs in UCB is justified because it can be hypothesised that both HSCs and MSCs travel from the liver via cord blood to the bone marrow. However, Mareschi et al. (2001) reported the absence of MSCs in full-term umbilical blood. Wexler et al. (2003) came to similar conclusions to those of Mareschi et al.. They suggested that since Erices et al. used preterm blood, presence of MSCs might be due to gestational age; however later findings of Lee et al. and Bieback et al., who both used full-term blood, disagree with this hypothesis. Lee et al. (2004) reported it was possible to obtain MSCs from UCB with the potential to differentiate into multiple lineages of mesodermal and non-mesodermal origin. Bieback et al. (2004) concluded that MSC-like cells could be isolated from full-term cord blood with high efficiency. MSCs are an attractive stem cell source for regeneration of damaged tissues in clinical applications because they are characterized as undifferentiated cells, able to self-renew with a high proliferative capacity, and possess a mesodermal differentiation potential (Kern et al., 2006). Consequently, further investigation is needed to clearly determine the presence or absence of MSCs in UCB. Different culture conditions need to be assessed and samples from both preterm and full-term UCB need to be investigated.

A form of stem cell has been discovered in UCB to have pluripotent properties. Having a pluripotent plasticity means the cells can differentiate into cell types of all three germ layers, giving them an even wider potential than MSCs. Kögler et al. (2004) described a rare population of unrestricted somatic stem cells (USSCs) capable of differentiating into bone, cartilage, hematopoietic cells, neural, liver, and heart tissue in vivo. More recently, Harris and
Rogers (2007) discovered UCB pluripotency, and identified primitive, plastic stem cells in cord blood. They reported that UCB contained multiple populations of pluripotent stem cells, capable of giving rise to hematopoietic, epithelial, endothelial and neural tissues both in vitro and in vivo. Their pluripotency and ability to be expanded may lead to these USSCs and pluripotent stem cells serving as a valuable alternative to the controversial embryonic stem cells and becoming a universal stem cell source for development of tissue repair and regenerative therapies.

Recently, yet another new form of stem cell has been discovered in UCB. McGuckin and Forraz (2008) report the first reproducible production of stem cell populations with an embryonic stem cell phenotype from UCB. They named these cells cord blood-derived embryonic-like stem cells (CBEs) and have developed them for tissue engineering and transplantation. They suggest UCB may host rare multipotent and extremely primitive stem cells that, up to birth, had been involved in embryonic development and which may remain in UCB in small frequencies. These unique CBEs offer another ethically acceptable alternative to the use of embryonic stem cells with strong potential for clinical application in tissue bio-engineering in the future (McGuckin and Forraz, 2008).

As well as its potential use in regenerative therapies, UCB has been investigated for use in gene therapy. Genetic manipulation of human cells has been of great biomedical interest because of its potential relevance in treatment of specific disorders through gene therapy such as thalassemia, sickle cell anaemia, Gaucher’s disease and several other metabolic/storage diseases. It has been documented that UCB cells are more adequate for genetic manipulation than bone marrow, thus making them attractive for gene therapy (Mayani and Lansdorp, 1998). UCB is an attractive candidate as a vector for gene transfer due to its attainability, proliferation rate, and engraftment potential. Fasouliotis and Schenker (2000) suggest autologous cord blood HSCs could be used to correct genetic deficiencies at birth after successful gene transduction and autologous UCB transplantation. The idea is that if early-stage stem cells in UCB can take up modified genes, they are likely to live longer than peripheral blood cells and give rise to a large progeny of genetically modified daughter cells. Gene therapy using autologous stem cells has the added benefit of no immunological complications (Willert et al., 2008). UCB in gene therapy offers significant clinical potential which is the subject of much on-going research.
Economic Implications:

Saving UCB in blood banks, particularly private banks, is a practice that has expanded rapidly in recent years. Private companies offer parents the opportunity to store UCB for future use by their child or other family members (Hollands and McCauley, 2009). However this offer does not come cheap. Initial collection of cord blood costs approximately $1,500 in the USA, with storage fees per year of approximately $100 (Smith and Thomson, 2000; Willert et al., 2008). If the UCB unit should later be needed, processing and shipment fees are billed to the health care insurance provider (Moise Jr, 2005). These costs may be considered a fair price if the blood is needed by the donor or their family but if it is never required, storage fees for the lifetime of the donor can mount up significantly. Private banking is a successful business, with one UK company reporting an income of around £2.6 million in just two years of operation, from storing approximately 2000 samples (Brown and Kraft, 2006).

On the other hand, public banks store UCB that is donated by the public for use by anyone who may need it. Donation to public cord blood banks is free for the donor’s family. But there is still a cost for the bank: approximately $1000 per unit stored for initial processing of the blood, as well as additional costs of running the bank. Public banks are allowed to recover some costs by charging fees (e.g. in the USA of $15,000 to $35,000 per unit) to the patient’s insurance provider for units used in transplants (Moise Jr, 2005). Patients undergoing a UCB transplant may not be required to pay a fee if the cord blood unit is acquired from a federally funded UCB bank or is transplanted through clinical trials (Smith and Thomson, 2000). Cord blood bank networks such as Netcord based in Europe, and the National Marrow Donor Program in the USA collaborate and work together to provide the most appropriate and high quality cord blood unit for a specific patient inside or outside of their home base (Gluckman, 2011). Establishment of these networks provide fair access to all members of society to a suitable cord blood unit, should they need it.

Arguably, greater Government investment in public cord blood banks would yield significant social and economic benefits in the long run. On the economic front, costs of caring and maintaining patients using traditional or non-UCB methods would be significantly reduced, especially for former chronic conditions; with a consequent lessening of the strain on government funding of health budgets. From a social perspective, the potential value of enabling patients regain a quality of health which enables them participate earlier and more fully in social and economic activity is self-evident.
Ethics:

Fortunately, saving and using UCB has none of the major ethical and moral issues that surround embryonic stem cells. Nonetheless, several controversial issues remain unresolved which serve to impede greater public acceptance. These range from issues concerning consent and privacy in the banking process to social inequality and commercialisation.

One of the main issues with UCB collection is whom consent should come from and the timing it is obtained. If UCB is obtained while the placenta is still in the uterus, consent from the mother is sufficient as it is an extension of her body, if the blood is obtained after removal of the placenta the father’s wishes should also be considered (Petrini and Farisco, 2011). The expectant mother should be given accurate and timely information about saving/donating UCB and its potential uses. Consent from the mother is seen by some as a “surrogate” form of consent since the biological owner of UCB is the child not the mother (Petrini and Farisco, 2011). Many view UCB as a waste product from the birth process. In this case consent would not be required since the blood would have been discarded anyway but is instead being stored in a public bank. This could lead to medical problems since the medical history of the donor or its family would not be known.

An important ethical concern occurs when a baby is specifically conceived to serve as a donor for a sibling/relative with a disease. A mother may conceive through in vitro fertilisation and only the embryo that tests negative for the disease and is an adequate HLA match to the patient is implanted. The issue raised is whether the child was used as a commodity, i.e. an item specifically produced to satisfy a need/want, (Fadel, 2009) and whether it is appropriate to selectively conceive a baby to be a donor. A parent’s decision to use stored UCB for treatment of anyone other than the baby raises questions of conflict of interest (Fasouliotis and Schenker, 2000). Technically the blood belongs to the newborn and parents have limited rights to control their child’s cord blood (Smith and Thomson, 2000). A further issue raised is whether the child has any property rights on the blood when they become of legal age. If the blood is being stored publically, the child would have the right to remove it from the bank as they did not give consent personally.

Linkage of the UCB unit to the identity of the donor is another topical issue. Blood banks require personal and family medical history from the mother which is kept with stored blood.
This insures unsafe units can be identified after collection and not used for transplantation should a donor develop a disease that was not identified at birth (Fadel, 2009). However this poses a risk to the donor’s privacy about their state of health. A positive outcome of this invasion of privacy is that UCB banks routinely test blood for a variety of diseases potentially leading to earlier notification of the donor and intervention.

Private versus public harvesting and storage of UCB can give rise to social inequality. Private banking, with its commercial focus, can be quite expensive and consequently can lead to discrimination or exclusion on financial grounds. Public banks provide a better and fairer service, giving all members of society access to the resource regardless of social status. Public banks focus on collecting UCB of rare immunological types, particularly ethnic minorities, for whom it is often difficult to find a donor (Brown and Kraft, 2006). Access should not be determined by demographic or economic features such as ethnicity, gender, or wealth (Giacomini et al., 2007). Greater investment in public blood banks would ensure adequate racial and ethnic diversity resulting in equality of access across all demographic groups to this valuable resource.

On the commercial front, advertising claims made by private blood banks have given rise to considerable controversy. Private banks have been known to advertise UCB as being capable of both real and imaginary or unproven clinical uses, with some claims in relation to the latter being equivalent to false advertising. Some cord blood banks suggest stem cells like HSCs can only be collected at birth, and seek to persuade parents that collecting and storing these cells may save their child’s life in the future (Brown and Kraft, 2006). However, most HSC transplants are allogeneic because if the patient’s own blood was used it could introduce diseased cells that were removed by treatment back into the body. Private banks also promote allogeneic use of UCB as a form of insurance for the whole family. Some claim a probability of 1 in 400 of using UCB, for allogeneic or autologous use, within the first 20 years of storage, while more conservative estimates put the figure closer to 1 in 20,000 (Brown and Kraft, 2006). Much work still needs to be done to ensure that the public are better educated about true potential of UCB and protected by regulation from misleading advertising.

The issues surrounding harvesting UCB and its use are primarily of a legal and social nature, and are therefore more amenable to being resolved and managed by regulatory intervention.
Rapid progress in regulation is likely to remain the main obstacle to greater public acceptance of the value of UCB as an alternative source of stem cells.

Conclusions:

It is clear that saving UCB has great clinical potentials, especially in the area of hematopoietic transplantations where successful transplants have been carried out for over 20 years. UCB is becoming an alternative source of HSCs for transplants to bone marrow due to lower risk of GVHD and ability to use partially HLA-mismatched donors which increases the patient’s chance of finding a donor. Other advantages of saving UCB include ease of collection without harm to the donor with a lower chance of contamination, ease of transport and availability on demand for patients. Advantages of UCB outweigh the few disadvantages such as low number of cells in each unit and the fact that it is unknown how long units can be stored for. UCB cells thawed after 15 years have been found to be viable, but there is not sufficient data after this time (Ballen, 2010). It is also unknown exactly how many stem cells, and of what type, are in a typical unit of UCB or exactly how many units are needed to successfully treat patients, particularly adults. However as previously outlined, methods such as expanding cells or using double-unit transplants are being investigated to counteract these difficulties.

While advantages and potentials of UCB are attractive, on-going research needs to be continued to discover its full potential. These studies are moving the application of UCB stem cells from strictly hematopoietic treatments to regenerative medicine and gene therapy. The identity of other types of stem cells hold promise for regenerative medicine applications to treat damaged and diseased cells and tissues outside of hematopoietic lineage including cardiovascular, endocrine, neurological and orthopaedic disorders, many of which currently have no effective medical treatments (Willert et al., 2008). The real test of the potential of these cells will be determined by how successfully they can be transplanted in humans and if they produce an improvement in patients without side-effects.

There are no major ethical objections to UCB use making it a more publicly accepted option for use in stem cell therapies. However there are still some controversial issues relating to privacy, inequality and commercialisation that need to be addressed.
Public cord blood banking, with its greater focus on accessibility and inclusiveness, should be encouraged over private banking. There are strong financial and economic arguments to support this. Additionally, the whole market would benefit from tighter regulation.

With a global human population of just over 7 billion, births and therefore umbilical cord blood remains the largest untapped source of stem cells available to society every year. From a zoological perspective, while advances in UCB treatment in humans have used animal models, these treatments may be applied in the future for the care, protection and preservation of other mammal species.

References:


