

## Stem cell transfer in newborn infants through placental transfusion via delayed umbilical cord clamping

Until recent years, medicine had not been able to establish the adequate timing for umbilical cord clamping. For over two centuries, controversy persisted around immediate or early cord clamping (within the first 15 seconds) and delayed cord clamping (at 2-3 minutes or later).

Only in the first years of the 21<sup>st</sup> century, randomized controlled studies and systematic reviews were done that provided solid evidence on the clear benefits of delayed cord clamping and the absence of harmful effects.<sup>1-3</sup>

Still, several years passed before scientific societies decided to support the recommendations for the use of delayed cord clamping, probably because standards and guidelines that strongly recommended early clamping had been in place for several decades. This occurred at a time when there was still no evidence endorsing this practice, and it had spread to most Western countries after the publication of several inadequately-designed studies conducted with a small number of patients, which emphatically pointed out that delayed clamping was harmful.

Incredibly, such distant approaches were not questioned, as it usually occurs with discussions about any treatment or disease, which almost always result in controversy. On the contrary, what was at stake here was something absolutely natural to mammals, including us, human beings. Unfortunately this was not noticed, and ignorance on the physiological mechanisms involved in newborn adaptation to extrauterine life prevailed.

I would like to point out that it is regrettable that, in the era of modern medicine, replete with major advances, immediate cord clamping has remained in place for the past 50 years. There is no doubt that the mass recommendation of this practice in Western medicine was an unfortunate and serious mistake that caused tremendous damage to many newborn infants and children.

Luckily, in recent years, there has been an increasing and marked interest in the study of physiological processes in the first minutes after birth, on which depends an adequate transition to extrauterine life. Several studies found that delayed cord clamping (at 2-3 minutes) is highly beneficial because it promotes the functioning of the physiological mechanisms involved in adaptation at birth. It is known that if the newborn infant

does not breathe spontaneously, it is critical to leave the cord unclamped until the baby's first breath given that the blood received from the placenta will improve his/her cardiovascular function by increasing pulmonary blood flow. This will prevent cardiac output from decreasing, which is essential for an adequate cardiovascular and respiratory transition in the first minutes of life.<sup>4,5</sup> These measures are related to the findings of a research that demonstrated that delayed clamping improved brain oxygenation in the first 24 hours of life of small preterm infants.<sup>6</sup>

On the contrary, immediate or early clamping hinders the establishment of every physiological mechanism provided by nature to mammals ever since we have been on planet Earth.

Now that I have made this introduction, I would like to approach another incredibly relevant aspect of newborn, child and even adult development. Placental transfusion is not only part of what we have briefly mentioned above; it also makes it possible for newborn infants to receive a considerable amount of stem cells from the umbilical cord blood.

Such amazing and fascinating physiological process may only take place only if the cord is clamped after some minutes, thus allowing the passage of a higher number of stem cells which, once again, nature has decided correspond to newborn infants. It has been estimated that the number of hematopoietic stem cells received by newborn infants go from zero with immediate clamping to 1100-45,000 with clamping at 3 minutes.<sup>7</sup>

We should bear in mind a greatly significant point: very small preterm infants (less than 31 weeks of gestation) receive a remarkable amount of erythropoietic stem cells through placental transfusion. Haneline et al. observed that stem cell proliferation in the blood of small preterm infants was significantly higher than in that of term infants, and also surprisingly higher than in the bone marrow of adults. This means that these preterm infants had a higher stem cell proliferation rate than any other human being. The authors also pointed out a very relevant aspect: fetal cord blood cells may be useful targets for genetic manipulation and autologous transplantation.<sup>8</sup>

An interesting article on this subject had a very suggestive title “*Mankind’s first natural stem cell transplant*”.<sup>9</sup> The article’s authors underscored the important proliferation of pluripotent stem cells in the fetus after birth and afterwards, and this may only be achieved through the large volume of blood (25-35 mL/kg) received by newborn infants via delayed clamping. The authors also highlighted that umbilical cord blood contains sufficient hematopoietic stem cells to be used for transplantation, although further experience is required in this regard. They also pointed out that umbilical cord blood may play a significant and transcendental role as a pluripotent cell reservoir for a variety of stem cells, such as hematopoietic, endothelial progenitor, mesenchymal progenitor, and pluripotent stem cells, together with multipotent lineage stem cells.

I would like to note that the first human umbilical cord blood transplant was done in a 16-year-old boy with acute lymphoblastic leukemia in 1972. After this, cord stem cells have been successfully transplanted to treat different pediatric, genetic, blood, immune, metabolic, and oncological disorders.

Also, and independently, from a very long time before birth, stem cells play a critical role in the development and maturity of many organs, including the central nervous, respiratory, endocrine, immune and hematological systems. They are also involved in fetus and newborn infant maturation, anti-inflammatory and anti-infectious actions, and the reduction of several diseases.

The confirmed benefits of stem cells in newborn infants include their effect on respiratory distress syndrome, anemia of prematurity, intraventricular hemorrhage, sepsis, and periventricular leukomalacia. They are also very likely beneficial against chronic pulmonary disease, apnea of prematurity, retinopathy of prematurity, and necrotizing enterocolitis.

These actions, especially in very small preterm infants, underline the fact that delayed clamping is greatly transcendental for the reduction of morbidity and mortality in the first months of life. Therefore, there are no arguments against

such safe, inexpensive practice that only takes a few minutes.

It is worth repeating that most benefits of umbilical cord stem cells occur not only in the neonatal period but later in child and adult life.

Undoubtedly, it is a captivating research line that in future years will provide new outcomes among newborn infants and children. In the meantime, in our role as obstetricians, neonatologists and pediatricians, we should promote delayed cord clamping based on its massive benefits.

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