

COVID-19 Pandemic Impact on Cord Blood Collection for Stem Cell Use and Actual Perspectives

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ABSTRACT

Cord blood collection for stem cell storage remains a popular procedure due to the advantages associated to it. In the last ten years, the therapeutic potential of umbilical cord stem cells was demonstrated in the treatment of bone pathologies, neuropsychiatry, metabolic and genetic diseases. There are several factors with direct influence on the quality and quantity of cord blood collection for stem cell storage. The collection principles should be individualized according to the maternal and fetal characteristics. Furthermore, in the context of COVID-19 pandemic, additional information can be obtained through this procedure. We present a specific case-adapted strategy for the collection of umbilical cord blood and its application in analyzing the transplacental transfer of maternal COVID-19 antibodies after vaccination. We suggest that the informed consent offered to the future parents prior to the procedure should include the history of COVID-19 during pregnancy, the vaccination status of the mother and the gestational age at the time when this event occurred.

Keywords: stem cells, collection principles, COVID-19.

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INTRODUCTION

Stem cells are characterized by multipotency, capacity for self-renewal and ability to undergo differentiation and become specialized progeny cells (1). Treatment with hematopoietic stem cell transplants relies on the principle that bone marrow reconstitution can have a curative potential in malignant and non-malignant diseases such as acute and chronic leukemia, lymphoma, aplastic anemia, thalassemia major, sickle cell anemia and a wide variety of genetic disorders. Autologous hematopoietic stem cells offer the advantage of perfect compatibility and the disadvantage of disease presence in the collected tissue (1). Compared with other sources of hematopoietic stem cells, umbilical cord blood (UCB) can be easily procured with lack of donor attrition, there is no need for a complete human leukocyte (HLA) match and graft *versus* host disease is unusual and rare (2).

The main recommendation stipulated in protocols for UCB collection is to avoid interference with the delivery process while maintaining sterility and obtaining a maximally possible volume. So, the collection of cord blood should never affect the process of childbirth, the way of birth and timing of cord clamping, the safety of both mother and child always being a priority (3). Despite the advantages of delayed cord clamping for the newborn and improvement of iron stores, respectively, this technique has a negative impact on the quality of cord blood cell collection, affecting the blood volume and cell sizes. In cases of term newborns when cord blood collection is desired, avoidance of delayed clamping is recommended (4).

There are several factors with direct influence on the cord blood unit volume, number of CD34+ cells and total nucleated cell count. Maternal and fetal characteristics with positive influence include a larger fetal weight at birth and, implicitly, a voluminous placenta as well as a low number of previous births. By contrast, post-term pregnancies and pregnancies complicated with fetal distress results in a lower cord blood volume (5).

After collecting all cord blood units, they undergo a procedure of complete characterization of the volume, weight, number of nucleated cells with differential and the hematopoietic potential reflected in the number of CD34+ cells or colo-

ny forming units (6). Also, the ABO and Rh blood type along with HLA class I and II haplotypes are mandatory. All collected cord blood samples are tested prior to banking for hepatitis B and C, HIV 1, 2 and p24, syphilis, cytomegalovirus and bacterial culture. If a hemoglobinopathy is suspected in the collected specimen, it can be confirmed through hemoglobin electrophoresis. According to some studies (7), storage and administration after 11 and 12 years did not have any influence on the rate of engraftment failure.

MATERIAL AND METHOD

We analyzed the frequency of cord blood collection in a tertiary care setting – the University Emergency Hospital of Bucharest – in the last 10 years (2011-2020) and compared how the pandemic situation affected this procedure.

Informed consent for UCB collection and testing was obtained from each parent prior to procedure.

Also, we aimed to find out whether the modality of birth had an influence on the UCB collection rate. Descriptive statistics was performed using two-tailed t test (Excel). Additionally, some specifics of cord blood collection will be presented in the context of a particular clinical case.

RESULTS

During the last ten years, at the University Emergency Hospital of Bucharest there was a constant decrease in the number of births associated with a similar tendency for the number of vaginal births (Figure 1). Correlated with the number of births, the highest rate of the procedure for UCB collection was observed in 2015 (6.5%). Opposite to this, the lowest number of cord blood collection procedures (4.2%) was registered in 2020, as expected (Figure 2). There was a statistically significant difference between the rates of UCB collection during C-sections compared to vaginal delivery ($p=0.045$, t test for proportions, two-tailed), which confirmed our observation that mothers giving birth via C-sections were also more likely to choose UCB collection at birth. Regarding the number of this procedure performed during vaginal birth, the average value of stem cells collection for the period 2011-2021 was 21.82 (+/- 10,880), with a

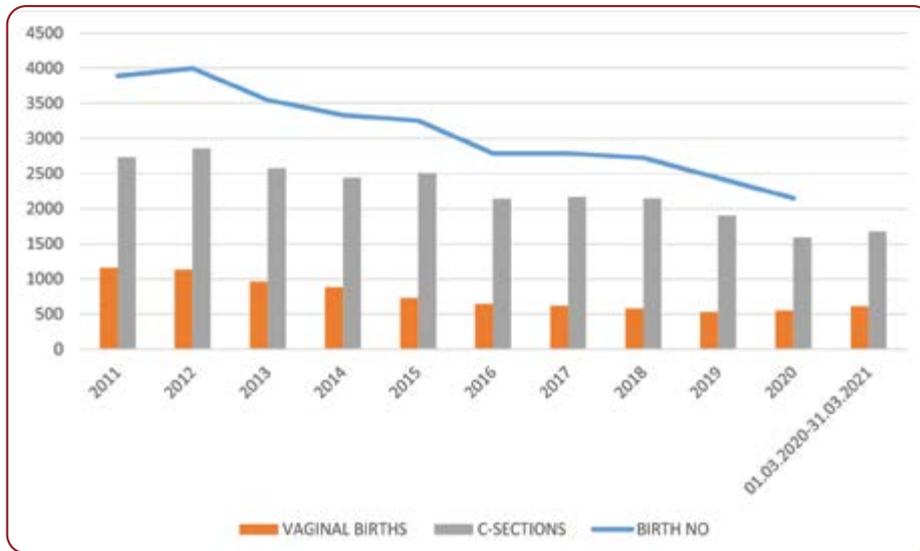


FIGURE 1. The trend of birth rate in the last decade in the University Emergency Hospital of Bucharest

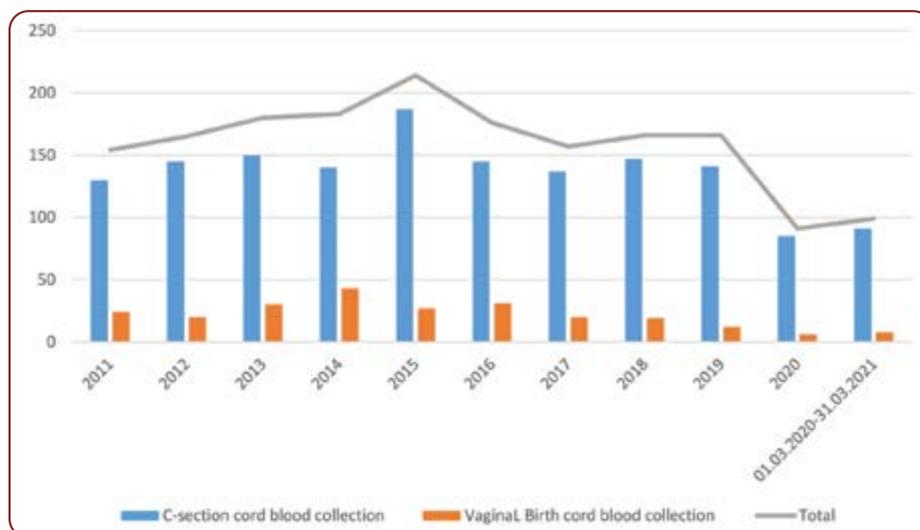


FIGURE 2. Numbers and trend of cord blood collection for stem cell storage

minimum value of six procedures and a maximum value of 43, while the number of UCB collections from C-sections ranged between 80-180.

Collection principles

Regarding the collection principle, there are a series of aspects that need to be established in order to obtain a sufficient quantity of cord blood. Furthermore, in the context of COVID-19 pandemic, additional information can be obtained through this procedure. The collection technique needs a case-by-case adaptation and, in order to emphasize this aspect, we present the following clinical case.

A 33-year-old primiparous gravida, with 38 weeks of gestation pregnancy required intrapartum UCB collection for stem cell banking in two

separate collection kits. Her pregnancy was complicated with recurrent genital infections, urinary infections and lack of toxoplasmosis protective antibodies. As a particularity, this patient was voluntary vaccinated in the late second trimester with a mRNA SARS-CoV-2 vaccine, with no adverse secondary effects. The birth through C-section was inevitable due to triple nuchal cord with associated dynamic dystocia. Regarding the cord blood collection strategy, as this case required the filling of two bags of approximately 400 cc, the specific approach was the blood collection directly from the placental most prominent vessels in order to obtain a sufficient quantity (Figure 3) after the complete collection from the umbilical cord was performed (Figure 4).

Specifically for this case, another cord blood sampling was performed for the serologic analy-

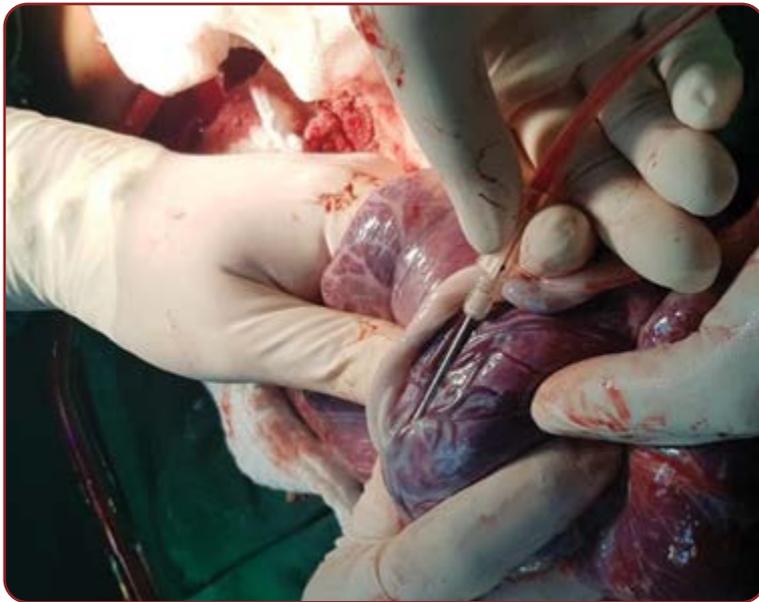


FIGURE 3. Personalized strategy for obtaining the sufficient amount of cord blood after placental delivery



FIGURE 4. Typical cord blood collection

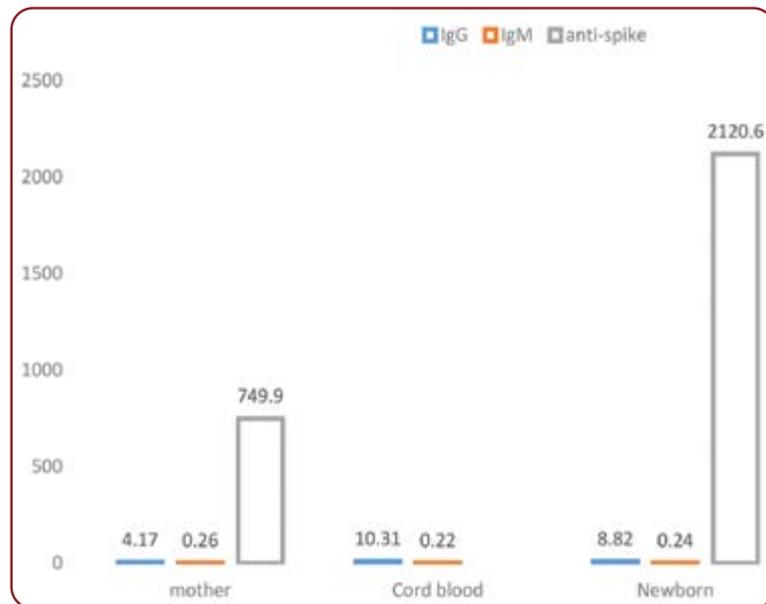


FIGURE 5. Comparative levels of SARS-CoV-2 serum antibodies in the mother, cord blood and newborn

sis of SARS-CoV-2 IgM and IgG levels. The results, along with the mother's levels of antibodies, neonatal level and specific neonatal anti-spike levels are summarized in Figure 5.

As presented, the highest value of protective antibodies for COVID-19 were at the placental level. The newborn had twice the value of mother's protective antibodies (IgG) and specific anti-spike antibodies were about three times higher.

DISCUSSIONS

The pandemic situation has been having a significant impact on the medical system worldwide and many countries implemented specific management protocols for facing all medical emergencies.

Cord blood collection for stem cells storage remains a popular procedure due to the advantages associated to it. During the last ten years, the therapeutic potential of the umbilical cord was demonstrated in the treatment of bone related deficits and metabolisms genetic diseases. Compared with stem cells obtained through other techniques, umbilical cord stem cells do not require perfect HLA matching, thus offering an expanded donor pool and the ability to use partially HLA-matched UCB units (8). In case of cell donation in unrelated recipients, the possibility of an acute and severe graft-versus-host disease development is much lower than in recipients of unrelated matched donor marrow or family member marrow allograft (8). Also, UCB is substantially tested prior to storage and offers the advantage of being rapidly ready for use without the donor direct implication.

Several cases of significant favorable neurological outcome after autologous stem cell transplant were reported. One example is the remission of a cerebral lesion in a four-year-old male child with neonatal encephalopathy. Also, there were two successful neurological improvements in two five-year-old children diagnosed with autism spectrum disorder, after single autologous transplantation, with evident verbal progress and increased interaction skills seen two months after the procedure (9).

Stem cell transplantation is now regarded as a standard approach for beta-thalassemia. An innovative procedure, respectively a mixed transplantation with auto- and allogenic transplantation in a five-year-old male child with a severe

form of beta-thalassemia, was successfully performed, with no side effects and no graft rejection. Further investigations are planned for documenting the biological response (9).

In contrast, umbilical cord blood as a hematopoietic stem cells source has several limitations, including an increased risk of graft failure and the unavailability of the donor for extra donations. Also, after UCB transplantation a delayed immune reconstitution reaction develops, so infectious complications are common. The median duration of induced neutropenia is approximately 30 days (10).

The large-scale study of Daikeler *et al* (11) is not to be ignored – according to it, the incidence of autoimmune diseases, such as autoimmune hemolytic anemia, immune thrombocytopenia and Evans syndrome, have an increased incidence after UCB transplantation.

Clearly due to the COVID-19 pandemic, the unstable financial status of many people negatively influenced the rate of cord blood collection for storage in private banks. Adapted to this situation, the procedure offers the possibility of investigating the impact of a new disease and a new vaccine at the placental level and in the newborn. This information is essential, offering an objective argument and an important basis for further studies. Also, we suggest that the informed consent given by future parents prior to the procedure should include information re-

garding the history of COVID-19 during pregnancy and the vaccination status of the mother. The gestational age when this event happened is also to be noted.

CONCLUSION

The indications for umbilical cord blood collection and the collection principles should always be individualized. The possibility for having this procedure, with equal insignificant side effects for the mother and newborn, even if the birth occurs by C-section or vaginal, is mandatory to be presented to all future parents as an existing possibility. Furthermore, the intention of the expectant parents for UCB collection and storage should not be discouraged.

We believe that more utilizations and therapeutic benefits for stem cell treatments will ensue in the near future as the collection of UCB becomes more widespread, and especially in the post-COVID-19 era, where their benefit is two-fold: for organ tissue regeneration (pulmonary) and modulation of the immune system. □

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