



## The impact of delayed cord clamping (DCC) and umbilical cord milking (UCM) on neonatal anemia

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### Abstract

Delayed cord clamping is done at least 1 to 9 minutes after birth. On the contrary, early cord clamping is done less than 91 seconds after birth (1). The proper time for clamping the umbilical cord has been discussed since the mid-1950s, and despite many studies that have taken place on the benefits of delayed clamping in comparison to the early form, the ideal and appropriate time to do so has not yet been agreed upon. Searches were conducted by two independent researchers in international (PubMed, Web of science, Scopus and Google scholar) and national (SID, Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were scanned. The specific search strategies were created by a Health Sciences Librarian with expertise in systematic review search using the MESH terms and free terms according to the PRESS standard. Delayed cord clamping in term newborns can increase the level of hemoglobin and ferritin in early infancy and it can be considered as a safe way to prevent anemia in infancy. In some studies, a slight increase in bilirubin levels without jaundice, and the need for phototherapy and the creation of benign polycytosis are considered as possible complications for delayed cord clamping in term neonates. Using delayed cord clamping technique provides several advantages in preterm and LBW infants, including increased levels of hemoglobin, volume and blood pressure in the infant, resulting in reduced blood transfusion and complications.

**Keywords:** delayed cord clamping, umbilical cord milking, neonatal, anemia

### Introduction

#### Delayed cord clamping

Delayed cord clamping is done at least 1 to 9 minutes after birth. On the contrary, early cord clamping is done less than 91 seconds after birth<sup>[1]</sup>.

The proper time for clamping the umbilical cord has been discussed since the mid-1950s, and despite many studies that have taken place on the benefits of delayed clamping in comparison to the early form, the ideal and appropriate time to do so has not yet been agreed upon<sup>[2]</sup>.

Delayed cord clamping in term newborns can increase the level of hemoglobin and ferritin in early infancy and it can be considered as a safe way to prevent anemia in infancy. In some studies, a slight increase in bilirubin levels without jaundice, and the need for phototherapy and the creation of benign polycytosis are considered as possible complications for delayed cord clamping in term neonates. Using delayed cord clamping technique provides several advantages in preterm and LBW infants, including increased levels of hemoglobin, volume and blood pressure in the infant, resulting in reduced blood transfusion and complications. Also, delayed cord clamping leads to a 50% reduction in intrahepatic hemorrhage and neurological complications due to anemia in these infants<sup>[3]</sup>.

### Methods

#### Search strategy

Searches were conducted by two independent researchers in

international (PubMed, Web of science, Scopus and Google scholar) and national (SID, Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were scanned. The specific search strategies were created by a Health Sciences Librarian with expertise in systematic review search using the MESH terms and free terms according to the PRESS standard. After the MEDLINE strategy was finalized, it was adapted to search in other databases. Accordingly, PROSPERO was searched for ongoing or recently related completed systematic reviews. The key words used in the search strategy were "Delayed cord clamping, umbilical cord milking, neonatal, anemia" and Iran which were combined with Boolean operators including AND, OR, and NOT.

#### Study selection

Results of the Literature review were exported to Endnote. Prior to the formal screening process, a calibration exercise was undertaken to pilot and refine the screening. Formal screening process of titles and abstracts were conducted by two researchers according to the eligibility criteria, and consensus method was used for solving controversies among the two researchers. The full text was obtained for all titles that met the inclusion criteria. Additional information was retrieved from the study authors in order to resolve queries regarding the eligibility criteria. The reasons for the exclusion

criteria were recorded. Neither of the review authors was blinded to the journal titles, the study authors or institutions.

## Discussion

Umbilical cord milking includes the transfusion of milk from placenta to the baby during which about 20 to 40 ml of blood and 30 to 35 mg of iron are injected into the baby's body. During umbilical cord milking, the baby can be kept at the same level of placenta if it is a cesarean section and below the placenta if it is natural delivery. In most studies, the umbilical cord is milked 3 to 5 times. Delayed cord clamping and umbilical cord milking can be done one after the other, depending on priority <sup>[4]</sup>. In a group of studies, the umbilical cord was first clamped at a distance of 25 cm from the baby's body, placed the baby under the heater, and the cord is milked three times at a speed of 10 centimeters per second. In most cases, the umbilical cord is milked to a maximum of 9 times, because there remains no noticeable amount of blood in the umbilical cord after 3 times. In some other studies, the cord is milked before getting clamped. Shaking before the clamping may result in the transfer of excess blood from placenta to the baby and provide a higher level of hemoglobin <sup>[5]</sup>. Eventually, "placenta transfusion" and blood transfusion to the embryo from birth to umbilical cord can cause higher hemoglobin levels and less anemia <sup>[6]</sup>.

## Hemoglobin

The production of hemoglobin begins in the prothryoid blisters and continues until the reticulocyte stage. Therefore, reticulocytes continue to make small amounts of hemoglobin for about a day after they leave the bone marrow and enter the blood, so that the red blood cells eventually mature <sup>[7]</sup>.

## Production processes

Each molecule is combined with a polypeptide chain called "globin" that is made up of ribosomes, creating a subunit of hemoglobin called the hemoglobin chain. A loose bonding of four hemoglobin chains creates a complete hemoglobin molecule <sup>[8]</sup>.

Different hemoglobin chains have several brief differences depending on the composition of the amino acids of the polypeptide region. Different types of chain include alpha, beta, gamma and delta chains. Hemoglobin A, the most abundant form of hemoglobin in humans, is a combination of two alpha and two beta chains <sup>[9]</sup>.

To solve the embryo's problem, oxygen is derived from maternal blood and a specific type of fetal hemoglobin develops in the body. The hemoglobin in the embryo red blood cells is slightly different from that of adults. Of the four peptide-forming hemoglobin sequences, the two alpha chains in the fetus and adults are similar, but embryonic hemoglobin has two gamma chains in its structure instead of two beta chains. The beta chain binds to a natural regulator of diphosphoglycerate, which helps to remove oxygen <sup>[10]</sup>. If the gamma-chain isoforms are not linked to phosphoglycerate, then they have a greater oxidation desire and oxygen is released from adult hemoglobin in a low-oxygen environment; if embryonic hemoglobin not only does not release oxygen but is attached to it, the same difference in oxygen demand makes oxygen transfer from mother to fetus. Embryonic hemoglobin

does not disappear after birth, and in humans, complete replacement of the red blood cells containing fetal hemoglobin continues through the red blood cells containing adult hemoglobin up to about 6 months after birth <sup>[11]</sup>.

## Factors lowering hemoglobin level

Anemia, severe hemorrhage, hemolysis, hemoglobinopathy, cancer, nutritional deficiency, lymphoma, systemic lupus erythematosus, sarcoidosis, kidney disease, chronic bleeding, splenomegaly, sickle cell anemia, malignancy and the use of medications such as antibiotics, anti-neoplastic drugs, aspirin, indomethacin, rifampin, and sulfonamides are agents that reduce hemoglobin levels <sup>[12]</sup>.

## Factors elevating hemoglobin level

Congenital heart disease, real polycythemia, blood condensation, chronic obstructive pulmonary disease, congestive heart failure, life at high altitudes, severe burns, dehydration, and the use of medications such as gentamicin and methyl dope are factors that increase hemoglobin levels <sup>[13]</sup>.

## Ferritin

Ferritin is a macromolecular weighing at least 440 kDa (depending on the iron content). This molecule consists of a crude protein (apophyrite) with 24 subunits and a molecular weight of 460 kDa and an iron core of about 2500 ions of Fe <sup>[14]</sup>. Serum ferritin is a good indicator of iron reserves availability. Ferritin is the main source of iron storage and its serum levels are directly dependent on the concentration of iron in the body. In normal people, serum ferritin levels of 1 ng/ml represent approximately 8 milligrams of iron stored in the body <sup>[15]</sup>. Ferritin levels go down in men and women after menopause. The levels remain the same in women before menopause. Reducing levels of ferritin is a sign of a reduction in iron stores due to iron deficiency anemia, so that ferritin below 10ng / 100ml has a diagnostic value for iron deficiency anemia. Often, decreases in serum ferritin levels occur before other signs of iron deficiency, such as decreased serum iron levels, or changes in size, shape, and number of red blood cells. Ferritin will be affected only in case of severe protein denaturation. Also, pregnancy reduces the level of ferritin and increased ferritin can be a sign of hemochromatosis, hemosiderosis, iron poisoning, or recent blood transfusion. There is also an increase in ferritin in Megaloblastic anemia, hemolytic anemia and chronic hepatitis. However, ferritin is artificially increased in people with chronic illnesses such as malignancy, alcoholism, collagen disease, or chronic liver disorder. Ferritin is also used to monitor chronic renal failure <sup>[16]</sup>. Serum ferritin levels increase in other conditions, which do not correlate with body iron stores, such as inflammatory disease, infections, metastatic cancers, and lymphomas. Increasing ferritin occurs 1-2 days after the onset of acute illness and reaches the peak within 3-5 days. Since ferritin levels are false, iron deficiency is not detectable in these patients <sup>[17]</sup>.

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