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Cord Clamping Practices and its Effect on Red Cell Indices.

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ABSTRACT

The need to maintain adequate blood volume at the point of delivery is critical to the smooth transition from intrauterine to extra uterine life. There is a dynamic balance between blood flow from baby to mother via the placenta, and when the umbilical cord is cut at birth, this flow is interrupted. How long after birth that this flow is permitted to go on determines how well adjusted physiologically the newborn is. Delaying cord clamping for a few minutes has been shown to be advantageous to the newborn as it improves the haematocrit and haemoglobin values as was elucidated in various studies. Circulatory stability was also proven by the higher oxygen saturation got when immediate and delayed cord clamping were compared. This effect has been proven for both term and preterm babies alike. The World health organization recommends delayed cord clamping. This review aims to elucidate the dynamics of placental transfusion, highlight the red cell indices and do an analysis of several studies done on how timing of cord clamping affects some of these red cell indices.

Keywords: Cord clamping, oxygen saturation, placental transfusion, red cell indices

INTRODUCTION

The newborn period is a vulnerable time in the life of all babies:[1,2] they are completing many of the physiologic adjustments for extra uterine life. The first few weeks of life are characterized by dramatic physiologic and anatomic changes.[3] Many common peripartum practices impact the fetal to neonatal transition.[4] Such practices include suctioning protocols, umbilical cord clamping, strategies to prevent heat loss and use of 100% oxygen for resuscitation.[4]

The transition from fetus to newborn is a normal physiologic process, 4 and cord clamping after birth is a routine obstetric procedure.[5] As part of active management of the third stage of labour, administration of a uterotonic agent at delivery of the shoulder and clamping of the umbilical cord shortly following the birth of the neonate has been practiced in both developed and developing nations.5,6 The decision on how long to wait before cord clamping is usually determined by existing protocols and the clinical state of the newborn. Cord clamping could be classified as early (or immediate) and late (or delayed).[7]

Immediate cord clamping (ICC) refers to the process whereby the connection between the baby and placenta is severed (double clamped and cut between the clamps) in the first sixty seconds following complete expulsion of the fetus.[7] Delayed cord clamping (DCC) refers to the same procedure but with a prolongation of the time beyond one minute after birth, or until the co rd stops pulsating.[7]

Current practices require that cord clamping is delayed to allow more blood to flow from placenta to baby.[8] This procedure, called placental transfusion, increases the newborn blood volume by up to 50%.[9] Allowing a placental transfusion to occur by delaying the clamping of the umbilical cord is an extremely effective method of enhancing arterial oxygen content, increasing cardiac output, and improving oxygen delivery.[10] Documented advantages include fewer incidences of anaemia, intraventricular haemorrhage, early onset sepsis in neonatal life,[11] and iron deficiency in infancy.[12]

This review article gives a general overview of how cord clamping practices have a profound effect on the circulatory stability of neonates at birth. It elucidates how delaying cord clamping (thereby increasing time for placental transfusion) gives the aforementioned positive effects.

The placental circulation:

The placenta, the barrier between maternal and fetal circulation, comprises of the maternal (utero-placental) and fetal (feto-placental) components.[13] The placenta is a reservoir of fetal blood, which could be equally useful to the neonate.[14]

At birth, blood flow in the umbilical arteries and veins usually continues for a few minutes. The additional blood volume transferred to the newborn during this time is known as placental transfusion.[15] For a term neonate, placental transfusion gives the newborn an additional 80–100 ml of blood.[16] For the fetus, blood volume/kilogram of body weight is similar to that of an adult. At birth, this rises to

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around 90 ml/kg but the rise is reduced by 20–35% if the cord is clamped immediately.[17,18]

The physiology behind the effects of placental transfusion is to facilitate the transfer of blood volume from the placenta to the newborn.[10] Owing to the relatively large size of the placenta compared with the fetus at mid-term, blood is equally distributed between the fetus and placenta. By term gestation, about one-third of the blood flows through the placenta and two-thirds flows through the fetus at any point in time.[10] It follows that immediate cord clamping (ICC) results in one-third of total blood volume remaining in the placenta. Delaying clamping of the cord (DCC) for 60 s decreases the residual placental blood to 20% and by 3–5 min the residual placental volume is approximately 13%.[10]

When cord clamping is delayed at birth, the infants experiences placental transfusion as whole blood is transferred (or transfused) from the placenta to the infant during the first few minutes of life.[8] This blood contains not only plasma and red blood cells but also millions of stem cells important in re-pairing tissue and building immunocompetence. The red blood cells are a major source of iron during the first few months of life. When the cord is cut rapidly, the infant has no access to approximately 30 mL/kg (of birth weight) of blood—about 30% of the fetal-placental blood volume.8 Placental transfusion facilitates an increase in the circulatory bed at the same time that the infant's various organs (lung, liver, kidney, etc) assume the many functions maintained by the placenta during fetal life. This additional blood volume may reduce the vulnerability of infants to inflammatory processes and infections.[8]

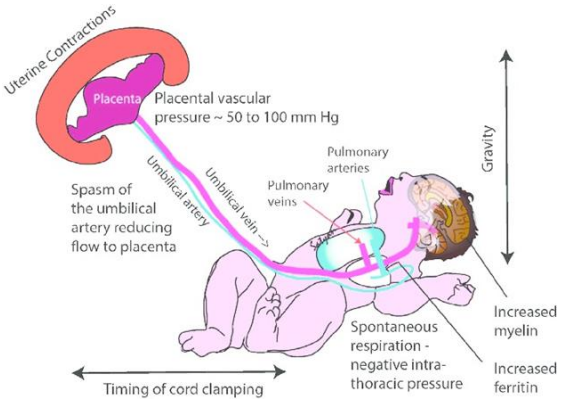

Figure 1: schematic drawing of placental transfusion. Adapted from Placental transfusion: a review.[22]

If the cord is left unclamped, the physiologic expectation of the umbilical arteries to constrict on account of the increased oxygen saturation of the blood and the pressure gradient from the pulmonary vasculature ensures the flow of blood between the newborn and the placenta is unidirectional (from placenta to the newborn via the still patent umbilical vein which is relatively insensitive to oxygen).[16] This was extensively studied by Yao et al in several publications.[18-21]

Blood circulates via the umbilical artery for about twenty-five seconds after birth, but this becomes negligible by about forty-five seconds after birth, indicating a cessation of blood flow from fetus to placenta.[19] In contrast, blood flow from the placenta to the newborn through the umbilical vein is maintained through the first three minutes of life , largely influenced by uterine contractions.[19] [Figure 1]

Total placental transfusion is about 30ml/kg body weight.[20] It is worthy of note that placental transfusion occurs mainly within the first minute18; the cord has been found to cease pulsating in majority of cases within the first two minutes,[23] and placental transfusion is usually completed after three minutes.[18] Studies with cord clamping beyond three minutes did not show any significant change in the placental residual blood volume.[18,19]

These studies on placental transfusion were carried out in the late sixties and early seventies,[17–20] and were recently corroborated by Farrar et al24 in 2011, who determined the volume of placental transfusion using the weight of newborns with intact cord, and measuring the average weight every two seconds, using a digital scale. Placental transfusion was then calculated from the change in weight between birth and either cord clamping or when weighing stopped. Placental transfusion contributed about 32 ml/kg (95% CI, 30 to 33 ml) to blood volume.[24]

Red cell indices:

The red cell (erythrocyte) is structurally the simplest cell in the body.[25] Its basic function is the creation and maintenance of an environment salutary to the physical integrity and functionality of haemoglobin.[25]

Several parameters related to the red cell size, volume and haemoglobin concentration are used to determine disease states.[26] These parameters, called the red cell indices include the haemoglobin concentration, erythrocyte count, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and the red cell distribution width.

Haemoglobin: This is the iron-globin moiety that imparts oxygen carrying capacity on erythrocytes.[3] Its value is dependent on both gestational and chronological age.[25,27] Further variation may be due to timing of cord clamping and sampling sites.[25,27] In most term neonates, there is a rise in haemoglobin by two hours of life due to postnatal fluid shifts.[3] Haemoglobin concentration declines onwards and continues to fall over the next several weeks, reaching its nadir in term infants at approximately eight weeks, and four to six weeks in preterm neonates.[25] The unit of measurement is grammes per decilitre (g/dL).[26]

Haematocrit: Also referred to as packed cell volume (PCV), measures the total volume of the erythrocyte relative to the total volume of whole blood in a sample.[25] Similar to haemoglobin, it is

also affected by gestational age, timing of cord clamping and sampling site.[25,27] It is usually presented as a percentage.[25]

Erythrocyte count: This involves counting the number of erythrocytes per unit volume of whole blood. The unit is cell/microliter.[25]

Mean corpuscular volume: This is the mean volume of all erythrocytes counted in the sample. It can be manually derived from the formula, MCV= haematocrit/ RBC count. The unit is femtoliters (fL).[26] It is noteworthy that it only measures average cell volume. Newborn erythrocytes are markedly macrocytic at birth, with a sharp decline occurring within the first 24 hours of birth.[27]

Mean corpuscular haemoglobin: This measures the mean mass of haemoglobin in the erythrocytes. It is calculated using the formula, MCH = haemoglobin(g/dl) /RBC count.[26] It is expressed in picogrammes (pg).

Mean corpuscular haemoglobin concentration: This is the mean concentration of haemoglobin in the red cell. Its formula is MCHC = Haemoglobin/Haematocrit.26 It is reported in grammes per decilitre (g/dL), and it is fairly constant in all gestational ages.[27]

Red cell distribution width (RDW): Is a measure of the variations in red blood cell volume.[3,27] It is mathematically calculated as RDW = (standard deviation of MCV/ mean MCV) x 100. It is reported in percentages.

Effect of cord clamping practices on red cell indices:

Physiological and health effects of cord clamping in relation to time after delivery have been studied since the late nineteenth century and arguments to support either method abound.[28] Many randomized controlled trials of term and preterm infants have evaluated the benefits of immediate umbilical cord clamping versus delayed umbilical cord clamping,

A systemic review of studies on babies born prematurely, demonstrated that delaying cord clamping for just a very short time helped the babies to adjust to their new surroundings better. This was the conclusion of a Cochrane review by Rabe et al in 2004.[29]

Table 1: summary of studies on cord clamping.

Author	Year	Study population	No of subjects	Delay duration	Conclusion	SignifIcant value
McDonnell et al	1994	Preterms 23 – 36 wks	46	30 secs	30 secs delay did not give any dsignificant difference in hct.	Not significant.
Chapparo et al	1997	Term	358	120 secs	Significant increase in Hb and Hct, with increased body iron at 6 months of life.	P=0.007
Rabe et al	2000	Preterms <33 weeks	40	45 secs	DCC reduced need for transfusion within first 6 weeks of life.	P <0.05
Emhamed et al	2004	Term	104	After cord stopped pulsating	DCC increases red cell mass	P= 0.0035
Rabe et al	2004	Preterms <37 comp weeks.	297 (Cochrane review)	30-120 seconds	DCC associated with fewer needs for transfusion	RR 2.01 95%CI 1.24 - 3.27
Ceriani Cernadas et al	2006	Term	276	I minute and 3 minutes	DCC at birth increases neonatal mean venous hematocrit within a physiologic range	P=0.0014 & 0.0027
Van Rheenen et al	2007	Term	91	When cord stopped pulsating	Reduces risk of early infant anaemia up to 6 months of life	CI 0.2-2.1
Ultee et al	2008	Preterms 34-36 weeks	37	>180secs	DCC had higher hb at 1 hr and 10 weeks of life	P < 0.05
Rincon et al	2009	Term	242	1 – 2 minutes and 2 – 3 minutes.	Significant increase in Hct and Hb with DCC.	P < 0.01
McDonald et al	2013	Term	3911(Cochrane review)	1-3 minutes.	Increase in early hb conc and iron stores in infants with DCC.	CI -1.78 to -1.21
Jibril et al	2015	Term	300	60 – 90 secs	DCC increased hb,Hct and oxygen saturation.	P < 0.001

Key : Hb – haemoglobin, Hct – Haaenatocrit, CI – confidence interval, DCC – delayed cord clamping.

McDonnell et al,[30] in an Australian study of forty-six preterm infants born at 26-33 weeks of gestation, assessed the size of placental transfusion following a thirty second delay in cord clamping after both vaginal and Caesarean births and determined the feasibility of delaying cord clamping in the labour ward and particularly in the operating theatre. They concluded that although delaying cord clamping in both situations was feasible, a thirty second delay did not give the predicted difference in hematocrit values. However, it was suggested that further studies should delay cord clamping for more than thirty seconds or alter the position of the fetus relative to the uterus, to facilitate the expected physiologic transfusion of up to 15-20 ml/kg of blood within that time frame. 30 It is noteworthy that even from the conclusion, it is clear that the duration used for delayed cord clamping was innacurate.

Rabe et al,[31] in Germany studied forty infants born mainly through caesarian section at gestation age of less than thirty-three weeks, and at forty-two days of age, ten in the immediate cord clamping group compared to three in the delayed cord clamping group had required transfusion. The conclusion was

that delaying cord clamping reduced the need for transfusion within the first six weeks of life in preterm infants.[31] Again, delayed cord clamping duration was not adequate for significant impact following current definition of delayed cord clamping by WHO.

A study done in the Netherlands by Ultee et al,[32] on thirty-seven infants between the gestational ages of 34-36 weeks where immediate cord clamping was within thirty seconds of birth and delayed cord clamping was after three minutes of birth showed a consistently higher haemoglobin value in the delayed clamping group both at one hour of life and at ten weeks of age. Conclusion was to discourage early clamping of the cord.

Despite all these studies, concerns still exist regarding the universal adoption of delayed umbilical cord clamping.[33] The issue is further complicated by the fact that term babies, preterm babies and very premature babies could behave as different cohorts, making it difficult to develop an empiric guideline for timing of cord clamping across all gestations.[34]

Several debates have emerged on the effects of delayed cord clamping in normal healthy term infants. Van Rheenen et al,[35] in 2007 studied the effect of delayed cord clamping on term neonates in a mission hospital in Zambia, and the babies were followed up monthly for six months. Cord was clamped after it had stopped pulsating. A more rapid decline in haemoglobin levels in ICC group was noted, though the total effect was said to have waned by six months of age. The conclusion was that DCC was a simple, free and safe delivery procedure which might offer a strategy to reduce the risk of early infant anaemia when other interventions are not yet feasible.[35] The sample size however was small (91 babies).

A study of term babies in Libya by Emhamed et al,[36] in 2004 showed a significantly higher mean infant haemoglobin and haematocrit levels in the delayed cord clamping group at twenty-four hours of life. In that study, the cord was clamped after it was deemed to have stopped pulsating. No significant differences were found in clinical jaundice or plethora. The conclusion from the study was that delaying cord clamping increases the red cell mass in term infants, and it is a safe, simple and low cost delivery procedure that should be incorporated in integrated programmes aimed at reducing iron deficiency anaemia in infants in developing countries.[36]

Chapparo et al,[37] in a randomized controlled study in Mexican infants in 2006 showed that waiting two minutes before clamping the umbilical cord provided the infants with more body iron at six months of age without causing any harm at birth. There was a significant increase in haematocrit and haemoglobin at birth in DCC babies compared to ICC babies. More babies in the DCC group had haematocrit > 70% and more infants had clinical jaundice but the difference was not statistically significant.[37]

Ceriani Cernadas et al,[38] in 2006 also prospectively studied Argentinian neonates and divided them into three groups based on duration before cord clamping (<15 seconds, at one minute and at three minutes of life) and was able to prove that delayed cord clamping at birth increases neonatal mean venous hematocrit within a physiologic range. Neither significant differences nor harmful effects were observed among groups.[38]

Similar three group study was carried out in Spain by Rincón et al,[39] in 2009 (<60seconds, 1-2 minutes and 2-3 minutes timing intervals) with the conclusion that though there was an increase in the incidence of polycythemia, there were no appreciable clinical correlates as none of the neonates required treatment. They also recorded significant increase in haemoglobin and haematocrit with increasing delay.[39]

McDonald et al,[40] in a bid to explore the benefits of delayed cord clamping in term infants, carried out a systematic review in 2013. This focused on randomized controlled trials comparing early and late cord clamping, and a total of fifteen trials were analyzed, including four of the aforementioned five studies in term neonates. Despite some variation in the timing of delayed cord clamping in the included studies, and the wide variation in outcome indices for each study, the authors were able to show an increase in early haemoglobin concentrations and iron stores in infants with delayed cord clamping. The authors concluded that delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.[40]

These studies demonstrate significant differences in the red cell indices when cord clamping is delayed, and the advantages have been demonstrated to be beneficial to both preterm and term neonates. However, considering the fact that increasing the clamping time lead to increased blood volume via enhanced placental transfusion which in turn results in an enhanced circulatory volume and oxygen carrying capacity of the blood, none of the afore mentioned studies went further to determine how this affects the oxygen saturation of the different cohorts.

The study carried out by Jibril et al in 2015, a study done on 300 term newborn, was able to corroborate the effect of timing of cord clamping on haematocrit and haemoglobin (there was significant difference in the values favouring DCC), she was also able to show that oxygen saturation (measured with a pulse oximeter) was significantly better in children who had cord clamping delayed compared to those who had their cord clamped immediately. See [Table 1] above for summary of a twenty year review of various studies on cord clamping.

CONCLUSION

Placental transfusion ensures autologous provision of whole blood to a newborn with its attendant effects. The longer the delay before the cord is clamped, the more blood transferred to the baby from the placenta, up until the third minute of life or the cord stops pulsating.

Thus, Delayed cord clamping has been advocated as the new standard of care at the point of delivery. The advantages are numerous, and studies have gone on to show that it does not have any significant side effects. The above review focused primarily on the effect on red cell indices, particularly haemoglobin and haematocrit values. The advantages are even greater for preterm babies in terms of other benefits beyond the improved red cell indices and oxygen saturation. It also significantly reduces the incidence of intraventricular haemorrhage, neonatal sepsis and necrotizing enterocolitis.

The benefits of delayed cord clamping, a procedure which has been shown to be cost effective and requiring no special skills, to newborn babies is numerous. Improved red cell indices and circulatory volume (as evidenced by improved oxygen saturation) is just one of them. Improved neonatal morbidity and mortality statistics can be achieved with this simple intervention. It is a World Health Organization recommendation, and thus delayed cord clamping should be universally accepted as the method of choice for cord clamping at delivery in the absence of a strong need to do otherwise, This will go a long way in modifying our health indices in the developing world.

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