Physiological measurements of the effect of cord clamping strategies

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GENERAL INTRODUCTION

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UMBILICAL CORD CLAMPING: PAST, PRESENT, FUTURE

Clamping and cutting of the umbilical cord after birth is a normal and necessary procedure during the third stage of labour, yet the exact timing has been debated for millennia, at least back to the time of Aristotle in 350BC.(1) However, the timing and method of umbilical cord clamping and cutting has changed over time: ranging from how to tie the umbilical cord in the Trotula (a medieval compendium of women's medicine) to only cutting the umbilical cord after the placenta had been delivered in primitive cultures.(2, 3) It is still unclear when the timing of umbilical cord clamping shifted from after placental delivery to before it, although the first description of this change dates from the 17th century.(3)

Of note: umbilical cord clamping and cutting are used interchangeably in the literature, but as cord clamping is an internationally accepted term to describe both simultaneously this will henceforth be the term used in this thesis, indicating clamping and cutting.

Another important change in the timing of cord clamping occurred after the 'active management of the third stage of labour' was implemented into clinical practice in the 1960s.(4) Active management of the third stage of labour was aimed at reducing post-partum haemorrhage (PPH), although there was no scientific evidence suggesting delaying cord clamping was related to excessive maternal blood loss. Nevertheless, early cord clamping was included in the active management trias together with the use of prophylactic uterotonics upon delivery of the anterior shoulder and controlled cord traction to deliver the placenta. A later review of the data showed the positive effect of implementing this new strategy was solely due to the use of uterotonics and not related to early cord clamping.(5)

Postponing (delaying) the moment of cord clamping has been the subject of numerous research projects over the last decades, demonstrating that both term and preterm infants could benefit from this.(6, 7) The beneficial effects of delayed cord clamping (DCC) led to changes in both obstetrical and neonatal resuscitation guidelines(8-10) that currently recommend delaying umbilical cord clamping for at least 1 minute, but only when the infant is uncompromised.(9, 10) However, infants who were compromised after birth, i.e. who were in need of respiratory support, were excluded from most trials on DCC. Consequently, due to absence of evidence, when infants are compromised guidelines either suggest immediately clamping the cord, to establish effective ventilation, or no recommendations are given.(9, 10)

Most preterm infants are in need of respiratory support at birth and immediate clamping is still recommended. Prematurity markedly increases the risk of neonatal morbidities and remains the main cause of neonatal mortality. These morbidities entail, but are not limited to, respiratory distress syndrome, intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, and retinopathy of prematurity, influencing both short- and long-term outcomes. As the risks of morbidity and mortality are directly related with gestational age (GA) at birth, infants born <28 weeks GA (extremely preterm) are at the highest risk for adverse outcomes.[11] Additionally, as they often fail to achieve lung aeration and sufficient gas exchange due to the immaturity of their respiratory system, these infants require respiratory support. Currently, the cord needs to be clamped immediately or within 30-60 seconds to provide effective respiratory support and monitor the clinical condition of the infants, denying these infants the benefits of DCC.

However, new resuscitation tables have been developed that enable effective neonatal resuscitation at the maternal bedside, while the umbilical cord remains intact. Implementing this new approach in clinical practice will allow preterm infants to receive DCC and, thereby, also receive the accompanying benefits. Additionally, as both maternal and neonatal care can be assured, the moment of umbilical cord clamping no longer has to remain time-based. Instead, cord clamping can be delayed until after the infant has been stabilised, as is done during physiological based cord clamping (PBCC; detailed explanation below).

THE BENEFITS OF DELAYED CORD CLAMPING

The beneficial effects seen after DCC have been the basis for current guideline recommendations. Studies have shown that DCC for term-born infants can lead to an increase in haemoglobin in the first hours after birth, a decrease in the risk of developing iron-deficiency in the first months of life, and improvements in neurodevelopmental outcomes.[6, 12] For preterm-born infants, DCC is associated with a reduction in the risk of hospital mortality and the need for blood transfusions, and with improved blood pressures.[7, 13] These beneficial effects as a result of performing DCC have all been attributed to placental transfusion.

Placental transfusion

Placental transfusion, or the net shift in blood volume from placenta to neonate during DCC, is a widely accepted phenomenon and has been the subject of several studies. To demonstrate placental transfusion, either neonatal blood volume was calculated using ^{125}I-tagged human serum albumin, remaining placental blood volumes were measured, or neonatal weight was used.[14-16] These studies demonstrated that placental transfusion occurred at an average rate of 2-3ml/kg/

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min, with the majority of blood being transfused in the first minute and transfusion likely to be completed within 3 minutes of birth. Based on these results, guidelines recommend DCC for 1-3 minutes if no resuscitation is needed; in other words, DCC has become time-based.(9)

Although placental transfusion is an accepted effect of DCC, the physiology causing the net shift in blood volume remains unclear. Early studies suggested both gravity and uterine contractions as the driving factors for placental transfusion. The gravity theory was later refuted by showing a similar placental transfusion for infants that were held higher than the introitus compared to infants held at the level of the introitus, using gain in weight as a measure of placental transfusion.(17) Additionally, the hypothesis on uterine contractions was deemed unlikely based on a study showing that uterine contractions cause reductions in uterine or fetal placental blood flow rather than increasing it.(18-20)

Uterine contractions, however, might still affect placental transfusion in a different way. A new hypothesis suggests that uterine contractions during labour might increase pressure within the fetus, leading to a shift in blood volume from the neonate into the placenta. This creates an accumulation of blood within the placenta, whereas after birth, this accumulated blood volume shifts back into the infant to rebalance the blood volume when the pressures are relaxed. This increase in blood flow towards the infant after birth is known as placental transfusion.

It is also possible that spontaneous breathing provides the driving force for placental transfusion by generating a sub-atmospheric (negative) intrathoracic pressure during inspiration. It is proposed that this negative intrathoracic pressure creates a greater influx of umbilical venous blood flow, while restricting arterial outflow, resulting in a net increase in blood volume.(19) This theory could explain why experimental studies have consistently failed to simulate placental transfusion, as those studies have employed positive pressure ventilation strategies to aerate the lungs, which generates positive intrathoracic pressures.

PHYSIOLOGICAL-BASED CORD CLAMPING

To understand the association between the timing of cord clamping and transitional changes at birth, we first need to explain the physiology of the fetal-to-neonatal transition.

Prior to birth

Before birth, the placenta is the primary site of both nutrient and respiratory gas exchange for the fetus. Deoxygenated blood leaves the fetus through the umbilical arteries to the placenta. After passing through the placenta blood is oxygenated and flows back to the fetus through the umbilical vein and ductus venosus towards the right atrium. Due to the funnel-shaped form of the ductus venosus and the Eustachian valve/ridge in the right atrium, the majority of oxygenated blood flows via the open foramen ovale to the left atrium and left ventricle to guarantee oxygenation of the myocardium and brain.[21] Approximately 30-50% of left ventricular preload is provided by the placenta, i.e. cardiac output is dependent on placental venous return.[22, 23] Most of the deoxygenated blood of the fetus coming from the inferior and superior vena cava is directed via the right ventricle towards the common pulmonary trunk. As the pulmonary vascular resistance (PVR) is high, most of the blood is then directed to the systemic circulation (aorta) via the ductus arteriosus (R to L shunt)(figure 1).[22] As the placenta has a very low vascular resistance, most of this blood then flows to the placenta where oxygenation will take place.

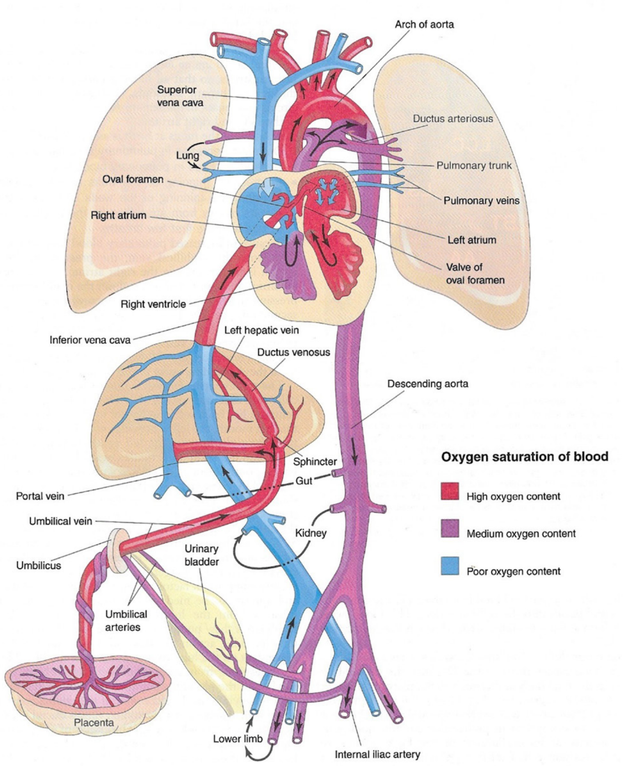

Figure 1 | Fetal circulation (prior to birth)
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After birth

According to international guidelines, the umbilical cord is clamped 1-3 minutes after birth in healthy term-born infants.[9] As the infant starts breathing or crying spontaneously, lung liquid is cleared across the distal airway walls due to the pressures gradients generated by breathing. As a result, the lungs aerate, which decreases PVR and increases pulmonary blood flow (PBF). Once PBF has increased, cardiac output is no longer dependent on placental venous return for preload, which is now provided by pulmonary venous return. When the umbilical cord is clamped after the lungs are aerated, cardiac output can therefore remain stable as preload is now provided by pulmonary return, while the lungs also function as the primary source of gas exchange (figure 2). However, when the umbilical cord is clamped prior to lung aeration, which is often the case in preterm infants, cardiac output is compromised as PBF remains low and placental venous return is absent, thus compromising preload to the left ventricle.

The cardiovascular instability resulting from cord clamping prior to lung aeration entails great fluctuations in cardiac output, blood pressures, and blood flow.[23] Consequently, these fluctuations may increase the risks for adverse outcomes in preterm infants such as IVH, NEC, and death. These detrimental outcomes could potentially be avoided if cord clamping is delayed until after lung aeration has been established.

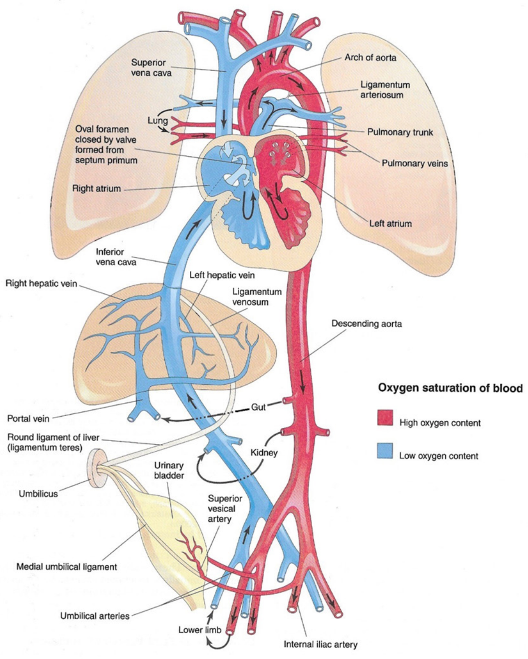

Figure 2 | Neonatal circulation (after birth)
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Physiological-based cord clamping

Physiological-based cord clamping (PBCC) is defined as delaying umbilical cord clamping until lung aeration has commenced. Instead of delaying cord clamping based on a specific amount of time, as with DCC, the umbilical cord is now clamped based on the infant's clinical and physiological status. The cardiopulmonary stability (described above) that results from PBCC has been demonstrated in experimental studies, but while the benefits are clear in theory[20, 23] and look promising for improving neonatal outcomes, neither the benefits nor physiology have yet been demonstrated in a clinical setting.

As performing PBCC is not feasible using the standard resuscitation tables, a new resuscitation table was constructed: the Concord birth trolley. This mobile resuscitation table is designed to provide the highest standard of care for preterm infants while the umbilical cord remains intact (figure 3). All equipment needed for stabilisation and/or resuscitation is built in to ensure that even infants in need of immediate resuscitation are able to receive the potential beneficial effects of PBCC. In addition to the potential cardiovascular benefits, the PBCC approach allows for both parents to remain close to their baby in the first minutes of life.

Figure 3 | Physiological-based cord clamping approach using the Concord resuscitation table
Image by Sophie Cramer

As mentioned before, the PBCC approach has so far only been investigated in experimental settings and clinical data is lacking. When translating this to the clinical setting it is important to confirm that similar beneficial physiological effects can be observed before performing large trials investigating the important clinical outcomes. The Concord resuscitation table allows us to investigate PBCC in a clinical setting, while closely monitoring neonatal parameters such as heart rate, oxygen saturation, and need for additional oxygen. Monitoring these parameters is pivotal to investigating the physiological changes during PBCC and to confirm the cardiovascular results seen in experimental studies.

AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to investigate the physiological changes that occur with physiological and time based cord clamping strategies, to obtain a better understanding of the optimal cord clamping moment and factors of influence. More specifically, this thesis will focus on the effect of spontaneous breathing on placental transfusion (part two) as well as the effects of PBCC on preterm neonates during and directly after resuscitation (part three). This thesis comprises experimental and observational studies and a randomised controlled trial.

In part one of this thesis a **general introduction** of umbilical cord clamping strategies are presented over time as well as the physiological and (beneficial) clinical effects that accompany these strategies.

Part two of this thesis focuses on placental transfusion and includes studies assessing the mechanisms that are responsible for this net blood volume shift as well as the effects of spontaneous breathing. While various theories have been put forward to explain the phenomena of placental transfusion, most of these theories have been refuted. However, there seems merit to the theory of spontaneous breathing as the driving force underpinning placental transfusion. To further investigate this, we collaborated with Professor Hooper's research group and investigated the effects of spontaneous breathing on umbilical venous blood flow in preterm born lambs, which is described in **chapter 1**. In this study blood flow measurements, intrapleural pressure and body weight were continuously measured to obtain a better understanding of the effect of spontaneous breathing on umbilical blood flow and placental transfusion. In addition, to investigate the effect of breathing during DCC an observational study was performed in healthy term born infants, described in **chapter 2**. Echocardiographic ultrasound measurements of the inferior vena cava (IVC), hepatic vein (HV) and ductus venosus (DV) were obtained while simultaneously visualizing diaphragm movement in order to correlate flow patterns to the related respiratory phase. Both HV and DV flow were used as a derivative of umbilical blood flow and therefore placental transfusion. In **chapter 3** an observational study is described in which both preductal and umbilical pulse oximetry measurements were obtained in infants who were stabilised after birth. Cardiac generated pressure pulses continue to reach the cord even after cord clamping and umbilical pulsatility can be palpated. Less motion artefacts and less vasoconstriction potentially make the umbilical cord a favourable location to quickly obtain heart rate (HR) measurements.

Part three of this thesis focusses on the implementation of PBCC in a clinical setting and the physiological changes during fetal-to-neonatal transition that occur with PBCC. In **chapter 4** an observational study is described in which the feasibility and safety of the PBCC approach are assessed when using the Concord resuscitation trolley. Both neonatal and obstetric teams were extensively trained and both briefing and debriefings were completed in order to improve this approach. During neonatal stabilisation vital parameters such as HR and oxygen saturation (SpO_2) were continuously monitored which enabled us to observe physiological changes in neonatal transition during PBCC and potentially improve hemodynamic stability. **Chapter 5** describes a non-inferiority randomised controlled trial on the effectiveness of the PBCC approach. The aim of this approach is to establish lung aeration prior to cord clamping and to provide full standard of care in neonatal stabilisation. This study compares the time needed to complete stabilisation to determine whether the PBCC approach was non-inferior to the time-based cord clamping (TBCC) approach. While transition is currently observed and measured during neonatal stabilisation, the infant's transitional status after birth could potentially be used as a predictor for (adverse) neonatal outcome. In **chapter 6** an observational echocardiographic ultrasound study is described focused on measuring the infant's transitional status after birth. DA flow measurements were obtained at 1 hour after birth in infants who received PBCC or TBCC and correlated with oxygenation parameters, which can currently be used to assess transitional status. Additionally, as infants received either PBCC or TBCC, measurements could be compared to observe if the increased hemodynamic stability of PBCC would still be present.

In part four, we provide an overall discussion on the main findings of the studies performed in this thesis, in regard to the current literature (**General discussion**). Future perspectives are contemplated with suggestions for further research. This thesis concludes with a summary of the discussed studies, which is provided in both English and Dutch.

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