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Effect of Deferred Cord Clamping on Respiratory Function in Neonates

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ABSTRACT

Background: the optimal timing of clamping of the umbilical cord after birth have been a subject of controversy and debate, However, there is insufficient evidence to date to support a recommendation as regards the impact of DCC on respiratory function in preterm neonates to delay cord clamping.

Aim of the work: this study aimed to evaluate the effect of deferred cord clamping on respiratory function in preterm neonates born vaginal.

Methods: The study was randomized controlled trial, including 100 Pregnant women (age 20-35 years old) had spontaneous preterm birth vaginal from 34-36^{+6} weeks, 50 subjected to ECC and 50 subjected to DCC.

Results: neonates in the two-randomization group differed significantly in requirement of O2 and ventilatory support, and neonates in the ECC group had a mean that was higher than neonates in the DCC group in both CPAP and nasal O2 (ECC 6 (12.0%) vs. DCC 1 (2.0%) – ECC 27 (54.0%) vs. DCC 18 (36.0%) in CPAP and O2 requirement respectively. Apgar scores at 1 and 5 min were significantly different in the two groups, and in general higher in DCC than ECC, reflecting better respiratory symptoms in group DCC.

Conclusion: the existing literature on delayed cord clamping has consistently demonstrated benefit especially for preterm neonates in facilitating placental transfusion. Improved physiologic stability in transition (blood pressure), better respiratory outcome, reduced need for transfusion is valuable improvements in outcome.

Keywords: DCC; ECC; preterm; respiratory.

INTRODUCTION

• **Charles White: 1773.** "The common method of tying and cutting the navel string in the instant the child is born, is likewise one of those errors in practice that has nothing to plead in its favour but custom".

• **Darwin E: 1801** "Another thing very injurious to the child, is the tying and cutting of the navel string too soon; which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be, a portion of the blood being left in the placenta, which ought to have been in the child" [(1)].

Traditionally, the umbilical cord is clamped and cut immediately after birth, but in 2010, the Inter-national Liaison Committee on Resuscitation (ILCOR) recommended that the cord should not be cut for at least 1min after birth in infants not requiring resuscitation. Recently the need of resuscitation is not acontraindication for DCC bedside resuscitation can be done. This recommended change in practice is to facilitate blood transfer from placenta to baby to reduce iron deficiency and later anemia[(2)].

Umbilical cord clamping (CC) and sub-sequent cutting are routine procedures performed at all facility-based deliveries, but the optimal time for clamping remains unclear. After decades with focus on immediate or early cord clamping (ECC), the past

15 years have seen a shift toward delayed cord clamping (DCC). This issue has provoked intense international debate and is further complicated from a lack of what defines both ECC and DCC[(3)].

ECC has been described as CC performed from 10 seconds and up to 60 seconds post delivery, whereas DCC is defined as CC performed after 30 to 60 seconds or extending up to 2 to 3 minutes of birth, and/or after cessation of pulsations in the cord. Accumulating evidence suggests that CC beyond 30 to 60 seconds after birth is of benefit for most infants[(3)].

Multiple studies have demonstrated that delayed clamping of the umbilical cord at delivery, with consequent flow of autologous placental blood into the neonate, will provide up to 30 percent more blood volume and 60 percent more red blood cells (RBCs) to the neonate than after immediate cord clamping. For preterm neonates, several clinical trials of delayed versus immediate cord clamping have reported mixed results sometimes favorable with improved circulatory hemodynamics, better cardiopulmonary adaptation to extrauterine life, diminished need for RBC transfusions, and less intraventricular hemorrhage after delayed cord clamping. For term infants, however, concerns have been raised that delayed clamping results in hypervolemia with respiratory distress, erythrocytosis with plethora and hyperviscosity, and hyperbilirubinemia. Thus, delayed cord clamping is not widely practiced in the United States because favorable clinical endpoints of delayed umbilical cord clamping trials have been inconsistent and because delayed cord clamping precludes prompt resuscitation of preterm neonates and may cause problems of "overtransfusion" in term infants[(4)].

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For the first few minutes after birth, there is still circulation from the placenta to the infant. Waiting to clamp the umbilical cord for 2–3 min, or until cord pulsations cease, allows a physiological transfer of placental blood to the infant (the process referred to as "placental transfusion"), the majority of which occurs within 3 min. This placental transfusion provides sufficient iron reserves for the first 6–8 months of life, preventing or delaying the development of iron deficiency [(1)].

METHODS

Participants and study protocol:

This was randomized controlled trial is carried out in the period from (June 2016 – February 2017), including 100 Pregnant women (age 20-35 years old) had spontaneous preterm birth vaginal from 34-36^{+6} weeks according to inclusion and exclusion criteria. **The study was approved by the Ethics Board of Ain Shams University.**

All women were subjected to Personal history, Complaint, present history, past history, Family history, Obstetric history, Physical examination and Investigations as needed.

All patients having inclusion criteria (age 20-35 years old, GA 34-36^{+6} weeks and spontaneous PTL) were randomly assigned to either one of two groups:

1) Group A: in which ECC.
2) Group B: in which DCC.

Exclusion criteria:

Any maternal or fetal condition associated with the need of immediate neonatal resuscitation were excluded as:

1- High risk pregnancy like hypertension (PIH), gestational diabetes mellitus (GDM), pre-eclampsia and placental insufficiency (cyanotic heart disease, pulmonary disease).
2- Infants with antenatal diagnosis of congenital malformations of any system (CVS, GIT, RENAL, CNS, RESP) .
3- Fetal distress.
4- Multiple gestation.
5- Fetal illness(fetal hydrops, Rhesus sensetization, IUGR).
6- RH negative pregnant.
7- PROM(premature rupture of membranes).

Data analysis and clinical observation

Steps were integrated DCC, ENC and AMTSL at vaginal birth for preterm births:

1. Baby was delivered and placed below mother's level, and immediate ENC initiated thoroughly drying baby and assessing breathing.
2. Immediately, or within 1 minute of delivery, we gave the mother an uterotonic drug (ensuring absence of second baby before giving uterotonic). Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug. An uterotonic was offered to all women.
3. Clamping of the umbilical cord was deferred until separation of placenta following the birth for all births.
4. During that time, we continue with ENC ensuring baby is kept dry, and ensuring normal breathing or crying. Covering the baby with dry cloth or blanket, including the head (with hat, if possible).
5. If the placenta separated, we clamp the cord.

Primary and secondary outcome

Primary outcome: Neonatal respiratory symptoms were assessed immediately, 1hr, 6hrs after birth in both groups.

Respiratory symptoms include:

- Respiratory rate above 60 (tachypnea), presence of nostril flaring, grunting or intercostal retraction.
- Oxygen requirements.
- Requirement of ventilatory support.

Secondary outcome

- Neonatal death.
- 1 min Apgar [Time Frame: at 1 minute of life].
- 5 min Apgar [Time Frame: at 5 minutes of life].
- Need for manual removal of placenta.
- Need for therapeutic Oxytocin.
- Length of hospital stay.
- Requirement of phototherapy.
- Duration of phototherapy [Time Frame: 1 month].
- Number and volume of blood transfusions.

Both primary and secondary outcomes was recorded for every case 50 case with early cord clamping and 50 case with deferred cord clamping chosen according to the randomly distributed appendex.

Initial newborn assessment (Apgar score):

We evaluated newborn Appearance, Pulse, Grimace, Activity, Respiratory rate and effort. At one, five minutes 1hour and 6 hours, a numerical score of 0, 1, or 2 is assigned each parameter. A score of 0 indicates maximum distress/dysfunction for that parameter. A score of 2 means the opposite.

Appearance is an evaluation of the neonate's color. Cyanotic, pale babies receive a 0. A condition of acrocyanosis (pink body, blue extremities) receives a 1. (Acrocyanosis is normal for newborns). Babies who are completely pink receive a 2. This is rare because it usually takes several hours to make the necessary change from neonatal circulation and adequately perfuse the extremities.

Table 1: APGAR scoring system [5]

APGAR SCORING SYSTEM

SCORE	0	1	2
APPEARANCE (color)	blue, pale	body pink, extremities blue	pink
PULSE (heart rate)	absent	below 100	above 100
GRIMACE (response to stimulation)	none	cry, some motion	vigorous cry
ACTIVITY (muscle tone)	flaccid	some flexion	well-flexed and active
RESPIRATION (rate, effort)	absent	slow, irregular	good, deep inspiration

After assigning a numerical score for each category, the scores are added. Normal neonates are usually scored from 7 to 10. Moderately depressed neonates receive scores of 4, 5 and 6. Severely depressed neonates receive lower scores less than 4. The one minute score determines what type of care and/or resuscitation is required. The six minute score establishes how stable the newborn is and how successful your care has been. The six minute score may be higher or lower than the one minute score. As the baby makes the successful transition to extrauterine life, the score may increase. Meconium babies also can have a low one minute score due to intubation during that first minute. As they get over this trauma, the six minute score is higher. On the other hand, upon cessation of the massive stimulation associated with birth, both activity and respiration of the neonate may decrease. This results in a lower six minute score in some neonates.

Statistical Methods

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.
- Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.
  - Sensitivity = (true +ve)/ [(true +ve) + (false –ve)].
  - Specificity = (true –ve) / [(true –ve) + (false +ve)].

- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.

P-value >0.05 was considered insignificant

RESULTS

Characteristics of the subjects

Table 2 shows the characteristics of the study participants.

Table 2: demographic characteristics of the studied patients

characteristics		N	%
Parity	Primigravida	41	41%
	Multigravida	59	59%
		Mean±SD	Range
Gestational Age (weeks)		35.78±0.44	34-36
Maternal age (years)		23.65±4.92	17-38

Comparison between groups according to respiratory symptoms at 1hr and 6hrs:

This table showed statistically significant difference between groups according to respiratory symptoms 1hr after birth.

Table 3: Comparison between groups according to respiratory symptoms at 1hr

Respiratory symptoms	Group(I) ECC	Group (II) DCC	t/x2*	p-value
Respiratory rate Mean±SD Range	 41.88±6.64 30-54	 38.16±5.19 30-52	9.743	0.002
Nostril flaring Negative Positive	 21 (42.0%) 29 (58.0%)	 35 (70.0%) 15 (30.0%)	7.955*	0.005
Grunting Negative Positive	 21 (42.0%) 29 (58.0%)	 35 (70.0%) 15 (30.0%)	7.955*	0.005
Intercostal retraction Negative Positive	 20 (40.0%) 30 (60.0%)	 34 (68.0%) 16 (32.0%)	7.89*	0.005

Relative risk of respiratory symptoms: 1.93 [1.19-3.14]

Table 4: comparison between groups according to respiratory symptoms at 6 hrs

Respiratory symptoms	Group(I) ECC	Group (II) DCC	t/x2*	p-value
Respiratory rate Mean±SD Range	 42.01±6.64 30-55	 37.89±5.12 30-52	9.743	0.002
Nostril flaring Negative Positive	 22 (43.0%) 28.9(57.0%)	 35 (70.0%) 15 (30.0%)	7.955*	0.005
Grunting Negative Positive	 22 (44.0%) 28 (56.0%)	 36 (72.0%) 14 (28.0%)	7.955*	0.005
Intercostal retraction Negative Positive	 21 (42.0%) 29 (58.0%)	 34 (68.0%) 16 (32.0%)	7.89*	0.005

Relative risk of respiratory symptoms: 1.93 [1.19-3.14]

This table shows statistically significant difference between groups according to respiratory symptoms at 6hrs.

Comparison between groups according to O2 and ventilatory support

Table 5: comparison between groups according to requirement of O2 and ventilatory support

Requirement of O2 and ventilatory	Group (I) ECC	Group (II) DCC	x2	p-value
O2 requirements				
CPAP	6 (12.0%)	1 (2.0%)		
Nasal O2	27 (54.0%)	18 (36.0%)	9.455	0.009
Negative	17 (34.0%)	31 (62.0%)		

This table showed statistically significant difference between groups according
to requirement of O2 and ventilator.

Neonates in the two-randomization group differed significantly in requirement of O2 and ventilatory support, and neonates in the ECC group had a mean that was higher than neonates in the DCC group in both CPAP and nasal O2 (ECC 6 (12.0%) vs. DCC 1 (2.0%) – ECC 27 (54.0%) vs. DCC 18 (36.0%) in CPAP and O2 requirement respectively) Table (4), so in requirement of O2 and ventilatory support there was significant difference between both groups Fig. (1).

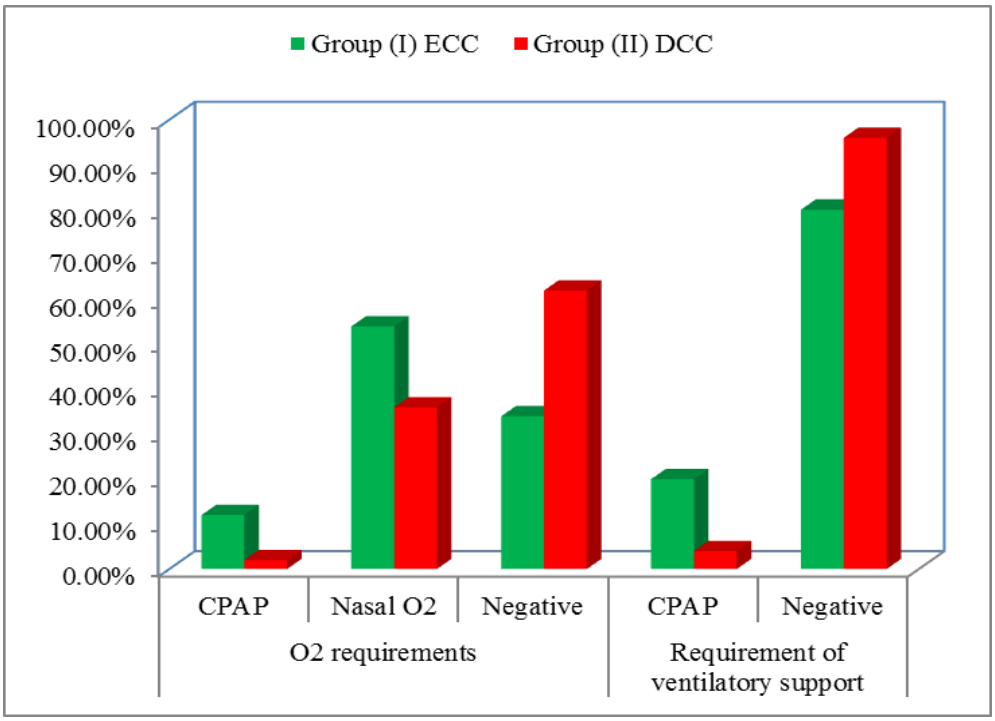

Fig. 1: bar chart between groups according to requirement of O2 and ventilator.

Comparison between groups according to Apgar score

Table 6: comparison between groups according to Apgar score

Apgar score	Group (I) ECC	Group (II) DCC	z-test	p-value
Apgar 1 min.				
Median (IQR)	5 (5)	10 (4)		
Mean±SD	6.82±2.50	8.44±2.06	4.517	0.002
Range	3-10	5-10		
Apgar 5 min.				
Median (IQR)	6 (5)	10 (4)		
Mean±SD	7.36±2.38	8.74±2.00	3.861	0.003
Range	3-10	5-10		

This table showed statistically significant difference between groups according to Apgar score.

Apgar scores at 1 and 5 min were significantly different in the two groups, and in general higher in DCC than ECC, reflecting better respiratory symptoms in group DCC as shown in table (6).

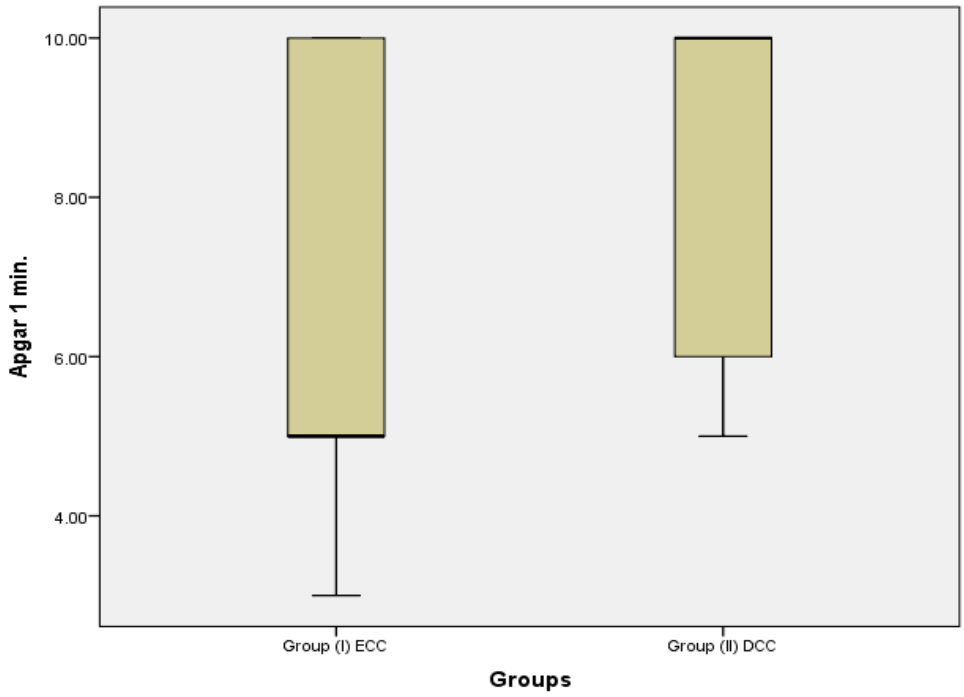

Fig. 2: box plot between groups according to Apgar score 1 Min.

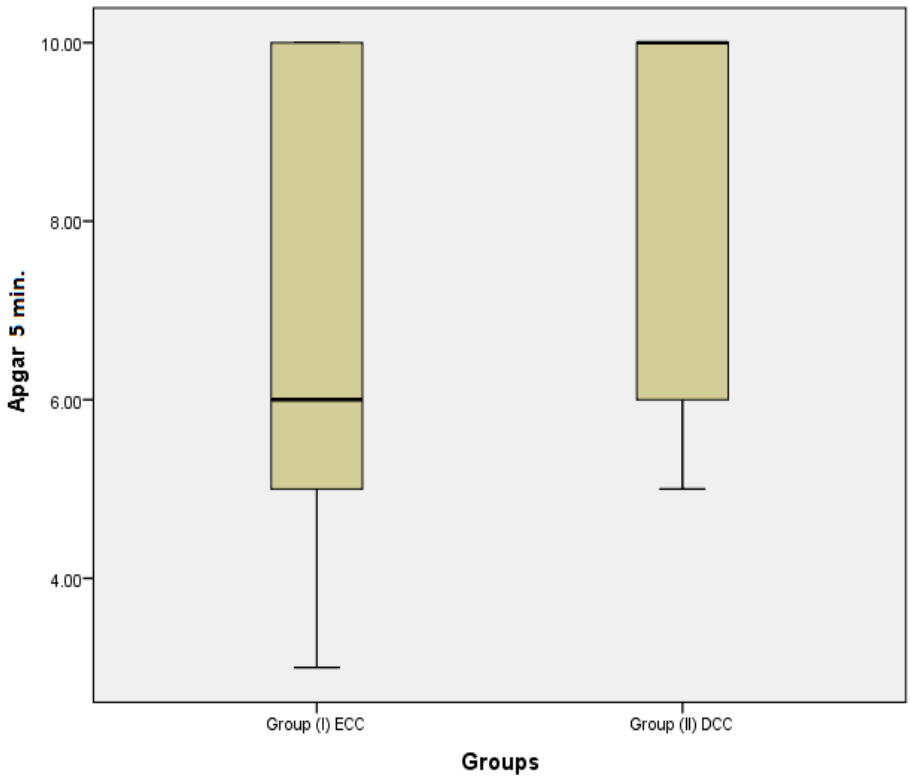

Fig. 3: box plot between groups according to Apgar Score 5 min.

Comparison between groups according to NICU admission (days)

Table 7: comparison between groups according to NICU admission (days)

Length of NICU admission (Days)	Group (I) ECC	Group (II) DCC	t-test	p-value
Mean±SD	8.19±9.03	2.94±4.66	13.362	<0.001
Range	0.33-30	0.33-18		

This table showed highly statistically significant difference between groups according to length of NICU admission (days).

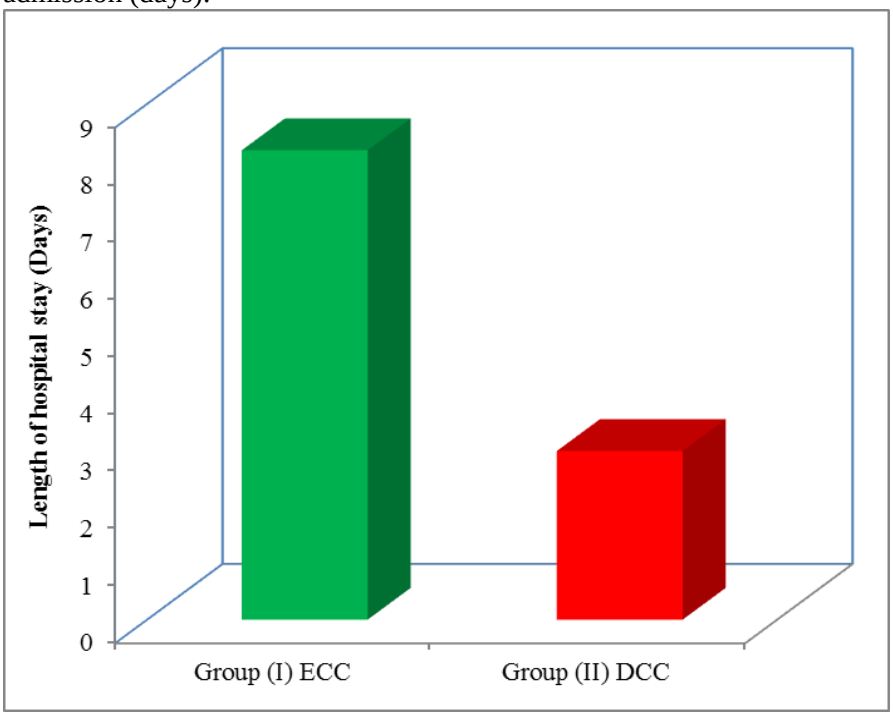

Fig. (4): Bar chart between groups according to length of NICU admission (days).

There was no relative difference between the need of manual removal of placenta, need of therapeutic oxytocin and need for blood transfusion as this study focus on respiratory symptoms in early hours of neonatal life.

DISCUSSION

This study was a prospective, randomized, clinical trial that was conducted in obstetrics and gynecology department Ain-Shams university maternity hospital (June 2016 – February 2017). The aim was to study immediate versus delayed clamping of the umbilical cord regarding respiratory function mainly in early neonatal life.

The study included pregnant women (age 20-35 years old) had spontaneous preterm vaginal birth of preterm neonates 34-36+6 weeks' gestation with no obstetrical complications such High risk pregnancy like hypertension، gestational diabetes mellitus, pre-eclampsia and placental insufficiency، antenatal diagnosis of congenital malformations, Fetal distress or illness, Multiple gestation, RH negative pregnant and premature rupture of membranes.

100 pregnant ladies in spontaneous preterm labor were enrolled in the study and divided into 2 groups group A (50 cases of ECC) were the cord was clamped within 30 seconds and group B (50 cases of DCC) were the cord clamping was deferred until separation of placenta.

Comparison between groups according to respiratory symptoms 1hr and 6 hrs after birth, according to requirement of O2 and ventilatory support، according to Apgar score 1min and 5 min after birth, according to NICU admission (days), and Comparison between groups according to requirement of phototherapy and duration. Each of these comparisons shows results in the favor of DCC showing improvement of respiratory symptoms.

The time to umbilical cord clamping may have important impact on newborn respiratory function, as shown by the results in this thesis and previous data. This study was set out to make a broad approach to the subject, and tried to evaluate a wide array of proposed effects of delayed versus early cord clamping. Furthermore, we wanted to focus much more on respiratory symptoms than

previous studies . Yet, very few human studies have explored the physiologic changes around respiration and cord clamping in preterm births. This study focus on respiratory symptoms 1 hr and 6 hrs after birth observing respiratory symptoms as primary outcome. In these few minutes of DCC the 30% more blood volume an infant receives from a placental transfusion contains iron rich red blood cells, stem cells, and plasma volume and other substances which all play a role in the infant's adaptation to life outside the womb.

In this thesis we admit that we had to exclude number of maternal and fetal conditions which might represent relative contraindications to facilitated placental transfusion. Growth restriction, especially if a result of chronic intrauterine hypoxia, may be associated with higher risk for polycythaemia and hyperviscosity. Maternal diabetes and pre-eclampsia also represent circumstances associated with intrauterine hypoxia. Non-vigorous infants born through meconium stained amniotic fluid have historically undergone immediate intubation for tracheal suctioning, prompting immediate cord clamping.

We documented a significant improvement in respiratory symptoms after delayed cord clamping. This finding supports a report by others in which neonatal whole respiratory symptoms was improved after delayed cord clamping versus immediate clamping.

This improvement in respiratory symptoms was reflected, immediately‹
by a significant increase in blood volume to the baby as the cord pulsates and the placenta continues providing oxygen, red blood cells, stem cells, immune cells in the delayed umbilical cord clamping. About half of the blood volume of preterm babies is contained in the placenta, and delaying cord clamping can result in an increase in blood volume, particularly after vaginal birth. Placental transfusion as an important part of the birthing process is facilitated by delayed cord clamping and can ensure safe oxygen levels and blood volume for the baby. Neonates in the two-randomization group differed significantly in requirement of O2 and ventilatory support, and neonates in the ECC group had
a mean that was higher than neonates in the DCC group in both CPAP and nasal
O2 (ECC 6 (12.0%) vs. DCC 1 (2.0%) – ECC 27 (54.0%) vs. DCC 18 (36.0%) in CPAP and O2 requirement respectively).

Apgar scores at 1 and 5 min were significantly different in the two groups, and in general higher in DCC than ECC, reflecting better respiratory
symptoms in group DCC.

There was no relative difference between the need of manual removal of placenta, need of therapeutic oxytocin and need for blood transfusion as this study focus on respiratory symptoms in early hours of neonatal life.

A transiently higher respiratory rate after DCC was shown by studies in 1971, but neither Hutton & Hassan or the Cochrane report did find any
significantly higher risks of respiratory symptoms associated with DCC [(6)]. In our study, we observed infants for signs of respiratory distress at 1 and 6 hours, and we observed differences between the two groups. Other study stated that effects of Delayed versus Early Cord Clamping on Healthy Term Infants they observed infants for signs of
respiratory distress at 1 and 6 hours, and did not find any differences between
the two groups **[(6)]**.

The Royal College of Obstetricians and Gynecologists published a very interesting paper recorded:

Timing of cord clamping for births before 37 weeks of gestation has been evaluated in 15 randomized trials involving 738 babies. Recruitment was between 24 weeks and 36 weeks of gestation, although most were before 33 weeks. Risk of bias was unclear in many of the trials. Primary outcomes for the babies were death, death or neurosensory disability at 2 years of age, grade 3 or
4 intraventricular hemorrhage, and periventricular leukomalacia **[(7)]**.

Preterm babies allocated to deferred cord clamping had higher serum bilirubin levels, but there was no clear difference in jaundice requiring phototherapy in the three trials reporting this outcome and no clear difference between the groups in oxygen requirement at 36 weeks of postmenstrual age [(7)]. For preterm births the evidence is less clear than for term births‹ although data from the trials suggest potential benefit by deferred rather than immediate cord clamping. Strategies and equipment for providing initial neonatal care and resuscitation at the woman's bedside with the cord intact should be developed further and evaluated **[(7)]**.

International Childbirth Education Association published**[(8)]** Delayed cord clamping and premature infants, Infants weighing < 1500 g with DCC tended to have higher mean BP, and needed less mechanical ventilation and surfactant compared with ICC neonates. Infants with DCC did not experience more polycythaemia (Hct > 60%), but had a trend toward higher bilirubin levels with no differences in the phototherapy needs. DCC seems to be safe and may be beneficial when compared with ICC in premature neonates. Buckley sites a 1993 study where premature babies experienced 30 second DCC and showed a reduced need for transfusion, less severe breathing problems,

better oxygen levels and indications of probable improved long-term outcomes [8].

Mayri Sagady Leslie[9] published Perspectives on Implementing Delayed Cord Clamping**:**

In a classic study, Yao and Lind demonstrated that DCC provides as much as a 30 percent increase in blood volume for term infants and a 50 percent increase for preterm infants. Cochrane review on preterm infants and DCC shows that waiting to clamp the cord improves systemic blood pressure, increases the cerebral oxygen index, reduces the number of blood transfusions required, lessens the need for inotropic support, and lowers the risk of necrotizing enterocolitis and results in nearly a twofold reduced risk for intracranial hemorrhage of all types[9].

The practice of rapid cord clamping has been questioned. There is evidence supporting a clinical benefit of delayed umbilical cord clamping (30–60 s) in preterm infants. About half of the blood volume of preterm babies is contained in the placenta, and delaying cord clamping can result in an increase in blood volume, particularly after vaginal birth. Meta-analysis of fifteen trials of delayed cord clamping in preterm babies showed that this practice results in higher haematocrit, less need for later transfusion, less NEC and an almost 50% reduction in intraventricular hemorrhage. A large multicentre trial is underway to determine if this practice genuinely improves short- and long-term outcome [10].

Current ILCOR (International Liaison Committee on Resuscitation (guidelines recommend that cord clamping should be delayed by 1 min in babies not requiring resuscitation, but state that there is insufficient evidence to support or refute a recommendation to delay clamping in babies requiring resuscitation. Our study shows that delaying cord clamping until after ventilation begins could have marked beneficial effects in infants requiring respiratory support [11].

The reported cardiovascular benefits in the neonate include higher haematocrit, reduced blood transfusions, improved blood pressure and superior vena cava flow, increased blood volumes, improved respiratory function, reduced incidence of necrotizing enterocolitis, reduced intraventricular hemorrhage and better cerebral oxygenation. However, there is much debate as to the length of time after birth that umbilical cord clamping should be delayed [11].

Healthy self-breathing neonates are more likely to die or be admitted if CC occurs before or immediately after onset of SR. These clinical observations support the experimental findings of a smoother cardiovascular transition when CC is performed after initiation of ventilation. Infants who had their cord clamped before the initiation of SR were more likely to die or exhibit early medical issues after delivery. Conversely the risk of death and/or admission decreased to a minimum if CC was delayed for 2 minutes after initiation of breathing, an effect independent of BW, GA, FHR, and pregnancy complications [12].

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