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Optimal umbilical cord management in different clinical situations; evidence of short and long term neonatal outcomes

Ola Andersson
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Norsk Perinatalmedisinsk Forening
faglig webinar onsdag 11.11.2020

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Guidelines

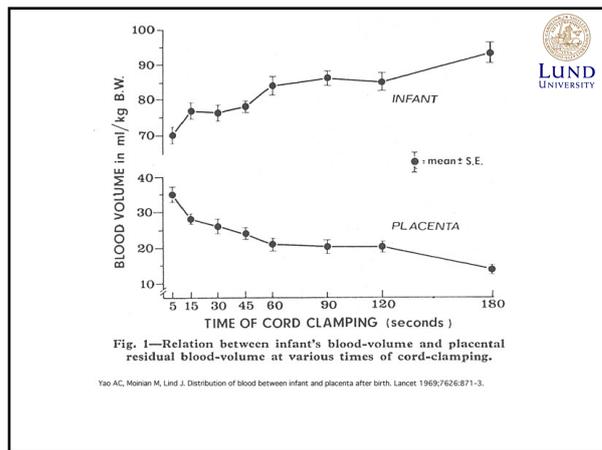
		Term	Preterm
Sweden	2008	2-3 min	30-120 s
WHO	2014	> 1 min	=
Norway	2014	1-3 min	=
UK (NICE)	2014	1-5 min	=
USA (ACOG)	2017	> 30-60 s	=
Italy	2018	1-3 min	60 s (< 29w) > 90 s (> 29w)
ERC/ILCOR	2020	> 1 min	=

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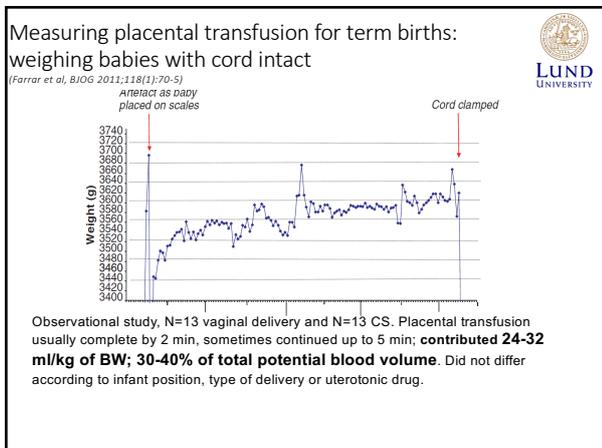
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What happens during delayed cord clamping?

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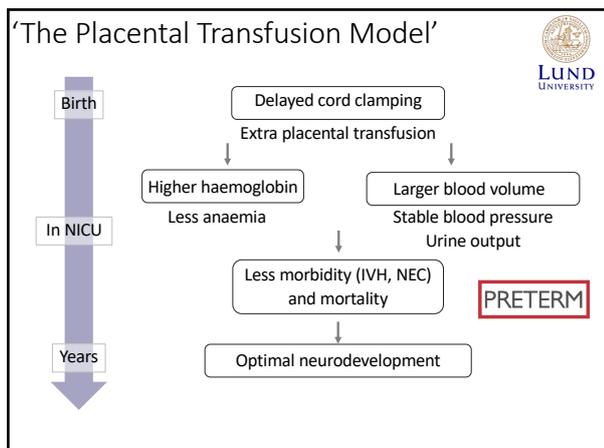


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Effects on preterm infants?

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Cochrane Library
Cochrane Database of Systematic Reviews

Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Review)

Rabe H, Gyte GML, Díaz-Rossello JL, Duley L

Rabe H, Gyte GML, Díaz-Rossello JL, Duley L
Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes.
Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD003248.
DOI: 10.1002/14651858.CD003248.pub4.

Rabe & al. Cochrane 2012

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Main findings

P: Twentyfive studies (3100 infants) between 24 and 36+6 weeks' gestation at birth
I: maximum delay in cord clamping 180 seconds.
C: early cord clamping
O: Delaying cord clamping was associated with

- probably reduced the numbers of babies who die before discharge, 20 studies, 2680 babies
RR 0.73, 95% CI 0.54 to 0.98 (moderate certainty)
- slightly reduced numbers of babies with any grade IVH, 15 studies, 2333 babies
RR 0.83, 95% CI 0.70 to 0.99 (high certainty)

Rabe & al. Cochrane 2019

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Cardiovascular effects

- Mean arterial blood pressure** in the early hours after birth (in mm Hg):
average MD 2.87, 95% CI 1.09 to 4.64, 4 studies, 208 babies, random-effects model, (low-certainty evidence, downgraded due to serious imprecision).
- Inotropics** for low bloodpressure during first 24 hours of life:
RR 0.37, 95% CI 0.17 to 0.81, 5 studies, 250 babies, random-effects model, very low-certainty evidence, downgraded due to unclear risk of bias and serious imprecision

Rabe & al. Cochrane 2019

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Haematological effects

- Hyperbilirubinemia** (treated by phototherapy)
RR 1.05, 95% CI 0.95 to 1.16, 8 studies, 495 babies, random-effects model, high-certainty evidence
- Blood transfusion** in infant:
RR 0.66, 95% CI 0.50 to 0.86, 11 studies, 2280 babies, random-effects model). moderate-certainty evidence, downgraded as some studies seemed to be missing, suggesting potential publication bias).

Rabe & al. Cochrane 2019

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No differences in

- PVL: **RR 0.58**, 95% CI 0.26 to 1.30, 4 studies, 1544 babies
- NEC: **RR 0.91**, 95% CI 0.64 to 1.28, 11 studies, 2010 babies
- CLD: **RR 1.04**, 95% CI 0.94 to 1.14, 6 studies, 1644 babies
- Home oxygen: **RR 0.47**, 95% CI 0.06 to 3.72, 2 studies, 101 babies
- Treatment of ROP: **RR 0.83**, 95% CI 0.62 to 1.12, 8 studies, 1827 babies
- Late sepsis: **RR 0.79**, 95% CI 0.56 to 1.10, 10 studies, 2017 babies

Rabe & al. Cochrane 2019

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Milking

Delayed cord clamping (DCC) with immediate neonatal care after cord clamping versus umbilical cord milking (UCM)
(three studies, 322 babies and their mothers)

UCM versus early cord clamping (ECC) (11 studies, 1183 babies and their mothers)

There are **insufficient data for reliable conclusions** about the comparative effects of UCM compared with delayed or early clamping (mostly low or very low certainty).



Rabe & al. Cochrane 2019

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Research

JAMA | Original Investigation

Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants

Anup Katheria, MD, Frank Reister, MD, Jochen Essers, MD, Marc Mendler, MD, Helmut Hummler, MD, Akila Subramaniam, MD, Waldemar Carlo, MD, Alan Tita, MD, Giang Truong, MD, Shareece Davis-Nelson, MD, Georg Schmolzer, MD, Radha Chari, MD, Joseph Kaempf, MD, Mark Tomlinson, MD, Toby Yanowitz, MD, Stacy Beck, MD, Hyagriv Simhan, MD, Eugene Dempsey, MD, Keelin O'Donoghue, MD, Shazia Bhat, MD, Matthew Hoffman, MD, Arif Falsh, MD, Kathy Arnell, RN, Wade Rich, RRT, Neil Fine, MD, Yvonne Vaucher, MD, MPH, Paritosh Khanna, MD, Mariana Meyers, MD, Michael Varner, MD, Philipp Altmann, MS, Jeff Szychowski, PhD, Gary Cutter, PhD

Planned enrollment was 750 per group. However, a safety signal comprising an imbalance in the number of severe intraventricular hemorrhage events by study group was observed at the first interim analysis; enrollment was stopped

INTERVENTIONS Participants were randomized to umbilical cord milking (n = 236) or delayed umbilical cord clamping (n = 238).

Katheria & al. 2019. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. JAMA. doi:10.1001/jama.2019.16004

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Death or Severe IVH

Table 2. Primary Composite Outcome Overall and in Prespecified Subgroups

	Umbilical Cord Milking No./Total No. (%)	Delayed Umbilical Cord Clamping No./Total No. (%)	Risk Difference, % (95% CI)	P Value*
Overall	29/236 (12)	20/238 (8)	4 (-2 to 9)	.16
By gestational age at birth strata				
23 wk 0 d through 27 wk 6 d	26/93 (28)	17/89 (19)	9 (-3 to 21)	.16
28 wk 0 d through 31 wk 6 d	3/143 (2)	3/149 (2)	0 (-3 to 3)	.99
By mode of delivery subgroups				
Cesarean	17/180 (9)	13/159 (8)	1 (-5 to 7)	.68
Vaginal	12/56 (21)	7/79 (9)	12 (0 to 25)	.04

Katheria & al. 2019. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. JAMA. doi:10.1001/jama.2019.16004

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Severe IVH

Table 3. Secondary Outcomes by Treatment Group, Overall, and Within Specified Subgroups

	Umbilical Cord Milking No./Total No. (%)	Delayed Umbilical Cord Clamping No./Total No. (%)	Risk Difference, % (95% CI)	P Value*
Severe Intraventricular Hemorrhage (Grade 3 or 4), No./Total No. (%)				
Overall	20/236 (8)	8/238 (3)	5 (1 to 9)	.02
By gestational age at birth strata				
23 wk 0 d through 27 wk 6 d	20/93 (22)	5/89 (6)	16 (6 to 26)	.002
28 wk 0 d through 31 wk 6 d	0/143	3/149 (2)	-2 (-4 to 1)	.24
By mode of delivery subgroups				
Cesarean	10/180 (6)	6/159 (4)	2 (-3 to 6)	.44
Vaginal	10/56 (18)	2/79 (3)	15 (5 to 26)	.004

Katheria & al. 2019. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. JAMA. doi:10.1001/jama.2019.16004

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Preterm infants <33 weeks of gestation admitted to the Canadian Neonatal Network between January 2015 and December 2017

9729 included; 4916 (50.5%) ECC, 394 (4.1%) UCM, and 4419 (45.4%) DCC.

ECC group compared with UCM group
Mortality or major morbidity: aOR, **1.18**; 95% CI, 1.03-1.35).

ECC as compared with DCC
Mortality: aOR, **1.6** [95% CI, 1.22-2.1]
IVH: aOR, **1.29** [95% CI, 1.19-1.41].

UCM compared with DCC
Severe IVH were **higher with UCM**: aOR, **1.38**; 95% CI, 1.05-1.81)

Peak serum bilirubin levels were not significantly different.

Conclusions
Both DCC and UCM were associated with better short-term outcomes than ECC; however, the odds of severe intraventricular hemorrhage were higher with UCM compared with DCC.

El-Naggar, WJ, Afi, J, Dorling, J, Bodani, J, Gieslak, Z, Canning, R, Ye, X, Y, Crane, J, Lee, S, K, Shah, P, S. 2020. A Comparison of Strategies for Managing the Umbilical Cord at Birth in Preterm Infants. The Journal of Pediatrics. doi:10.1016/j.peds.2020.05.018

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Neurodevelopment?



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Randomised trial of cord clamping at very preterm birth: outcomes at 2 years

Lindsay Armstrong-Buisseret, Kate Powers, Ian Darling, Lucy Bradshaw, Samantha Johnson, Elaine Mitchell, Lella Duley

	Clamp \leq 2 min+neonatal care with cord intact n=115 (%)	Clamp \geq 20 s+neonatal care after clamping n=103 (%)	Risk difference (95% CI)	Risk ratio (95% CI)
Death or adverse neurodevelopmental outcome	24 (21)	35 (34)	-33% (-25% to -1%)	0.61 (0.39 to 0.96)
Death	8 (7)	16 (16)	-9% (-17% to 0%)	0.45 (0.20 to 1.00)
Adverse neurodevelopmental outcome	16 (14)	19 (18)	-5% (-14% to 5%)	0.75 (0.41 to 1.39)

Armstrong-Buisseret L, Powers K, Darling J, Bradshaw L, Johnson S, Mitchell E, Duley L, 2020. Randomised trial of cord clamping at very preterm birth: outcomes at 2 years. Archives of Disease in Childhood - Fetal and Neonatal Edition. doi:10.1136/archdischild-2019-316812

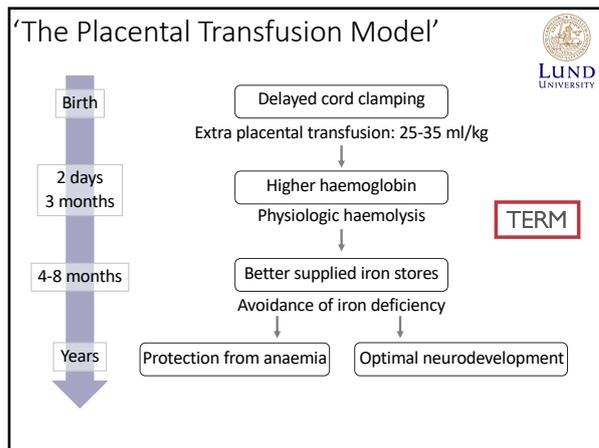


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Effects on term infants?



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Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes (Review)

McDonald SJ, Middleton P, Downswell T, Morris PS



THE COCHRANE COLLABORATION®

This is a review of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2013, Issue 7
<http://www.thecochranelibrary.com>

McDonald & al. Cochrane 2013



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P: 15 trials involving a total of 3911 term infants
 I: Later (delayed) cord clamping > than one minute after birth or when cord pulsation has ceased
 C: Early clamping within 60 seconds of the birth of the infant
 O: **Early cord clamping** was associated with

- lower birth weight, 12 trials, 3139 infants
101 g decrease, 95% CI 45 to 157
- Lower hemoglobin at 24-48 hours, 884 infants
Mean difference -14.9 g/L, 95% CI -17.8 to -12.1
- Increased risk for iron deficiency, five trials, 1152 infants
RR **2.65** 95% CI 1.04 to 6.73



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Two RCTs on cord clamping

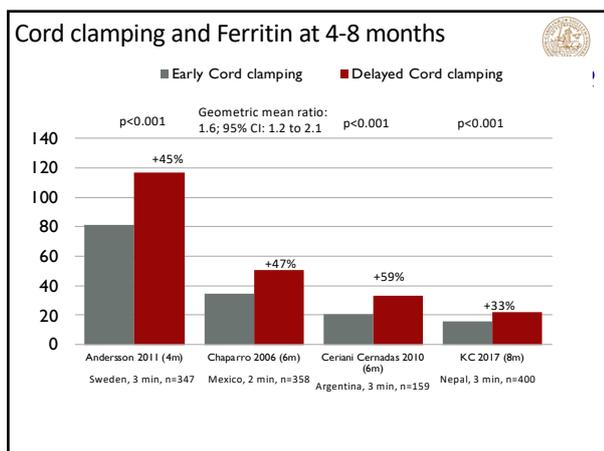
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Study

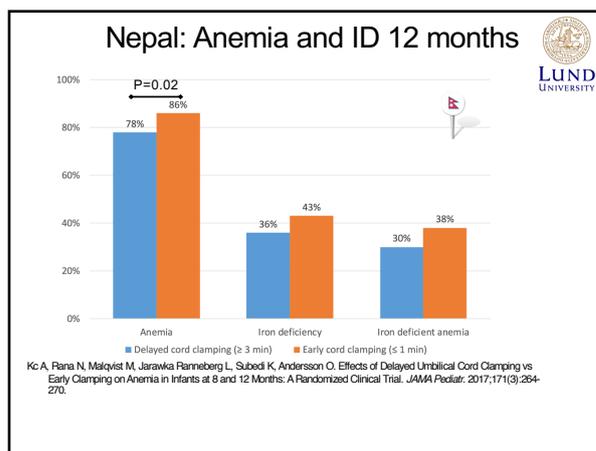
- Inclusion**
 - 400 (200 ≥ 180 s; 200 ≤ 10 s)
 - April 2008 to May 2009
 - 13 months
- Follow-up**
 - Blood and iron status
 - Birth, 48-72 h, 4 months, 12 months
 - Bilirubin (blood)
 - 48-72 h
 - Development (ASQ)
 - 4, 12 months
 - 48 months (also WPPSI & MABC)

- Inclusion**
 - 540 (270 ≥ 180 s; 270 ≤ 60 s)
 - Oct 2014 to Nov 2014
 - 8 weeks
- Follow-up**
 - Blood and iron status (Hb+Fer)
 - 8 and 12 months
 - Bilirubin (transcutaneous)
 - 6-24 h
 - Development (ASQ)
 - 12 months

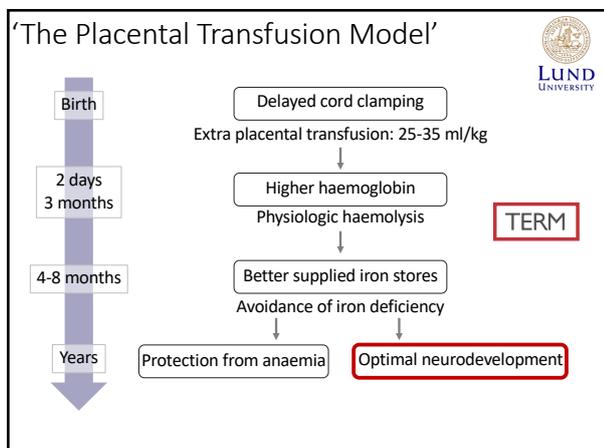
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Why worry about iron and development?

- Hippocampus
- Myelin
- Dopaminergic neurons

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ORIGINAL ARTICLES www.jpeds.com • THE JOURNAL OF PEDIATRICS

The Effects of Delayed Cord Clamping on 4-Month Ferritin Levels, Brain Myelin Content, and Neurodevelopment: A Randomized Controlled Trial

Justin S. Murray, PhD^{1,2,3,4}, Debra A. Erickson-Owens, PhD^{1,2,3,4}, Sean C. L. Dixon, PhD^{1,2,3,4}, Douglas C. Dean, II, PhD^{1,2,3,4}, Jennifer Collins, MD^{1,2,3,4}, James B. Paster, MD^{1,2,3,4}, Wai-Hing Ip, MD^{1,2,3,4}, Sarah Jensen, MD^{1,2,3,4}, Emily B. Moore, MD^{1,2,3,4}, and James F. Padbury, MD^{1,2,3,4}

The Effects of Delayed Cord Clamping on 12-Month Brain Myelin Content and Neurodevelopment: A Randomized Controlled Trial

Justin S. Murray, PhD^{1,2,3,4}, Debra A. Erickson-Owens, PhD^{1,2,3,4}, Sean C. L. Dixon, PhD^{1,2,3,4}, Douglas C. Dean, II, PhD^{1,2,3,4}, Jennifer Collins, MD^{1,2,3,4}, Richard Tucker, MD^{1,2,3,4}, Ashley B. Parker, MD^{1,2,3,4}, Sarah Jensen, MD^{1,2,3,4}, Emily B. Moore, MD^{1,2,3,4}, Jennifer Collins, MD^{1,2,3,4}, James F. Padbury, MD^{1,2,3,4}

P: 73 healthy term pregnant women and their singleton fetuses
 I: Delayed umbilical cord clamping (DCC, >5 minutes)
 C: Immediate clamping (ICC, <20 seconds).
 O: At 4 months of age, blood was drawn for ferritin levels.
 Brain myelin content was measured with magnetic resonance imaging at 4 and 12 months.

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ORIGINAL ARTICLES www.jpeds.com • THE JOURNAL OF PEDIATRICS

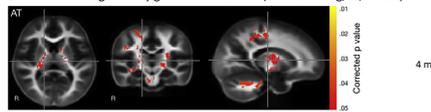
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Ferritin:
 At 4 months, infants with DCC had significantly greater ferritin levels (96.4 vs 65.3 ng/dL, $P = .03$)

Myelin:


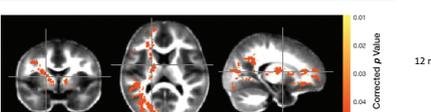
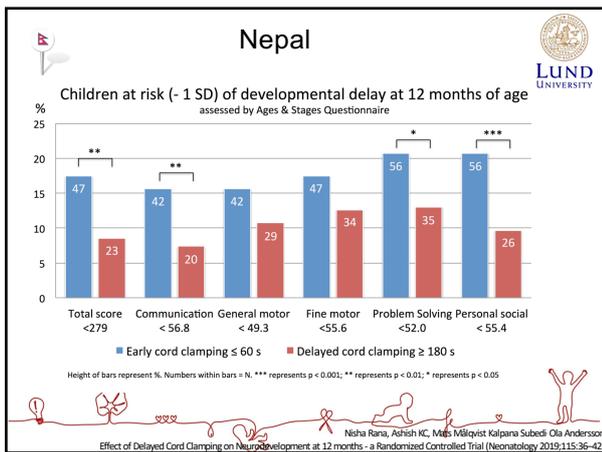
 At 12 months:


Figure 3. Group differences in myelin content between infants with DCC vs ICC by actual treatment. Significance is indicated by the color scale on the right with yellow at P value of .01 and red at a P value of .05. The color represents areas in which myelin is greater in infants who had DCC compared with those who had ICC. DCC, delayed cord clamping; ICC, immediate cord clamping; MRI, magnetic resonance imaging.

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Neurodevelopment in Sweden at 4 years

- 263 children (68.8%)
- Delayed CC improved the adjusted mean differences (AMDs) in the ASQ
 - **fine-motor** (AMD, 2.1; 95% CI, 0.2-4.0) domains
 - **personal-social** (AMD, 2.8; 95% CI, 0.8-4.7)
- Strengths and Difficulties Questionnaire
 - **prosocial subscale** (AMD, 0.5; 95% CI, >0.0-0.9).
- Fewer children in the delayed-CC group had results **below the cutoff** in the
 - ASQ fine-motor domain (11.0% vs 3.7%; $P = .02$) and
 - Movement ABC bicycle-trail task (12.9% vs 3.8%; $P = .02$).

Andersson & al. JAMA Peds 2015

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What about jaundice?

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Jaundice and phototherapy

- Phototherapy 1.61 [1.04, 2.44]
- 4.4% (52/1193) vs 2.7% (31/1131)
- Unpublished data (one study, 1996)
 - 7.7% (37/483) vs. 4.6 % (22/480)
- Published data
 - 2.1% (15/710) vs. 1.4% (9/651)

McDonald & al. Cochrane 2013

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Argentinian study



	Early CC (n=91)	Delayed CC (n=90)	p
Laboratory data at 24-48 hours of age			
Bilirubin (µmol/L)	124	122	n.s.
median (first quartile–third quartile)	(95-153)	(85-153)	
Bilirubin > 275 µmol/L, n (%)	2 (2.2)	0 (0.0)	n.s.

Ceriani Cernadas & al 2006

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Sweden: Bilirubin




	Early CC (n=129)	Delayed CC (n=136)	p
Laboratory data at (mean) 2.4 days of age			
Bilirubin (µmol/L)	144 (62)	145 (67)	0.96
Bilirubin > 275 µmol/L, n (%)	3 (2.3)	1 (0.7)	0.36
Treated with phototherapy , n (%)	2 (1.1)	1 (0.5)	0.62

p value calculated by: Student's t test for continuous variables and Fischer's exact test for dichotomous variables.

Andersson & al. BMJ 2011

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Nepal: Bilirubin




- No differences at discharge (n=540)
 - ECC 87.3 vs DCC 85.4 µmol/L, p=0.6
- At high risk of needing phototherapy
 - ECC 22 (8.6%) vs DCC 25 (9.7%), p=0.4

Rana & al. Submitted

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Cesarean section



Neonatology Original Paper
Neonatology 2018;14(2):202-209
DOI: 10.1186/s13052-018-0262-2

Received: March 11, 2018
Accepted: February 28, 2018
Published online: July 2, 2018

Delayed Cord Clamping versus Early Cord Clamping in Elective Cesarean Section: A Randomized Controlled Trial

Francesco Cavallini¹, Beatrice Galazzo², Vittoria Lorenti³, Stefania Madella³, Martina Pizzoloto³, Silvia Visentini³, Daniele Trevisanato³

¹Hospital of Obstetrics, Bologna, Italy; ²Department of Women's and Children's Health, University of Padua, Padua, Italy

JAMA | Original Investigation

Effect of Delayed vs Immediate Umbilical Cord Clamping on Maternal Blood Loss in Term Cesarean Delivery: A Randomized Clinical Trial

Stephanie E. Parizich, MD, Candice V. Ananth, PhD, MPH, Brittany Arditi, MD, MSCR, Logan Mauney, MD, Barouq Ajemian, MD, Amy Heiderich, MD, Tina Leone, MD, Cynthia Gyamfi-Bannerman, MD, MSc

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Cesarean section



Neonatology Original Paper
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Delayed Cord Clamping versus Early Cord Clamping in Elective Cesarean Section: A Randomized Controlled Trial

Francesco Cavallini¹, Beatrice Galazzo², Vittoria Lorenti³, Stefania Madella³, Martina Pizzoloto³, Silvia Visentini³, Daniele Trevisanato³

¹Hospital of Obstetrics, Bologna, Italy; ²Department of Women's and Children's Health, University of Padua, Padua, Italy

N 40 + 40

Conclusions: Delaying cord clamping beyond 60 s increases the hematocrit at day 2 in neonates born through elective CS, without affecting maternal blood losses.

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Cesarean section



JAMA | Original Investigation

Effect of Delayed vs Immediate Umbilical Cord Clamping on Maternal Blood Loss in Term Cesarean Delivery: A Randomized Clinical Trial

Stephanie E. Parizich, MD, Candice V. Ananth, PhD, MPH, Brittany Arditi, MD, MSCR, Logan Mauney, MD, Barouq Ajemian, MD, Amy Heiderich, MD, Tina Leone, MD, Cynthia Gyamfi-Bannerman, MD, MSc

N 57 + 56

Delaying cord clamping beyond 60 s increases the hematocrit at 24-72 h in neonates born through elective CS, without affecting maternal blood losses.

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Intact cord resuscitation

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Intact cord resuscitation



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Bhatt 2013

J Physiol 591, 8 (2013) pp 2113-2126

Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs

Sasmira Bhatt^{1,2}, Beth J. Alison¹, Euan M. Wallace^{1,2}, Kelly J. Crossley^{1,2}, Andrew W. Gill³, Martin Kluckow⁴, Arjan B. te Pas⁵, Colin J. Morley⁶, Graeme R. Polglase^{1,2} and Stuart B. Hooper^{1,2}

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⁴Department of Neonatal Medicine, Royal North Shore Hospital and University of Sydney, Sydney, New South Wales, 2065, Australia
⁵Department of Pediatrics, Leiden University Medical Centre, Leiden, The Netherlands
⁶Department of Neonatal Research, The Royal Women's Hospital, Melbourne, Australia

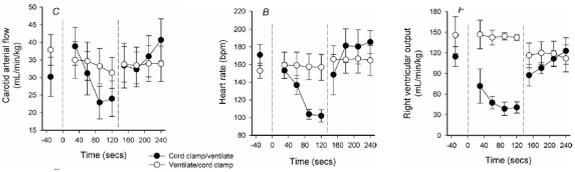
6 preterm (123 days) lambs in each group

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Clamping after ventilation resulted in:

- More stable carotid arterial flow
- More stable heart rate
- Higher right ventricular output



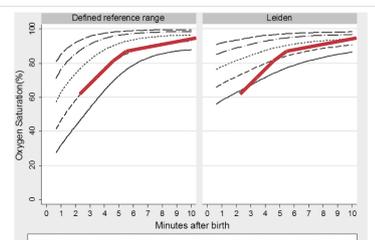
Bhatt, S. & al. *J Physiol*, 591(8), 2113-2126

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Cardiovascular effects in term infants

DCC higher O2 saturation



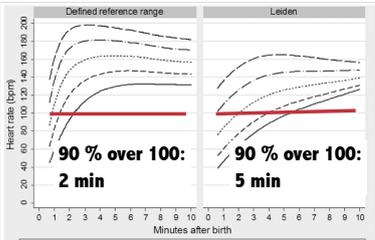
- Smit & al, 2014: DCC and immediate skin to skin contact
 - N=109
- Defined reference range (J.Dawson 2010, N=308)

Smit M, Dawson JA, Ganzeboom A, Hooper SB, van Roosmalen J, te Pas AB. Pulse oximetry in newborns with delayed cord clamping and immediate skin-to-skin contact. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2014 March 31, 2014

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DCC lower heart rate



- Smit & al, 2014: DCC and immediate skin to skin contact
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P: Infants identified at risk for resuscitation were randomized (n=30 per group)
 I: CC at 5 minutes.
 C: CC at one minute
 O: The need for resuscitation was 63% (19/30) in the 1-minute group and 43% (13/30) in the 5-minute group. The 5-minute group had greater cerebral oxygenation and blood pressure at 12 hours of life

Katheria AC, Brown MK, Faksh A, Hassen KO, Rich W, Lazarus D, et al. Delayed Cord Clamping in Newborns Born at Term at Risk for Resuscitation: A Feasibility Randomized Clinical Trial. *J Pediatr* 2017; 187:313-7 e1.



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P: Congenital diaphragmatic hernia, before and after design (n=20 in each group)
 I: DCC, intact cord resuscitation
 C: ICC, immediate cord clamping
 O: The pH was higher, and the plasma lactate concentration was significantly lower at one hour after birth in the intact cord resuscitation group. Mean blood pressure was significantly higher 1, 6 and 12 hours after birth in the intact cord resuscitation group

Lefebvre C, Rakza T, Weslinck N, et al. Feasibility and safety of intact cord resuscitation in newborn infants with congenital diaphragmatic hernia (CDH). *Resuscitation*. 2017;120:20-25



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Pilot study i Nepal

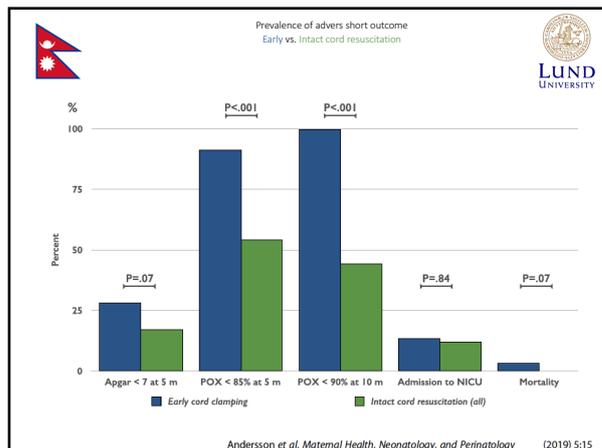


Included = 1560
 Randomisation at birth

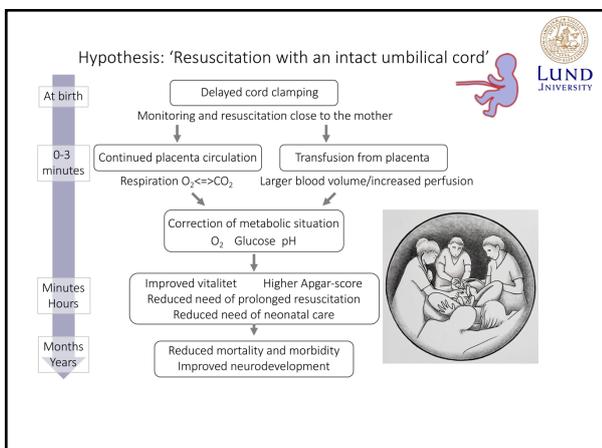
Delayed cord clamping total= 780	Early cord clamping total = 780
In need of resuscitation total= 231	



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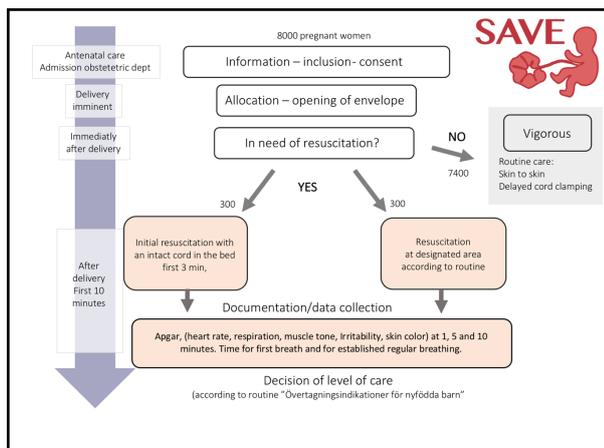
SAVE



Sustained cord clamping Awaiting VENTilation



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Acknowledgements

Whole team in Nepal, foremost **Dr Ashish KC** and **Nisha Rana**

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