

Umbilical Cord Clamping: First Do No Harm



**Audrey Harris Neonatal
Conference
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Disclosure

The presenter has an NICHD grant to study delayed cord clamping in term infants.

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THINK BIG



WE DO™



FUNDING SOURCES

Sigma Theta Tau – Delta Upsilon Chapter-at-Large (2008)

ACNM Foundation Graduate Scholarship (2008)

Women & Infants Hospital Department of Pediatrics

NIH – NINR K23 NR08027 (2003-2006)

NIH – NINR RO1 NR100015 (2008-2013)

Thrasher Research Foundation (2011-2014)

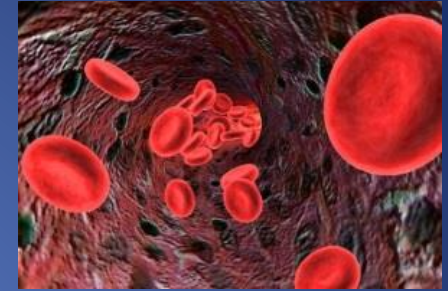
Bill and Melinda Gates Foundation (2012-2013)

NIH – NICHD – R01 HD076589 (2012-2017)

BILL & MELINDA
GATES foundation



Objectives

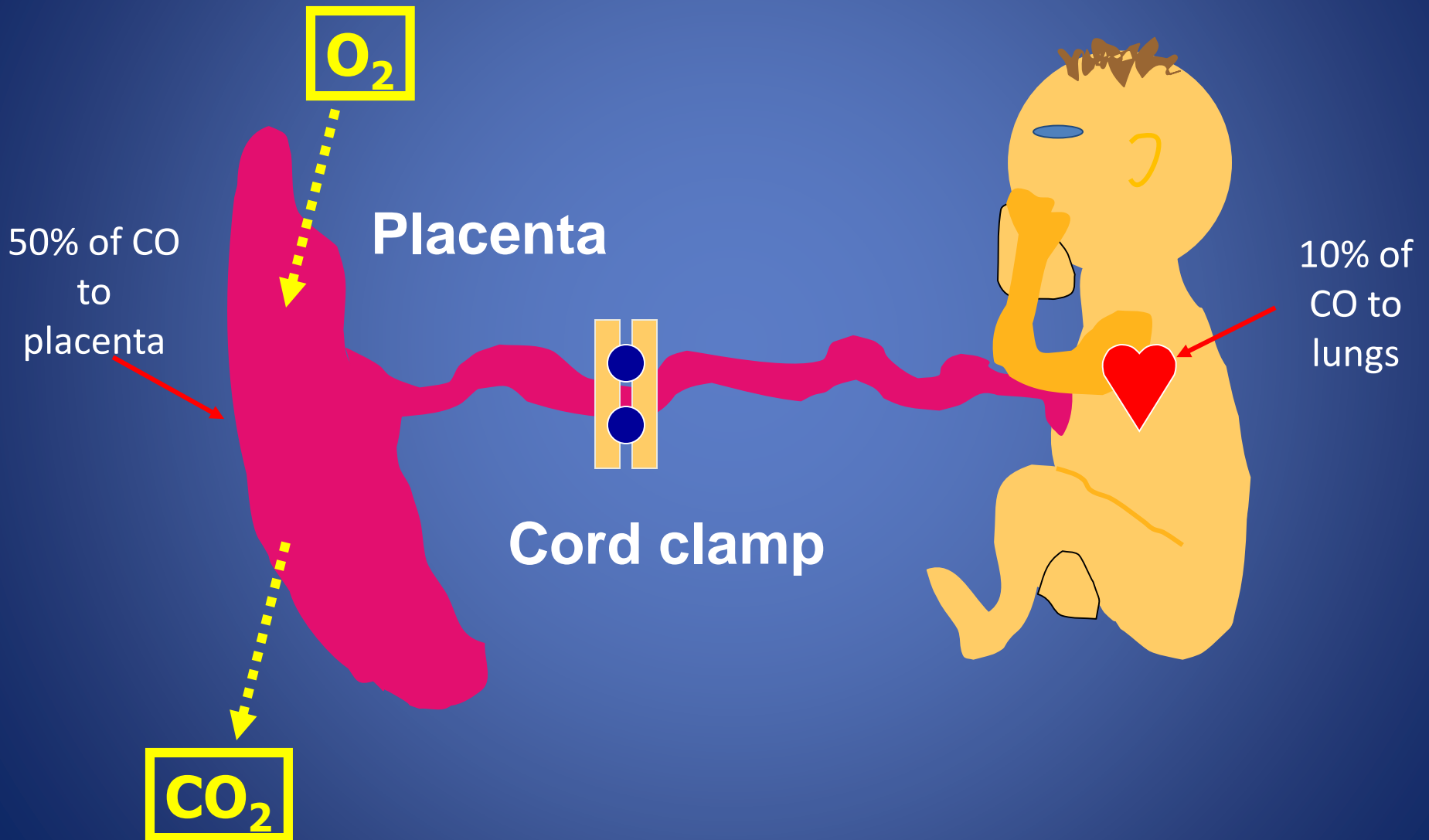


- Review effects of immediate and delayed cord clamping on fetal to neonatal transitional physiology
- Examine the current evidence about umbilical cord clamping in term and preterm infants and potential risks
- Describe methods to ensure delayed cord clamping and/or cord milking at birth, and when complex situations occur

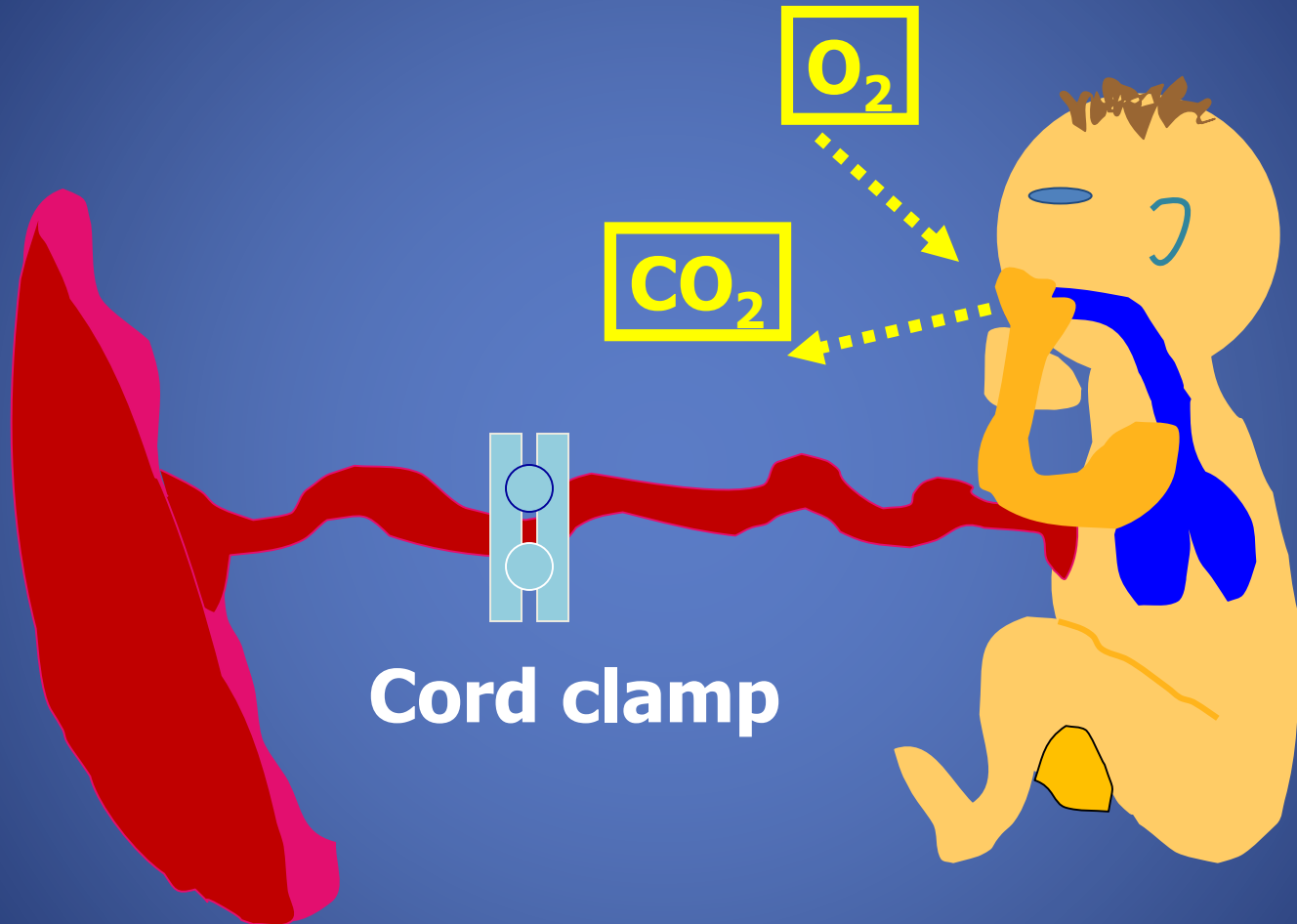
Review effects of cord clamping time on fetal to neonatal transitional physiology



Immediate Cord Clamping (ICC)



Delayed Cord Clamping (*DCC*)



1/3rd blood volume
returned to the newborn

Placental Transfusion

- The transfer of residual placental blood to the baby during the 1st few minutes of life
- Techniques:
 - Delayed Cord Clamping
 - Umbilical Cord Milking
 - Cut and milk by pediatric provider



Factors that Affect Amount of Placental Transfusion

- Time of Cord Clamping
- Gravity
- Uterine contractions
- Cord milking
- Not pulsations

Forces behind Placental Transfusion

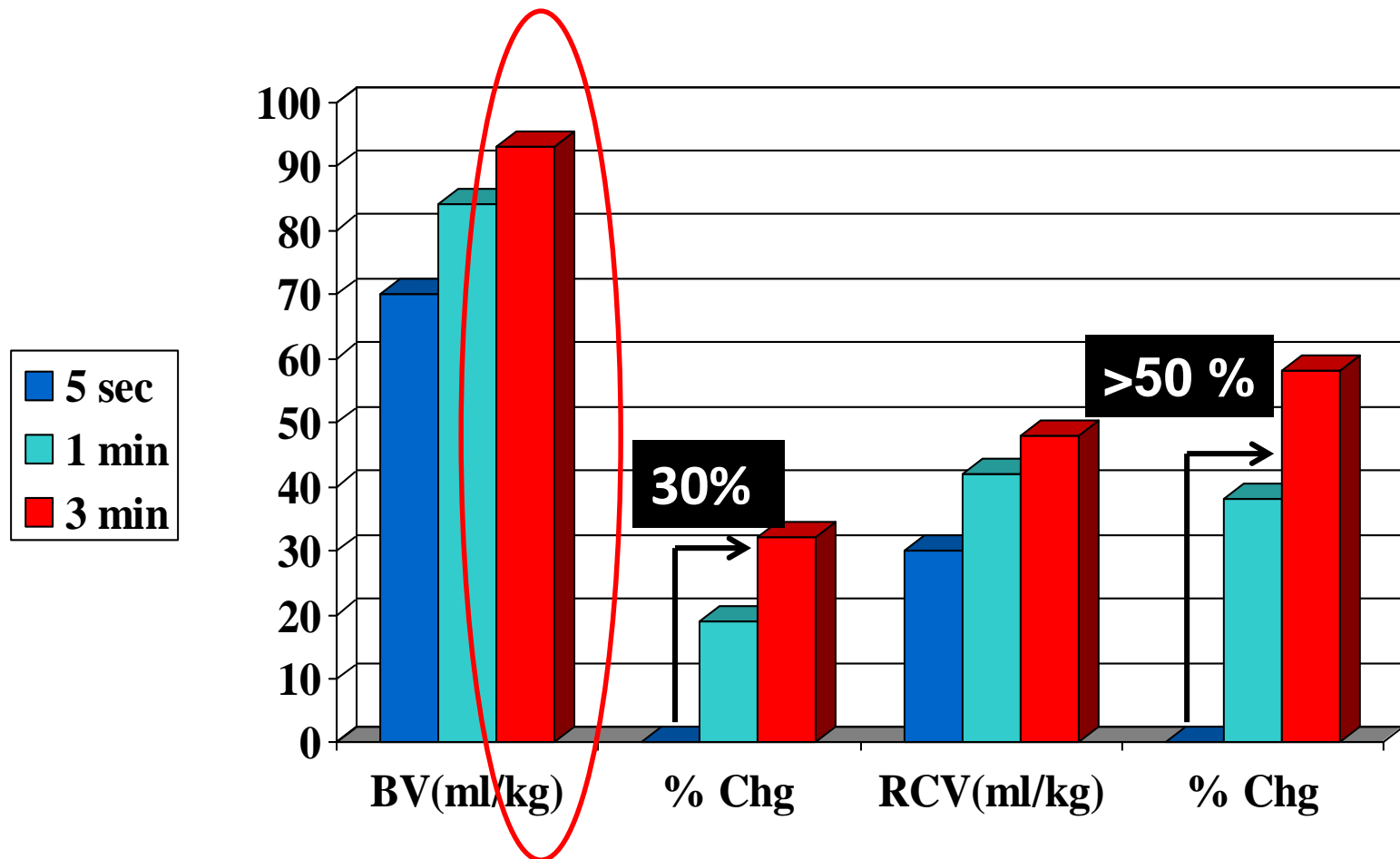
Step 1:

- Baby's heart continues to pump blood through cord & placenta
- Arteries close when O₂ reaches newborn levels and pulsations cease

Step 2:

- Uterine contractions squeeze placenta
- Remaining infant's blood transferred to the infant via umbilical vein

Percent Change in Blood Volume (BV) & Red Cell Volume (RCV) Due to Delayed Cord Clamping



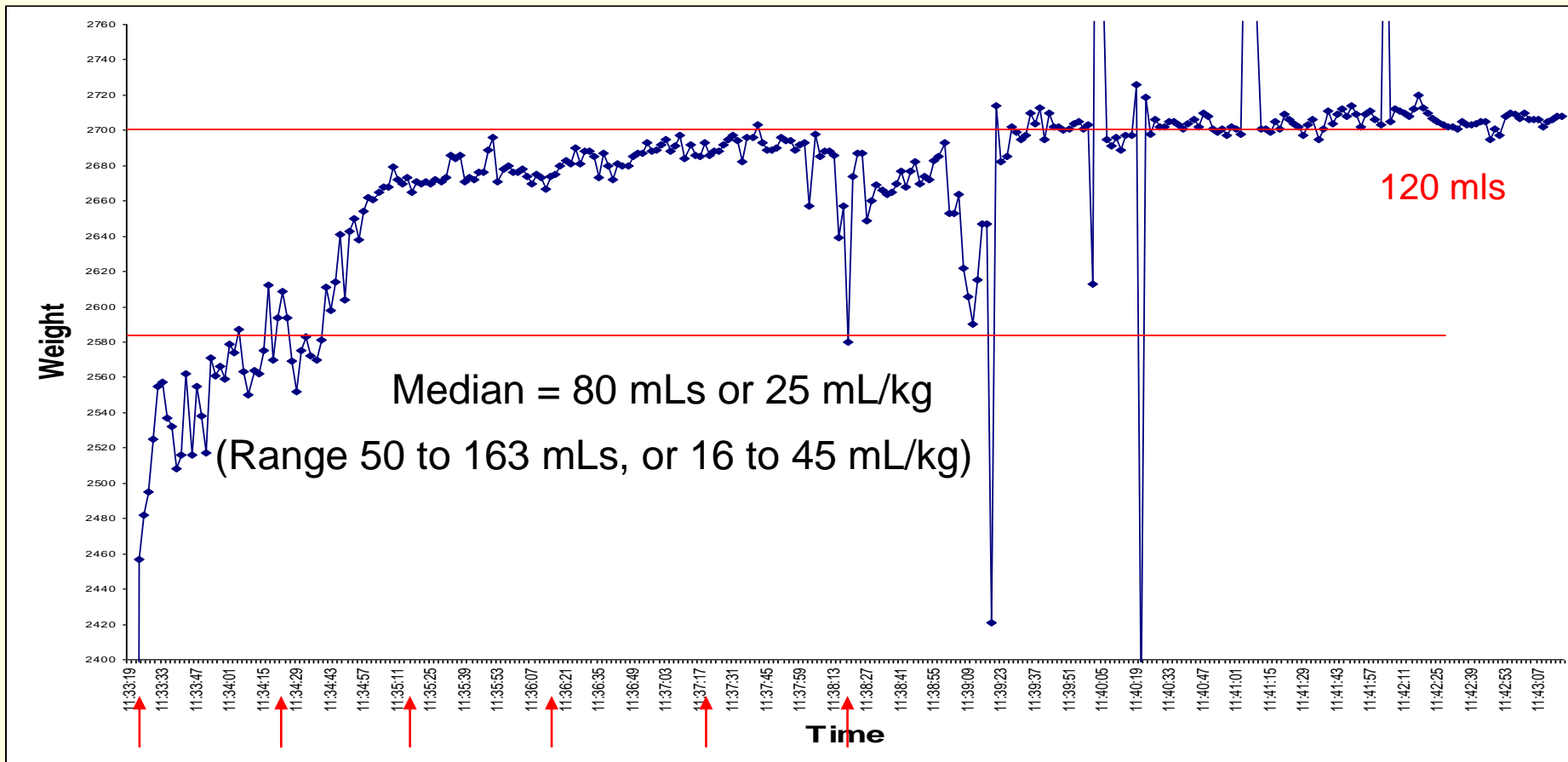
Adapted from Yao, Lind, et al, "Distribution of Blood between Infant and Placental after Birth,"
Lancet, Oct 25, 1969.

Vaginal Birth



Farrar D, (2011). Measuring placental transfusion for term births: weighing babies with cord intact. *BMJ*

Vaginal Birth



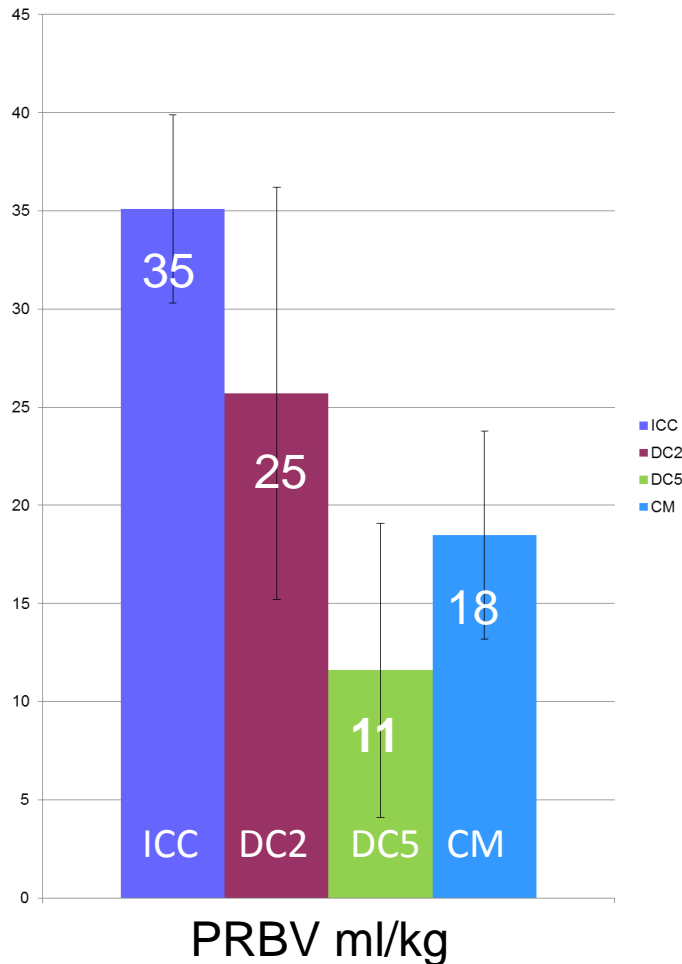
Red arrows indicate 1 minute intervals. Median = 80 mls (50-163)

Immediate Cord Clamping (ICC)

- A practice that leaves a large amount of the baby's blood volume behind in the placenta
- Does not support placental transfusion
- Developed without scientific evidence or study
- Remains the most common practice across the US



Placental Residual Blood Volume (PRBV) with Skin-To-Skin Placement



PRBV ml/kg

ICC vs. DC 2 min $p = .14$

ICC vs. DC 5 min $p < .0001$

ICC vs. Cord Milking $p < .0001$

DC2 vs. DC5 $p < .005$

Skin-to-skin placement slows
transfusion, delay longer if
using skin-to-skin

Erickson-Owens, Mercer & Thulier, 2012, JPNN

What Does the Baby Receive with a placental transfusion?

- Warm oxygenated blood with:
- RBCs - 15 mL/kg
- Iron: 30 to 75 mg (enough for 3 to 6 mo's need)
- Stem Cells - millions (1st autologous transplant) and other factors
- Plasma for volume expansion - 20 to 30 mL/kg

Stem Cells and Progenitor Cells In Cord Blood

- Hematopoietic stem cells
- Non-hematopoietic stem cells
 - Mesenchymal
 - unrestricted somatic
 - multilineage progenitor
 - embryonic-like
 - oligodendrocyte progenitor cells

Cotton, MC et al, 2014

What Stem Cells Do

- Secrete neurotropic factors
 - growth factors and cytokines
- Prevent cell death
- Decrease microglial activation
- Engraft and differentiate
- Promote endogenous stem cell self-renewal

Factor Isolated from Cord Blood Could Treat Harmful Inflammation, Sepsis

A factor found in umbilical cord blood could become the basis for developing a new therapy to fight harmful inflammation.

The newly discovered factor countered signs of inflammation and sepsis, such as fever, fluctuations in respiratory rate, and death.

Christian C. Yost, et al, Neonatal NET-inhibitory factor and related peptides inhibit neutrophil extracellular trap formation

J Clin Invest. doi:10.1172/JCI83873

REVIEW

Rescuing the neonatal brain from hypoxic injury with autologous cord blood

Y Liao¹, M Cotten², S Tan³, J Kurtzberg² and MS Cairo^{1,4,5,6,7}

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL
ARTICLES

Feasibility of Autologous Cord Blood Cells for Infants with Hypoxic-Ischemic Encephalopathy

C. Michael Cotten, MD¹, Amy P. Murtha, MD², Ronald N. Goldberg, MD¹, Chad A. Grotegut, MD², P. Brian Smith, MD¹, Ricki F. Goldstein, MD¹, Kimberley A. Fisher, PhD¹, Kathryn E. Gustafson, PhD³, Barbara Waters-Pick, BS, MT(ASCP)⁴, Geeta K. Swamy, MD², Benjamin Rattray, MD¹, Siddhartha Tan, MD⁵, and Joanne Kurtzberg, MD⁶

NEURAL REGENERATION RESEARCH

September 2015, Volume 10, Issue 9

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● INVITED REVIEW

Enhancing endogenous stem cells in the newborn *via* delayed umbilical cord clamping

Christopher Lawton, Sandra Acosta, Nate Watson, Chiara Gonzales-Portillo, Theo Diamandis, Naoki Tajiri, Yuji Kaneko, Paul R. Sanberg, Cesar V. Borlongan*

Center of Excellence for Aging and Brain Repair, Department of Neurosurgery and Brain Repair, University of South Florida College of Medicine, Tampa, FL, USA

Physiologic Studies



Physiologic Outcomes in Studies of Delayed Cord Clamping

Hematologic

- ↑ RCV, Hct, Hb
- ↓ Hypovolemia

Iron Stores

- ↑ Ferritin (4-6 mos)
- ↑ Total Body Iron (6 mos)

Cardiovascular

- ↑ BP
- ↓ Vascular resistance
- ↓ Heart murmurs
- ↑ RBC flow to brain (18%)
- ↑ RBC flow to gut (15-20%)

Body Weight

- ↑ Heavier 100 g

Skin

- ↑ Cutaneous perfusion
- ↑ Peripheral temps

Renal

- ↑ Renal blood flow
- ↑ Urine output
- ↓ Sodium excretion

Respiratory

- ↑ Pulmonary vasodilatation

DCC Before and After Ventilation Onset*

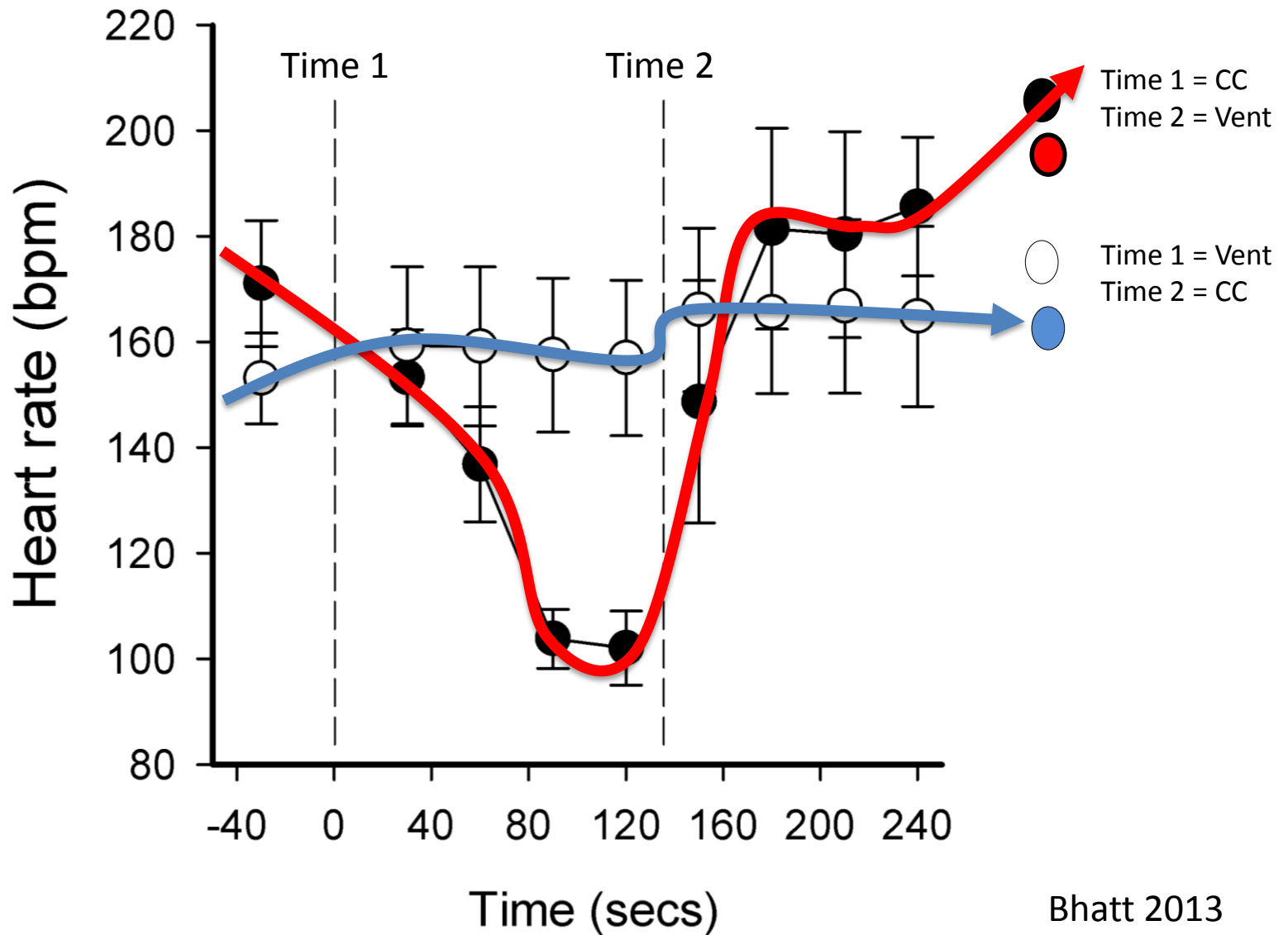
Using preterm lambs, Bhatt et al compared effects of ventilation before and after cord clamping.

"Delayed cord clamping allows time for the infant to aerate its lungs and increase pulmonary blood flow (PBF) before venous return from the placental circulation is lost."

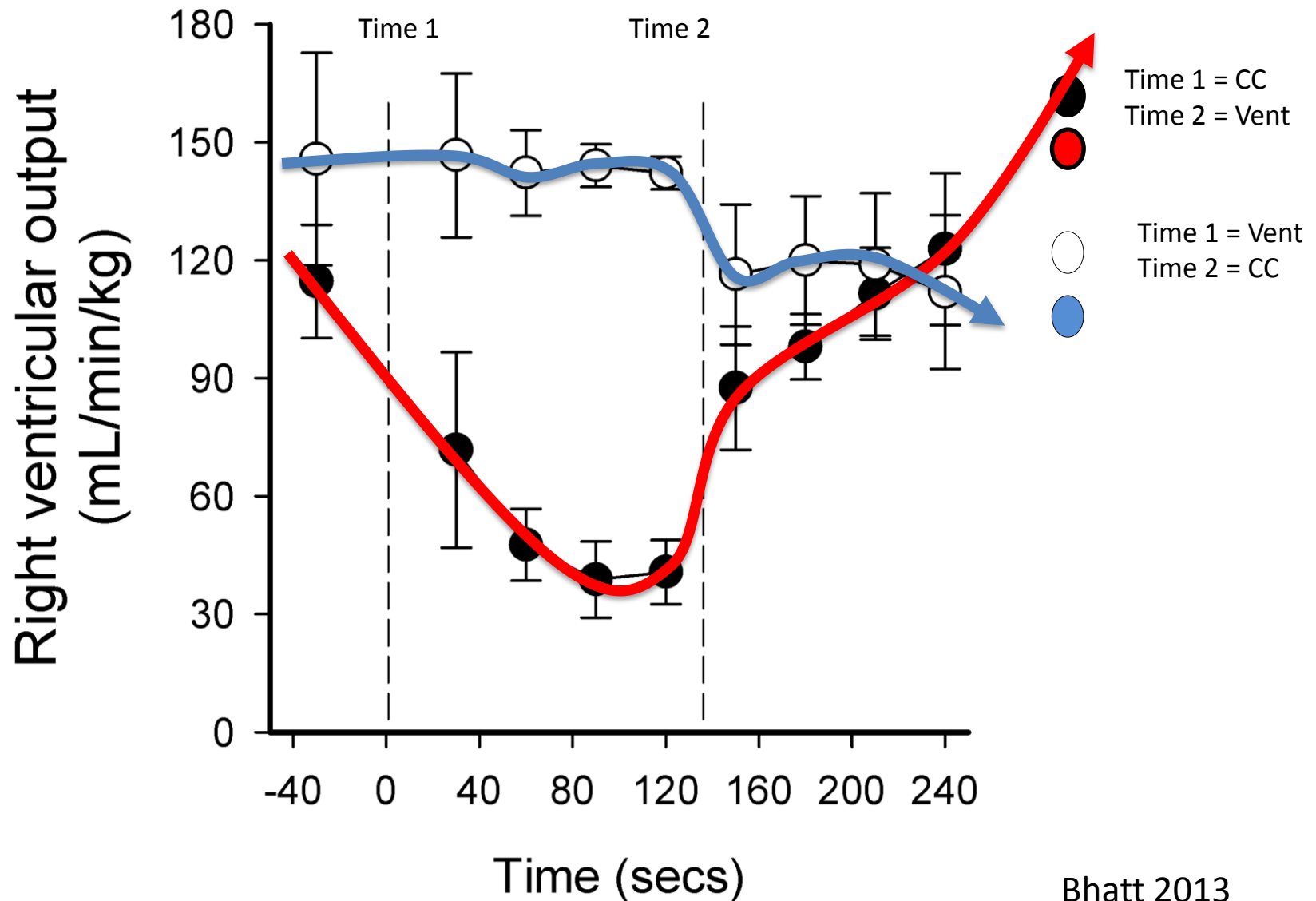
"...it avoids large swings in cardiovascular function."

*Bhatt, Kluckow, Morley, Polglase, Hooper, et al. J Physio 2013

Effects on Heart Rate



Effects on R Ventricular Output



**Examine the current evidence
from trials on DCC**

Meta-Analyses: Studies on Term Infants

- **15 RCT & CTs (1912 newborns)**
 - Delayed cord clamping: at least two minutes (n=1001)
 - Early cord clamping: immediately (n=911)
- **Results at birth**
 - Hematocrit: WMD 3.7; (CI 2 to 5.4)
 - Asymptomatic Polycythemia: RR 3.8 (CI 1.1 to 13)
- **Results: Ages 2 to 6 months**
 - Iron status (ferritin): WMD 17.9 (CI 16.6 to 19)
 - Stored iron: 19.9 (CI 7.7 to 32)
 - Less anemia: RR .53 (CI .4 to .7)
- **No harm from Jaundice or Symptomatic Polycythemia**

Cochrane Review on Term Infants and Delayed Cord Clamping

- Review of 15 trials (n=3911 infants)
- **Results (DCC)**
 - Higher birthweight by 101 grams (12 trials, n=3139)
 - More infants requiring phototherapy (2%) but no difference in clinical jaundice
 - Higher hemoglobin levels after birth
 - 2x less likely to be iron deficient at 3 to 6 months
 - Ferritin levels were not assessed but were higher with DCC in all studies

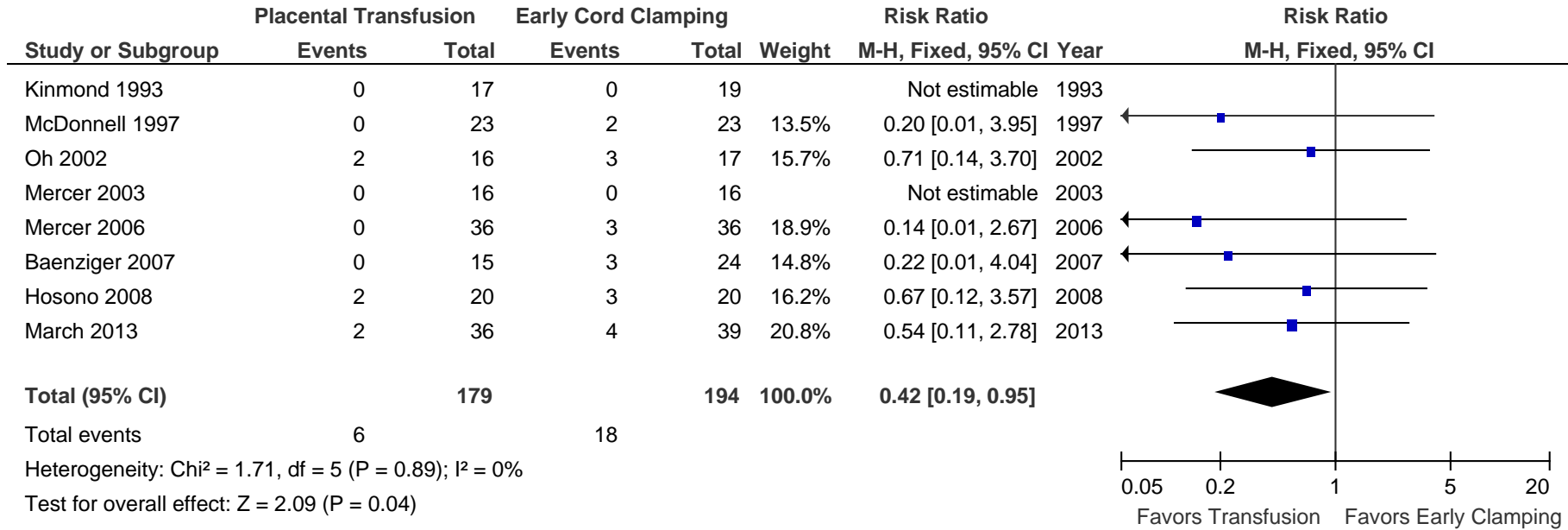
Meta-Analysis: Preterm Infants

- 3rd Edition: Meta-analysis on Delayed Cord Clamping or Cord Milking in Preterm Infants
 - 15 RCT studies (n= 738 infants 24 to 36 weeks)
 - Delay = 30 to 120 seconds
 - 1 RCT on cord milking
 - 2 RCTs report on blood volume measurement

Reported Benefits for Preterm Infants

- Higher circulating blood volume for 24-48 h
- Fewer blood transfusions
- Better systemic blood pressure
- Reduced need for inotropic support
- Increased blood flow in the superior vena cava
- Higher cerebral oxygenation index
- Lower frequency of any intracranial hemorrhage
 - No difference in rates of severe IVH

Mortality



Umbilical Cord Milking: Term & Preterm Infants

- 5 Systematic Reviews
- 15 Randomized Controlled Trials
- 8 Non Randomized Controlled Trials
- 3 Secondary Analysis
- 3 Review Articles
- Same benefits as DCC
- Absence of harm with milking

Meta-Analysis of Cord Milking Studies*

- 7 RCTs with 501 infants
- **Results**
- Preterm: (277 infants)
 - higher H&H; less BPD; less IVH
 - No diff in mortality, hypotension, inotrope support
- Term: (224 infants)
 - higher Hemoglobin at 48 hrs and 6 wks
 - Higher ferritin levels at 6 wks of age

No differences in jaundice or polycythemia

Our Women & Infants Studies

- Pilot Preterm Study 1999 - 01
- Preterm Infants 2003-06
- Cord Milking at C/S term infant 2008-09
- Preterm Infants 2008 – 14
- Term Infants 2012 - 17



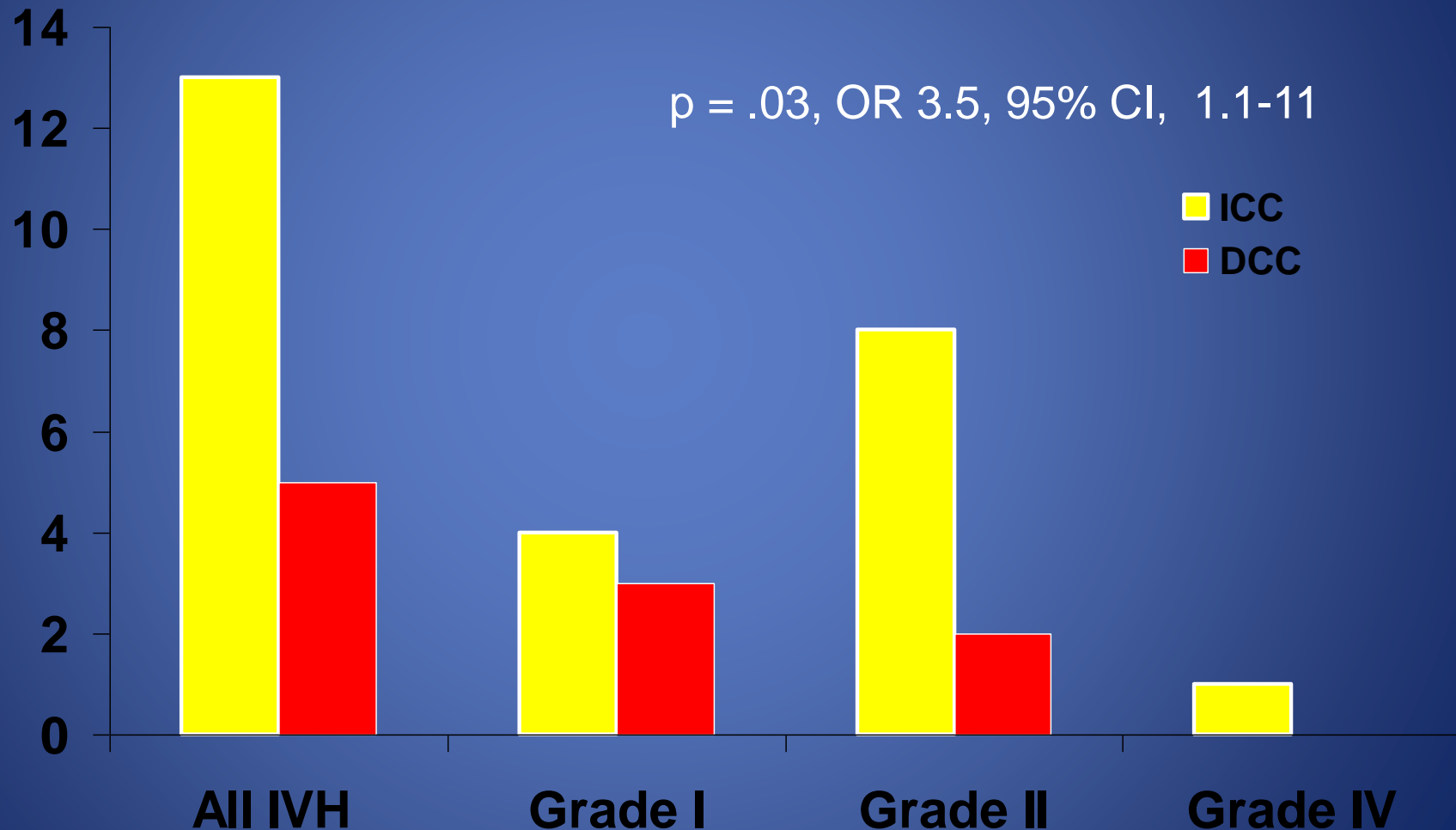
Phase I Study 2003-2006

- 72 VLBW infants between 24 and 31⁶ wks
 - ICC or DCC of 30 to 45 seconds
 - No difference in maternal and newborn demographics
 - No difference in safety variables (temp, Apgar, jaundice) or need for resuscitation

Mean CC times – ICC = 7 sec (\pm 4); DCC = 32 sec \pm 13

*Effects of Delayed Cord Clamping in VLBW Infants, K23NR08027, NIH (2003-2006)

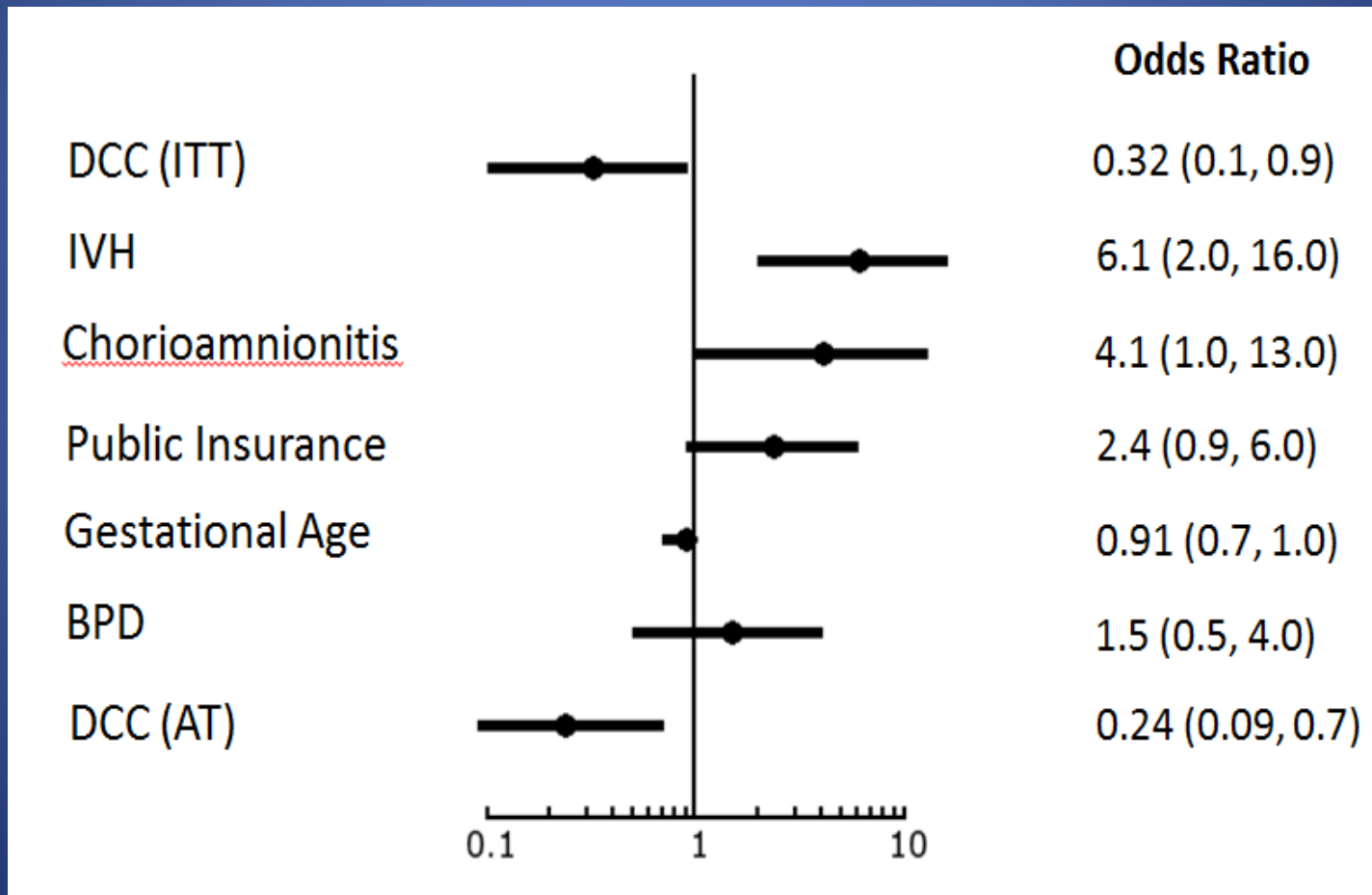
Intraventricular Hemorrhage



Preterm Study 2008-2014

- RO1, 5 year RCT of 211 preterm infants
 - 24 to <32 weeks
 - ICC versus 30 to 45 sec delay – lowered & 1 milking of the cord before clamping
- Primary outcomes:
 - IVH and Sepsis
 - Biologic markers (cytokines, stem cells, red cell volume)
 - Motor function at 18 months corrected age
- No difference in IVH or Sepsis, but...

Logistic Regression: Effects of DCC, IVH, Chorio, BPD, & GA on Bayley Motor Score <85 at 18 months



Mercer, et al, 2016 J of Pediatrics

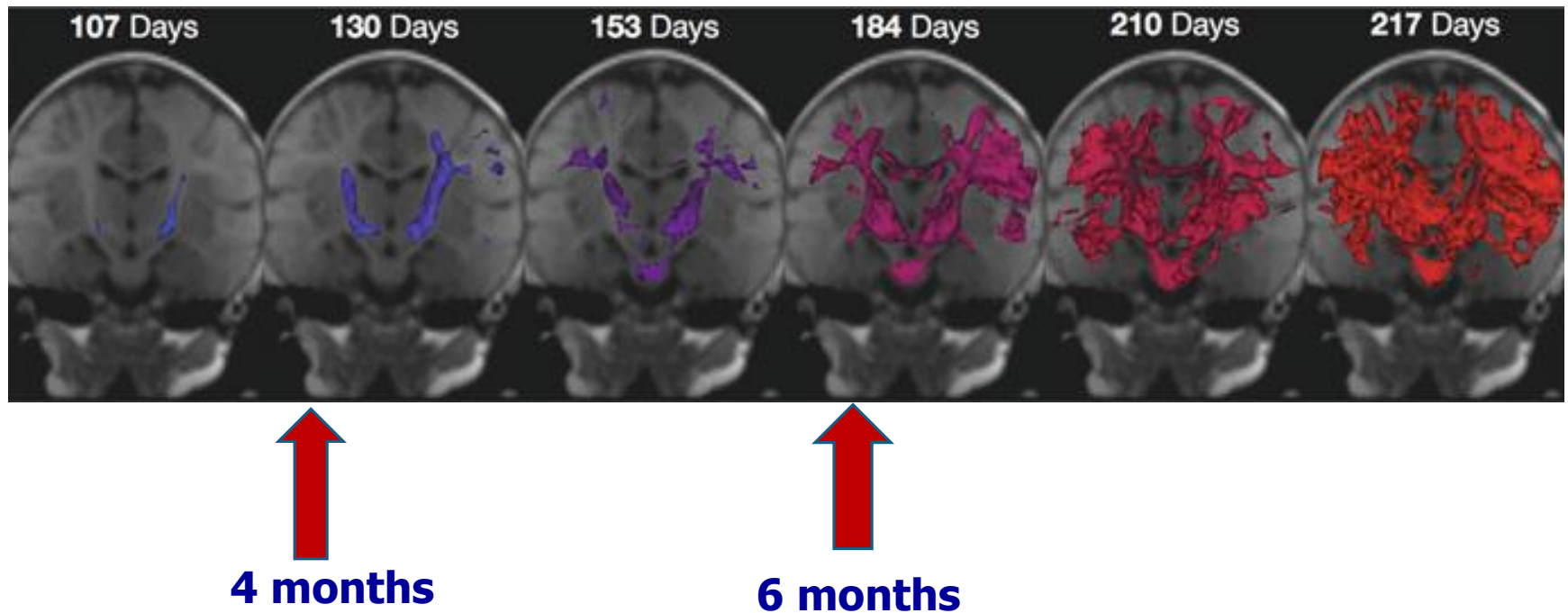
Why term study?

- High percentage of babies world-wide are anemic or iron deficient (ID) by 6 to 9 months
- Cord blood, an excellent source of iron, is available to every infant at birth via placental transfusion (DCC)
- Anemia and ID in infancy are associated with decreased cognitive abilities and behavioral problems
- Good evidence for safety and benefits of DCC exists*



*McDonald, S. Cochrane Review (2013)

Normal Myelination in Infants from 3 to 7 Months



Deoni SL et al. Mapping Infant Brain Myelination with Magnetic Resonance Imaging.
J Neuroscience 2011;31(2):784-791

Effects of Placental Transfusion on Early Brain Development*

- 73 normal healthy women delivering at term and planning to breastfeed with healthy fetuses
- Randomized to ICC (immediate) or DCC (5 or more minutes) and stratified by gender
- Milking as a proxy when one cannot delay
- Blood samples: cord blood, 48 hrs, 4 & 12 mo (iron levels)
- Quantitative Myelin scans at 4, 12, & 24 mo
- Developmental assessments at 4, 12, 24 months of age

*Bill & Melinda Gates Foundation, 2012-2013

*NIH – NICHD – R01 HD076589 : 2012-2017 (Mercer, Erickson-Owens, Deoni)

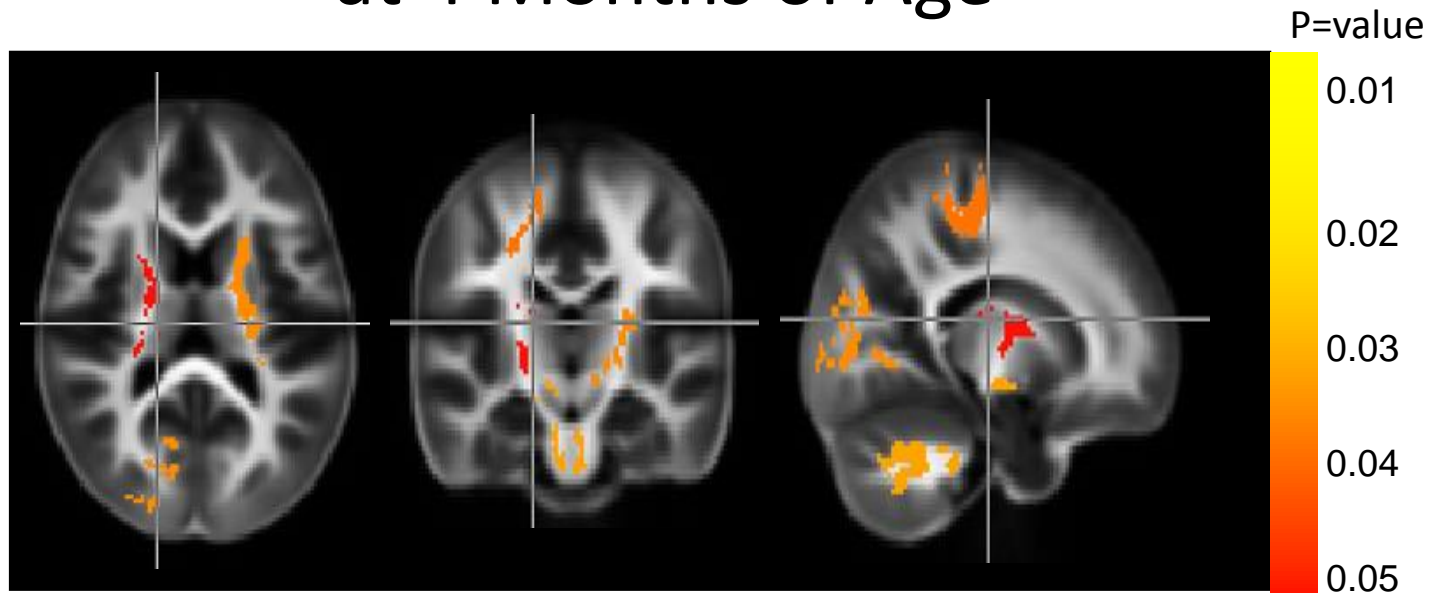
RESULTS TO DATE

Clinical Outcomes of Infants with MRI

	MRI Cohort	
	DCC (n=22)	ICC (n=21)
Cord Clamp Time, seconds	209 ± 185***	11 ± 5
Two-Day Hemoglobin, g/dL	19.4 ± 2*	17.8 ± 2
Bilitool high risk zone	1 (5)	3 (14)
Peak total bilirubin, mg/dL	8.6 ± 3.4	9.3 ± 3
RPBV, mL/kg**	20 ± 8**	28 ± 7
Ferritin at 4 months, ng/mL	90.7 ± 46	71.5 ± 53
Log Ferritin at 4 months	4.4 ± 0.44*	4.1 ± 0.6

mean ± SD or n (%); *p<0.05; **p<0.01; ***p<0.001

Correlations between Ferritin and Myelin at 4 Months of Age*



Axial: Left & Rt posterior arms of the Internal Capsule; Rt occipital cortex

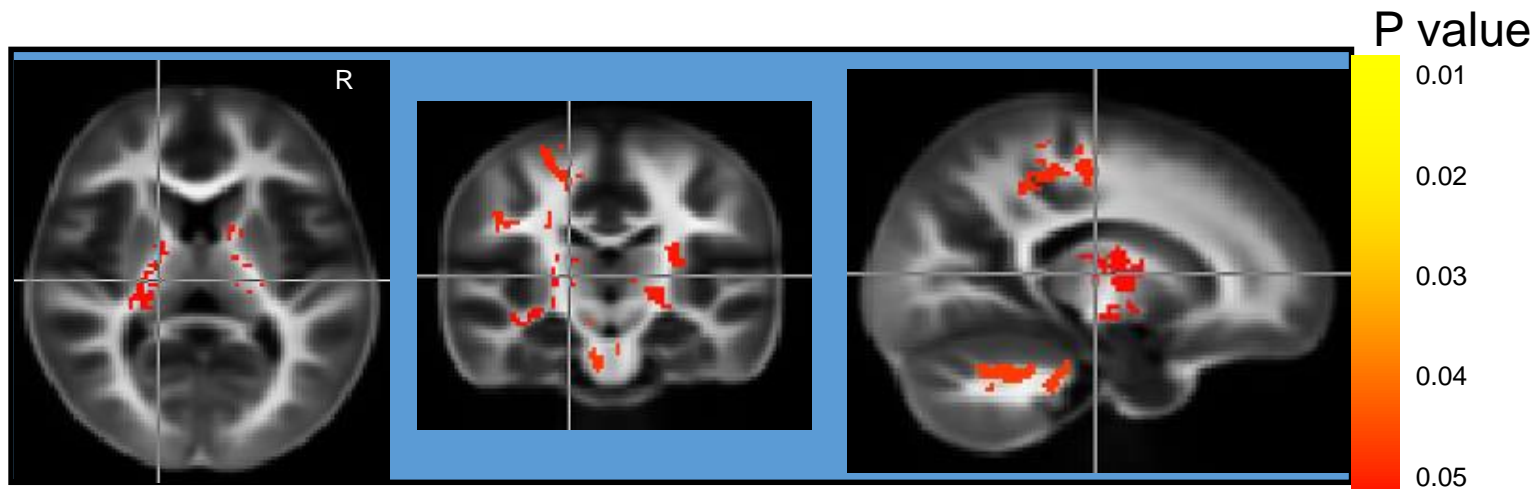
Coronal: brain stem, internal capsule, parietal white matter

Sagittal: Internal capsule, cerebellum, occipital cortex, parietal white matter

These are early myelinating areas involved in motor function and sensory processing

*p-value, corrected, shown at color axis on right denotes areas of significant differences

Group Differences in Myelin Volume Between Infants with DCC vs ICC



Axial: Left & Rt posterior arms of the Internal Capsule

Coronal: brain stem, internal capsule, parietal white matter

Sagittal: Internal capsule, cerebellum, parietal white matter

These are similar early myelinating areas involved in motor function and sensory processing

DCC > ICC denoted by red coloring ($p < 0.05$)

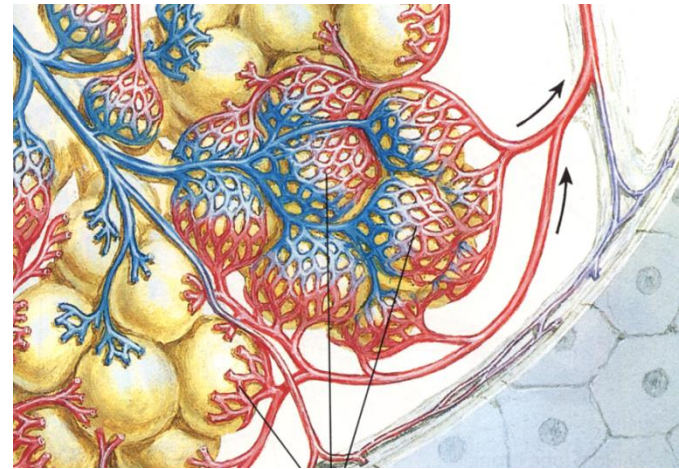
Impression

- Delayed cord clamping/cord milking (placental transfusion) increases iron stores and myelin content at 4 months of age
- DCC (or milking) is a low tech, no cost approach to increase ferritin levels and myelin content at 4 mo
- Further study includes scans for myelin content at 12 and 24 months along with developmental testing.

Are there Risks from Placental Transfusion?

- Theoretical Risks
 - Over-transfusion?
 - Symptomatic Polycythemia?
 - Jaundice?
 - Hypothermia?
 - Delayed resuscitation?
- Actual Risks – none seen in meta-analyses

Fears of Overtransfusion... Where does all the blood go?



- The lung must change immediately: an organ of fluid excretion → an organ of gas exchange
- To exchange gases, 50% of the CO needs to flow through the lung instead of 10% in utero
- Placental transfusion creates an ↑ in circulatory bed in the lung
- No evidence of overtransfusion in any recent RCTs

Symptomatic Polycythemia

- **Concern:** The infant gets too many RBCs
- **Actual:** The infant's whole blood and red cell volume expands & infant receives more iron
- **No Difference**
 - Hutton & Hassan⁰⁷; McDonald, Middleton, Dowswell & Morris¹³

Jaundice & Hyperbilirubinemia

Concern: Excess RBCs → breakdown → excess bilirubin

Actual: Clinical jaundice similar between ICC & DCC

Hutton & Hassan⁰⁷

8 Studies (n=1009)

Outcome: Risk of jaundice within 24-48 hours

- No significant difference

McDonald, Middleton, Dowswell & Morris¹³

5 Studies (n=1828)

Outcome: Clinical Jaundice

- No significant difference

Other Potential Issues

Hypothermia

- No differences were noted in the meta-analyses in:
 - infants' temperatures on arrival to nursery
 - or after 15 min in term infants

Delay in Resuscitation

- No differences in
 - Apgar scores at 1 and 5 min in any of the studies
 - number of infants with an Apgar score of < 4 between the ICC or DCC groups

Describe methods to ensure delayed cord clamping and/or cord milking at birth

DCC at Term Birth (≥ 36 weeks)

“Vaginal Birth”

- **First 30 secs-** Evaluate breathing & tone
- Spontaneous breathing & good tone
 - Place infant skin-to-skin and leave cord intact for at least 5 mins-

—“WAIT for WHITE”



- Poor respiratory effort & poor tone
 - Milk the cord 3 to 5 times, pass off infant if no response

“Wait for White”



Cord Milking at ≥ 36 weeks

“Cesarean Section”

- Place newborn on maternal thighs (on the sterile drapes)
- Milk cord 3 to 5 times
- Pass newborn to pediatric provider
- Usual care at warmer

DCC at Preterm Birth

“Vaginal Birth”

- **First 30 secs**- Evaluate breathing & tone
 - Hold baby at or below perineum & wrap in warm blanket
- Spontaneous breathing & good tone
- (<32 wks) Leave cord intact for up to 60 seconds
- (>32 – 36 wks) 120 seconds
- Poor respiratory effort & poor tone
- Milk the cord 3 to 4 times
- Then cut cord and pass baby off to pediatric provider

Cord Milking at < 36 weeks

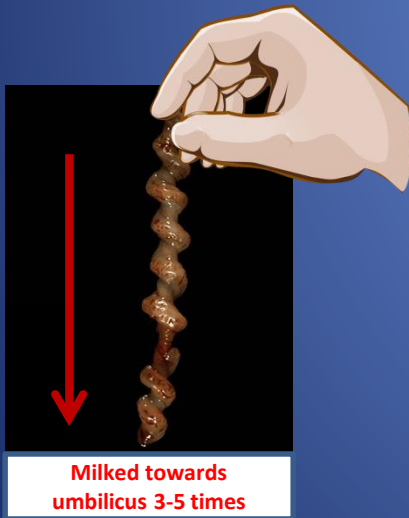
“Cesarean Section”

- Wrap newborn in warm sterile blanket
- Gently dry and stimulate
- Milk the cord 3 to 4 times
- Pass newborn to pediatric provider
- Usual care at warmer

How To Milk the Umbilical Cord

- Grasp the cord between your thumb and forefinger and milk the length of cord towards infant's umbilicus 3-5 times
 - **Vaginal birth** - start at introitus
 - **Cesarean birth** - start near insertion site on placenta

Take about 2 seconds to move over the length of the cord; wait about 2 seconds for cord to refill after milking and milk again



Challenges:

- Cord is slippery
- Can be tightly coiled and difficult to milk entire cord
- Potential to tear (rare)

Use of Uterotonics and Active Management of 3rd Stage of Labor



- No harm is associated with the use of uterotonics
 - May speed the placental transfusion somewhat
 - NO need to change cord clamping practice

Farrar D, 2011; Yao A, 1969

Umbilical Cord Gas Collection

Can be collected on an intact cord



“The proportion of valid blood gas samples were similar between

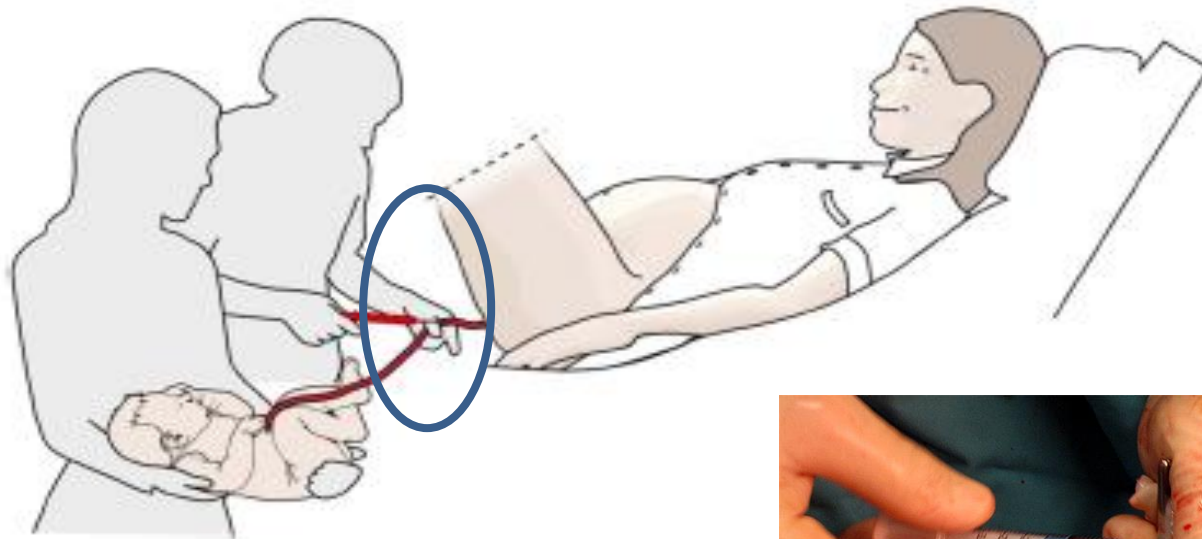
Infants with DCC (67%, $n = 130$) and

Infants with ICC (74%, $n = 139$) groups...

with 6% ($p = 0.2$) fewer valid samples after DCC.”

Blood Gas Sampling

Figure 1. Blood gas sampling from an unclamped umbilical cord.



Things to consider

- Cord blood, an excellent source of iron, is available to every infant at birth via placental transfusion (DCC)
- Team work important
- Cord milking for depressed infants when one feels the need to **“Cut & Run”**
- Umbilical Cord Gases can co-exist with a delay or milking of the cord

“Lost” Knowledge

Current research evidence has re-examined some “old fashioned” practices such as....

- Early initiation of breast-feeding
- Skin-to-skin placement

Not only are these practices safe,
they are important for promoting mother
and infant health and well-being.

Delayed cord clamping is another “lost” practice that has been found to be beneficial and is now being implemented worldwide.



KEEP THE CORD INTACT



Questions?