



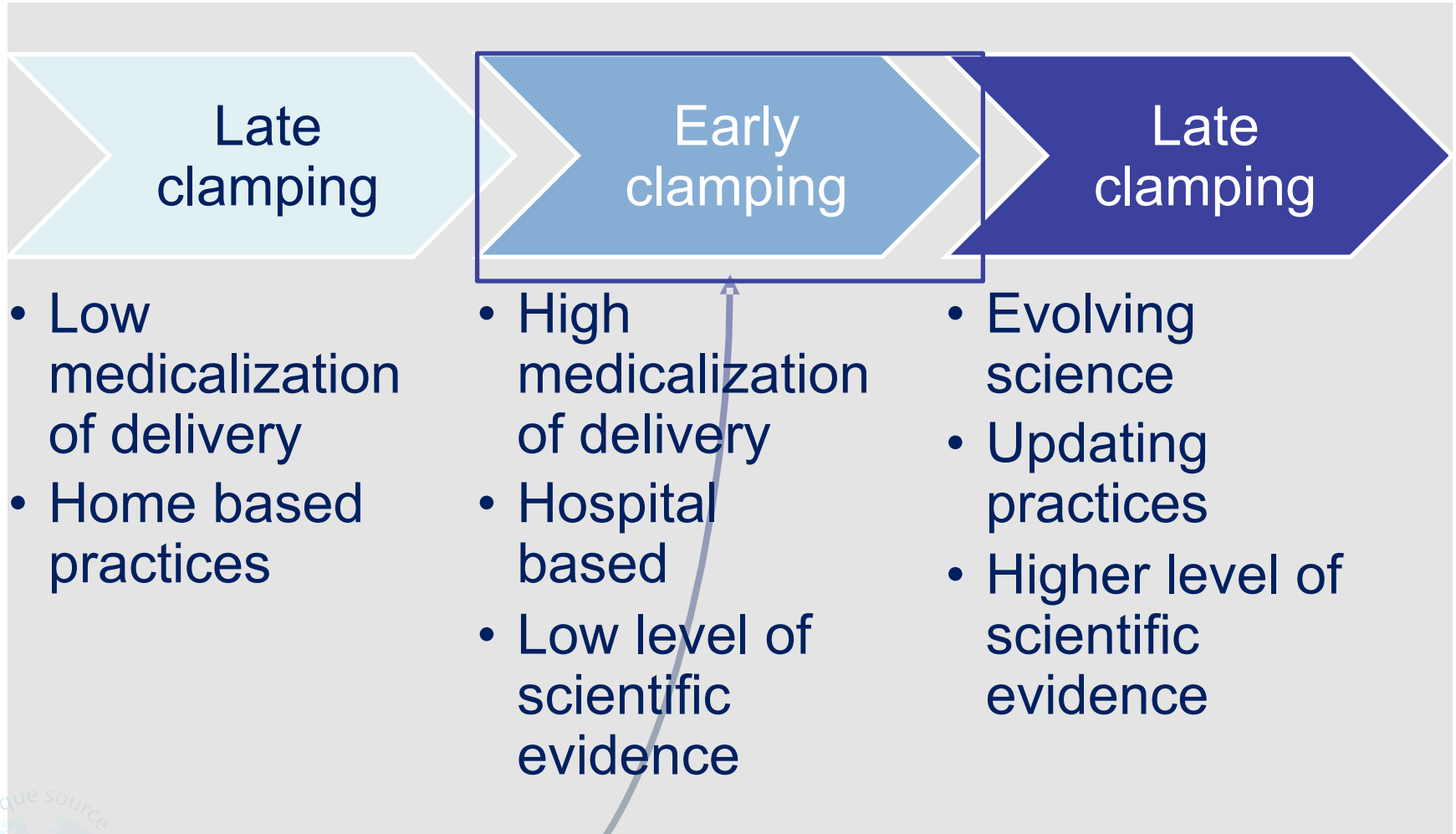
CORD DONOR SAFETY

E. Baudoux

C. Lefèbvre

A. Fasth

3 steps in history



**CORD BLOOD
COLLECTION**

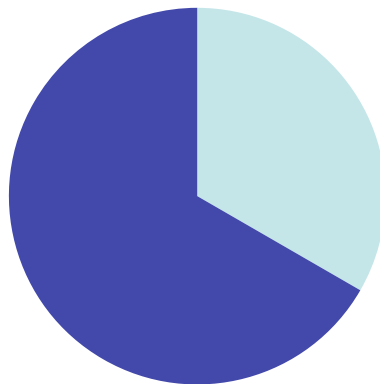
PHYSIOLOGY OF CORD CLAMPING



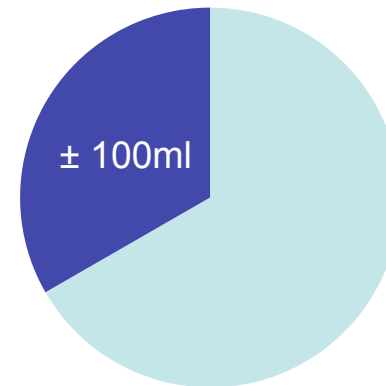
Physiology of cord clamping

- Feto-placental blood volume
100 - 120 mL/kg
- Distribution of blood volume

Premature



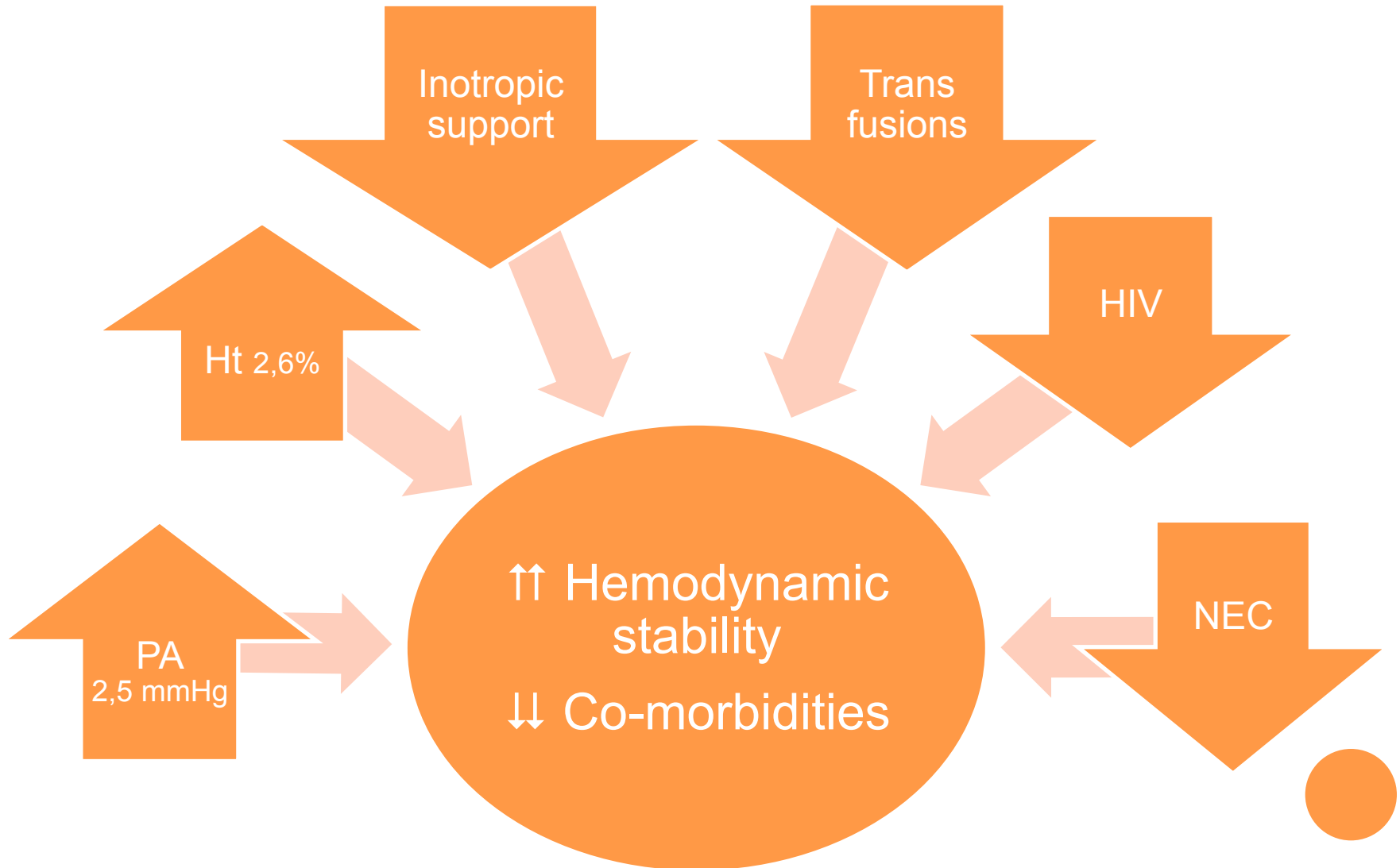
Term



■ Fetus
■ Placenta

→ Late clamping more efficient in premature babies?

EFFECTS OF LATE CLAMPING ON THE PRETERM BABY



EFEFCTS OF LATE CLAMPING FOR THE FULL TERM INFANT

BENEFITS

RISKS

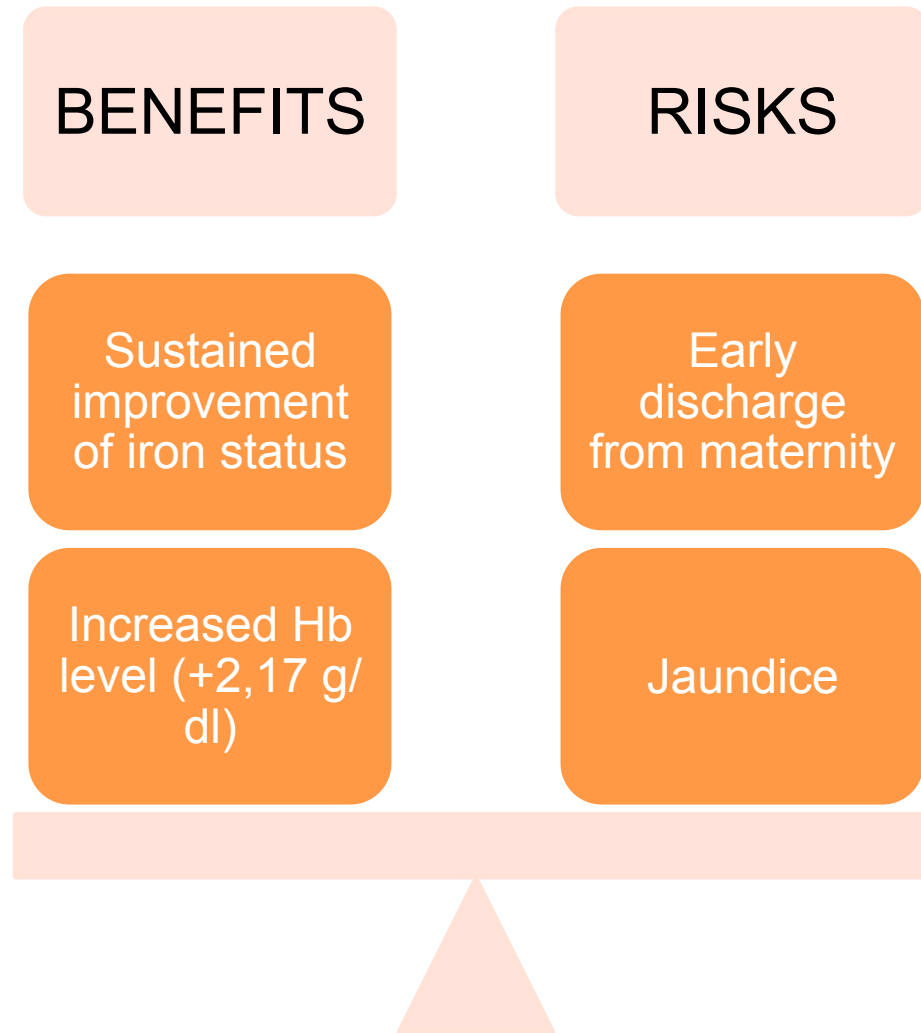
Sustained improvement of iron status

Increased Hb level (+2,17 g/dl)

Jaundice

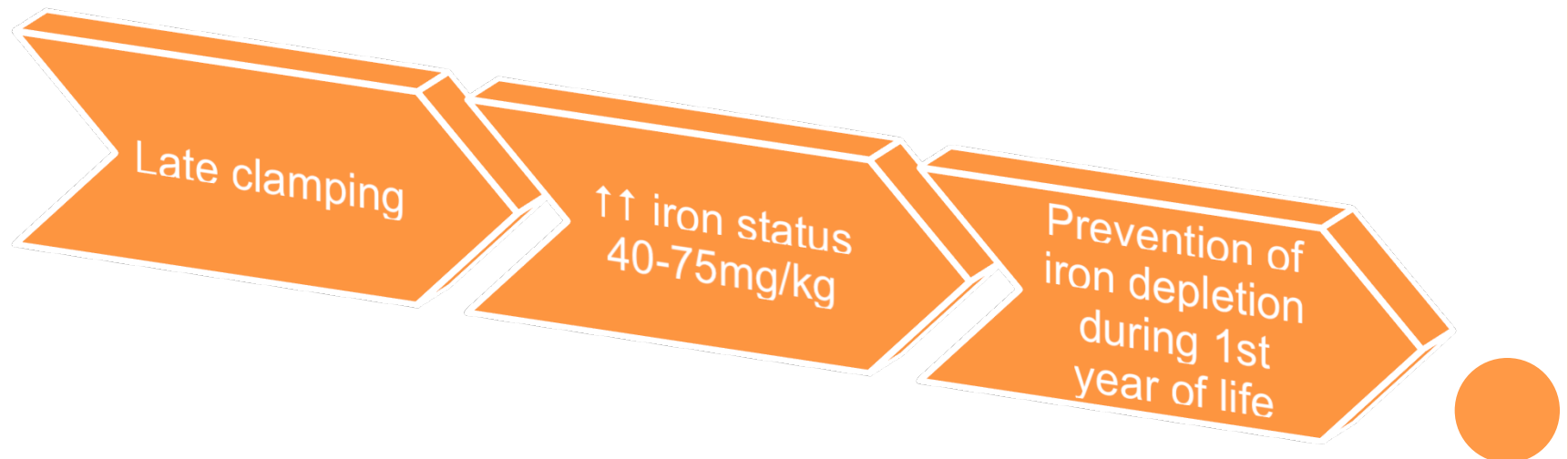


EFFECTS OF LATE CLAMPING ON THE FULL TERM BABY



HYPOCHROMIC ANEMIA

- Public health issue in developing countries
 - 3,6 billion people are iron depleted
 - 2 billion people have iron deficient anemic
- Prevalence in Europe 3 to 7%



Iron depletion

- ↓ growth (height/weight)
- ↑ sensitivity to infection
- Brain development
 - Myelinisation
 - Dendriogenesis
 - Neurotransmission
 - Energy supply to glial cells

Iron and the Newborn

- Iron stores accumulate during 3rd trimester
 - At birth about 75 mg/kg for full terms
- Factors associated with iron deficiency
 - Severe maternal iron deficiency with anemia
 - Maternal diabetes
 - Maternal smoking
 - Maternal hypertension

Iron is essential for neurogenesis

- Animal models - Iron deficiency
 - alters synthesis and catabolism of neurotransmitters → behavioral alternations
 - Decreases dendritic growth and reduces interneuronal connections in hippocampus → learning difficulties
 - Altered composition and amount of myelin

Iron is essential for neurogenesis

- Human studies
- Many confounders such as disadvantaged environment and quality of parent-child interactions
- An association between iron deficiency with anemia and neurological performance suggested from many trials

Iron Deficiency and Neurological Outcome

- Infants and toddlers with iron deficiency with anemia (case-control studies)
 - Have 1-15 IQ point difference to iron-repleted
 - Are less leashed, more hesitant, less playful etc.
 - Might be long-lasting (one study from Costa Rica)

Andersson et al. BMJ 2011

Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial

- Design
 - ❖ 400 Full term infants, low risk pregnancies
 - ❖ Arm 1: Early cord clamping (ECC) ≤ 10 secs
 - ❖ Arm 2: Delayed cord clamping (DCC) >180 secs
- Improved Iron status in DCC arm
 - ❖ Higher ferritin
 - ❖ Lower incidence of NN anemia
 - ❖ Lower incidence of iron deficiency at 4 months
- Neurodevelopment: NA
- No AE
- Conclusions
 - ❖ Looking at consequences of iron deficiency (with or without anemia), DCC benefits full term infants
 - ❖ DCC considered standard of care

Andersson et al. Acta paediatrica 2013

Effects of delayed cord clamping on neurodevelopment and infection at 4 months of age: a randomised trial

- Design
 - ❖ 382 Full term infants, low risk pregnancies
 - ❖ Arm 1: Early cord clamping (ECC) ≤ 10 secs
 - ❖ Arm 2: Delayed cord clamping (DCC) >180 secs
- IgG levels and symptoms of infection in DCC arm
 - ❖ IgG: transient increase at day 2-3, disappears later
- Neurodevelopment: Age and stages questionnaire (ASQ)
 - ❖ Differences in ITT analysis for DCC arm, not confirmed by per protocol analysis
 - \uparrow Problem solving
 - \downarrow Personal-social
 - ❖ Not the best test to assess neurodevelopment at 4 months
 - ❖ Study underpowered for fine neurodevelopmental analysis
- No AE

• Conclusions

- ❖ More data needed

Andersson et al. JAMA Pediatrics 2014

Effect of delayed vs early umbilical cord clamping on iron status and neurodevelopment at age 12 months: a randomized clinical trial

- Design
 - ❖ 382 Full term infants, low risk pregnancies
 - ❖ Arm 1: Early cord clamping (ECC) ≤ 10 secs
 - ❖ Arm 2: Delayed cord clamping (DCC) >180 secs
 - ❖ Follow up after 12 months
- Iron status
 - ❖ NSS difference
- Neurodevelopment: Age and stages questionnaire (ASQ)
 - ❖ NSS difference
- Conclusions
 - ❖ DCC does not affect iron status or neurodevelopment as assessed by ASQ

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

McDonald SJ, Middleton P, Dowswell T, Morris PS



PLAIN LANGUAGE SUMMARY

Effect of timing of umbilical cord clamping of term infants on mother and baby outcomes

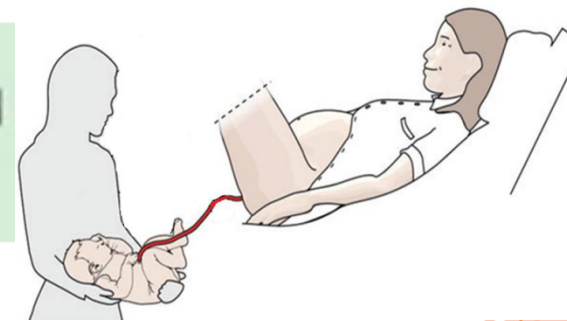
At the time of birth, the infant is still attached to the mother via the umbilical cord, which is part of the placenta. The infant is usually separated from the placenta by clamping the cord. This clamping is one part of the third stage of labour (the time from birth of the baby until delivery of the placenta) and the timing can vary according to clinical policy and practice. Although early cord clamping has been thought to reduce the risk of bleeding after birth (postpartum haemorrhage), this review of 15 randomised trials involving a total of 3911 women and infant pairs showed no significant difference in postpartum haemorrhage rates when early and late cord clamping (generally between one and three minutes) were compared. There were, however, some potentially important advantages of delayed cord clamping in healthy term infants, such as higher birthweight, early haemoglobin concentration, and increased iron reserves up to six months after birth. These need to be balanced against a small additional risk of jaundice in newborns that requires phototherapy.

TIMING OF UMBILICAL CORD CLAMPING AFTER BIRTH FOR OPTIMIZING PLACENTAL TRANSFUSION *RAJU, CURRENT OPINION IN PEDIATRICS 2013*










Table 4. Recommendations from professional organizations

Professional entity (year)	Recommendations
World Health Organization (2006, updated 2012) [31**]	In preterm births, delay cord clamping for 30–120 s after birth; and in term births, up to 3 min after birth, also observe uterine contractions.
Society of Obstetricians and Gynaecologists of Canada (2009) [32]	Delaying cord clamping for at least 60 s for preterm births.
International Liaison Committee on Resuscitation (2010) [33]	Delay umbilical cord clamping for at least 1 min for newborn infants not requiring resuscitation. There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.
European Association of Perinatal Medicine (2010) [34]	If possible, delay clamping of the cord for at least 30–45 s with the baby held below the mother (evidence grade A).
The American College of Obstetricians and Gynecologists (2012) [35**]	Evidence exists to support delayed umbilical cord clamping in preterm infants, when feasible (by 30–60 s). Evidence is insufficient to confirm or refute the potential for benefits from delayed umbilical cord clamping in term infants, especially in settings with rich resources.

The American College of Obstetricians and Gynecologists recommends that timing of umbilical cord clamping should not be altered for the purpose of collecting cord blood for banking [17].



Recommendations

Term	Premature
 <p>OMS: 3 min</p>	 <p>OMS: 3 min</p>
	 <p>EUROPEAN ASSOCIATION OF PERINATAL MEDICINE</p> <p>EAPM: >1min</p>
 <p>ILCOR: 1 min</p>	 <p>ILCOR: 1 min</p>
  <p>(ACOG) (SOGC)</p>	  <p>ACOG: 30-60 s SOGC: 60 s</p>

Royal College of Midwives

July 2013

RCM supports delayed cord clamping

Thursday 11th July 2013

Commenting on research to be published today by the Cochrane Library on delaying of cord clamping, Louise Silverton, director for midwifery at the Royal College of Midwives, said: "This is welcome research that is adding to the increasing body of evidence for delayed cord clamping which the RCM supports.

"This and other evidence is suggesting that delayed clamping of the cord is overall beneficial to the baby. It is estimated that this normally would be between one to three minutes, though more research needs to be done to determine the optimum time for this. We would also stress that midwives will need time in the postnatal period to detect jaundice in the newborn which may occur as a result of delayed clamping"

- 1-3 minutes
- Optimal time to be determined
- Recommends NOT TO perform in utero collections (to be confirmed)



Vain et al. Lancet 2014

Effect of gravity on volume of placental transfusion: a multicenter, randomized, non-inferiority trial

- Design

- ❖ 546 Normal, term, uncomplicated pregnancies with expected vaginal delivery
- ❖ DCC (2 minutes)
 - Below placenta level
 - Direct contact with mother's abdomen

- Conclusions

- ❖ Hct and bilirubin NSS
- ❖ Volume of placental transfusion (based on infant's weight) NSS
- ❖ Tends to reconcile DCC and enhanced bonding linked to direct contact with the mother

New guidelines for PREMATURE BIRTHS

Department of pediatrics-UH Liège

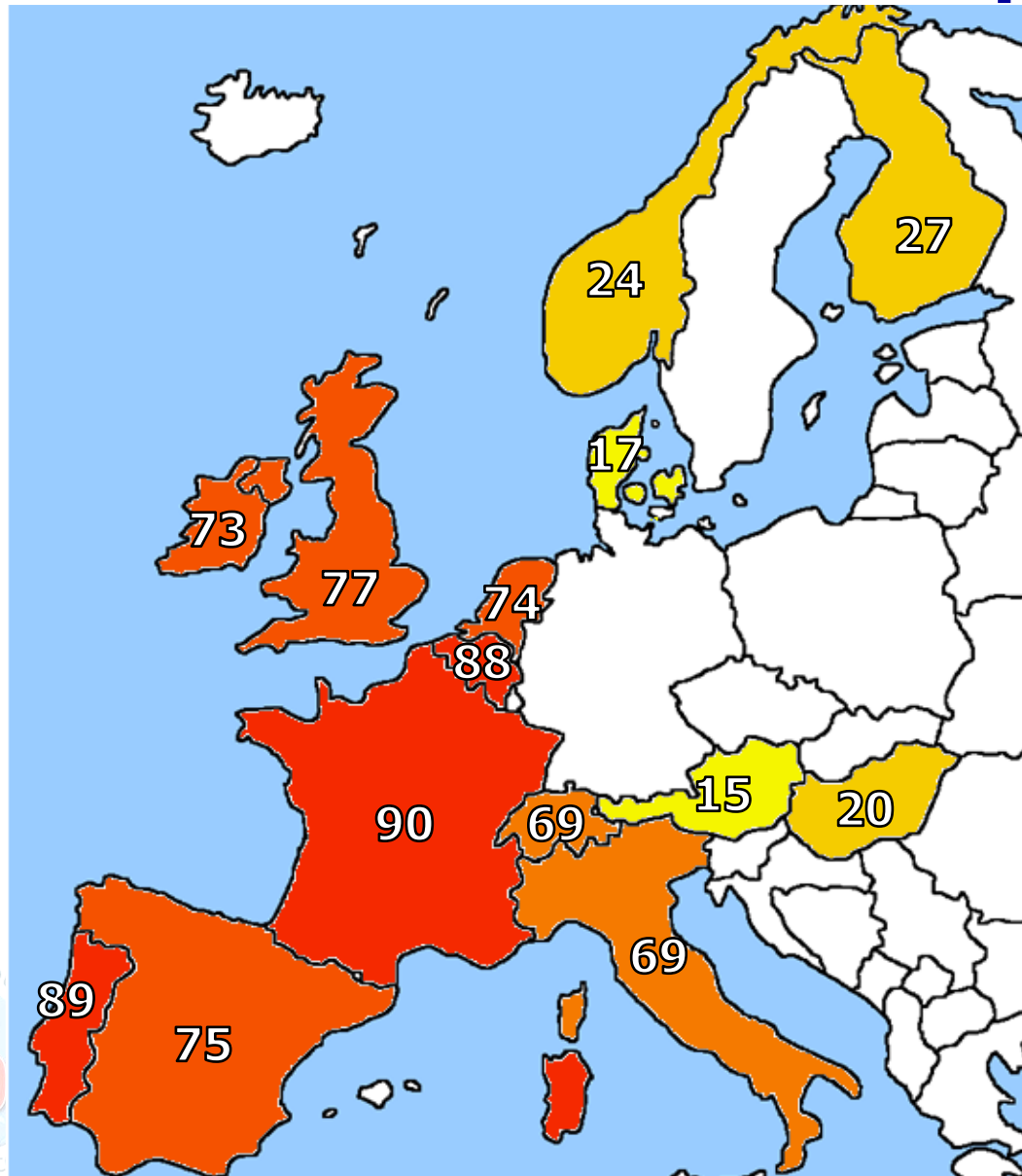
- Preterm births (<37 wks)
- Paediatric support needed
- Late clamping is critical
- Manage late clamping:
 - ❖ 60 sec
 - ❖ 20-30 cm below placenta level
 - ❖ Clamp after 1st breathing movement
 - ❖ C/S → milking
- Due to heterogeneous obstetrical practices, not applied in all centers, but active efforts are made to promote late clamping

Tentative guidelines for TERM BIRTHS

Department of pediatrics-UH Liège

- Whenever possible:
 - ❖ 60 sec
 - ❖ 20-30 cm below placenta level
 - ❖ Clamp after 1st breathing movement
 - ❖ C/S → milking
- Developing countries: should be systematic (Iron stores, anemia)
- Due to heterogeneous obstetrical practices, not applied in all centers
- Data against early clamping are still missing at this stage

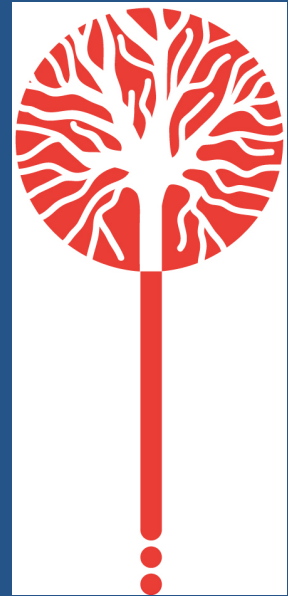
ECC in Europe



% maternities practicing ECC in 2007

Early clamping and possible harm to full term baby

Anders Fasth
The Swedish National Cord Blood
Bank at
Sahlgrenska University Hospital



Frequency of early clamping

- In Scandinavia and Austria 20%
- The rest of Europe 60 – 90 %
- Many developing countries practice early clamping

The Swedish debate

- Early clamping is against the The Convention on the Rights of the Child
- Early clamping is causing brain damage
- The child loses important stem cells

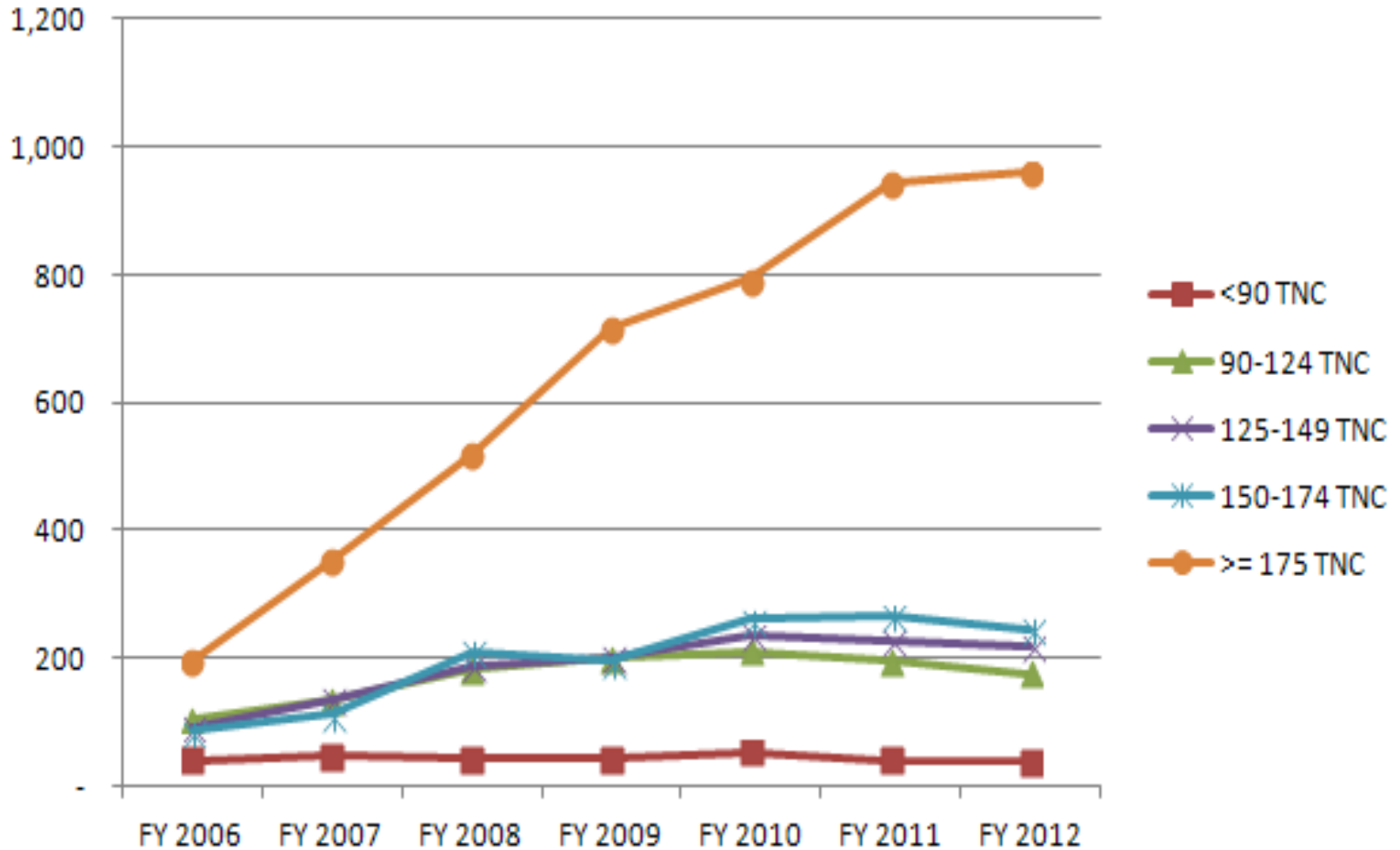
FROM THE CORD BLOOD BANK VIEWPOINT



Need to adapt banking strategies

- CB donation had the reputation of being safe, as it takes place after the baby has been delivered and the cord cut
- Not much attention paid to time of clamping, until...
- Seek maintenance of inventories with focus on:
 - ❖ High quality
(acceptance criteria, standardisation of processes)
 - ❖ Genetic diversity
 - ❖ Concept of operational inventory
- Optimise search and release processes
 - ❖ Evolution of upfront unit characteristics
 - ❖ Access to high performance and uniform data exchange networks
 - ❖ Speed up release process (off the shelf CBUs)
 - ❖ ? Open to non hematopoietic cells/byproducts

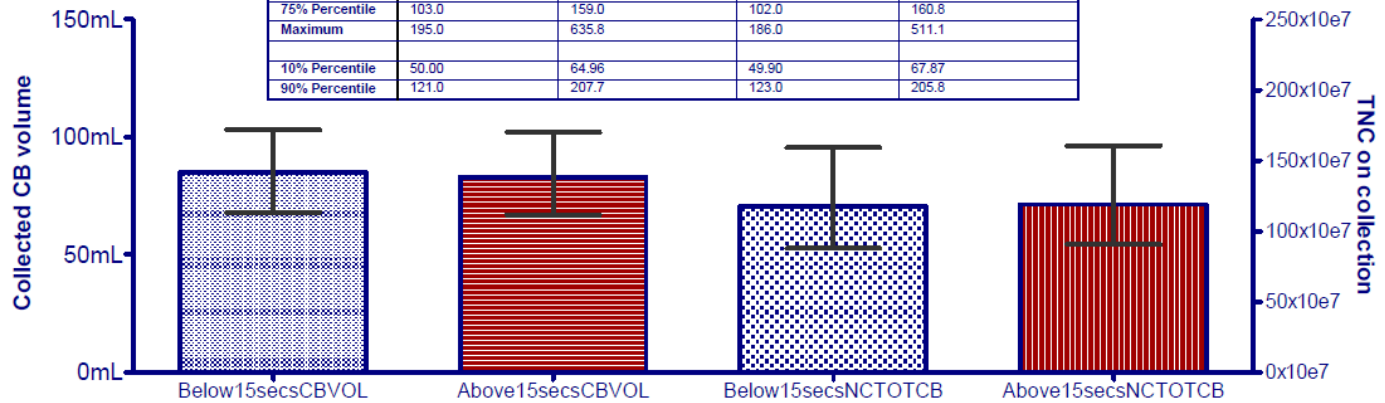
NMDP Cord Shipments By TNC



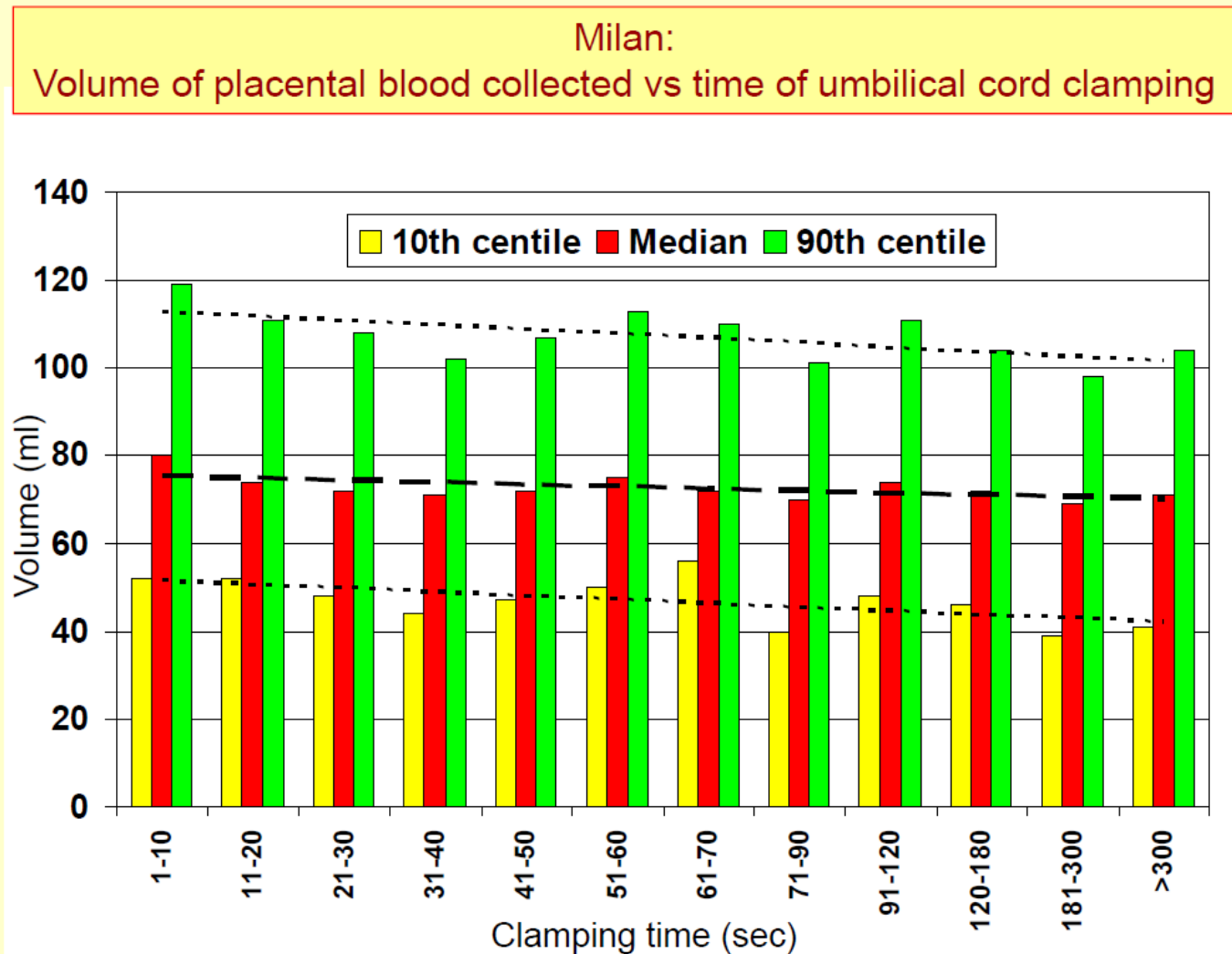
Impact on banking activities

Liège CBB

	Below15secsCBVOL	Below15secsNCTOTCB	Above15secsCBVOL	Above15secsNCTOTCB
Number of values	3918	3918	838	838
Minimum	5.000	6.800	7.000	16.92
25% Percentile	68.00	87.86	67.00	90.77
Median	85.00	117.4	83.00	118.9
75% Percentile	103.0	159.0	102.0	160.8
Maximum	195.0	635.8	186.0	511.1
10% Percentile	50.00	64.96	49.90	67.87
90% Percentile	121.0	207.7	123.0	205.8

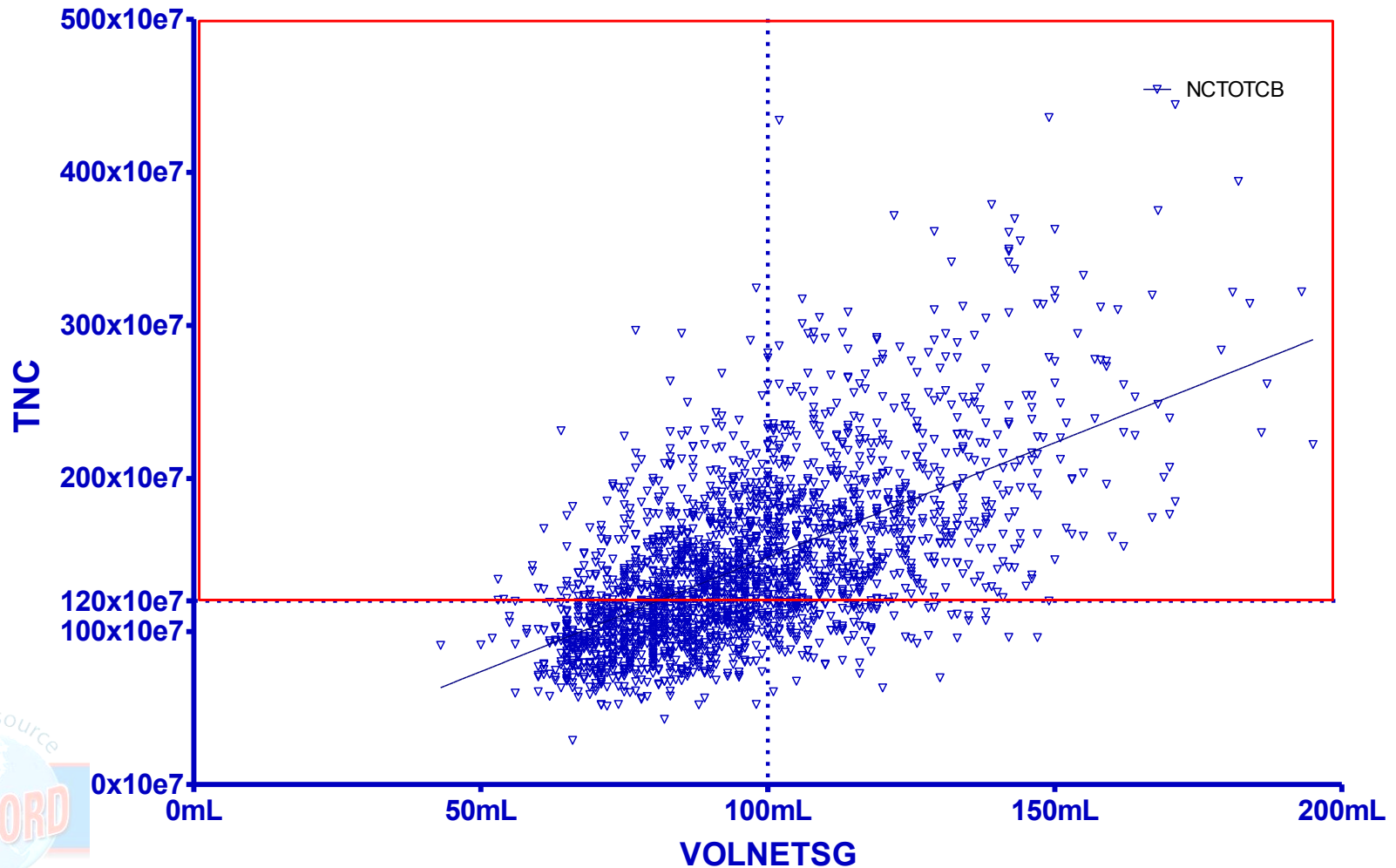


Impact on banking activities 2



Collected volume and cell contents

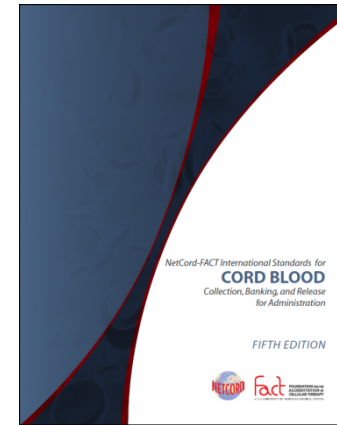
TNC/VOLUME
(N=2291)



Impact on banking activities 3

- Average collected volumes decrease → potential loss of corresponding high TNC units
- Emotional reactions to inadequate press coverage/extrapolation of scientific data
 - ⇒ **Mothers:** decrease in willingness to donate
 - ⇒ **Maternity staff:** wide range of positions from indifference to upfront refusal

FACT



- CB collection procedures and practices shall protect the mother and the infant donor and have no impact on obstetric practice or patient care.
- Delivery practices shall not be modified in an attempt to increase CB unit volume.
- When in utero CB collection is performed, there shall be additional safeguards in place to ensure the safety of the mother and the infant donor.

Safety of cord blood donation

- Collection takes place as long as it is safe for the mother and infant donor
 - ❖ Concept of uncomplicated pregnancy/delivery
 - ❖ Safety to be assessed by health professional in charge with the delivery
- FACT NetCord standards (*FIFTH EDITION*)
C6 CORD BLOOD COLLECTION
 - ❖ Guideline:
"It is expected that CB collection would not occur if there is any difficulty during delivery (e.g., excessive maternal bleeding, difficult delivery, fetal/newborn distress, and/or serious maternal medical problems)."
 - ❖ Special handling/exclusion of multiple pregnancies
- Directed donation: priority to infant donor safety

FACT and National Policies

- Informed consent shall be obtained and documented while the mother is able to concentrate on the information and is not distracted by aspects of labor.
- All aspects of participation in CB donation shall be discussed with the mother in a language and with terms that she understands.
- The mother shall have an opportunity to ask questions.
- Consent for at least the collection procedure shall be obtained and documented prior to delivery, including the following information at a minimum:
 - An explanation of the collection procedure in terms the mother can understand.
 - The possible risks and benefits of CB collection.
 - The right of the mother to refuse the collection without prejudice at any time.
 - The mother will be approached at a later time for complete consent, including consent to process, bank, and release the CB unit for administration and all of the elements in Section C4.5.

Take home messages

- Target population = **full term** deliveries from **uncomplicated** pregnancies
 - ❖ DCC has potential benefits (iron stores, anemia), even in developed countries, **BUT**
 - ❖ On the long run, studies don't show significant difference between DCC and ECC
- Efforts must be continued towards
 - ❖ **Literature watch** to foresee impact on CBB activities
 - ❖ **Multidisciplinary approach** of CB banking
 - ❖ Giving **accurate and balanced information** to mothers and families (ie brochures, consents, interviews)

- **Rabe H. et al.** ; Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Review) , Cochrane 2012
- **McDonald SJ et al.**; Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes (Review), Cochrane 2013
- **Raju TN** ; Timing of umbilical cord clamping after birth for optimizing placental transfusion, Current Opinion in Pediatrics. 25(2):180-187, Avril 2013
- **Hooper et al** ; Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs, *J Physiol J Physiol*, 591.8 pp 2113–2126, 2013
- **Upadhyay A et al**; Effect of umbilical cord milking in term and near term infants: randomized control trial, Am J Obstet Gyneco, 208:120.e1-6., 2013
- **Andersson O et al.**; Effects of delayed cord clamping on neurodevelopment and infection at four months of age: a randomised trial, Foundation Acta Pædiatrica 102, pp. 525–531, janvier 2013
- **Andersson O et al** ; Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial, Bmj, 343 November 2011
- **Downey et al** ; Historical perspectives on umbilical cord clamping and neonatal transition, J R Soc Med, 105 325-329, 2012
- Timing of Umbilical Cord Clamping After Birth ,**The American College of Obstetricians and Gynecologists**, December 2012
- **Rabe et al.** ; Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates, The American College of Obstetricians and Gynecologists, février 2011
- **Mercer et al.** ; Seven Month Developmental Outcomes of Very Low Birth Weight Infants Enrolled in a Randomized Controlled Trial of Delayed versus Immediate Cord Clamping ,J Perinatol, 30(1): 11–16, janvier 2010
- **Andersson O et al.** *Effect of delayed vs early umbilical cord clamping on iron status and neurodevelopment at age 12 months: a randomized clinical trial* JAMA Pediatrics 2014
- **Vain et al.** *Effect of gravity on volume of placental transfusion-a multicentre randomised non-inferiority trial* Lancet April 2014

Aknowledgements

- Caroline Lefèbvre, University of Liège
- Anders Fasth, Swedish National Cord Blood Bank, NetCord

- Michael Boo, NMDP, WMDA
- Paolo Rebutta, Milan CBB, NetCord
- Vincent Rigo, Neonatology CHU Liège
- Susana Gomez, Anthony Nolan CBB