Delayed Cord Clamping: Worth the Wait?

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Objectives

• Discuss risks and benefits of delayed cord clamping in term and preterm infants
• Understand the effects of cord clamping at different times on maternal and neonatal outcomes
• Apply this information to improve patient outcomes

Assumption of evidence

• Immediate umbilical cord clamping (CC) after delivery is the current practice in U.S.
• CDC estimates 3,952,937 births in 2012
• Early CC practiced on millions of babies
• What is the evidence for this practice?

Image

Live births and fertility rates: United States, 1920–2010
Etiology of current practice

• Not totally clear
• Early 1900’s, pregnant mothers routinely given general anesthesia before delivery
• Newborns had severe respiratory depression
• Doctors quickly clamped and cut the umbilical cord to prevent babies from receiving further chloroform or ether being given to their unconscious mothers
Umbilical Cord Clamping (CC)  
3rd stage of labor  
• Active management to reduce postpartum hemorrhage:  
  – Prophylactic uterotonic drug  
  – Immediate umbilical CC  
  – Controlled cord traction  
• Prophylactic uterotonic drugs clearly reduce risk of major hemorrhage  
• Umbilical CC timing does not appear to have a major impact on the risk of hemorrhage  
  – Cochrane review of 15 trials, 3911 women and infant pairs  
  – No significant difference in postpartum hemorrhage rates when early & late CC compared (RR 1.04, 95% CI 0.65 to 1.65)  

Timing of Umbilical CC  
• Deferring CC will allow a larger placental transfusion that may affect the newborn  
• A neglected topic for decades, there is now growing interest in assessing the effects of placental transfusion for both term and preterm infants  

The umbilical cord (UC)  
• In a full term neonate  
  – ~50 cm (20 in) in length  
  – 2 cm (0.75 in) in diameter  
• Umbilical artery: 3 mm intravital diameter  
• Umbilical vein: 6 mm intravital diameter  
• Blood flow  
  – 115 ml / min / kg at 20 weeks  
  – 64 ml / min / kg at 40 weeks  

In absence of external interventions  
• The UC occludes shortly after birth  
  – Explained both by a swelling and collapse of Wharton’s jelly in response to a reduction in temperature  
  – Vasoconstriction of the blood vessels by smooth muscle contraction  
• In air at 18°C, this physiological clamping will take three minutes or less
Umbilical vessel closure after birth

• Umbilical artery closure begins after 15 sec
  – Functional closure by 45 sec
• Umbilical vein closure begins after 15 sec
  – Diameter decreases significantly by 1-2 min

Term baby and placenta blood volumes

• Term fetus blood volume is ~70 ml/kg
• Placenta contains 45 ml/kg of blood
• Total fetoplacental volume 115 ml/kg

Preterm baby and placenta blood volumes

• Premature infants have larger placenta compared to term neonates
• Preterm fetus blood volume is ~90 ml/kg
• Fetoplacental volume is 150 ml at 26 weeks’ gestation
• Up to 2/3 of the preterm infant’s blood amount can be distributed in the placenta at the time of delivery

Placental transfusion after birth

• One quarter (40 ml) of blood enters the term infant within 15 sec
• One half (80 ml) within 60 sec
• The corresponding volume for a 70 kg adult would be 1600 ml in a minute

Factors influencing placental transfusion

• Timing to clamp the umbilical cord
• Position at which the delivered infant is held relative to the placenta in utero
• Timing of onset of breathing by the infant
• Strength of uterine contractions with or without use of oxytocin
Uterine Contraction and Maternal Hypotension

- Oxytocin given at the onset of 3rd stage of labor augments placental transfusion
- In the absence of uterine contraction, placental transfusion occurs if the infant is in the dependent position
- Residual placental blood volume shown to correlate inversely with maternal blood pressure during the first 20 to 40 sec


Delayed cord clamping (DCC)

- Allows extra transfer of fetal blood from the placenta to the infant
- Results in ~10 - 15 ml/kg of additional whole cord blood for a VLBW infant
- 8% - 24% increase in blood volume with DCC of 30 - 45 sec in preterm infants


Premature Infants

- Preterm birth:
  - Affects 11.99% of US pregnancies (2010 data)
- Global Statistics (2005 data)
  - 9.6% of all births preterm (12.9 million births)
    - 10.9 million (~85%) in Africa and Asia
    - ~0.5 million in Europe
    - ~0.5 million in North America
    - 0.9 million in Latin America and Caribbean

Preterm births in the US

- ~10,000 infants born prematurely per wk
- 600 (6%) of these are ELBW
- ~90% of ELBW neonates will receive at least one RBC transfusion


Premature infants at risk for:

- Respiratory problems
- Blood pressure instability
- Intraventricular hemorrhage (IVH)
- Neurodevelopmental delays
- Cerebral palsy
  - Reported CP prevalence rates vary from 19 to 152 per 1,000 live births for very premature and very low-birth-weight infants

Premature infants at risk for:

- Anemia of prematurity (AOP)
- Hyperbilirubinemia
- Necrotizing Enterocolitis
- Longer hospital stays

Anemia

- Neonatal anemia and low iron stores not immediately seen as serious or life-threatening
- If more serious consequences of CC considered, the need for timing and documentation of the intervention would be obvious
Anemia of prematurity (AOP)

• Typically occurs at 4 to 6 weeks after birth in infants < 32 weeks gestation.
• Onset inversely proportional to GA at birth
• Causes:
  – Reduced RBC life span
    • 60 to 80 days: Term infants
    • 45 to 50 days: Extremely low birth weight infants
  – Blood loss from phlebotomy
    • 2 to 4 ml/kg per week
  – Iron depletion
    • May impair recovery from AOP


AOP

• Many infants asymptomatic despite having Hgb values < 7 g/dL
• Other infants symptomatic at similar or even higher Hgb levels
  – Tachycardia, poor weight gain, requirement of supplemental oxygen, or episodes of apnea or bradycardia

The Anemia Argument

• Blood is a scarce and costly resource
• Risk of multiple donor exposures
• Iron stores at birth show large individual variations, but correlate with later iron status in infancy
• Iron deficiency & anemia in infancy may be associated with later cognitive deficits


### Placental transfusion
- Immediately after birth placental blood continues to flow in the direction of the baby.
- For a term infant, placental transfusion increases total volume of blood by ~ 30%.
- Within a few hours, additional plasma is lost to the circulation, leaving a high red cell mass.
- Red cell mass broken down in 1st 2 mo of age and iron is re-used or stored.

### Differences in clinical trial designs
- Associated with imprecision in quantitating the increase in RBC volume/mass achieved by DCC.
- Placental blood volume transfused into the neonate varied depending on clamp time.
- No consensus about definition of ECC or DCC regarding time intervals.

### How early is early?
- **Term infants**
  - Most trials: <15 s
  - “Immediately” following birth
- **Preterm infants**
  - Immediately
  - Up to 10 s
  - Up to 20 s


How delayed is delayed?

- Term Infants
  - 30-45s
  - 3 min (most common)
  - Up to 10 min
  - Until cessation of cord pulsations
- Preterm Infants
  - 20-30 s or 45 s

Early Cord Clamping (ECC):
Studies from the 1960’s

- Infants with decreased
  - Blood volume, red cell volume and hematocrits
  - Central venous and atrial pressures
  - Pulmonary and aortic pressures
- Differences well compensated for and tolerated in full-term newborn infants
- Theoretical risk in premature infants, in cesarean section babies and following complicated deliveries

Polycythemia and CC

- Concerns about polycythemia raised repeatedly
- DCC so frequently identified as a cause of polycythemia that it has become accepted as an unsubstantiated fact in the literature
- Symptomatic polycythemia not seen in any RCTs

Polycythemia and CC

- Blood volume being denied to baby unknown and unpredictable
- What is higher risk?
  - ECC: A baby with decreased blood viscosity and low blood pressure due to hypovolemia
  - DCC: A baby with increased blood viscosity and a normal blood pressure

Clinical trials
DCC versus ECC

- Preterm neonates, several clinical trials with mixed results
  - Favorable (pro-DCC):
    - Improved circulatory hemodynamics
    - Better cardiopulmonary adaptation to extrauterine life
    - Diminished need for RBC transfusions
    - Decreased IVH after DCC
- Term infants
  - Concerns*: (anti-DCC)
    - Results in hypervolemia with respiratory distress,
    - Erythrocytosis with plethora and hyperviscosity
    - Hyperbilirubinemia

*Theoretical

DCC vs ECC in preterm infants: Major benefits based on RCTs

- Improved circulatory hemodynamics
- Better cardiopulmonary adaptation to extrauterine life
- Diminished need for RBC transfusions
- Decreased IVH after DCC
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*Theoretical

DCC: Benefits in term infants

- **Increased**
  - Hgb and Hct in early neonatal period
  - Total body iron stores, 2–4 mo of age
  - Circulating ferritin level, 2–4 mo of age

- **Decreased**
  - Incidence of iron-deficiency anemia, around 4 mo of age

DCC: Benefits in preterm infants

- **Increased**
  - Hgb and Hct during the early neonatal period
  - Systemic blood pressure between 4 and 24 h of age
  - Blood volume
  - Urine output during the first 48 h
  - Cerebral oxygenation
  - Transfer of autologous stem cells
  - Myocardial function (systolic time intervals and cardiac output)

DCC: Benefits in preterm infants

- **Decreased**
  - Need for inotropic medications
  - Need for blood transfusions for anemia
  - Incidence of intraventricular hemorrhage (all grades)

DCC: Adverse outcomes

- **Increased**
  - Peak bilirubin values during the first week in preterm infants
  - Need for phototherapy in both preterm and term infants

Maternal and neonatal outcomes unchanged by DCC vs. ECC

- **Maternal**
  - Any or severe postpartum hemorrhage
  - Incidence of retained placenta
  - Need for maternal blood transfusions, operative delivery, episiotomy

- **Newborn**
  - Apgar scores, need for resuscitation, or umbilical cord pH values
  - Frequency of respiratory distress
  - Severe intraventricular hemorrhage or periventricular leukomalacia
  - Incidence of polycythemia
  - Requirement of exchange transfusions
  - Bayley II Scale of Development at 7 months of age

What has prevented DCC from becoming routine practice?

- Cord blood gases
- Resuscitation
- Concern regarding nuchal cord
- Cord blood banking
- Need for neonatal blood group in rhesus negative mothers
- Pediatricians waiting to get the baby
Not ‘All or None’

- Likely situations where ECC is indicated
  - Ruptured vasa previa results in fetal blood loss & need for urgent delivery
  - Baby likely hypovolemic
  - Waiting for a placental transfusion may be fruitless due to continued loss of blood from the cord vein
  - May create a placental transfusion by cord milking and lowering the baby below the placenta
- RCTs unlikely to study these situations
- Assuming that ECC will always be the best management not evidence based

Unresolved issues

- What is the optimal position to hold the infant in relation to the placenta, especially after cesarean birth?
- What is the optimal time to CC in high-risk mothers?
  - HIV, hepatitis A, B, C positive
  - Placental abruption or previa

Unresolved issues

- What is the optimal time to CC for high-risk infants?
  - Multiple gestations
  - At risk fetal polycythemia
  - IUGR, LGA, IDM
- What will the effect of DCC be on umbilical cord blood gases?
- Should NRP be started before CC?

Delay is preferable to error.

Thomas Jefferson

Conclusions: Changing Times

- One of the problems of evidence-based medicine is how to handle interventions that entered medical practice without proper evidence
- To avoid negating clinical experience (>100 yrs with ECC) evidence is needed to remove these interventions from clinical practice

Changing Times

- DCC since the 1st human birth
- ECC is the newer intervention
- Introducing a new intervention requires evidence “beyond a reasonable doubt” that it will produce a benefit
- Removing an intervention does not require the same level of proof if harm is being caused
Conclusions

- Clamping of the umbilical cord soon after birth has no physiological rationale and may cause harm (regarding iron status)

- The terms *early* and *delayed* cord clamping should be abandoned since they are misleading, suggest unsafe practice, and are inconsistent
  - Describe the procedure: e.g., CC at <15 s, CC at 45 s

Documenting timing of CC

- Record CC time in the medical records of the mother and her infant
  - Alert pediatric/NICU team to monitor infants’ bilirubin status and to implement appropriate follow-up plans
  - Possible increased need for phototherapy, in settings where early discharge of term and late preterm infants is a common practice

**Wait a Minute**

- Incorporate the practice of cord clamping after at least 30 s, whenever feasible, especially for preterm infants
- Benefits outweigh risks
- Motto should be to, “*Just wait a minute,*” and not, “*Just wait a second.*”
- The *Iron Minute* should precede the *Golden Minute*

**References**

- Philip AGS, Saigal S. When should we clamp the umbilical cord? *NeoReviews* 2004;5:e142–53.