Title: Maternal blood loss with delayed cord clamping during cesarean delivery at term
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Objective:
To evaluate maternal blood loss associated with delayed cord clamping during cesarean delivery at term

Background and Rationale:
The optimal timing of umbilical cord clamping remains a topic of controversy. The common obstetric practice of active management of the third stage of labor involves immediate clamping of the umbilical cord in an effort to reduce the risk of maternal hemorrhage. On the other hand, a delay in umbilical cord clamping has potential neonatal benefits by virtue of allowing transfusion of additional blood from the placenta to the neonate and ultimately increasing the circulating blood volume in the neonate (1). There are a variety of practice patterns with regard to delayed clamping, with the time of cord clamping ranging from 30 seconds up to five minutes after birth, or when cord pulsation ceases.

Multiple studies have demonstrated that delayed cord clamping is beneficial for preterm infants (2). Delayed umbilical cord clamping in preterm infants is associated with decreased rates of intraventricular hemorrhage, necrotizing enterocolitis, and blood transfusion. Similar studies in term infants have failed to show a difference in major morbidity or mortality, but do demonstrate more modest benefits - an increase in hematocrit at 24 to 48 hours after birth and increased iron stores later in infancy (3). Improved iron stores may have a favorable impact on developmental outcomes in childhood, particularly in low resource settings. Of note, delayed cord clamping is associated with higher rates of hyperbilirubinemia in preterm infants and higher rates of jaundice requiring phototherapy in term infants (2, 3). A number of professional societies worldwide (World Health Organization, American Academy of Pediatrics, Royal College of Obstetricians and Gynaecologists, American College of Nurse–Midwives) recommend delayed clamping of the umbilical cord for anywhere from 30 seconds up to 5 minutes after birth for both preterm and term infants. In line with these recommendations, the American College of Obstetrics and Gynecology recently published a Committee Opinion that recommends a "delay in umbilical cord clamping in vigorous term and preterm infants for at least 30–60 seconds after birth"(4). The Committee Opinion does note that "the ability to provide delayed umbilical cord clamping may vary among institutions and settings; decisions in those circumstances are best made by the team caring for the mother-infant dyad."

Currently at our center, immediate cord clamping is the standard of care for term deliveries. As we consider implementing this new recommendation, we must recognize that the impact of delayed cord clamping on maternal health outcomes is understudied. To date, only five studies have examined maternal outcomes related to delayed cord clamping (3). These studies found no difference in postpartum hemorrhage, mean blood loss, postpartum Hgb, or need for blood transfusion. However, these studies generally included healthy women expected to give birth vaginally, with only three studies including women who delivered by cesarean. There are no published data specific to women (or neonates) undergoing cesarean delivery.

There is physiologic reason to be concerned about the potential impact of delayed cord clamping on maternal health, and specifically maternal blood loss, at the time of cesarean delivery. Uterine blood flow at term is 17% of cardiac output (450-650mL/min). Thus, there may be a high potential for significant blood loss from delayed hysterotomy closure with delayed cord clamping during cesarean (which differs from vaginal delivery). For what is a relatively small neonatal benefit, delayed cord clamping at term cesarean may come possibly at the expense of increased maternal blood loss, which is a great concerns considering that postpartum hemorrhage remains a leading cause of maternal morbidity and mortality. If we are to implement ACOG's recommendations into practice, it is critical that we understand the implications for maternal health in addition to neonatal health.

We propose a prospective randomized controlled trial which will compare maternal blood loss associated with immediate versus delayed cord clamping during cesarean delivery at term. We hypothesize that delayed cord clamping in cesarean delivery at term is associated with increased maternal blood loss compared to immediate cord clamping.

Primary Research Question:
Is delayed cord clamping at the time of scheduled cesarean delivery at term associated with increased maternal blood loss (based on primary outcome of maternal hemoglobin drop from preop to postoperative day #1)?

Hypothesis
Delayed cord clamping in cesarean delivery at term is associated with increased maternal blood loss compared to immediate cord clamping.

Secondary Research Question:
Is delayed cord clamping at scheduled cesarean delivery in term infants associated with improved neonatal hemoglobin and hematocrit levels?

Study Design and Statistical Procedures:
This is a randomized controlled trial of patients undergoing scheduled (daytime) cesarean section at term at CHONY and The Allen.

For our primary research question, we will compare the change in maternal hemoglobin from pre-op to postoperative day #1. Based on existing literature for elective cesarean section, the mean +/- SD Hgb pre-op is 12.24 +/- 1.09 and post-op 10.87 +/- 1.2, with a mean Hgb drop 1.37 +/- 0.87 (5).

For a hypothesized effect size of a 1 SD (0.9g/dL) difference in blood loss (change in Hgb) between the two groups, with an alpha of 0.05 and 90% power, and 1:1 randomization, the required sample size is 40 patients (mother-baby pairs) per group.

Planned analysis is by intention-to-treat. We anticipate 20% differential crossover (from the delayed cord clamping group in cases where the cord is clamped sooner than planned due to maternal or fetal status). With a 20% crossover rate, the sample size per group is 53 patients to maintain an alpha of 0.05 and 90% power. We therefore plan to enroll 55 patients per group for a total of 110 mother-baby pairs.

Type I error = 0.05
Type II error = 0.1 (90% power)

Study Arms
Intervention group:
- Delayed cord clamping (60 seconds)

Control group:
- Immediate cord clamping (<15 seconds)

Study Procedures
Consented patients who remain eligible for study participation on the day of their scheduled cesarean delivery will be randomized 1:1 by trained research personnel to one of two groups (Intervention group/Delayed cord clamping or Control group/Immediate cord clamping). Randomization will occur on labor and delivery while the patient is in the pre-operative area prior to delivery.

Once the patient is randomized, the obstetric providers/surgical team will be notified of the patient's assignment to the immediate or delayed cord clamping group. The patient will be taken to the operating room where anesthesia will be administered and cesarean delivery will be performed in routine fashion until delivery of the baby. A trained member of the research team will be present in the operating room, and upon delivery of the neonate, management will proceed based on randomization assignment.

For the immediate cord clamping group, the obstetric surgical team will clamp and cut the cord immediately (goal within 15 seconds of delivery of the baby) and hand the neonate to the pediatric team for routine assessment. For the delayed cord clamping group, the obstetric surgical team will clamp and cut the cord 60 seconds after delivery, unless cord clamping is indicated sooner to expedite neonatal resuscitation by the pediatric team.

In the interval from delivery to cord clamping, oxytocin will be administered (by the anesthesia team) in routine fashion immediately upon delivery. Umbilical cord milking may not be performed. The neonate should rest between the mother's legs on the sterile operating field. Immediate newborn assessment and stimulation should be performed. This includes wrapping the neonate in warm, dry towels and drying/stimulating the neonate (performed by the obstetric team). There will be ongoing visual assessment by the pediatric team present at delivery. For the delayed cord clamping group, if the neonate is not breathing and crying at 30 seconds of life, despite initial stimulation and drying, the cord should be clamped prior to the planned 60 seconds and given to the pediatric team for further resuscitation. If the neonate is vigorous at 30 seconds of life, cord clamping will be delayed until 60 seconds as planned. If at any time the pediatric team feels the neonate requires more urgent resuscitation, the cord should be clamped and the neonate given to the pediatric team. The neonates in the immediate cord clamping group will also receive initial resuscitation with drying/stimulating, but this will be performed by the pediatric team as per routine care.

The trained research team member who is present in the operating room will record the time from delivery to cord clamping. The APGAR timer will be used for timing. For the delayed cord clamping group, the research team member will use the timer to instruct the surgical team when to clamp and cut the cord (60 seconds after delivery).

After the neonate is handed to the pediatric team, an umbilical cord segment will be obtained by the obstetric surgical team for routine arterial and venous cord gas collection. After cord gases specimens are collected by the RN, the research team member will collect an additional venous cord specimen and run point-of-care Hgb/Hct testing.

The remainder of the cesarean will proceed in routine fashion per surgical team. Uterotonics/blood transfusion may be administered per routine care as judged necessary by the surgical team. Blood loss at completion of the surgery will be estimated by the obstetric, nursing, and anesthesia teams with a final estimated blood loss (EBL) agreed on by all providers and recorded in the routine fashion in the medical record.

All mothers will receive routine postoperative/postpartum care. A maternal POD#1 CBC will be collected in the routine manner.

All newborns will receive routine newborn care. At the time of the routine newborn heel stick for NY State Newborn Screening, the research team personnel will collect one additional drop of blood and run point-of-care Hgb/Hct testing. Of note, this sample/result will be obtained for the research record only. However, if an abnormal neonatal Hgb/Hct result is obtained, the pediatric team will be notified by the research team so they may repeat testing through the NYP/CHONY lab to confirm results and respond accordingly.

Aside from the aforementioned timing of cord clamping and point-of-care Hgb/Hct measures (which will be obtained using the Hemocue Hb 201+ instrument), the research team member will also record operative time and the time of the first breath and cry for the neonate. All other data will be abstracted by the research team by review of both the maternal and neonatal medical records.

Study Outcomes

Primary Outcome:

- Maternal drop in Hgb on POD#1

Secondary Outcomes:

- Postpartum hemorrhage
- Estimated blood loss
- Need for additional uterotonics

- Maternal blood transfusion

- APGAR scores
- Time of first breath/cry
- Resuscitative interventions
- Birthweight
- Newborn temperature (within 1st hour of life)
- Placental weight
- Neonatal Hgb/Hct
- Neonatal hyperbilirubinemia/jaundice/phototherapy
- NICU admission
- Neonatal blood pressure if admitted to NICU

- Umbilical cord venous Hgb/Hct
- Umbilical cord gas (arterial and venous)
- Operative time

Study Subjects

Inclusion Criteria:

- Singleton gestation
- Scheduled cesarean delivery at term (>=37 weeks)

Exclusion criteria:

- Placenta previa, abruption
- IUGR with abnormal Dopplers
- Fetal anomalies
- Known fetal anemia
- Planned cord blood banking
- Preeclampsia
- Significant maternal anemia (Hgb <=7)
- Maternal coagulopathy/bleeding disorder
- Jehovah's Witness/refusal of blood products

Recruitment

Participants will be recruited in-person by trained research personnel either at a prenatal visit (at or beyond 35 weeks gestation) or in the pre-op area on labor and delivery (at CHONY or The Allen) prior to administration of sedatives, anesthetics, or other mental-altering medications (note: all patients included in study will be undergoing scheduled cesarean delivery and therefore should not be in pain or laboring at the time of pre-op consent). Of those recruited at a prenatal visit, some patients will ultimately be ineligible for inclusion in the study. If a patient goes into spontaneous labor or has rupture of membranes prior to the scheduled term cesarean delivery, they will no longer qualify for the study. Additionally, if the scheduled cesarean is delayed until the late afternoon or evening, they not qualify for the study either. Given this, the goal is to recruit a total of 150 women for a final sample size of 110 patients (110 mother-baby pairs for a total of 220 study subjects).

We will abide by the CUMC policy that researchers cannot directly approach a patient for recruitment until that patient has been informed of the study by a care provider who has ascertained that the patient is willing to discuss the study with the investigators. This will be documented in the research record.

Patient written informed consent and HIPAA authorization to participate in the study will be collected on an iPad. In-person electronic signature will be captured on the electronic informed consent form. Study personnel obtaining

consent will be physically present at time of signature. A paper copy of the signed informed consent form is given to the patient. If consent is being obtained in the pre-op area, copy of the signed consent form will also be placed in the patient's inpatient paper chart. The time of consent will be documented on the consent form and in the medical record.

Informed Consent Process:
Study personnel will consent participants in person, face to face, when they receive notification by a provider of an eligible patient. Participants will be consented in English or Spanish by personnel fluent in that language or with the use of NYP translators and a full consent in their language. Recruitment will occur in a private setting, in a non-coercive manner, with ample time to ask questions and receive satisfactory answers.

Patient written informed consent and HIPAA authorization to participate in the study will be collected on an iPad. In-person electronic signature will be captured on the electronic informed consent form. Study personnel obtaining consent will be physically present at time of signature. A paper copy of the signed informed consent form is given to the patient. If consent is being obtained in the pre-op area, copy of the signed consent form will also be placed in the patient's inpatient paper chart. The time of consent will be documented on the consent form and in the medical record.

Consent forms will be available in both English and Spanish to accommodate our expected population.

Confidentiality of Study Data
Data and research records will primarily be stored electronically in a study database. This study database will be developed and maintained with support from Columbia University's Department of Obstetrics and Gynecology CORE Data Team. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University.

REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the OB/GYN Division of Research Informatics Support Team. The iterative development and testing process results in a well-planned data collection strategy for individual studies. With the assistance of the OB/GYN Division of Research Informatics, the research team work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data.

REDCap servers are securely housed in an on-site limited access data center and is managed by the OB/GYN IT Division. The data is all stored on a private, protected university managed server. All users are authenticated via the CU and NYP LDAP servers and their access is restricted on a role-specific basis. Access can only be granted by administrators of the system. REDCap@OBGYN was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Columbia University and New York Presbyterian guidelines. All collected data are backed up daily. REDCap@OBGYN system id is 4283.

REDCap Reference:
P.A. Harris, R. Thielke, R. Taylor, J. Payne, N. Gonzalez, J.G. Conde. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 2008 (doi:10.1016/j.jbi.2008.08.010).

Source data will be stored on encrypted, password protected servers maintained by OBGYN IT at the CUMC server farm; system id is 3959.

Some data may be collected on paper case report forms, which will be stored in a locked file cabinet in the MFM fellow office and will be accessible only to named research personnel.

Privacy Protections
Patient information will be collected by trained research personnel in a private setting. Patient confidentiality will be maintained following HIPAA rules and regulations.

Potential Risks
If patients are randomized to delayed cord clamping, there is a potential maternal risk of increased maternal blood loss during cesarean delivery (as per our primary research question and hypothesis). In all cases, obstetric providers will take standard precautions to minimize blood loss. Medications to decrease blood loss are readily available in the operating room to use when indicated. As part of routine postoperative care, all patients will have vital signs, urine output, blood count, and symptoms monitored closely after delivery to quickly identify and treat patients with anemia.

There is a neonatal risk for increased jaundice requiring phototherapy in the delayed clamping group. Data from the literature suggests that the incidence of phototherapy for jaundice is 2.74% for early clamping and 4.36% for delayed clamping (3). Monitoring for jaundice is a component of routine neonatal care and our institution has phototherapy readily available for neonates. When infants with hyperbilirubinemia are identified and treated appropriately, outcomes are excellent.

For both randomization groups, there is no additional maternal or neonatal risk to cord blood collection because a cord segment is routinely collected at all deliveries, and is ultimately discarded tissue. We will be obtaining an additional sample of blood from the cord segment after collection prior to tissue disposal. There is no added neonatal risk to collecting an additional one drop of blood at the time of neonatal heel stick, because the heel stick procedure is already a part of routine neonatal care for all babies. If an abnormal neonatal Hgb/Hct result is obtained from the heel stick sample, the pediatric team will be notified by the research team so they may repeat testing through the NYP/CHONY lab to confirm results and respond accordingly.

Although unlikely, it is possible that participating in this study may involve risks to the patient and her baby that are not expected.

There is a risk of improper release or misuse of personal information or specimens. The chance of this happening is very small. The research team has many protections in place to lessen this risk.

Data and Safety Monitoring
To ensure safety of the subjects, local monitoring will be completed by the Quality Assurance Monitor for the Department of Obstetrics and Gynecology for this Investigator/Peer study. At each scheduled monitoring visit, the QA will randomly select a representative number of study subject charts to be reviewed. Additional monitoring will be based on the initial monitoring review.

Potential Benefits
If patients decide to participate in this research study, they (and/or their newborn) may or may not directly benefit from their participation. If the patient is randomized to the delayed clamping arm, the neonate may benefit from an increased hemoglobin level in the newborn period and increased iron stores in the first six months of life. This may have a positive impact on child neuro-development.

In addition, the data gathered on maternal outcomes will serve to increase the general knowledge regarding the timing of cord clamping at cesarean and may benefit mothers and babies in the future.

Alternatives
The alternative to this study is not to participate and to continue receiving standard care during delivery and postpartum.

References

1. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet. 1969;2(7626):871-3.

2. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. The Cochrane database of systematic reviews. 2012(8):CD003248.

3. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. The Cochrane database of systematic reviews. 2013(7):CD004074.

4. Committee Opinion No. 684 Summary: Delayed Umbilical Cord Clamping After Birth. Obstet Gynecol. 2017;129(1):232-3.

5. Horowitz E, Yogev Y, Ben-Haroush A, Rabinerson D, Feldberg D, Kaplan B. Routine hemoglobin testing following an elective Cesarean section: is it necessary? The journal of maternal-fetal & neonatal medicine. 2003;14(4):223-225.