Background

The primary objectives are to assess whether timing of cord clamping and other strategies to alter placental transfusion at preterm birth influence (i) the composite outcome of death or serious morbidity at discharge from hospital, and (ii) disability-free survival in early childhood (aged 2-3years).

Methods

The Chief Investigators of potentially eligible studies will be contacted to invite them to collaborate in this prospective meta-analysis. Eligible trials identified in January 2013 are listed in Table 1. The Cord Clamping and other measures to influence Placental Transfusion at Preterm birth collaboration (CCPTP collaboration) will undertake this prospective meta-analysis using individual participant data according to the methods recommended by the Cochrane Collaboration Prospective Meta-Analysis Methods Group.[1]

Criteria for potentially eligible studies

Study design: Studies will be included if they are randomised trials. Studies will be included if they are individual or cluster randomised. Quasi-random studies will be excluded.

Publication and unblinding of outcome data: Studies will only be included in the prospective meta-analysis if the investigator/s were blind to outcome data by intervention group at the time this protocol was agreed (i.e. when the objectives, aims and hypotheses, eligibility criteria, subgroup and sensitivity analyses, and main outcomes were agreed). If short term data are unblinded by allocation group but follow-up data remain blinded at the time the protocol is agreed, only the follow-up data from such trials will be included.

Types of participant: Participants will be women giving birth preterm (before 37 completed weeks gestation) and their babies. Studies will be eligible for inclusion if they recruited women and their babies, or babies alone.

Types of intervention: Studies will compare early or immediate cord clamping (standard care) with deferred cord clamping, with or without other strategies to influence placental transfusion (such as position of the baby whilst cord intact, use of uterotonic drugs, and umbilical cord milking). Studies will also be included if they compare any alternative strategies for influencing placental transfusion without a timing of cord clamping arm.

Studies evaluating collection and storage of residual placental blood that is then used for transfusion after birth will be excluded.

The comparisons included in the prospective meta-analysis will be:

1. Immediate cord clamping versus deferred cord clamping (trials with no cord milking in either allocated group)
2. Immediate cord clamping versus deferred cord (with subgroups by whether umbilical cord milking)
3. Immediate cord clamping versus umbilical cord milking
4. Umbilical cord milking versus deferred cord clamping

There is no consensus about the definition of 'immediate' and 'deferred' cord clamping. Whenever possible immediate clamping will be defined as within 20 seconds, and deferred clamping as at least 60 seconds. However, one objective of this PMA will be to explore the potential impact of alternative timings of cord clamping.

Types of outcome: Primary outcomes will be for the children:

- Death or serious morbidity at discharge from hospital. Serious morbidity will be defined as one or more of (i) brain injury on cranial ultrasound, (ii) necrotizing enterocolitis ≥ Grade 2, (iii) late onset sepsis (>48 hr after birth), (iv) chronic lung disease, and (v) retinopathy requiring treatment
- Disability-free survival at age 2-3 years

Secondary outcomes will be:
For the women: postpartum haemorrhage (blood loss >500ml), any breast feeding, postnatal depression

For the children: Death , Brain injury on cranial ultrasound, Necrotizing enterocolitis ≥ Grade 2, Late onset sepsis (> 48 hr after birth), Chronic lung disease, Retinopathy requiring treatment, Blood transfusion, Hypothermia, Jaundice requiring treatment, Long term neurodevelopment: cerebral palsy, neurosensory disability, deafness, blindness.

Search strategy for potentially eligible studies

We will identify ongoing trials that may be eligible by searching for published protocols in Medline and Embase, searching online registries of clinical trials, web searches of other sources, and personal contacts (for example by asking all collaborators to check conference abstracts). The Chief Investigators of ongoing trials will be invited to join the PMA provided the data remain blind and the study meets the eligibility criteria.

Assessment of study quality

Potentially eligible studies will be assessed for risk of bias using the criteria described in the Cochrane Handbook.

Planned subgroup analyses

To assess whether the results are comparable for different groups of infants, and for different levels of intervention, the following subgroup analyses will be conducted for the primary outcomes, if data are sufficient, based on:

For all comparisons:

- Gestation at birth: <37 completed weeks to 32 weeks; <32 weeks to 28 weeks, <28 weeks
- Type of pregnancy: singleton; multiple
- Mode of birth: caesarean; vaginal
- If caesarean birth, by type of anaesthesia: general anaesthesia, regional anaesthesia, type of anaesthesia not known

For comparisons of timing of cord clamping

- Timing of uterotonic drug: before cord clamping; after/at cord clamping
- Duration of deferred cord clamping: >30 seconds but ≤1 minute; >1 minute but ≤2 minutes; >2 minutes
- Whether cord milking: cord milking; no cord milking; not known whether cord milking

Planned sensitivity analyses

To assess whether results are robust to trial quality and different methods of analysis the following sensitivity analyses will be conducted for the primary outcomes, if data are sufficient:

- excluding studies with high risk of bias
- for trials comparing alternative strategies for timing of cord clamping: excluding studies where the mean difference between timing in the intervention arms was <45 seconds, or where the difference is not known
- comparing analyses using fixed effects and random effects models
- analysis of outcomes weighted by degree of difference between birth weights in treatment and control

Analysis plan

Analysis will include all randomised participants with available data and be based on intention-to-treat. Missing data will be described and reasons for missing data explored. The impact of missing data on conclusions about the comparative effects on the primary outcomes will be explored where possible (for example by using sensitivity analyses or imputation techniques). Multilevel models will be considered to examine how much variation in the outcomes is attributable by subgroup variables, and to estimate effect sizes with adjustment for subgroup variables as well as uncountable random effects among individual studies where necessary.[5] The full analysis plan will be agreed by the Collaboration before any analyses are undertaken.

Project management

Membership of the CORD Collaboration will include representatives from each of the trials contributing data to the project, plus representatives from the project coordination group, and invited experts in IPD prospective meta-analysis. The project coordination group will be responsible for data management and analysis and communication within the Collaboration, including newsletters and email updates.

Ethics issues

Participants in the individual trials have previously consented to participation in their respective trial. The data will be available through an agreement between all Chief

Investigators of the included trials, and ethics approval for each of the trials has been given by their respective Research Ethics Committees. The trialists remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time. Data will be de-identified before being shared with the CCPTP Collaboration.

Publication policy

Each trial has the right to publish the main results of their trial prior to the CCPTP Collaboration results being published. When publishing individual study results the authors for participating trials will acknowledge within the publication their involvement in the CCPTP Collaboration. Before publication of any CCPTP manuscripts, drafts will be circulated for comment, revision and approval by a nominated representative of each of the participating trials. Publications using these data will be authored on behalf of the CCPTP Collaboration, either with specific named authors, or on behalf of the Collaboration as a whole and names of other participating Collaborators will be listed in the Acknowledgements.

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Table 1: Trials eligible for collaboration in CCPTP at January 2013

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
El-Nagare, W	70 infants <31 weeks gestation	Cord milking - infants in the cord-milked group will be placed at or below the level of the placenta, and about 20 cm of the umbilical will be vigorously milked towards the umbilicus three times before clamping the cord	Systemic blood flow as reflected by mean SVC flow measured by echocardiographic study at 4-6 hours after birth.	Immediate cord clamping at birth
Mercer, S	212 pregnant women in preterm labour between 24 and 31.6 weeks	Delayed cord clamping - at birth, the obstetrical provider delays the cord clamping for 45 sec while lowering the infant. At 45 sec the cord is milked once and then clamped and cut	Very low birth weight infants in the delayed cord clamping group will have better motor function at 18-22 months corrected age when compared with VLBW infants in the ICC group.[Time Frame: 18-22 months]	Immediate cord clamping at birth
Josephsen, J	80 pregnant women in preterm labour between	Cord milking - the neonate will be placed below the level of the placenta and approximately 20cm	• To evaluate and compare hemoglobin and hematocrit concentrations in extremely	Immediate Cord clamping at birth

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
	24 0/7 and 27 6/7 weeks	of umbilical cord will be milked three times over 10-20 seconds total from the placental end to the neonate before clamping the cord	low birth weight infants (ELVW) after cord milking intervention to ELBW infants receiving immediate cord clamping • To evaluate and compare the incidence and numbers of blood transfusions after cord milking	
Katheria, A	60 Infants <32 weeks gestation	Cord milking – the delivering obstetrician will hold the infant below the mother's introitus at vaginal delivery or below the level of the incision at caesarean section and about 20cm of the cord will be milked over 2 seconds and repeated two additional times	Superior Vena Cava Flow. Researchers hypothesize that infants who receive umbilical cord milking (UCM) compared to infants who receive immediate cord clamping (ICC) will have higher SVC flow at 6 hours. [Time Frame: 6 hours]	Immediate cord clamping at birth without milking

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
Datta, V	120 infants between 34 weeks 0 days to 36 weeks +6 days gestation	Delayed cord clamping - delayed by 30 to 60 seconds	Short term neurobehavioral outcome using N.A.P.I. (neurobehavioural assessment of preterm infant).	Early cord clamping within 20 sec
Mercer, J	212 pregnant women between 24 and 31.6 weeks at risk of delivery	1-Delayed cord clamping - delayed 30 to 45 seconds while the infant is held lower than the placenta. 2-Cord milking -At the end of the time, the cord is milked once and the cord is clamped. If the obstetrician feels he cannot delay the cord clamping, then the cord can be milked 2 to 3 times.	• Very low birth weight (VLBW) infants in the delayed cord clamping (DCC) group will have less intraventricular haemorrhage (IVH) compared to VLBW infants in the immediate clamped (ICC) group [Time Frame: December, 2012] • Very low birth weight infants in the delayed cord clamping group will have less late onset sepsis than those in the immediate clamping group	Immediate cord clamping at birth

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
			[Time Frame: December 2012]	
Hosono, S	566 infants between 24 and 28 weeks gestation	Cord milking - Umbilical cord is cut and clamped at 30cm from infants, baby is placed on a radiant warmer. Paediatrician then milks the umbilical cord once	1) the probability of not needing transfusion and death 2) amount of blood transfusion within the first 4 weeks	Early cord clamping within 30 seconds
Tarnow-Mordi, W	1600 pregnant women less than 30 weeks at risk of delivery	Delayed cord clamping - Infant held as low as possible below the level of the placenta for 60 seconds or more before cord clamped about 6 cm from the umbilicus.	Composite death and/or major morbidity at 36 weeks post menstrual age. Morbidity is defined by one or more of the following: Brain injury on ultrasound, Chronic lung disease, Severe retinopathy, Necrotising enterocolitis, Late onset sepsis. Timepoint: 36 weeks post menstrual age	Immediate cord clamping

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
Tarnow-Mordi, W	100 pregnant women less than 32 weeks at risk of delivery	Autologous placental transfusion 1. Cord milking – Cord clamped and cut long (3 cm from the placenta or the introitus of the vagina) then untwisted and milked during resuscitation. 2. Delayed cord clamping - Infant place as low as possible below the level of the introitus or placenta for 30 – 60 seconds then cord clamped 6 cm from the umbilicus. If the baby is in extremis, the previous step is omitted and the cord is clamped immediately 6 cm from the umbilicus.	Haemoglobin concentration will be measured using arterial or venous or capillary blood on the neonatal intensive care unit blood gas analysis machine or hospital laboratory using any method pragmatically available. Timepoint: at 6 hours after birth	Immediate cord clamping

Chief Investigator	Participants	Intervention	Primary outcome	Comparator
		3. Delayed cord clamping plus milking - Infant held as low as possible below the level of the introitus or the placenta for 30 – 60 seconds then cord clamped and cut long before being handed to neonatal team. After the delay step, cord untwisted and milked during resuscitation		