Final Mini-CAT **Alena Rakhman**

Brief description of patient problem/setting
34-year-old female G2P0101 underwent an emergent caesarean delivery after going into labor at 35-weeks gestation. Her first child was born premature as well through C-section, where immediate cord clamping was performed. Prior to going into labor for her second pregnancy, she was discussing with her Ob provider about delayed umbilical cord clamping as she heard of potential benefits from other mothers from her Mommy & Me class.

Search Question:
What is the efficacy and safety of delayed umbilical cord clamping compared with early/immediate cord clamping in preterm infants?

Additional Information:
- Immediate clamping of the umbilical cord – less than or equal to 10 seconds after delivery.
- Delayed clamping – greater than or equal to 60 seconds after delivery.
- Cord milking – milking the contents of the umbilical cord.

Question Type:

☐Prevalence	☐Screening	☐Diagnosis
☒Prognosis	☒Treatment	☐Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

- RCTs can offer great supporting evidence as they are carefully planned experiments, reduce the potential for bias, and allow for comparison between intervention and control groups.
- Retrospective cohort studies could also be utilized because they are below RCTs in terms of level of evidence in which study participants who receive a particular treatment can be followed over time and compared with another group of participants who did not receive the same treatment.

PICO search terms:

P	I	C	O
Preterm infants	Delayed umbilical cord clamping	Early umbilical cord clamping	Efficacy
Preterm neonates		Immediate umbilical cord clamping	Safety
Birth before 37th week of pregnancy			Complications
			Mortality
			Morbidity

Search tools and strategy used:
I was lucky enough to find a very recent systematic review and meta-analysis that focused on my research question and included many RCTs. After that, I tried finding studies that were not included in the systematic review, but I decided to include 1 of them, an RCT, since there was more focus on it. I explained my choice to include it in more details below.

Results found:
PubMed

- delayed vs early cord clamping in preterm infants (most recent) – 17
- delayed vs early cord clamping in preterm infants (most recent, within 10 years) – 15
- delayed cord clamping in preterm infants (most recent) – 204
- delayed cord clamping in preterm infants (most recent, within 10 years) – 175
- delayed cord clamping in preterm infants (most recent, within 10 years, systematic review) – 8
- delayed cord clamping in preterm infants (most recent, within 10 years, clinical trial) - 29

Google Scholar

- delayed vs early cord clamping in preterm infants (any time, sort by relevance) – 21,600
- delayed vs early cord clamping in preterm infants (2009-2019, sort by relevance) – 17, 200
- delayed vs early cord clamping in preterm infants (since 2015, sort by relevance) – 12, 500
- delayed vs early cord clamping in preterm infants 'systematic review' (since 2015, sort by relevance) – 9,190

Cochrane Library

- early versus delayed umbilical cord clamping in preterm infants (Cochrane reviews) – 1
- early versus delayed umbilical cord clamping in preterm infants (Trials) – 6
- early versus delayed umbilical cord clamping in preterm infants (Trials, 2010-2019) – 6
- delayed cord clamping in preterm infants (Cochrane reviews) – 2
- delayed cord clamping in preterm infants (Trials) – 106
- delayed cord clamping in preterm infants (Trials) – 106
- delayed cord clamping in preterm infants (Trials, 2010-2019) – 106

Citation:

1. Fogarty, M., Osborn, D. A., Askie, L., Seidler, A. L., Hunter, K., Lui, K., … Tarnow-Mordi, W. (2018). Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. American Journal of Obstetrics and Gynecology, 218(1), 1–18. https://doi.org/10.1016/j.ajog.2017.10.231

Type of article:

Systematic review and meta-analysis

Abstract:

Background:

The effects of delayed cord clamping of the umbilical cord in preterm infants are unclear.

Objective:

We sought to compare the effects of delayed vs early cord clamping on hospital mortality (primary outcome) and morbidity in preterm infants using Cochrane Collaboration neonatal review group methodology.

Study design:

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Chinese articles, cross-referencing citations, expert informants, and trial registries to July 31, 2017, for randomized controlled trials of delayed (!30 seconds) vs early (<30 seconds) clamping in infants born <37 weeks' gestation. Before searching the literature, we specified that trials estimated to have cord milking in >20% of infants in any arm would be ineligible. Two reviewers independently selected studies, assessed bias, and extracted data. Relative risk (ie, risk ratio), risk difference, and mean difference with 95% confidence intervals were assessed by fixed effects models, heterogeneity by I^2 statistics, and the quality of evidence by Grading of Recommendations, Assessment, Development, and Evaluations.

Results:

Eighteen randomized controlled trials compared delayed vs early clamping in 2834 infants. Most infants allocated to have delayed clamping were assigned a delay of !60 seconds. Delayed clamping reduced hospital mortality (risk ratio, 0.68; 95% confidence interval, 0.52e0.90; risk difference, e0.03; 95% confidence interval, e0.05 to e0.01; P 1⁄4 .005; number needed to benefit, 33; 95% confidence interval, 20e100; Grading of Recommendations, Assessment, Development, and

Evaluations 1⁄4 high, with I^2 1⁄4 0 indicating no heterogeneity). In 3 trials in 996 infants 28 weeks' gestation, delayed clamping reduced hospital mortality (risk ratio, 0.70; 95% confidence interval, 0.51e0.95; risk difference,

e0.05; 95% confidence interval, e0.09 to e0.01; P 1⁄4 .02, number needed to benefit, 20; 95% confidence interval, 11e100; I^2 1⁄4 0). In subgroup analyses, delayed clamping reduced the incidence of low Apgar score at 1 minute, but not at 5 minutes, and did not reduce the incidence of intubation for resuscitation, admission temperature, mechanical ventilation, intraventricular hemorrhage, brain injury, chronic lung disease, patent ductus arteriosus, necrotizing enterocolitis, late onset sepsis or retinopathy of prematurity. Delayed clamping increased peak hematocrit by 2.73 percentage points (95% confidence interval, 1.94e3.52; P < .00001) and reduced the proportion of infants having blood transfusion by 10% (95% confidence interval, 6e13%; P < .00001). Potential harms of delayed clamping included polycythemia and hyperbilirubinemia.

Conclusion:

This systematic review provides high-quality evidence that delayed clamping reduced hospital mortality, which supports current guidelines recommending delayed clamping in preterm infants. This review does not evaluate cord milking, which may also be of benefit. Analyses of individual patient data in these and other randomized controlled trials will be critically important in reliably evaluating important secondary outcomes.

Key points:

- Delaying umbilical cord clamping may improve outcome in preterm infants by increasing the volume of blood transferred from placenta to infant and by allowing time for physiologic transition.
- This was an updated systematic review of randomized clinical trials identified up to July 31, 2017.
- Eighteen randomized controlled trials compared delayed vs early clamping in 2834 infants.
- Delayed clamping reduced mortality and infant blood transfusions, both in preterm (<37 weeks' gestation) and very preterm (28 weeks' gestation).
- Additional subgroup analyses showed no significantly different effects on mortality according to duration of delay in cord clamping, mode of delivery (vaginal or cesarean), height infant held relative to the introitus or cesarean incision, timing of oxytocics, or timing of resuscitation (before or after cord clamping).
- Delayed clamping did not impact maternal postpartum hemorrhage or the need for maternal blood transfusion.
- For the infant, delayed cord clamping was well tolerated with no evidence of an adverse effect on Apgar scores, need for resuscitation, intubation at delivery, or temperature at admission to neonatal intensive care unit.
- Delayed clamping increased mean peak hematocrit in the first week confirming that placental transfusion occurred.
- Delayed clamping increased the incidence of polycythemia and jaundice.

Why I chose it:

I chose this article because it is a systematic review and meta-analysis providing me with highest level of evidence as well as because of its recent publication date (2018).

Citation:

2. Tarnow-Mordi, W., Morris, J., Kirby, A., Robledo, K., Askie, L., Brown, R., … Simes, J. (2017). Delayed versus Immediate Cord Clamping in Preterm Infants. New England Journal of Medicine, 377(25), 2445–2455. https://doi.org/10.1056/nejmoa1711281

Type of article:

RCT

Abstract:

Background:

The preferred timing of umbilical-cord clamping in preterm infants is unclear.

Methods:

We randomly assigned fetuses from women who were expected to deliver before 30 weeks of gestation to either immediate clamping of the umbilical cord (≤10 seconds after delivery) or delayed clamping (≥60 seconds after delivery). The primary composite outcome was death or major morbidity (defined as severe brain injury on postnatal ultrasonography, severe retinopathy of prematurity, necrotizing entero- colitis, or late-onset sepsis) by

36 weeks of postmenstrual age. Analyses were per- formed on an intention-to-treat basis, accounting for multiple births.

Results:

Of 1634 fetuses that underwent randomization, 1566 were born alive before 30 weeks of gestation; of these, 782 were assigned to immediate cord clamping and 784 to delayed cord clamping. The median time between delivery and cord clamping was 5 seconds and 60 seconds in the respective groups. Complete data on the primary outcome were available for 1497 infants (95.6%). There was no significant difference in the incidence of the primary outcome between infants assigned to delayed clamping (37.0%) and those assigned to immediate clamping (37.2%) (relative risk, 1.00; 95% confidence interval, 0.88 to 1.13; P=0.96). The mortality was 6.4% in the delayed-clamping group and 9.0% in the immediate-clamping group (P=0.03 in unadjusted analyses; P=0.39 after post hoc adjustment for multiple secondary outcomes). There were no significant differences between the two groups in the incidences of chronic lung disease or other major morbidities.

Conclusions:

Among preterm infants, delayed cord clamping did not result in a lower incidence of the combined outcome of death or major morbidity at 36 weeks of gestation than immediate cord clamping. (Funded by the Australian National Health and Medical Research Council [NHMRC] and the NHMRC Clinical Trials Centre; APTS Australian and New Zealand Clinical Trials Registry number, ACTRN12610000633088.)

Key points:

- This study was an unblinded, randomized, controlled trial comparing delayed versus immediate clamping with respect to a composite outcome of death or major morbidity in preterm infants.
- There was no significant difference in the primary composite outcome of death or major morbidity at 36 completed weeks of postmenstrual age between infants assigned to delayed cord clamping and those assigned to immediate cord clamping.
- There was also no significant difference in the primary outcome according to sex, gestational age, or method of delivery or in the originally defined primary composite outcome of death or major morbidity, which included chronic lung disease.
- Fewer infants in the delayed-clamping group than in the immediate-clamping group died by 36 weeks but this was not statistically significant.

Why I chose it:

Even though this article was included in the systematic review and meta-analysis above and focuses on the Australian population, I decided to include it anyway. The finding that delayed clamping reduced hospital mortality became statistically significant in 2016, until this study was published. Additionally, when this study was excluded from the systematic review above, the finding that delayed clamping reduced hospital mortality was also statistically significant. This RCT also however mentioned that the potential bias could be that the infants included in this study were less severely ill than earlier trial populations. I chose this study because it is an a recently published RCT from *The New England Journal of Medicine,* and offers different findings than included in prior RCTs.

Citation:

3. Zhao, Y., Hou, R., Zhu, X., Ren, L., & Lu, H. (2019). Effects of delayed cord clamping on infants after neonatal period: A systematic review and meta-analysis. International Journal of Nursing Studies, 92, 97–108. https://doi.org/10.1016/j.ijnurstu.2019.01.012

Type of article:

Systematic review and meta-analysis of RCTs

Abstract:

Background:

The majority of current evidences simply showed the short-term benefits of delayed cord clamping, mainly focusing on the first week after birth. Without follow-up data, we can hardly come to the conclusion that delayed cord clamping may do more harm than good.

Objective:

To evaluate the long-term effects of delayed cord clamping compared with early cord clamping on infants after neonatal period.

Design:
Systematic review and meta-analysis of randomized controlled trials (RCTs).
Data sources:
PubMed, EMBASE, and the Cochrane Library were systematically searched from inception date to June 22, 2018 for randomized clinical trials comparing early cord clamping with delayed cord clamping in infants beyond 1 month of age.
Review methods:
Two reviewers independently assessed trial eligibility and quality and extracted all infants' follow-up data after one month of age, which were divided into two groups for analysis, with follow-up periods of less than 6 months (<6 months) and beyond 6 months (!6 months) respectively.
Results:
A total of twenty RCTs were identified and included in this study. All data of the twenty studies were pooled for final meta-analysis (3733 infants). Among preterm deliveries, delayed cord clamping slightly increased hematocrit (6–10 weeks) and serum ferritin (6–10 weeks). For term infants, delayed cord clamping reduced the incidence of anemia after six months of age (!6 months), iron deficiency (< 6 months, !6 months) and iron deficiency anemia (4–12 months), while increased mean corpuscular volume before six months of age (< 6 months), hemoglobin after six months of age (!6 months), serum iron (2–4 months), total body iron (4–6 months), serum ferritin (< 6 months, !6 months) and transferrin saturation (2–12 months). There were no significant differences between early versus late cord clamping groups for other variables.
Conclusion:
Delayed cord clamping modestly improved hematological and iron status of both preterm and term infants after neonatal period. This affords cogent evidence on the practice of delayed cord clamping for medical staff, especially for countries and regions suffering from relatively higher prevalence rate of iron deficiency during infancy and childhood.

Key points:

- Among preterm deliveries, delayed cord clamping slightly increased hematocrit (6–10 weeks) and serum ferritin (6–10 weeks).
- No evidence of longer-term effects of delayed cord clamping on preterm infants is available.

Why I chose it:
Even though this study did not solely focus on preterm infants, I decided to include it because it is a systematic review and meta-analysis that was just published (2019) and examines the long-term effects of delayed cord clamping in preterm and term infants separately.

Citation:
4. Rabe, H., Diaz-Rossello, J. L., Duley, L., & Dowswell, T. (2012). Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.cd003248.pub3

Type of article:
Systematic review

Abstract:
Background:
Optimal timing for clamping the umbilical cord at preterm birth is unclear. Early clamping allows for immediate transfer of the infant to the neonatologist. Delaying clamping allows blood flow between the placenta, the umbilical cord and the baby to continue. The blood which transfers to the baby between birth and cord clamping is called placental transfusion. Placental transfusion may improve circulating volume at birth, which may in turn improve outcome for preterm infants.
Objectives:
To assess the short- and long-term effects of early rather than delaying clamping or milking of the umbilical cord for infants born at less than 37 completed weeks' gestation, and their mothers.
Search methods:
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (31 May 2011). We updated this search on 26 June 2012 and added the results to the awaiting classification section.

Selection criteria:

Randomised controlled trials comparing early with delayed clamping of the umbilical cord and other strategies to influence placental transfusion for births before 37 completed weeks' gestation.

Data collection and analysis:

Three review authors assessed eligibility and trial quality.

Main results:

Fifteen studies (738 infants) were eligible for inclusion. Participants were between 24 and 36 weeks' gestation at birth. The maximum delay in cord clamping was 180 seconds. Delaying cord clamping was associated with fewer infants requiring transfusions for anaemia (seven trials, 392 infants; risk ratio (RR) 0.61, 95% confidence interval (CI) 0.46 to 0.81), less intraventricular haemorrhage (ultrasound diagnosis all grades) 10 trials, 539 infants (RR 0.59, 95% CI 0.41 to 0.85) and lower risk for necrotising enterocolitis (five trials, 241 infants, RR 0.62, 95% CI 0.43 to 0.90) compared with immediate clamping. However, the peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping (seven trials, 320 infants, mean difference 15.01 mmol/L, 95% CI 5.62 to 24.40). For most other outcomes (including the primary outcomes infant death, severe (grade three to four) intraventricular haemorrhage and periventricular leukomalacia) there were no clear differences identified between groups; but for many there was incomplete reporting and wide CIs. Outcome after discharge from hospital was reported for one small study; there were no significant differences between the groups in mean Bayley II scores at age seven months (corrected for gestation at birth (58 children)). No studies reported outcomes for the women.

Authors' conclusions:

Providing additional placental blood to the preterm baby by either delaying cord clamping for 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion, better circulatory stability, less intraventricular haemorrhage (all grades) and lower risk for necrotising enterocolitis. However, there were insufficient data for reliable conclusions about the comparative effects on any of the primary outcomes for this review.

Key points:

- This review looked at delaying cord clamping to allow more placental transfusion compared with immediate cord clamping.
- The maximum delay in cord clamping was 180 seconds.
- Delayed cord clamping was associated with fewer babies needing transfusions for anemia, and with reduced risk of intraventricular hemorrhage and necrotising enterocolitis.
- Further studies are needed comparing different methods of delivering placental blood to babies.

Why I chose it:

This is another systematic review from Cochrane Reviews which are usually thorough. Even though this systematic review is from 2012, it is still a great addition to my choice of articles as it directly looks at my research question.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/studies, cohort definition etc.)	Outcomes(s) studied	Key Findings	Limitations and Biases
1. Fogarty, M., Osborn, D. A., Askie, L., Seidler, A. L., Hunter, K., Lui, K., … Tarnow-Mordi, W. (2018).	Systematic review and meta-analysis	- MEDLINE (1946 through week 4 of July 2017), EMBASE (classic 1947 through July 31, 2017), and Cochrane Central Register of Controlled Trials (July 2017) were searched, supplemented by searches for articles in Chinese, cross-referencing citations, trial authors, including Chinese authors, and trial registries - 18 RCTs (2834 infants) were included	- to evaluate the effect of delayed clamping without cord milking vs early clamping in reducing all-cause mortality (primary outcome) before hospital discharge in infants born less than 37 weeks' gestation - major neonatal secondary outcomes included severe intraventricular hemorrhage, retinopathy of prematurity receiving treatment or stage 4, chronic lung disease defined as respiratory support at greater than or equal to 36 weeks' postmenstrual age, necrotizing enterocolitis, late-onset sepsis (after first 48 hours), and number of infants receiving a blood transfusion - maternal secondary out-comes comprised of number of women with postpartum hemorrhage greater than 500 mL and number of women receiving a blood transfusion	- delayed clamping reduced hospital mortality compared to early clamping in preterm infants - there were no differences in major neonatal morbidities - delayed cord clamping reduced the number of infants receiving a later blood transfusion - delayed cord clamping increased peak hematocrit and increased the incidence of polycythemia - delayed cord clamping had no impact on the use of partial exchange transfusion for polycythemia - delayed cord clamping slightly increased peak bilirubin - delayed clamping reduced the incidence of Apgar score less than 4 at 1 minute but not of Apgar score less than 8 at 5 minutes - there was no difference in numbers of women with postpartum hemorrhage	- studies including cord milking were excluded (confirmed by 13 authors, but not by authors of remaining studies) - performance bias was not included as a criterion (due to the primary outcome being objective and the intervention difficult to blind) - only 3 trials reported outcomes that could be extracted for meta-analysis - potential bias in the additional subgroup analyses as the data that was extracted from the published reports was incomplete - this study was not preregistered in the international PROSPERO database (The International Prospective Register of Systematic Reviews) due to the fact that the goal was to achieve rapid submission for peer review

				(greater than 500 mL) or blood transfusion - additional subgroup analyses showed no significantly different effects on mortality according to duration of delay in cord clamping, mode of delivery (vaginal or cesarean), height infant held relative to the introitus or cesarean incision, timing of oxytocics, or timing of resuscitation (before or after cord clamping)	
2. Tarnow-Mordi, W., Morris, J., Kirby, A., Robledo, K., Askie, L., Brown, R., … Simes, J. (2017).	Large, multicenter, randomized trial	- of the 1634 fetuses that underwent randomization, 1566 were born alive before 30 weeks of gestation - of these, 782 were assigned to immediate cord clamping and 784 to delayed cord clamping. - the median time between delivery and cord clamping was 5 seconds and 60 seconds in the respective groups - participants were randomly assigned to immediate clamping, defined as clamping within 10 seconds after delivery, or delayed clamping,	- the primary composite outcome was death or major morbidity (defined as severe brain injury on postnatal ultrasonography, severe retinopathy of prematurity, necrotizing enterocolitis, or late-onset sepsis) by 36 weeks of postmenstrual age - secondary outcomes included death by 36 completed weeks of postmenstrual age, death or severe brain injury on postnatal ultrasonography, severe brain injury, late cerebral abnormality on ultrasonography, intraventricular hemorrhage (all grades, grade 3 or 4, and grade 4 only), severe retinopathy of prematurity,	- there was no significant difference in the incidence of the primary outcome at 36 weeks between delayed clamping and immediate clamping - the primary outcome did not differ significantly according to sex, gestational age, or method of delivery (cesarean section vs. vaginal delivery) - there was no significant difference between the two groups in other secondary outcomes - there were no significant differences between the two groups in tertiary outcomes	- infants of multiple births underwent randomization individually - this trial has not been powered for mortality, which would require international collaboration and a greater integration of clinical research with routine care - infants in this study were less severely ill than earlier cohorts (they received antenatal glucocorticoids, and their average systemic blood flow was higher than in infants enrolled in previous studies) - this trial minimized data collection to maximize enrollment (only short-term outcomes were included)

		defined as clamping 60 seconds or more after delivery, with the infant held as low as possible below the introitus or placenta and without palpation of the cord - no cord milking was intended in either group	necrotizing enterocolitis, late-onset sepsis, treated patent ductus arteriosus, and chronic lung disease - tertiary outcomes included birth weight, the number of red-cell transfusions by 36 weeks, the temperature of the infant on admission, the peak bilirubin level in the first week, the peak hematocrit in the first week		
3. Zhao, Y., Hou, R., Zhu, X., Ren, L., & Lu, H. (2019).	Systematic review and meta-analysis of RCTs	- PubMed, EMBASE, and the Cochrane Library were systematically searched from inception date to June 22, 2018 for randomized clinical trials comparing early cord clamping with delayed cord clamping in infants beyond 1 month of age - a total of 20 RCTs were identified and included in this study - all data of the twenty studies were pooled for final meta-analysis, which included 3733 infants - infants were divided into two groups with follow-up periods of less than 6 months and beyond 6 months	- to evaluate the long-term effects of delayed cord clamping compared with early cord clamping on infants after neonatal period	- among preterm deliveries, delayed cord clamping slightly increased hematocrit (6–10 weeks) and serum ferritin (6–10 weeks) - for term infants, delayed cord clamping reduced the incidence of anemia after six months of age, iron deficiency and iron deficiency anemia, while increased mean corpuscular volume before six months of age, hemoglobin after six months of age, serum iron, total body iron, serum ferritin and transferrin saturation - there were no significant differences between early versus late cord clamping groups for other variables	- higher iron or ferritin status at 4–6 months of age in preterm infants could be due to the high iatrogenic blood loss during the hospital stay after birth for this patient group - no analysis was performed on the subgroups due to the lack of reported data or relatively few trials with reported data - optimal timing of umbilical cord clamping is still not yet determined, which could have led to the omission of many trials that investigated the long-term effects of delayed cord clamping on infants as well, but did not fit the specific criteria of this study - the quality of some RCTs is relatively low, because the risk of bias is unclear or unknown

					- infants' data was divided into two groups and set to six months of age as the cut-off point when synthesizing and analyzing follow-up data, instead of providing all results at every month - data from different follow-up duration as well as from different umbilical cord clamping times in both experimental and control groups was combined and analyzed collectively, which in turn may make the findings of meta analyses less accurate and effective
4. Rabe, H., Diaz-Rossello, J. L., Duley, L., & Dowswell, T. (2012).	Systematic review	- Cochrane Pregnancy and Childbirth Group Trials Register (31 May 2011 were searched for RCTs comparing early with delayed clamping of the umbilical cord and other strategies to influence placental transfusion for births before 37 completed weeks' gestation - the search was updated on 26 June 2012 and added the results to the awaiting classification section - 3 review authors assessed eligibility and trial quality	- to assess the short and long-term effects of early rather than delaying clamping or milking of the umbilical cord for infants born at less than 37 completed weeks' gestation, and their mothers	- delaying cord clamping was associated with fewer infants requiring transfusions for anemia, less intraventricular hemorrhage, and lower risk for necrotising enterocolitis compared with immediate clamping - peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping - for most other outcomes (including the primary outcomes infant death, severe intraventricular hemorrhage and periventricular leukomalacia) there were	- included studies with cord milking - different clamping timing between studies was included - blinding after delivery of the baby was not possible, as the intervention had to be performed openly after birth

		- 15 studies (738 infants) were eligible for inclusion - participants were between 24- and 36-weeks' gestation at birth - the maximum delay in cord clamping was 180 seconds		no clear differences identified between groups - no studies reported outcomes for the women	

Conclusions(s):

1. Fogarty, M., Osborn, D. A., Askie, L., Seidler, A. L., Hunter, K., Lui, K., … Tarnow-Mordi, W. (2018).	- delayed clamping reduced all-cause mortality in preterm infants before discharge from hospital - delayed clamping did not impact maternal postpartum hemorrhage or the need for maternal blood transfusion - delayed cord clamping appears well tolerated with no evidence of an adverse effect on Apgar scores, need for resuscitation, intubation at delivery, or temperature at admission to neonatal intensive care unit - delayed clamping increased mean peak hematocrit in the first week by 2.7 percentage points, confirming that placental transfusion occurred - delayed clamping increased the incidence of polycythemia and of jaundice
2. Tarnow-Mordi, W., Morris, J., Kirby, A., Robledo, K., Askie, L., Brown, R., … Simes, J. (2017).	- delayed cord clamping did not result in a lower incidence of the combined outcome of death or major morbidity at 36 weeks of gestation than immediate cord clamping - the relative risk of death or major morbidity was not significantly lower in the delayed-clamping group than in the immediate-clamping group after adjustment for gestational age, sex, and method of delivery - the relative risk of death or major morbidity was not significantly reduced with each 10-second delay in clamping - there were no significant differences between the two groups in rates of intraventricular hemorrhage or late cerebral abnormality on ultrasonography - more infants in the delayed-clamping group than in the immediate-clamping group had polycythemia and fewer infants in the delayed-clamping group received red-cell transfusions - among infants who were assigned to delayed clamping, those who had a delay of less than 60 seconds before clamping were of a younger mean gestational age, had a lower mean birth weight, and had lower Apgar scores at 1 minute and 5 minutes than those who had a delay of 60 seconds or more
3. Zhao, Y., Hou, R., Zhu, X., Ren, L., & Lu, H. (2019).	- among preterm deliveries, delayed cord clamping slightly increased hematocrit (6–10 weeks) and serum ferritin (6–10 weeks) - delayed cord clamping can lead to improved follow-up hematocrit only in preterm infants but not term infants - no evidence of longer-term effects of delayed cord clamping on preterm infants is available
4. Rabe, H., Diaz-Rossello, J. L., Duley, L., & Dowswell, T. (2012).	- delaying cord clamping was associated with fewer infants requiring transfusions for anemia, less intraventricular hemorrhage, and lower risk for necrotising enterocolitis compared with immediate clamping - peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping - for most other outcomes (including the primary outcomes infant death, severe intraventricular hemorrhage and periventricular leukomalacia) there were no clear differences identified between groups
The overall conclusion is that delayed umbilical cord clamping may improve outcome in preterm infants by increasing the volume of blood transferred from placenta to infant and by allowing time for physiologic transition.	

Clinical Bottom Line:

What is the efficacy and safety of delayed umbilical cord clamping compared with early/immediate cord clamping in preterm infants?

According to UpToDate, cord clamping is delayed for at least 30 seconds in vigorous preterm infants, but the available data does not strongly support one approach over another. The American College of Obstetricians and

Gynecologists recommends delaying umbilical cord clamping for 30 to 60 seconds after birth in both vigorous term and preterm infants.

In the past, immediate cord clamping was a normal practice in preterm infants because of concerns about harm from delayed resuscitation, hypothermia, hyperbilirubinemia, or polycythemia. However, delayed cord clamping in preterm infants could provide more time for the physiological transition from fetal to newborn life. According to UpToDate, "approximately 75 percent of blood available for placenta-to-fetus transfusion is transfused in the first minute after birth" and "delaying cord clamping increases the volume of placental blood transfused to the fetus and thereby increases neonatal blood volume, improves neonatal and infant iron stores, and decreases neonatal and infant anemia." Additionally, delayed clamping can help to avoid unnecessary and potentially harmful interventions. Delaying clamping for 60 second may increase the number of infants breathing before the cord is clamped as nearly all preterm infants begin breathing by 60 seconds, which may stabilize hemodynamic transition and reduce endotracheal intubation and invasive mechanical ventilation. Lastly, delayed cord clamping is a simple procedure requiring no training and costs nothing.

My first article, a systematic review and meta-analysis included 18 RCTs and concluded that delayed clamping reduced hospital mortality. My third article, which looked at long-term effects of delayed cord clamping found that among preterm deliveries, delayed cord clamping slightly increased hematocrit at 6–10 weeks and serum ferritin at 6–10 weeks. However, my second article, and RCT, seems to be an odd study out, and the authors concluded that among preterm infants, delayed cord clamping did not result in a lower incidence of the combined outcome of death or major morbidity at 36 weeks of gestation than immediate cord clamping. However, when this RCT was excluded from the meta-analysis of my first article, the finding that delayed clamping reduced hospital mortality was also statistically significant.

I would weight my first article as the most important one, as it is a recent systematic review and meta-analysis, which answered my question fully. Since it is a systematic review, there is expected to be some bias, but the authors went through great lengths to address it and it is also published by a reputable source. I would not put too much emphasis in my second study as it is only one RCT that came up with different results compared to the first article with 18 RCTs. The second study also addressed a potential bias for such results. My fourth article also included cord milking which I was trying to avoid, and the third article also looked at term infants.

At this point, I would take the recommendation of The American College of Obstetricians and Gynecologists into consideration, but I believe that healthcare providers should use their judgement about whether and how long to delay cord clamping in individual preterm infants until there is definitive data available. Therefore, more RCTs should be performed to include large sample sizes of diverse, generalizable population. Additionally, the studies I have included excluded studies with cord milking technique, which should also be examined further for its potential benefits or harms.