Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis

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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, 0.52—0.90; risk difference, −0.03; 95% confidence interval, −0.05 to −0.01; $P = .005$; number needed to benefit, 33; 95% confidence interval, 20—100; Grading of Recommendations, Assessment, Development, and Evaluations = high, with $I^2 = 0$ indicating no heterogeneity). In 3 trials in 996 infants ≤28 weeks' gestation, delayed clamping reduced hospital mortality (risk ratio, 0.70; 95% confidence interval, 0.51—0.95; risk difference, −0.05; 95% confidence interval, −0.09 to −0.01; $P = .02$, number needed to benefit, 20; 95% confidence interval, 11—100; $I^2 = 0$). 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, 1.94—3.52; $P < .00001$) and reduced the proportion of infants having blood transfusion by 10% (95% confidence interval, 6—13%; $P < .00001$). 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 words: delivery, infant, mortality, obstetric, premature, time factors, umbilical cord

Introduction

The death of a child is among the most profoundly stressful events that an adult can experience.[1-3] About 15 million children are born <37 weeks' gestation annually, of whom about 1 million die.[4] Several publications in this journal have addressed whether enhanced placental transfusion—by delayed clamping of the umbilical cord, milking the cord before or after clamping, or a combination of these measures—can reduce adverse neonatal outcomes, including death.[5-10]

Delaying umbilical cord clamping may improve outcome in preterm infants by increasing the volume of blood transferred from placenta to infant[11] and by allowing time for physiologic transition.[12] Previously early clamping was normal practice in preterm infants, reflecting concerns about harm from delayed resuscitation, hypothermia, jaundice, and polycythemia.[13-15] Systematic reviews of randomized controlled trials (RCT) in babies born <37 weeks[11,15] suggested that a longer delay in clamping improved blood pressure and reduced blood transfusions,[11,15] intraventricular hemorrhage,[11,15] necrotizing enterocolitis, and infection.[11] There were no differences in infant mortality, severe intraventricular hemorrhage, or periventricular leukomalacia, but these were incompletely reported, with imprecise estimates.[11,15] A more recent systematic review[16] of 12 RCTs in 531 preterm infants <32 weeks' gestation was the first to conclude that placental transfusion, defined as delayed clamping or cord milking or both, reduced mortality ($P = .04$). It also reported that delayed clamping reduced infant blood transfusions ($P < .01$) and intraventricular hemorrhage ($P = .01$). Current recommendations are to delay clamping by >30 seconds,[17] 30-60 seconds,[18] at least 60 seconds,[19] or 30-180 seconds,[20] if resuscitation is considered unnecessary[17-19] or if mother and infant are stable.[20] After completing the Australian Placental Transfusion Study (APTS),[21] which compared delayed cord clamping (≥60 seconds) vs early cord clamping (<10 seconds), both with minimal cord milking, in 1566 infants born <30 weeks' gestation, we placed the results in the context of other trials[22,23] of placental transfusion with minimal cord milking by combining APTS with RCTs in the most recent Cochrane Review.[11] This meta-analysis suggested that delayed clamping reduced the relative risk of mortality in preterm infants to hospital discharge (relative risk, 0.71; 95% confidence interval [CI],

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0.53−0.95; $P = .02$) (Supplementary Materials at ajog.org). However, this Cochrane Review had not been updated since 2012,[11] so it was likely that more trials had been completed since then.

We therefore designed a protocol (Supplementary Materials) for the present study: an updated systematic review of randomized clinical trials identified up to July 31, 2017. This aimed to evaluate the effect of delayed clamping without cord milking vs early clamping in reducing all-cause mortality before hospital discharge in infants born <37 weeks' gestation using Cochrane Review neonatal group methods[24] according to PRISMA guidelines.[25] Because of their implications for practice, we submitted APTS and the present systematic review to their respective journals for rapid peer review and sequential publication.

Materials and Methods

Materials and methods were prespecified using a protocol dated July 21, 2017 (Supplementary Materials) that is summarized below. Although delayed clamping is more closely aligned to natural birth, for the purposes of analysis, delayed cord clamping was regarded as the experimental treatment, as in previous systematic reviews.[11,15,16]

Criteria for considering studies for this review

RCTs including cluster-randomized trials were considered eligible. Quasirandomized trials were excluded. Abstracts of studies were included only if data were verified by authors. Trials were eligible if they enrolled preterm infants born <37 completed weeks' gestation and their mothers, and compared delayed (≥30 seconds) vs early (<30 seconds) umbilical cord clamping at delivery. We planned in advance to exclude trials in which we estimated that cord milking was performed in >20% of infants in any arm. We contacted all authors for details of cord milking and other characteristics (Supplementary Materials).

The primary outcome measure was all-cause mortality at any time before hospital discharge. If rates of all-cause mortality were reported at different time points we planned to use the latest mortality rate before hospital discharge and >36 weeks' postmenstrual age. Major neonatal secondary outcomes included severe intraventricular hemorrhage (Papile-Burstein grade 3 or 4[26]), retinopathy of prematurity receiving treatment or stage 4, chronic lung disease defined as respiratory support at ≥36 weeks' postmenstrual age, necrotizing enterocolitis, late-onset sepsis (after first 48 hours), and number of infants receiving a blood transfusion. Other neonatal morbidities included intraventricular hemorrhage (all grades); periventricular leukomalacia; any combination of periventricular leukomalacia, porencephaly, or echodense intraparenchymal lesions or ventriculomegaly (≥97th percentile plus 4 mm); mechanical ventilation; patent ductus arteriosus (medical or surgically treated); peak hematocrit (%); polycythemia (hematocrit >65%); partial exchange transfusion for polycythemia; peak bilirubin (μmol/L) and exchange transfusion for hyperbilirubinemia; and outcomes of infant resuscitation: namely, proportions with Apgar score <4 at 1 minute, Apgar score <8 at 5 minutes, cardiorespiratory support (mask, intermittent positive pressure, cardiac compression, or adrenaline), endotracheal intubation in the delivery room, and mean temperature on admission. Maternal secondary outcomes comprised: (1) number of women with postpartum hemorrhage >500 mL; and (2) number receiving a blood transfusion.

We planned to analyze outcomes by intention to treat by: (1) keeping participants in the intervention groups to which they were randomized, regardless of the intervention they actually received and, if possible; (2) reporting outcome data on all participants; and (3) including all randomized participants in the analysis, as the least biased way to estimate intervention effects in randomized trials.[24,27]

Search methods for identification of studies

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 (via http://caod.oriprobe.com), cross-referencing citations, trial authors, including Chinese authors, and trial registries (clinicaltrials.gov). The search of MEDLINE included terms "umbilical-cord.mp or exp umbilical cord/" and "exp clamp/or clamp*.mp" and "exp premature labor/or exp prematurity/ or preterm.mp or premature.mp or infant, premature.mp" limit to (human beings and clinical trial, all). This search was adapted for EMBASE and Cochrane Central Register of Controlled Trials. We attempted to contact authors of all included studies, abstracts, and ongoing studies for additional details of methods and data (Supplementary Material, ajog.org). No language restrictions were applied.

Data extraction and synthesis

Standard methods of the Cochrane Collaboration were used.[24] Two authors (D.A.O. and M.F.) independently assessed eligibility and risk of bias and extracted data. Differences were resolved through consensus. All data were entered and cross-checked in Review Manager (RevMan), Version 5.3.[28] Risk of bias (low, high, or unclear) of all included trials was assessed[24] using the Cochrane risk-of-bias tool for the following domains: selection bias (sequence generation and allocation concealment); reporting bias; attrition bias; and any other bias. Disagreements were resolved by discussion or a third assessor (W.T-M.).

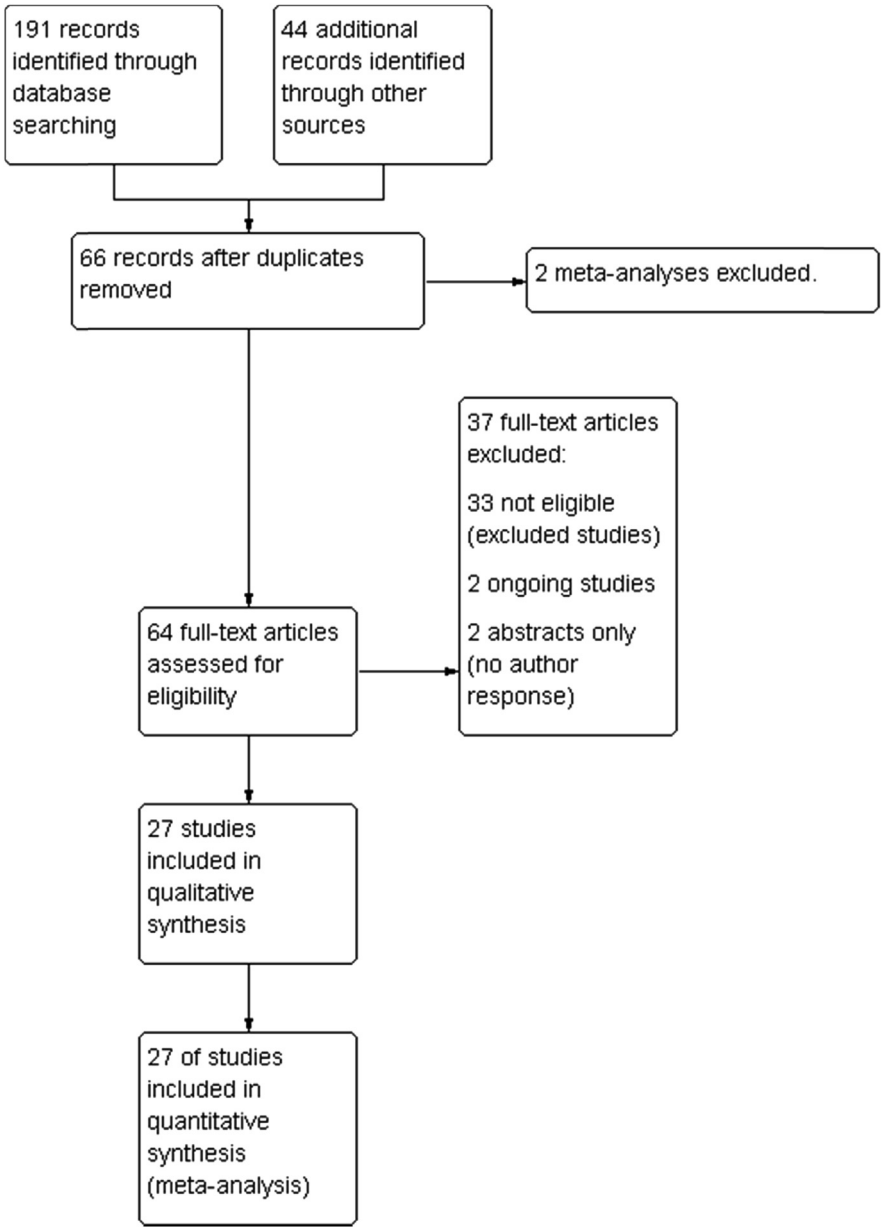
Results were analyzed using Review Manager (RevMan), Version 5.3[28] and reported using mean difference with a 95% CI for continuous variables and risk ratio (RR) with a 95% CI for dichotomous variables. For statistically significant results we report risk difference (RD) and use 1/RD to calculate the number needed to treat for an additional beneficial outcome or the number needed to treat for an additional harmful outcome.

Fixed effects models were used for meta-analysis.[24] Heterogeneity was

assessed using the χ^2 test ($P < .1$ being defined as significant heterogeneity) and quantified using the I^2 statistic. Degree of heterogeneity was assessed as: none (I^2 <25%); low (I^2 = 25-49%); moderate (I^2 = 50-74%); or high (I^2 ≥75%). Subgroup analysis and sensitivity analysis were performed to determine potential sources of heterogeneity.[24] Three prespecified subgroup analyses were performed according to: gestational age (≤28 vs 29-37 weeks); duration of delayed (≥30-45, ≥45-60, ≥60-120, ≥120 seconds) vs early (<30 seconds) cord clamping; and mode of delivery (vaginal vs cesarean). These subgroup analyses were restricted to 7 key outcomes: mortality, severe intraventricular hemorrhage (grade 3 or 4 by Papile-Burstein classification),[26] severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, late-onset sepsis (after first 48 hours), and number of infants receiving a blood transfusion. To inform practice further, 2 additional, post-hoc subgroup analyses were performed according to: height relative to the introitus or cesarean incision (above or on mother; at same level; >5-10, >10-20, >20 cm below) and timing of oxytocics (before or after cord clamping). Sensitivity analysis was performed according to risk of bias assessment, including only studies that were at low risk of selection bias, had low attrition bias, and used intention-to-treat analysis. As the primary outcome (hospital mortality) is objective and the intervention is difficult to blind, we did not include performance bias as a criterion.

A funnel plot was generated in Review Manager (RevMan) Version 5.3.5[28] to assess asymmetry, and hence possible publication bias or other small study effects, with the Egger test.[29,30] The Grading of Recommendations, Assessment, Development, and Evaluations approach[31] was used to assess quality of evidence (QoE) for the 7 predefined outcomes listed above. Five domains contributed to the QoE assessment: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Potential for publication bias was considered if there were unpublished studies, underreported outcomes, or an asymmetrical funnel plot.

FIGURE 1
Study search and eligibility



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Results

Selection, characteristics, and quality of studies

Figure 1 summarizes the process of identification and selection of studies. The search strategy identified 235 records, which resulted in 66 studies after removing duplications. In all, 64 full text articles were assessed, resulting in 27 trials eligible for inclusion and 37 studies excluded. Of these excluded studies, 2 were meta-analyses, 33 were not eligible, 2 are ongoing (total 550 infants), and 2 were published as abstracts with no response from the authors to our queries for confirmatory information to date (total 186 infants). Three excluded

TABLE 1
Characteristics of 27 eligible trials

Study	Inclusion criteria	Main exclusion criteria	Enrolled: delayed/ early cord clamping	Delayed cord clamping	Early cord clamping
APTS,[21] 2017	<30 wk gestation	No indication or contraindication to placental transfusion	Total: 784/782 Vaginal: 264/273 Cesarean: 520/509	≥60 s No cord milking Height: as low as possible Oxytocic: not specified Resuscitation: after clamping	Early: <10 s
Armanian et al,[33] 2017	≤34 wk gestation	Admission to NICU, singleton pregnancy, parent refusal to participate, major congenital anomalies, asphyxia	Total: 32/31 Vaginal: 5/10 Cesarean: 25/20	30–45 s Height: not reported Oxytocic: not reported Resuscitation: not reported	5–10 s
Backes et al,[43] 2016	Singleton 22.5–27.6 wk gestation	Placental abruption, placental previa, multiple gestations, chromosomal abnormalities, major congenital malformation, intent to withhold care	Total: 18/22 Vaginal: NR Cesarean: NR	30–45 s No cord milking Height: 10–15 in below introitus/incision Oxytocic: not reported Resuscitation: after clamping	Early: <10 s
Baenziger et al,[78] 2007	Singleton 24–32 wk gestation	Multiple deliveries, perinatal asphyxia, major fetal malformations	Total: 15/24 Vaginal: NR Cesarean: NR	60–90 s Height: 15 cm below introitus/incision Oxytocic: delivery of infant Resuscitation: after clamping	<20 s
Dai et al,[79] 2014	Preterm infants	Maternal diabetes, hypertension, anemia, blood group incompatibility	Total: 21/31 Vaginal: NR Cesarean: NR	Wait until cord pulsation ceased Height: between mothers' legs Oxytocic: not reported Resuscitation: after clamping	5–10 s
Datta et al,[34] 2017	Singleton 34–36+6 wk gestation	Congenital anomaly, hydrops and Rh-negative pregnancy	Total: 60/60 Vaginal: 41/33 Cesarean: 17/26	30–60 s No cord milking Height: not reported Oxytocic: not reported Resuscitation: not reported	<20 s
Dipak et al,[46] 2017	Singleton 27–31+6 wk gestation	Multiple gestation, Rh-negative mother, placenta previa, abruption-placenta, major congenital anomalies, hydrops, fetal growth restriction with abnormal Doppler waveforms, fetal distress	Total: 51/27 Vaginal: 43/23 Cesarean: 8/4	60 s Height: 10–15 in below introitus/incision Oxytocic: group 1: delivery of infant; group 2: after cord cut Resuscitation: after clamping	<10 s
Dong et al,[80] 2016	Singleton <32 wk gestation vaginal delivery	Congenital malformation, multiples, nonvigorous at birth, placental abruption or previa	Vaginal: 46/44	45 s Height: 10–20 cm below placenta Oxytocic: not reported Resuscitation: after clamping	<10 s
Duley et al,[44] 2017	<32 wk gestation	Monochorionic twins or clinical evidence of twin-twin transfusion syndrome, triplet or higher-order multiple pregnancy, and known major congenital malformation	Total: 137/139 Vaginal: 49/64 Cesarean: 87/74	>120 s No cord milking Height: at or below mothers' abdomen Oxytocic: not specified Resuscitation: before clamping	<20 s
Gokmen et al,[37] 2011	24 and 31.6 wk gestation	Vaginal bleeding, major fetal anomalies, intrauterine growth restriction, twin-twin transfusion syndrome or discordant twin growth, maternal drug abuse	Total: 21/21 Vaginal: NR Cesarean: NR	30–45 s Height: not reported Oxytocic: after clamping Resuscitation: after clamping	5–10 s

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TABLE 1
Characteristics of 27 eligible trials *(continued)*

Study	Inclusion criteria	Main exclusion criteria	Enrolled: delayed/ early cord clamping	Delayed cord clamping	Early cord clamping
Hofmeyr et al,[81] 1988	Singleton <35 wk' gestation	Multiple pregnancies	Total: 24/14 Vaginal: NR Cesarean: NR	>60 s No cord milking Height: not reported Oxytocic: group 1 after clamping; group 2 at delivery Resuscitation: not reported	Early
Hofmeyr et al,[82] 1993	Expected birthweight <2000 g (mean gestation 32.0 SD 2.3 wk)	None reported	Total: 40/46 Vaginal: 33/34 Cesarean: 7/12	60–120 s No cord milking Height: vaginal = "level of uterus"; cesarean = on mother Oxytocic: after clamping Resuscitation: after clamping	Early
Hu and Xu,[83] 2015	28–35 wk gestation	None reported	Vaginal: 90/30	30 s (n = 30); 60 s (n = 30); 120 s (n = 30) Height: between mothers' legs Oxytocic: not reported Resuscitation: not reported	Early <10 s
Hua et al,[84] 2010	Preterm births	Blood incompatibility and twin-twin transfusion	Total: 28/21 Vaginal: NR Cesarean: NR	Wait until cord pulsation ceased Height not reported Oxytocic: not reported Resuscitation: not reported	10 s
Kinmond et al,[38] 1992	27–33 wk gestation vaginal delivery	Hemolytic disease or major congenital malformations	Vaginal: 17/19	>30 s No cord milking Height: 20 cm below introitus Oxytocic: not reported Resuscitation: not reported	<25 s
Kugelman et al,[85] 2007	24–34+7 wk gestation	Vaginal bleeding, major anomaly, severe intrauterine growth restriction, gestational diabetes treated with insulin, twin-twin transfusion syndrome or discordant twins, maternal drug abuse	Total: 30/35 Vaginal: 10/12 Cesarean: 20/23	30–45 s No cord milking Height: as low as possible Oxytocic: not reported Resuscitation: not reported	5–10 s
McDonnell and Henderson-Smart,[86] 1997	23–33 wk gestation	Severe fetal distress, intrauterine growth retardation with abnormal umbilical arterial Doppler velocity waveforms, hemolytic disease or major malformations	Total: 23/23 Vaginal: NR Cesarean: NR	30 s No cord milking Height: between mother's legs (vaginal) or on thighs (cesarean) Oxytocic: before clamping Resuscitation: not reported	Early
Mercer et al,[39] 2003	Singleton 24 and 31+6 wk gestation	Intent to withhold or withdraw care, placenta previa or abruption, bleeding, major anomaly	Total: 16/16 Vaginal: 7/10 Cesarean: 9/6	30–45 s No cord milking Height: 10–15 cm below introitus Oxytocic: after clamping Resuscitation: after clamping	5–10 s
Mercer et al,[47] 2006	Singleton 24–31.6 wk gestation	Major congenital anomalies, multiple gestations, intent to withhold care, severe maternal illness, placenta abruption or previa	Total: 36/36 Vaginal: 21/22 Cesarean: 15/14	30–45 s No cord milking Height: 10–15 in below introitus/incision Oxytocic: not reported Resuscitation: after clamping	Early: <10 s

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TABLE 1
Characteristics of 27 eligible trials *(continued)*

Study	Inclusion criteria	Main exclusion criteria	Enrolled: delayed/ early cord clamping	Delayed cord clamping	Early cord clamping
Oh et al,[45] 2011	Singleton 24+0 −27+6 wk gestation	None reported	Total: 16/17 Vaginal: NR Cesarean: NR	30−45 s No cord milking Height: 10 cm below introitus/ incision Oxytocic: not reported Resuscitation: after clamping	<10 s
Rabe et al,[35] 2000	Singleton <33 wk gestation	Rh incompatibility, fetal hydrops, congenital abnormalities, Apgar <3 at 0 min, multiple pregnancy	Total: 19/20 Vaginal: NR Cesarean: NR	45 s No cord milking Height: 20 cm below introitus/ incision Oxytocic: on delivery Resuscitation: after clamping	20 s
Rana and Agarwal,[87] 2017	<34 wk gestation	Congenital malformations, serious maternal illness (severe preeclampsia or eclampsia, PPH, uncompensated heart disease), twins or triplets, babies requiring resuscitation	Total: 50/50 Vaginal: NR Cesarean: NR	120 s Height: not reported Oxytocic: not reported Resuscitation: not reported	<30 s
Ranjit et al,[88] 2015	30+0−36+6 wk gestation	Rh negative status, monoamniotic-monochorionic twins, need for resuscitation	Total: 50/50 Vaginal: 24/25 Cesarean: 20/25	120 s Height: mother's abdomen (vaginal) or thighs (cesarean) Oxytocic: on delivery Resuscitation: after clamping	Early
Shi et al,[48] 2017	Preterm infants	Sick mother (high blood pressure, anemia, blood group incompatibility, twin-twin transfusion)	Total: 30/30 Vaginal: NR Cesarean: NR	Wait until cord pulsation ceased Height: not reported Oxytocic: not reported Resuscitation: not reported	5−10 s
Strauss et al,[40] 2008	30−36 wk gestation	Unable to perform studies, nonsurvivors	Total: 45/60 Vaginal: NR Cesarean: NR	60 s Height: 10−15 in below introitus (vaginal); beside mother's thigh (cesarean) Oxytocic: not reported Resuscitation: after clamping	Early: <15 s
Tanprasertkul et al,[41] 2016	Singleton 34−36+6 wk gestation	Thalassemia, preeclampsia, gestational diabetes mellitus, renal impairment, placental abnormality, major congenital anomaly, multiple gestation, instrumental delivery, abnormal fetal tracing	Total: 50/50 Vaginal: NR Cesarean: NR	120 s Height: same level Oxytocic: not reported Resuscitation: after clamping	Early
Ultee et al,[87] 2008	34+0−36+6 wk gestation vaginal delivery	Diabetes, gestational diabetes, pregnancy-induced hypertension, congenital abnormality, twins, postrandomization Apgar scores < 5 at 1 min, <7 at 5 min	Total: 21/20 Vaginal: NR Cesarean: NR	180 s Height: mother's abdomen Oxytocic: not reported Resuscitation: not reported	<30 s

APTS, Australian Placental Transfusion Study; *NICU*, neonatal intensive care unit.

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studies did not report an outcome prespecified by the review (total 196 infants) and 1 study of late preterm and term infants (540 infants) did not report preterm outcomes separately.[32] The characteristics of the 27 eligible trials are summarized in Table 1. The methodological quality of the trials is summarized in Figure 2. Most studies reported that randomization occurred before delivery, except for 3[33-35] for which the timing of randomization is unclear. We excluded 1

study that reported allowing cord milking in all infants allocated to delayed cord clamping.[36] We classified as eligible for inclusion all trials of delayed vs early clamping that did not report if cord milking was used. We received responses from 13 authors confirming that no cord milking was used in any arm (Table 1). We could not obtain further details on the proportion of infants receiving cord milking from the remaining published reports.

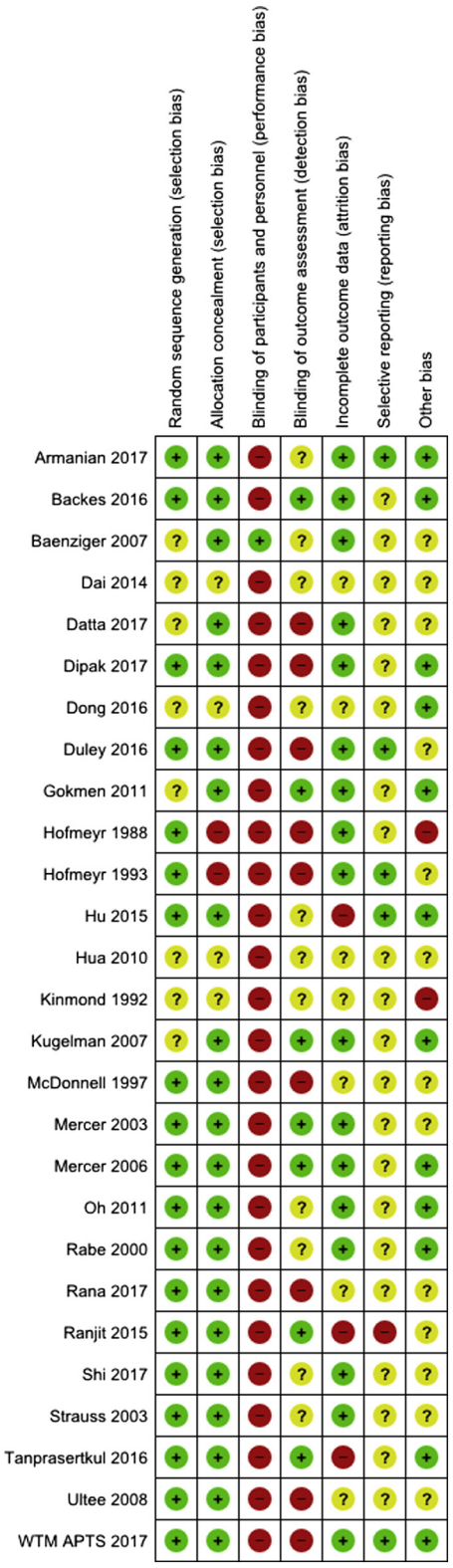
Primary outcome

Overall, meta-analysis showed that delayed clamping reduced hospital mortality (RR, 0.68; 95% CI, 0.52−0.90; RD, −0.03; 95% CI, −0.05 to −0.01; $P = .005$) compared to early clamping in preterm infants (Figure 3 and Table 2). There was no heterogeneity ($I^2 = 0\%$) and the funnel plot was symmetrical (Figure 4) with a nonsignificant Egger test. The Grading of Recommendations, Assessment, Development, and Evaluations QoE that delayed clamping reduced hospital mortality was assessed as high. Five studies had 0 mortality rates.[37-42] These 5 studies were excluded when meta-analysis was undertaken using RR (RR, 0.68; 95% CI, 0.52−0.90; total number of infants in the denominator excluding trials with 0 mortality = 2538; $P = .006$). However, they were included when meta-analysis was undertaken using RD (RD, −0.03; 95% CI, −0.05 to −0.01; $P = .005$; total number of infants in the denominator including trials with 0 mortality = 2834).

Neonatal secondary outcomes

There were no differences in major neonatal morbidities including severe intraventricular hemorrhage (QoE low), any intraventricular hemorrhage, periventricular leukomalacia, combined periventricular leukomalacia or porencephaly or echodense intraparenchymal lesions or ventriculomegaly, mechanical ventilation, chronic lung disease (QoE moderate), patent ductus arteriosus (medical or surgically treated), necrotizing enterocolitis (QoE low), late-onset sepsis (QoE low), and severe retinopathy of prematurity (QoE low). Delayed cord clamping reduced the

FIGURE 2
Risk of bias summary



Author judgements on each risk of bias item in each included study.

APTS, Australian Placental Transfusion Study.

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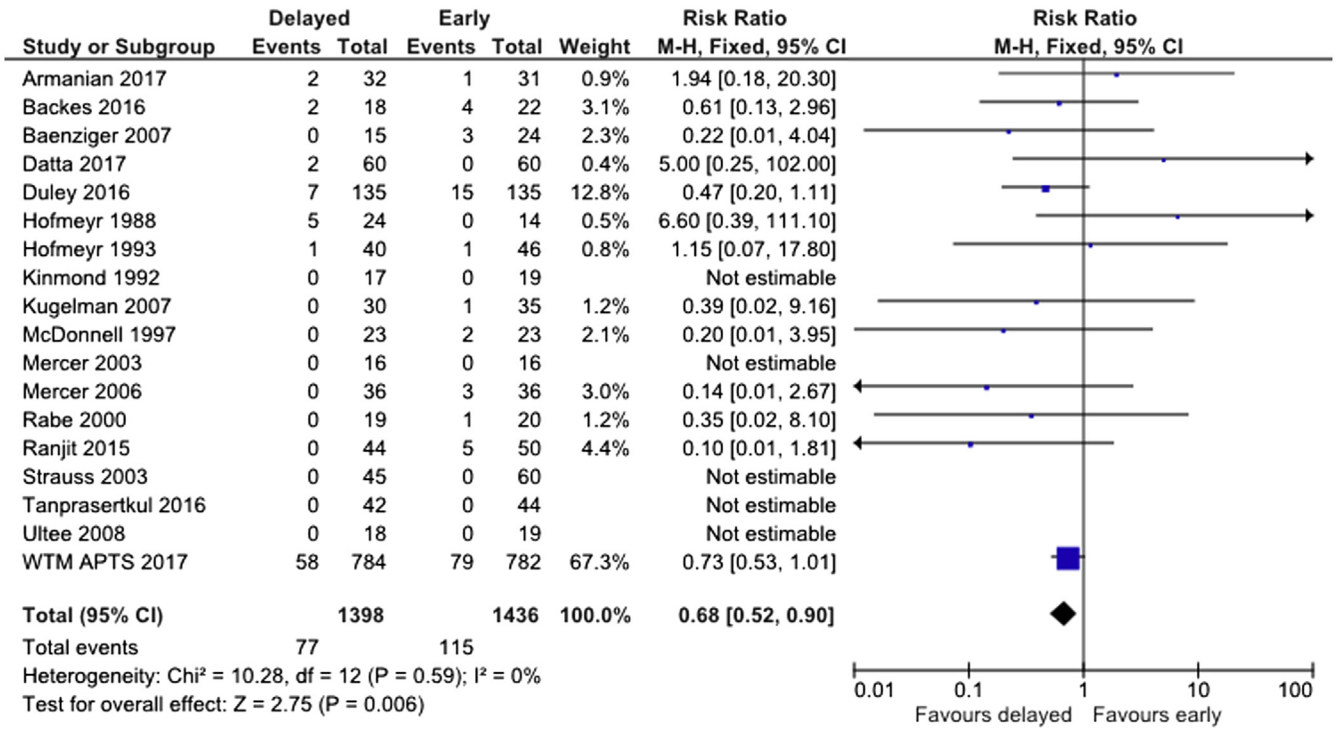
FIGURE 3
Meta-analyses showing effect of delayed clamping on mortality



Meta-analyses showing effect of delayed vs early cord clamping on risk ratio for hospital mortality in 18 trials in 2834 infants <37 weeks' gestation (top) and 3 trials in 996 infants ≤28 weeks' gestation (bottom).

APTS, Australian Placental Transfusion Study; *CI*, confidence interval; *M-H*, Mantel-Haenszel.

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number of infants receiving a later blood transfusion (13 trials; 2595 infants; RR, 0.81; 95% CI, 0.74−0.87; RD, −0.10; 95% CI, −0.13 to −0.06; $P < .00001$; number needed to benefit, 10; 95% CI, 8−17; with moderate heterogeneity between studies; $I^2 = 61\%$). Despite this, the QoE that delayed cord clamping reduced the number of infants receiving subsequent blood transfusions was assessed as high, due to the statistical significance ($P < .00001$) and magnitude of effect.

Delayed cord clamping also increased peak hematocrit (%) (2 trials; 1587 infants; mean difference, 2.73; 95% CI, 1.94−3.52; $P < .00001$) and increased the incidence of polycythemia (hematocrit >65%) (13 trials; 2529 infants; RR, 2.65; 95% CI, 1.61−4.37; RD, 0.03; 95% CI, 0.01−0.04; number needed to harm, 33; 95% CI, 25−100; $P < .0001$; $I^2 = 0\%$). However, delayed cord clamping had no impact on the use of partial exchange transfusion for polycythemia (4 trials; 1743 infants; RR, 0.14; 95% CI, 0.01−2.74).

Delayed cord clamping slightly increased peak bilirubin (15 trials; 2358 infants; mean difference, 4.43 μmol/L; 95% CI, 1.15−7.71; $P = .008$) although heterogeneity was high between studies ($I^2 = 77\%$). However, there was no difference in use of exchange transfusion (7 trials; 2139 infants; RR, 0.29; 95% CI, 0.05−1.73).

In Table 2, delayed clamping reduced the incidence of Apgar score <4 at 1 minute (RR 0.82, 95% CI 0.67-1.00, $P = .05$) but not of Apgar score <8 at 5 minutes, cardiorespiratory support at resuscitation or intubation in the delivery room. The temperature on admission was not significantly different (11 trials; 2317 infants; mean difference, −0.02°C; 95% CI, −0.07 to 0.03) although there was moderate heterogeneity between studies ($I^2 = 50\%$).

Maternal secondary outcomes

There was no difference in numbers of women with postpartum hemorrhage (>500 mL) or blood transfusion (Table 2).

Subgroup analyses for major neonatal morbidities

Infants born ≤28 weeks' gestation

Only 3 trials reported outcomes that could be extracted for meta-analysis in this group of very preterm infants (Table 2).[21,43,44] Delayed cord clamping reduced the incidence of hospital mortality for infants born ≤28 weeks' gestation (3 trials; 996 infants; RR, 0.70; 95% CI, 0.51−0.95; $P = .02$). No significant difference was found in

TABLE 2
Meta-analyses of delayed vs early cord clamping in preterm infants born <37 weeks' gestation and extremely preterm infants born ≤28 weeks' gestation

Outcome	Studies/ participants	Effect estimate: RR [95% CI]; heterogeneity I^2	RD [95% CI]; weighted mean % of events in early vs delayed group
All infants born <37 wk			
Hospital mortality	18/2834	0.68 [0.52–0.90]	−0.03 [−0.05 to −0.01]; 8% vs 5%
Maternal postpartum hemorrhage (>500 mL)	4/634	0.94 [0.72–1.23]	
Maternal blood transfusion	3/1906	0.84 [0.50–1.39]	
Apgar score <4 at 1 min	2/1600	0.82 [0.67–1.00]	
Apgar score <8 at 5 min	3/1683	1.03 [0.91–1.17]	
Cardiorespiratory support at resuscitation	10/748	0.89 [0.71–1.11]	
Intubation in delivery room	6/532	0.96 [0.82–1.13]	
Temperature on admission, °C	11/2317	MD −0.02 [−0.07 to 0.03]; 50%	
Severe intraventricular hemorrhage	11/2300	0.87 [0.59–1.27]	
Intraventricular hemorrhage—any	19/2871	0.87 [0.75–1.00]	−0.03 [−0.06 to 0.00]; 13% vs 10%
Periventricular leukomalacia	8/1977	0.71 [0.39–1.27]	
Combined periventricular leukomalacia or porencephaly or echodense intraparenchymal lesions or ventriculomegaly	6/1920	0.77 [0.56–1.06]	
Mechanical ventilation	9/686	0.95 [0.84–1.07]	
Chronic lung disease ≥36 wk	7/1951	1.02 [0.93–1.12]	
Patent ductus arteriosus	12/2397	0.96 [0.84–1.09]	
Necrotizing enterocolitis	12/2397	0.88 [0.65–1.18]	
Late-onset sepsis	10/2146	0.95 [0.80–1.13]; 19%	
Severe retinopathy of prematurity	5/1893	0.74 [0.51–1.07]	
Peak hematocrit, %	2/1587	MD 2.73 [1.94–3.52]	
Blood transfusion	13/2595	0.81 [0.74–0.87]; 61%	−0.10 [−0.13 to −0.06]; 50% vs 40%
Polycythemia (hematocrit >65%)	13/2529	2.65 [1.61–4.37]	
Partial exchange transfusion	4/1743	0.14 [0.01–2.74]	
Peak bilirubin, μmol/L	15/2358	MD 4.43 [1.15–7.71]; 77%	
Exchange transfusion	7/2139	0.29 [0.05–1.73]	
Infants born ≤28 wk gestation			
Hospital mortality	3/996	0.70 [0.51–0.95]	−0.05 [−0.09 to −0.01]; 17% vs 12%
Severe intraventricular hemorrhage	3/967	0.80 [0.51–1.25]	
Chronic lung disease ≥36 wk	3/869	0.99 [0.91–1.09]	
Necrotizing enterocolitis	4/977	0.87 [0.61–1.24]	
Late-onset sepsis	3/925	1.07 [0.87–1.31]	
Severe retinopathy of prematurity	2/839	0.72 [0.47–1.09]	
Blood transfusion	2/941	0.91 [0.85–0.97]; 39%	−0.07 [−0.13 to −0.02]; 82% vs 75%

CI, confidence interval; *MD*, mean difference; *RD*, risk difference; *RR*, risk ratio.
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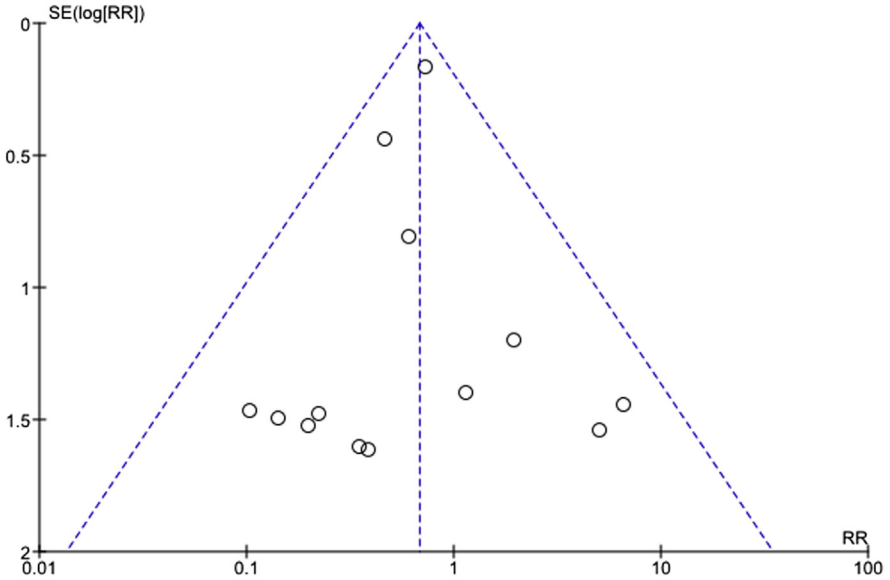
proportions of infants with severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, or late-onset sepsis. Delayed cord clamping reduced the numbers of very preterm infants receiving blood transfusions (2 trials; 941 infants; RR, 0.91; 95% CI, 0.85–0.97; RD, −0.07; 95% CI, −0.13 to

FIGURE 4
Funnel plot for hospital mortality



Funnel plot for hospital mortality showing that Egger test for small-study effects was not significant ($P = .6$).

RR, risk ratio (ie, relative risk); *SE*, standard error.

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−0.02; number needed to benefit, 14; 95% CI, 8−50; $P = .007$).

Duration of delayed cord clamping

Subgroup analysis (Table S1, Supplementary Material) of delayed (≥30-45, ≥45-60, ≥60-120; ≥120 seconds) vs early (<30 seconds) cord clamping showed no significant subgroup difference for mortality, severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, late-onset sepsis, or blood transfusion.

Vaginal vs cesarean delivery

Subgroup analysis (Table S1, Supplementary Material) of infants born by vaginal vs cesarean delivery showed no significant subgroup differences for mortality, severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, late-onset sepsis, or proportions receiving a blood transfusion.

Height relative to the level of the introitus or incision

Subgroup analysis (Table S1, Supplementary Material) of height relative to introitus or incision (above or on mother; at same level; >5-10, >10-20, >20 cm below) showed no significant subgroup difference for mortality, severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, or late-onset sepsis. However, delayed cord clamping led to increasing reductions in the RR of infants receiving later blood transfusion if the preterm infant was held at an increasingly low level below the introitus or incision ($P = .05$; $I^2 = 57.4\%$).

Timing of oxytocics

Subgroup analysis (Table S1, Supplementary Material) of oxytocics before or after cord clamping showed no difference for mortality, severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, late-onset sepsis, or blood transfusion.

Timing of cord clamping relative to onset of resuscitation

A single study[44] reported delayed cord clamping after onset of resuscitation. Subgroup analysis (Table S1, Supplementary Material) of timing of cord clamping relative to onset of resuscitation (before or after cord clamping) showed no significant subgroup difference for mortality, severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, late-onset sepsis, or blood transfusion.

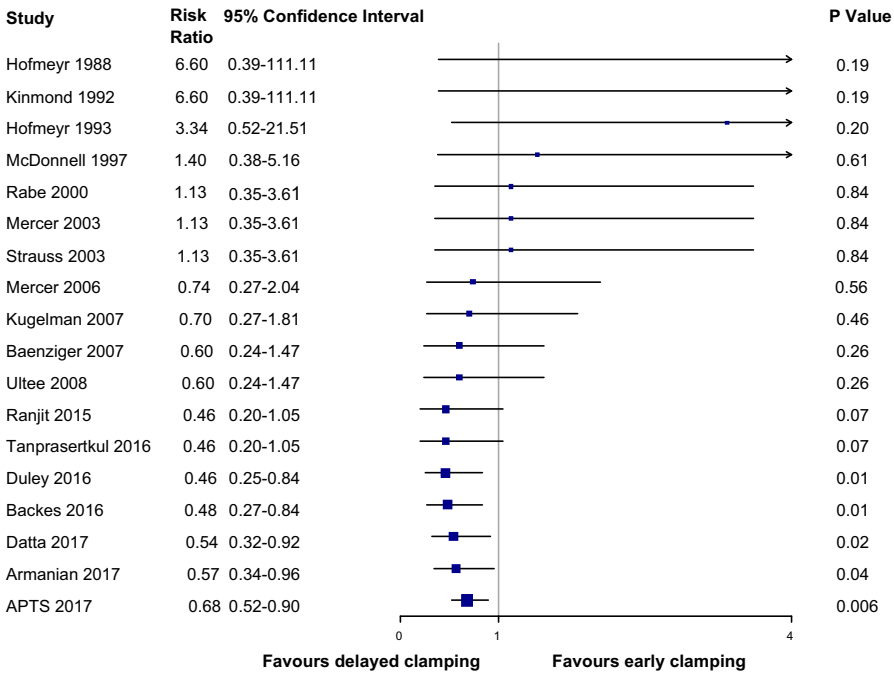
Sensitivity analyses in trials of high quality

Ten trials[35,36,39,43-48] were considered to be at low risk of selection and attrition bias and therefore of high quality. A sensitivity analysis, performed in 9 of these trials that reported hospital mortality, confirmed that death was reduced by delayed cord clamping (1233 infants; RR, 0.66; 95% CI, 0.50−0.89; $P = .006$; $I^2 = 0$), but there were no differences in the proportions of infants with important neonatal morbidities including severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, or late-onset sepsis. In these trials of high quality, delayed cord clamping also reduced the number of infants receiving blood transfusion (7 trials; 2172 infants; RR, 0.83; 95% CI, 0.77−0.90; $P < .00001$; $I^2 = 49\%$).

We performed 6 post-hoc sensitivity or additional analyses, whose results should thus be interpreted with caution. First, using a more conservative random effects model instead of a fixed effects model, delayed clamping significantly reduced hospital mortality in all 18 trials after meta-analysis using trial RR (RR, 0.69; 95% CI, 0.52−0.91; $P = .009$ and RR, 0.68; 95% CI, 0.52−0.90; $P = .006$) but not after meta-analysis using trial RD (RD, −0.02; 95% CI, −0.04 to 0.00; $P = .12$). Second, after excluding the 1566 infants in APTS, using random effects delayed clamping reduced hospital mortality in 1268 infants from 17 trials (RR, 0.56; 95% CI, 0.31−1.00; $P = .05$, $I^2 = 0$). Third, a cumulative

meta-analysis by date of publication (Figure 5)[49] shows that delayed clamping was associated with a significant reduction in hospital mortality in 2016, the year before APTS.[21] Fourth, a sensitivity analysis of all 18 trials in 2902 fetuses, including stillbirths after randomization,[27] showed that delayed clamping reduced mortality to discharge (RR, 0.69; 95% CI, 0.53−0.91; $P = .007$). Fifth, a sensitivity analysis showed that 18 additional null studies of average size would be required to create a nonsignificant effect for hospital mortality ($P > .05$) (Figure 6). Sixth, a cumulative meta-analysis of the effect of delayed clamping on any intraventricular hemorrhage was undertaken by year of publication (Figure 7).

FIGURE 5
Cumulative meta-analysis of effect of delayed clamping on hospital mortality



Cumulative meta-analysis of effect of delayed vs early cord clamping on risk ratio (RR) of primary outcome of hospital mortality, in 18 trials arranged in order of publication.

APTS, Australian Placental Transfusion Study; *CI*, confidence interval; *RR*, Risk ratio (i.e. relative risk).

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Comment

Main findings

Delayed cord clamping reduced hospital mortality

This systematic review of 18 RCTs of delayed vs early clamping, with minimal cord milking in either arm, enrolled 2834 infants born <37 weeks' gestation. Its primary finding is that delayed clamping reduced all-cause mortality before discharge from hospital (RR, 0.68; 95% CI, 0.52−0.90; $P = .006$; RD, 0.03; 95% CI, −0.05 to −0.01; $P = .005$; number needed to benefit, 33; 95% CI, 20−100), with no heterogeneity in the analysis of this result ($I^2 = 0$). Importantly, it remained highly significant in a sensitivity analysis of 9 studies of high quality at low risk of bias in 2233 infants ($P = .006$) consistent with enhanced precision. The QoE that delayed clamping reduced mortality was therefore assessed as high. These comparisons excluded fetuses who were stillborn after randomization. Although such exclusions violate the principle of analyzing all randomized participants by intention to treat, it does not introduce bias.[27] However, we also performed a post-hoc secondary sensitivity analysis of all 2902 fetuses randomized, including those subsequently stillborn, which did not materially affect the results.

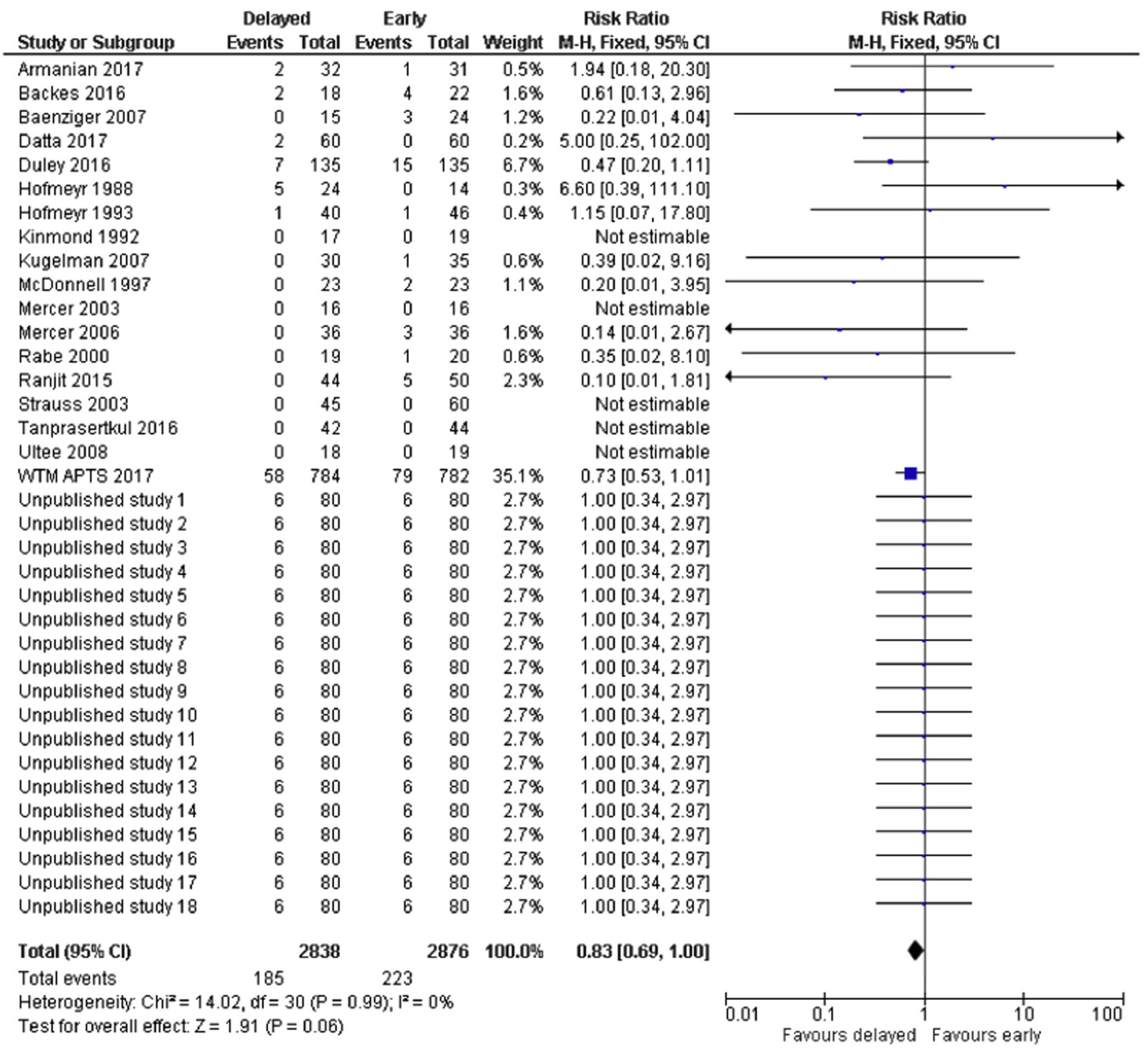
A predefined subgroup analysis showed that delayed clamping significantly reduced mortality for infants born ≤28 weeks' gestation (3 trials, 996 infants; RR, 0.70; 95% CI, 0.51−0.95; $P = .02$; RD, −0.05; 95% CI, −0.09 to −0.01; $P = .02$). Additional subgroup analyses showed no significantly different 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). However, all of these secondary analyses should be interpreted with caution because the data that could be extracted from the published reports were incomplete. This underlines the critical need for individual patient data analyses to investigate these and other important hypotheses reliably.

How generalizable are these findings? On one hand, delayed cord clamping is a simple procedure that requires no training; costs nothing; and could be widely applied in low-, medium-, or high-income countries. On the other hand, it is important to note that unanticipated complications might occur in populations different from those represented by the trials in this review. For example, in a large randomized cluster trial, antenatal corticosteroids were unexpectedly linked with excess neonatal deaths and infection in low-resource settings.[50,51] However, trials in this review were conducted in populations ranging across low-, middle-, and high-income settings, suggesting that the findings may be widely generalizable.

Delayed cord clamping is safe for mothers and newborns

Delayed clamping did not impact maternal postpartum hemorrhage or the need for maternal blood transfusion, so it is safe for the mother. For the infant, 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

FIGURE 6
Sensitivity analysis showing additional null studies needed for nonsignificant effect on mortality



Sensitivity analysis showing that 18 additional null studies of average size would be required to create nonsignificant effect for hospital mortality ($P > .05$).

APTS, Australian Placental Transfusion Study; *CI*, confidence interval; *M-H*, Mantel-Haenszel.

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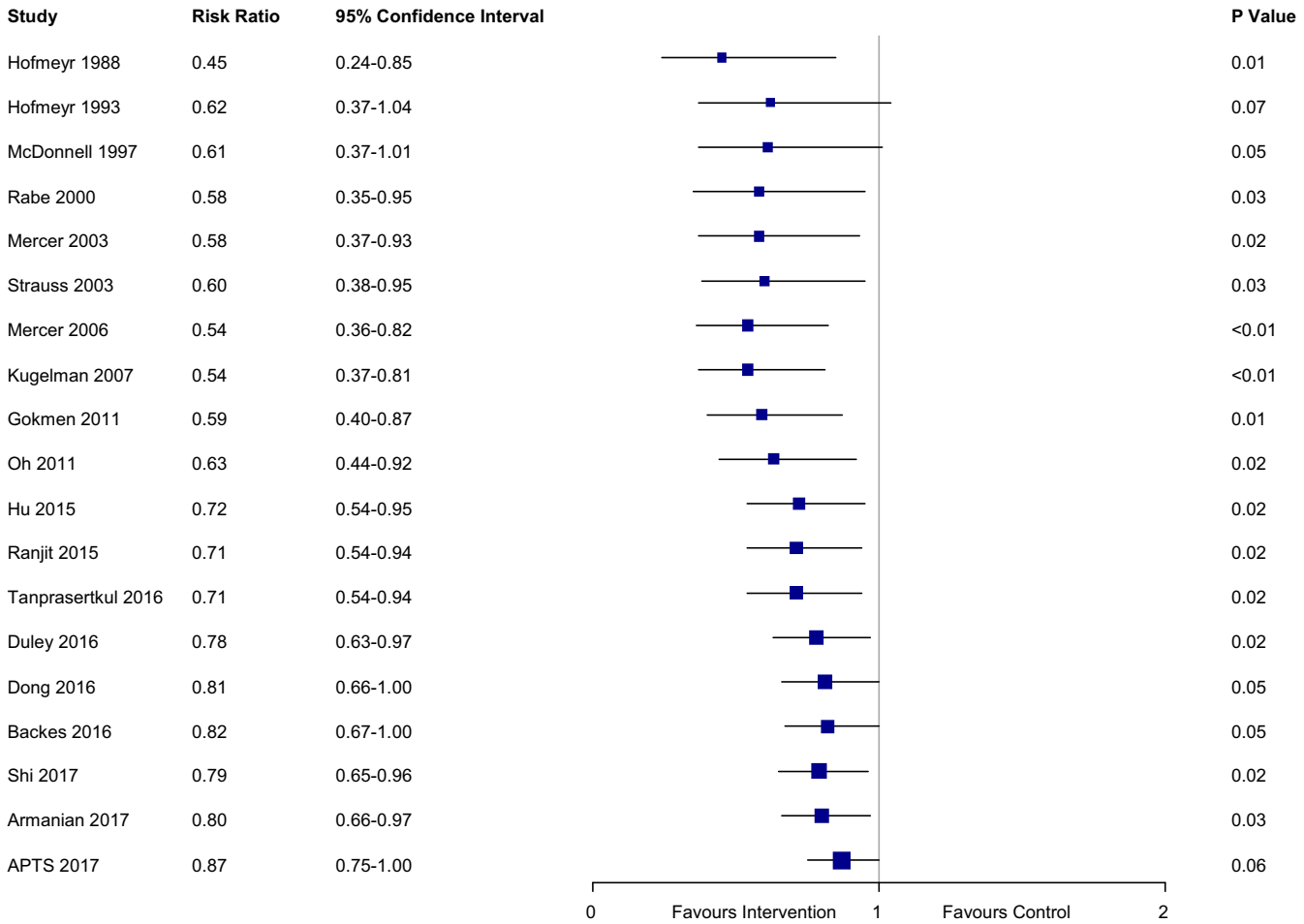
neonatal intensive care unit. The key neonatal morbidities of severe intraventricular hemorrhage, severe retinopathy of prematurity, chronic lung disease, necrotizing enterocolitis, or late-onset sepsis were not significantly different between randomized groups, although the QoE of these secondary analyses was substantially downgraded to low or moderate because of lack of precision and the potential for new studies to change the estimate of effect. These results contrast with those of previous systematic reviews of RCTs in smaller samples,[11,15] which reported that delayed cord clamping reduced intraventricular hemorrhage,[11,15] necrotizing enterocolitis, and infection[11] in babies born <37 weeks' gestation. A cumulative meta-analysis by year of publication (Figure 7) shows that the overall effect of delayed clamping on reducing all grades of intraventricular hemorrhage was no

FIGURE 7
Cumulative meta-analysis of effect of delayed clamping on intraventricular hemorrhage



Cumulative meta-analysis of effect of delayed vs early cord clamping on risk ratio (RR) of intraventricular hemorrhage of any grade in 19 trials arranged in order of publication.

APTS, Australian Placental Transfusion Study; *CI*, confidence interval; *RR*, risk ratio (i.e. relative risk).

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longer statistically significant after publication of the APTS.

Delayed clamping increased neonatal hematocrit, confirming placental transfusion

Delayed clamping increased mean peak hematocrit in the first week by 2.7 percentage points (95% CI, 1.9−3.5; $P < .00001$), confirming that placental transfusion occurred. This is consistent with the finding that delayed cord clamping reduces the proportion of infants receiving subsequent blood transfusions, with an absolute reduction of 10% (95% CI, 6-13%). The QoE for this effect on blood transfusions was assessed as high, owing to the magnitude and statistical significance ($P < .00001$) of effect. The effect of delayed clamping in reducing infant blood transfusions was also observed in infants born ≤28 weeks' gestation. Subgroup analysis showed a nominally statistically significant effect of the level at which the infant was held ($P = .05$), supporting the hypothesis that delayed cord clamping performed with the infant held at increasingly lower levels below the introitus or incision results in increasing reductions in subsequent blood transfusion. There were no significant subgroup effects for blood transfusion according to time of delay to cord clamping, mode of delivery (vaginal or cesarean), timing of oxytocics, and timing of resuscitation.

Are there potential harms from delayed cord clamping?

Delayed clamping increased the incidence of polycythemia, with an increased RD of 3% (95% CI, 1−4%), and it increased the incidence of jaundice (mean difference in peak bilirubin +4 μmol/L). However, there was no difference in partial exchange transfusions for polycythemia or in exchange transfusions for hyperbilirubinemia. The

increased incidences of polycythemia and peak bilirubin in delayed cord clamping infants were not associated with morbidity. Importantly, delayed clamping reduced the proportion of infants with Apgar score <4 at 1 minute with marginal statistical significance (N = 1600; RR, 0.82; 95% CI, 0.67−1.00; $P = .05$; $I^2 = 1\%$) and did not increase the proportions with Apgar score <8 at 5 minutes, or the proportions receiving cardiorespiratory support or endotracheal intubation in the delivery room (Table 2).

What are the potential risks of delayed clamping in low-income settings with a high risk of bilirubin encephalopathy and without access to phototherapy? As delayed clamping increased peak serum bilirubin by only 4 μmol/L without increasing partial exchange transfusions for polycythemia or exchange transfusions for hyperbilirubinemia its potential risks in low-resource settings seem unlikely to be large.

By which mechanisms may delayed clamping confer benefit?

(a) The increased mortality in the early clamping group is unlikely to reflect low systemic blood flow,[52] as this was not improved by delayed clamping in a subgroup of 266 infants in the APTS.[53]

(b) Increased red cell mass enhances total oxygen carrying capacity and oxygen saturation,[54] while lower oxygen saturations increase mortality in very preterm infants,[55,56] 2 observations which might explain, in part, how delayed cord clamping reduced mortality. In parallel with increased red cell mass, an increase in the number and concentration of mesenchymal stem cells may enhance the modulation of excessive inflammatory reactions,[57] perhaps explaining in part the lower sepsis-related mortality but similar incidence of sepsis in infants after delayed clamping.[58]

(c) Clamping the cord after the onset of breathing may improve outcomes[59-63] in preterm[62,64] and term[63] infants by maintaining cardiac output, oxygenation, and arterial blood pressure.[59,61]

(d) Perhaps most importantly, delayed clamping may avoid unnecessary and potentially harmful intervention. Nearly all preterm infants begin breathing by 60 seconds,[65] particularly if gently stimulated.[64] Delaying clamping for ≥60 seconds may thus increase the number of infants breathing before the cord is clamped, which may stabilize hemodynamic transition[66] and reduce endotracheal intubation and invasive mechanical ventilation. These interventions can be hazardous[67] and may initiate a cascade of potentially adverse events including release of inflammatory markers,[68] treatment with inotropes, arterial lines, delayed enteral feeds, and bronchopulmonary dysplasia,[69] predisposing to increased risk of death and neurodevelopmental impairment.[70]

(e) How can the reduced effect of delayed clamping on risk of intraventricular hemorrhage that is shown in the cumulative meta-analysis in Figure 7 be explained? This may reflect the impact of adding the 1566 infants in APTS,[21] if they were less severely ill than earlier trial populations. Consistent with this, all 266 patients in the APTS echo substudy[53] received antenatal glucocorticoids and their average systemic blood flow was higher than in previous studies.

Implications for clinical care

This review provides high-quality evidence that, in the trial populations represented, delayed clamping reduces mortality and infant blood transfusions, both in preterm (<37 weeks' gestation) and very preterm (≤28 weeks' gestation), without increasing the proportion with low Apgar scores or who received cardiorespiratory support or neonatal resuscitation at delivery (Table 2). In most infants in this review, delayed clamping was planned for ≥60 seconds. Assuming that 1 million infants are born ≤28 weeks' gestation globally,[4] using delayed instead of early clamping could achieve between 10,000 and 90,000 additional survivors each year, based on the RD of −0.05 and 95% CI of −0.09 to −0.01 that were observed in this group. Delayed cord clamping also led to increasingly greater reductions in likelihood of receiving subsequent blood transfusions as infants were held at increasingly lower levels below the introitus or incision ($P = .05$), which is consistent with a dose response (Table 2).

Implications for future research

(a) Further trials of delayed vs early cord clamping in similar settings and populations as these may be difficult to justify in view of the finding that, in trials that did not report cord milking, delayed clamping reduced hospital mortality. A post-hoc cumulative meta-analysis[49] shows that this result became statistically significant in 2016, before APTS was published (Figure 5). A post-hoc sensitivity analysis of all 17 trials excluding APTS also shows that delayed clamping reduced hospital mortality, confirming that this result is not driven solely by APTS.[21] Furthermore, mortality before hospital discharge accounts for >97% of all deaths of preterm infants aged <2 years.[55,71]

(b) Optimum management of the small proportion of infants who require early resuscitation remains uncertain. RCTs of cord milking vs delayed clamping, and of resuscitation with or without the umbilical cord intact, and before or after the onset of breathing are needed.

(c) Childhood follow-up will be essential, both in existing and future trials.

(d) As the time of onset of breathing is closely correlated with time after birth, the potential benefits of clamping the cord after onset of breathing could be substantiated if analyses of individual patient data from new and existing RCTs showed a dose response between incremental delays in the time of cord clamping (which, unlike time of onset of breathing, is accurately captured by nearly all studies) and

progressive improvements in mortality and other adverse outcomes. Individual patient data analyses of new and existing RCTs will also be of critical importance to identify the optimal duration and methods of placental transfusion and their relative effects at different gestational ages.

(e) How large would a future trial need to be, assuming that event rates continue to improve?[72] To detect a 20% reduction in RR (ie, relative risk) of hospital mortality from 8-6.4%, with 90% power and 10% noncompliance would require >11,000 patients.[21]

(f) Accordingly, the most important implication for future research is the need to achieve much larger sample sizes to resolve important clinical questions more rapidly.[72,73] Although the first trial of delayed vs early clamping was published nearly 30 years ago, <3000 patients of <37 weeks' gestation have been enrolled in the 18 trials identified in this systematic review—inevitably limiting its power. Furthermore if event rates continue to fall, increasingly large samples—of thousands rather than hundreds—will be needed to demonstrate further reductions in mortality, major morbidity, or disability reliably.[73] Addressing this challenge will require a transformation in perinatal practice through greater international collaboration and integration of clinical research into routine care with standardization of definitions of adverse outcome.[21,72,74-76] All are key aims of the newly conceived ALPHA Collaboration for **A**dvancing **L**arge **P**ublicly prioritized perinatal trials for **H**ealth outcomes **A**ssessment, a global initiative that plans to help publicly prioritize and promote perinatal megatrials.[74]

Strengths and limitations

The strength of this review is in its rigorous methods, as evidenced by:

(a) Strict adherence to the guidelines of the Cochrane Collaboration and PRISMA statement for the conduct and reporting of systematic reviews of interventions[24,25];

(b) A prospective protocol designed to address a highly specific research question that was not changed during the review process (Supplementary Material);

(c) A comprehensive literature search, including Chinese articles, without language restrictions;

(d) Attempts to obtain data from all authors, including those who wrote abstracts;

(e) Inclusion of a relatively large number of studies;

(f) Strict assessment of study quality using the Cochrane risk-of-bias tool[24];

(g) The performance of subgroup and sensitivity analyses;

(h) The focus on trials of delayed vs early clamping by excluding trials that reported cord milking in any arm;

(i) The exploration of potential sources of heterogeneity;

(j) The quantitative synthesis of the evidence; and

(k) The symmetric funnel plot and nonsignificant Egger test, suggesting no publication or related biases in meta-analyses including 18 studies.

Limitations of this systematic review are that:

(a) It was not preregistered in the international PROSPERO database,[77] because our focus was on achieving rapid submission for peer review. However, the prespecified protocol of July 21, 2017 (Supplementary Materials) used the standard template for Cochrane systematic reviews, whose criteria are identical to those of PROSPERO. In similar circumstances in future we would not omit registration in PROSPERO, which is relatively quick and simple and provides prior, publicly accessible information and accountability for the review.

(b) Secondary analyses were frequently underpowered to detect effects on mortality and morbidities, including subgroup analyses by duration of delayed cord clamping, height relative to the introitus or incision, mode of delivery, timing of oxytocics, and timing of cord clamping relative to onset of resuscitation.

(c) Further, this systematic review may not have captured all unpublished RCTs. However, there was no evidence of publication bias. Some data could not be included from ongoing studies, studies published as abstracts only, studies excluded because they did not report an outcome prespecified by the review, and from 1 study of late preterm and term infants that did not report preterm outcomes separately.[32] Nevertheless, it seems unlikely that publication of missing trials will change the conclusions that delayed cord clamping reduces mortality and infant blood transfusion. For example, it would require ≥18 null RCTs of similar size as in this systematic review to overturn the statistically significant result for mortality (Figure 6).

(d) Benefits may be greater for certain subgroups or periods of delayed clamping. Information for analysis of the effects of gestational age was limited by missing data in published studies, further underlining the need for individual patient data analysis to provide further evidence regarding the effects of delayed clamping in various subgroups.

(e) This review aimed to assess the effect of delayed vs early clamping of the umbilical cord and not the effect of other strategies, such as cord milking. APTS reported <2% incidence of cord milking in the delayed cord clamping group.[21] Twelve other trials reported no or minimal rates of cord milking in either arm. We acknowledge that trials whose authors did not respond to our enquiries may have included, but not reported, some cord milking. However, as their primary aim was to compare

delayed vs early cord clamping, we have classified them as eligible for this review. Potential benefits of cord milking in infants undergoing delayed cord clamping have not been assessed by this review and would require a detailed analysis of individual patient data.

Conclusions

This review shows, with high-quality evidence, that, in studies that do not report cord milking, delayed clamping reduces mortality in preterm infants and it confirms earlier findings that delayed clamping reduces subsequent blood transfusions. Delayed clamping had no impact on clinically significant neonatal or maternal morbidity, but these secondary analyses were substantially underpowered and analyses of individual patient data from new and existing RCTs will be critically important to evaluate them further. Trials are needed of cord milking vs delayed clamping, of combining cord milking with delayed clamping, and of resuscitation with or without the umbilical cord intact, before or after the onset of breathing. Childhood follow-up will be essential. ■

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