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Effects of delayed cord clamping on infants after neonatal period: A systematic review and meta-analysis

Yang Zhao, Rui Hou, Xiu Zhu, Lihua Ren, Hong Lu*

Peking University School of Nursing, #38 Xueyuan Road, Hai Dian District, Beijing, 100191, PR China

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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.

What is already known about the topic?

- There is mounting evidence that delayed cord clamping, compared with early cord clamping, is beneficial for both term and preterm infants, as well as low birthweight infants, but mostly in the short term and especially within the first week after birth.
- No up-to-date and reliable follow-up data of long-term effects of delayed cord clamping on infants is available, without which we can hardly conclude that delayed cord clamping may do more harm than good.

What this paper adds

- Delayed cord clamping is mainly proved to modestly improve hematological and iron status of term infants after neonatal period.
- For preterm infants, delayed cord clamping slightly increased hematocrit and serum ferritin between six and ten weeks old, whereas no evidence of longer term effects of delayed cord clamping on preterm infants is available.
- Among the effects of delayed cord clamping compared with early cord clamping on infants after neonatal period, infant mortality

* Corresponding author.
E-mail addresses: sonya915@pku.edu.cn (Y. Zhao), luhong@bjmu.edu.cn (H. Lu).

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and morbidity, which are of more clinical significance than hematological and iron status was seldom studied.

1. Introduction

The practice of delayed cord clamping with umbilical cord being clamped no earlier than one minute or after it stopped pulsating in the third stage of labour, is recommended by many international and national organizations or guidelines, such as World Health Organization (WHO), International Confederation of Midwives and Society of Obstetricians and Gynecologists of Canada, as well as Queensland Government, with a view to improve maternal and infant health and nutrition outcomes (International Confederation of Midwives, 2017; Leduc et al., 2009; Queensland Government, 2017; WHO, 2014, 2018). Delayed cord clamping allows for a transfer of blood from the placenta to the infant at birth, and approximately 25%–60% (54–160 mL) blood volume and up to 60% more red blood cells can be provided through this placental transfusion (Leduc et al., 2009; van Rheenen and Brabin, 2004). In addition, mounting evidence indicates that, compared with early cord clamping, delayed cord clamping is beneficial for both term and preterm and even extremely low birthweight infants in terms of improved hematological status (measured as hematocrit, hemoglobin concentration, anemia rate and transfusion requirement for anemia), better iron status (measured by ferritin concentration and stored iron), lower risk for necrotising enterocolitis, reduced overall mortality, less intraventricular hemorrhage, decreased blood transfusion incidence, reduced episodes of late-onset sepsis and better blood pressure in short term, especially within the first week after birth (Backes et al., 2014; Chapman et al., 2016; Fogarty et al., 2018; Garg et al., 2017; Ghavam et al., 2014; Leduc et al., 2009; McDonald and Middleton, 2008; McDonald et al., 2013; Rabe et al., 2012; van Rheenen and Brabin, 2004).

The majority of these evidences mentioned above simply showed the short-term benefits of delayed cord clamping, mainly focusing on the first week after birth. However, without follow-up data, we can hardly come to the conclusion that delayed cord clamping may do more harm than good. For example, in spite of short-term benefits, high dose steroids treatment for chronic lung disease, antibiotics and antenatal thyrotropin-releasing hormone used for women at high risk of preterm birth, and restriction of oxygen therapy concentrations to less than 40% were proved to be futile or even harmful in the long run (Tarnow-Mordi et al., 2014). Moreover, although two meta analyses mentioned the long-term effects of delayed cord clamping that it increased hemoglobin concentration and ferritin level in infants at two to three months and at six months of age respectively, as well as reduced the risk of anemia (Tarnow-Mordi et al., 2014; van Rheenen and Brabin, 2004), they all published ten years ago and failed to provide adequate evidence.

Given the current available meta analyses published more than 10 years ago as well as more recent research evidence available on the long-term effects of delayed cord clamping on infants, we evaluated the long-term effects of delayed cord clamping compared with early cord clamping on all kinds of infants after neonatal period, including preterm, term and low birthweight infants, in order to narrow this knowledge gap and gain a more comprehensive view of this issue.

2. Objectives

We conducted this systematic review and meta analysis with the aim to evaluate the long-term effects of delayed cord clamping compared with early cord clamping on infants after neonatal period.

3. Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011; Liberati et al., 2009).

3.1. Inclusion and exclusion criteria

Studies were included if they (1) had full-text articles available; (2) were randomized controlled trials; (3) provided infants' follow-up data beyond one month of age; (4) defined early cord clamping as clamping the cord at no later than 60 s after delivery; (5) defined delayed cord clamping as clamping the cord after the cord stopped pulsating or after placental separation or at no earlier than 60 s after delivery. We excluded commentaries, editorials, letters, case reports, reviews and non-randomized clinical trials (non-RCTs) such as observational and cohort studies. Also, animal studies and studies in which cord milking was employed instead of delayed cord clamping were not included.

3.2. Search strategy

A comprehensive literature search was performed in PubMed, EMBASE and Cochrane Library database from inception to June 22, 2018, without language restriction. Relevant text words and subject headings (MeSH Term and Emtree term) relating to "cord clamp*", umbilical cord clamp*, "cord ligat*", umbilical cord ligat*, "placental transfusion" and “umbilical cord” were combined. We searched for randomized clinical trials (RCTs) that compared early cord clamping with delayed cord clamping in infants. An additional search was done to identify original RCTs included in the systematic reviews or meta analyses utilizing the databases and keywords mentioned above. Full search terms and complete search strategy are provided in Table 1 in the appendix.

3.3. Study selection

Potentially relevant studies were imported into EndNote X7. After removal of duplicates, titles and abstracts were screened by two independent reviewers for relevance and eligibility. We reviewed full texts of the remaining results, if sufficient information could not be obtained from title or abstract, or if a final decision could not be made. Disagreements were resolved through discussion or consultation with a third reviewer. We put no limits on language and translated non-English records.

3.4. Data extraction

Two reviewers independently extracted data into a standardized data collection form. The data extracted from each study included first author, year of publication, country where the study was performed, characteristics of participants, number of participants (including total, delayed cord clamping group and early cord clamping group), time of cord clamping (both delayed cord clamping and early cord clamping), follow-up duration and primary outcomes (long-term effects of delayed cord clamping compared with early cord clamping on infants after neonatal period) of infants following up beyond 1 month of age. All the data from the same study yet collected at different follow-up time points were included. We combined means and standard deviations of two delayed cord clamping groups, which were consisted in the same study and whose cord clamping times were different (both$\geq$60 s), into one using Stat Tools. We used methods proposed by Cochrane Handbook and Wan X et al. to estimate missing sample mean or standard deviation (Higgins and Green, 2011; Wan et al., 2014).

Table 1
Characteristics of included studies.

First Author, Year of Publication	Country	Characteristics of Participants	Number of Participants (DCC Group/ ECC Group)	Time of cord clamping		Follow-up Duration	Primary Outcomes
				Delayed	Early		
Lanzkowsky, 1960	South Africa	Term infants Mother: no hemorrhagic episodes, vaginal delivery	112 (58/54)	After placental separation	Immediate	3 months	Hemoglobin, Weight
Nelson et al., 1980	Canada	Term newborn babies born at >36 weeks	54 (28/26)	After the cord stopped pulsating	<60 seconds	8 months	Infant's temperament (Carey Scales of Infant Temperament), Infant behaviour (Bayley Scales of Infant Development)
Grajeda et al., 1997	USA	Birth weight≥2000 g, gestational age≥37wk, singleton birth, vaginal delivery, no maternal gestational diabetes, no serious hemorrhages	69 (48/21)	After the cord stopped pulsating	Immediate	2 months	Ferritin, Hematocrit, Hemoglobin, Serum iron, Transferrin saturation, Total iron binding capacity (TIBC), Feeding mode, received vitamin supplement, received iron supplement, Illness since birth, Diarrhea in previous week, Upper respiratory infection
Geethanath et al., 1997	India	Term neonates born per vaginum to mothers with uncomplicated pregnancies and with hemoglobin more than 10 g/dl.	107 (59/48)	After the placenta descended into the vagina	Immediate	3 months	Hemoglobin, Ferritin
Gupta and Ramji, 2002	India	Term neonates born vaginally to pregnant women with hemoglobin (Hb) <100 g/L	58 (29/29)	After the placenta descended into the vagina	Immediate	3 months	Hemoglobin, Ferritin, Hb change
Chaparro et al., 2006	USA	Term pregnancy (gestational age 36 to 42 weeks)	358 (187/ 171)	2 minutes	10 seconds	2, 4 and 6 months	Dietary data/Breastfeeding (at 2, 4, and 6 months, food-frequency, dietary recall, use of nutritional supplements), Infant hematological and iron status (at 6 month; hemoglobin, anaemic, hematocrit, maen corpuscular hemoglobin, mean corpuscular hemoglobin concentration, ferritin, iron deficiency, iron deficiency anemia, transferrin receptor, ratio transferrin receptor/ferritin, stored iron, body iron)
Chaparro et al., 2007	USA	Term pregnancy (gestational age 36 to 42 weeks)	266 (139/ 127)	2 minutes	10 seconds	6 months	Weight gain, Blood lead concentration, Hgb, Anemic, Ferritin), Iron deficient, Iron deficiency anemia, TfR, Body iron, Body storage iron
van Rheenen et al., 2007	Zambia	Infants: weighed >2500 g, with gestational age above 37 weeks	72 (35/37)	After the cord stopped pulsating	<20 seconds	4 and 6 months	Dietary data (exclusively breastfed, iron supplements, diarrhoea), Infant hematological status (at 4 and 6 months of age, Hb, Hb change from baseline, anemia, zinc-protoporhyrin, iron deficient erythropoiesis, iron deficiency anemia, positive malaria smear)
Ultee et al., 2008	Netherlands	Infants born at 34 weeks and 0 days to 36 weeks and 6 days gestational age, delivered vaginally	34 (16/18)	180 seconds	30 seconds	10 weeks	Hemoglobin, Hematocrit, Ferritin
Ceriani Cernadas et al., 2010	Argentina	Term infants	252 (166/ 86)	3 minutes	15 seconds	6 months	Serum ferritin (μg/L), Hemoglobin (g/dl), Iron deficiency anemia (hemoglobin<105 g/ dl, ferritin<9 μg/L), Mean corpuscular volume (MCV), Feeding Supplementation with iron, Blood transfusion, Morbidity, Dermatitis, Ear, nose and throat infection, Urinary tract infection, Low respiratory infection, Upper respiratory infection
Andersson et al., 2011	Sweden	Term pregnancy (gestational age 37^{+0} to 41^{+6} weeks), non-smoking, normal Pregnancy, singleton	350 (176/ 174)	≥180 seconds	≤10 seconds	4 months	Infant hemoglobin and iron status (measured as hemoglobin, packed cell volume, mean cell volume, mean cell hemoglobin concentration, reticulocyte hemoglobin, reticulocyte count, iron, transferrin, transferrin receptors, transferrin saturation, logTfR/Fer-ratio, total body iron, iron deficiency and anemia) at 4 months of age Weight, Length, Breastfeeding (at 4 months)
Li et al., 2012	China	Gestational age 37 to 42 weeks, birth weight2500g-4000 g	158 (64/ 94)	60 seconds	<10 seconds	4 month	Hemoglobin, Serum ferritin (SF), Serum iron (SI), Soluble transferrin receptors (sTfR), Mean corpuscular volume (MCV), Hematocrit (HCT), Total iron binding capacity (TIBC), Weight, Body length, Development quotients
Al-Tawil et al., 2012	Egypt	Term gestation >37 weeks, received adequate prenatal care, singleton	160 (82/ 78)	180 seconds	15 seconds	3-5 months	Hb, Hematocrit, Iron status: serum ferritin, transferrin saturation, Mean corpuscular

3.5. Risk of bias assessment

Assessment of risk of bias for each included study was conducted by pairs of independent reviewers in duplicate utilizing the Cochrane Collaboration Risk of Bias tool (Higgins and Green, 2011). Overall risk of bias across seven domains was appraised as unclear, low, or high risk of bias by focusing on randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

3.6. Statistical analysis

We divided infants' data (primary outcomes presented in Table 1, except for feeding data which we considered to be influenced by individuals' behaviors and habits) into two groups with follow-up periods of less than 6 months (< 6 months) and beyond 6 months (≥6 months) respectively. When one outcome included two or more independent results from RCTs, but with one group or both groups only having one result available, we combined data from the two groups and subgroup analysis was conducted. When data from two or more studies were available, for

Table 1 (*Continued*)

First Author, Year of Publication	Country	Characteristics of Participants	Number of Participants (DCC Group/ ECC Group)	Time of cord clamping		Follow-up Duration	Primary Outcomes
				Delayed	Early		
		pregnancy, multigravida, without underlying maternal medical diseases, without antenatal complications, antenatal maternal Hb≥11gr/dL, planned for normal vaginal delivery					volume (MCV), Serum bilirubin, Iron deficiency, Anemia
Andersson et al., 2013	Sweden	Term pregnancy (gestational age 37^{+0} to 41^{+6} weeks), non-smoking, normal Pregnancy, singleton	365 (185/ 180)	≥180 seconds	≤10 seconds	4 months	Neurodevelopment (Ages and Stages Questionnaire), Immunoglobulin G level, Prevalence of symptoms of infection and other morbidities (Morbidity Questionnaire; including fever, diarrhoea, loose stools, hard stools, belly ache, vomiting, cough, breathing difficulties, rhinorrhea/runny nose, nasal congestion, otitis, rash, crying, tiredness, prescription of antibiotics, visit to paediatrician, visit to other doctor and hospitalization)
Andersson et al., 2014	Sweden	Term pregnancy (gestational age 37^{+0} to 41^{+6} weeks)	340 (172/ 168)	≥180 seconds	≤10 seconds	4, 12 months	Hemoglobin level, Hematocrit, Reticulocyte Hb equivalent, Iron status (as assessed by ferritin level, transferrin saturation [TS], soluble transferrin receptor [sTfR] level, mean cell volume [MCV] and iron deficiency), Anemia, Neurodevelopment (Ages and Stages Questionnaire), Weight (at 4 and 12months of age), Nutrition (food energy, protein, carbohydrates and iron)
Krishnan et al., 2015	India	Term (37-41 completed weeks of gestation); Singleton; Normal vaginal delivery with cephalic presentation; Maternal Hb>10 g/dl at admission for delivery; Exclusively breastfeed	76 (37/ 39)	180 seconds	10seconds	6 weeks	Serum ferritin
Andersson et al., 2015	Sweden	Infants: full-term newborns with a gestational age of 37 to 41 weeks Mothers: nonsmoker, vaginal delivery	255 (136/ 119)	≥180 seconds	≤10 seconds	48 months	Cognitive function (at 48 months/4 years of age, Wechsler Preschool and Primary Scale of Intelligence, WPPSI-III), Fine-motor skills (at 48 months and 4 years of age, manual dexterity area from the Movement Assessment Battery for Children, Second Edition, Movement ABC), Child's development (at 48 months and 4 years of age, Parents reported, Ages and Stages Questionnaire, Third Edition, ASQ), Breastfeeding (at 4 months)
Tiemersma et al., 2015	Netherlands	Low birthweight infant	73 (35/ 38)	120-180 seconds	30 seconds	2-3 months	Weight/Weight change, Length/Length change, Head circumference, Hemoglobin/ Hb change, Anemia, Mean corpuscular volume, Ferritin, Transferrin saturation, Feeding (breastfeeding, formula feeding, mixed feeding), Positive HIV PCR
Ranjit et al., 2015	India	Preterm infants born between $30^{0/7}$ and $36^{6/7}$ wk of gestation	34 (16/ 18)	120 seconds	immediate	6 weeks	Serum ferritin, Hematocrit
Kc et al., 2017	Nepal	Infants: full-term newborns with a gestational age of 37 to 41 weeks Mothers: vaginal delivery, singleton pregnancy	540 (270/ 270)	≥180 seconds	≤60 seconds	8 and 12 months	Hemoglobin level (at 12months of age), Ferritin level (at 8 and 12months of age), Anemia (at 8 and 12months of age), Iron deficiency (at 8 and 12months of age), Iron deficiency anemia (at 8 and 12months of age)

dichotomous outcomes of RCTs, we estimated the risk ratios (RRs) with corresponding 95% confidence interval (95% CI) using the Mantel-Haenszel statistical method. For continuous parameters, standard mean differences (SMDs) with 95% CI was calculated, given the heterogeneity between studies in terms of follow-up period. The weighted mean difference (WMD) with 95% CI was calculated when only one study was pooled for each outcome. According to Cochrane Handbook, studies with zero events in both delayed cord clamping and early cord clamping groups were excluded when calculating RRs.

Heterogeneity between studies was assessed using Cochran's Q test and Higgins' I^2, with I^2 greater than 50% considered to indicate significant heterogeneity. Either DerSimonian and Laird random effect model or Mantel-Haenszel fixed effect model was used, and model selection was determined by the degree of heterogeneity. When heterogeneity between studies was found to be significant as indicated by I^2 values greater than 50%, pooled estimates based on DerSimonian and Laird random effect model were reported. We performed complementary sensitivity analyses by excluding studies that had high risk of bias in at least one domain of the risk of bias tool, or studies recruiting participants with distinguishing features, or studies with weight of more than 30%.

All analyses were performed using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). All tests were calculated from two-tailed and a P value of less than 0.05 was considered statistically significant.

4. Results

4.1. Literature search results

From searches for individual trials, 1589 potentially eligible records were identified, of which 147 were reviewed in full text, and 18 met the inclusion criteria. Literature searches of systematic reviews or meta-analyses yielded 529 articles. After screening for titles and abstracts, 22 articles underwent full-text eligibility screening, out of which 13 RCTs were deemed relevant and were retained. After removing duplicates, data of 20 studies (3733 infants) were pooled for final meta-analysis. PRISMA flow diagram of the search process is shown in Fig. 1.

4.2. Characteristics of included studies

Characteristics of the included studies are shown in Table 1. Studies were conducted in Argentina, Canada, China, Egypt, India, Netherlands, Nepal, South Africa, Sweden, USA and Zambia. Two trials enrolled preterm babies between 30 and 36 weeks' gestation and between 34 and 36 weeks' gestation respectively (Ranjit et al., 2015; Ultee et al., 2008). Sybrich Tiemersma et al. enrolled low birth infants (weighed≤3000 g), who born between 29 to 42 weeks of gestation. Except the three studies mentioned above, the remaining others all recruited term infants (Tiemersma et al., 2015). In Rajesh Gupta et al.'s study, the pregnant women were anaemic with hemoglobin below 100 g/l and included data of infants born to human immunodeficiency virus positive mothers (Gupta and Ramji, 2002). Patrick van Rheenen's trial was conducted in a malaria endemic area (van Rheenen et al., 2007). Sample sizes for individual trials ranged from 54 to 476 participants. Follow-up duration ranged from 6 weeks to 4 years.

4.3. Risk of bias assessment

The assessments of risk of bias for each included study are shown in Table 2. Of the twenty included studies, eight (40%) were low risk of bias across all domains (Andersson et al., 2011, 2013, 2014, 2015; Ceriani Cernadas et al., 2010; Chaparro et al., 2006, 2007; Li et al., 2012). One (5%) was high risk of bias for random sequence generation (Grajeda et al., 1997). Sixteen (80%) trials described the random sequence generation process, the same amount (80%) as the trials described the methods used for allocation concealment. Because of the nature of cord clamping, neither the mother giving birth nor the midwife performing the intervention could be masked. But the majority outcomes were laboratory results recorded as objective numerical values and fourteen (70%) studies mentioned that all staff

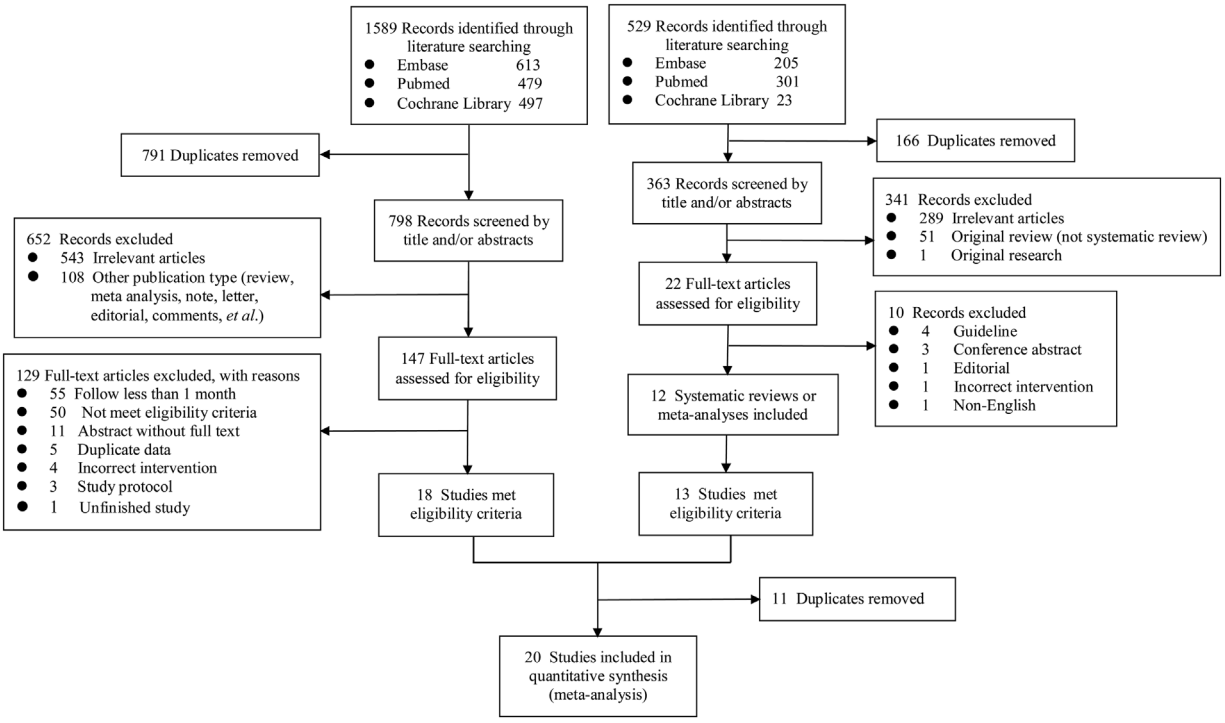


Fig. 1. PRISMA flow diagram of the search process.

Table 2
Risk of bias of included studies evaluated using the Cochrane Risk of Bias tool.

Study	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other
Lanzkowsky, 1960	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Nelson et al., 1980	Unclear	Unclear	Unclear	Low	Low	Low	Low
Grajeda et al., 1997	High	Unclear	Unclear	Low	Low	Low	Low
Geethanath et al., 1997	Low	Low	Unclear	Unclear	Low	Unclear	Low
Gupta and Ramji, 2002	Low	Low	Unclear	Unclear	Low	Unclear	Low
Chaparro et al., 2006	Low	Low	Low	Low	Low	Low	Low
Chaparro et al., 2007	Unclear	Low	Low	Low	Low	Low	Low
van Rheenen et al., 2007	Low	Low	Low	Low	Low	Low	Low
Ultee et al., 2008	Low	Low	Unclear	Low	Unclear	Unclear	Low
Ceriani Cernadas et al., 2010	Low	Low	Low	Low	Low	Low	Low
Andersson et al., 2011	Low	Low	Low	Low	Low	Low	Low
Li et al., 2012	Low	Unclear	Unclear	Unclear	Low	Low	Low
Al-Tawil et al., 2012	Unclear	Low	Unclear	Low	Low	Low	Low
Andersson et al., 2013	Low	Low	Low	Low	Low	Low	Low
Andersson et al., 2014	Low	Low	Low	Low	Low	Low	Low
Krishnan et al., 2015	Low	Low	Unclear	Unclear	Unclear	Unclear	Low
Andersson et al., 2015	Low	Low	Low	Low	Low	Low	Low
Tiemersma et al., 2015	Low	Low	Unclear	Unclear	Low	Low	Low
Ranjit et al., 2015	Low	Low	Low	Low	Low	Unclear	Low
Kc et al., 2017	Low	Low	Low	Low	Low	Low	Low

involved in collecting and analyzing data were blinded to group assignment. So we considered that the outcomes were less likely to be influenced by lack of this blinding, and rated the domain of blinding of participants and personnel as low risk of bias when it referred to relevant content on this aspect in the corresponding article. Most RCTs had a low risk of bias for incomplete data reporting (17, 85%), selective reporting (14, 70%), and other types of bias (19, 95%).

4.4. Meta-analysis results

After quality appraisal, all of the twenty studies we initially identified and included were remained. All data of the twenty RCTs were pooled for final meta-analysis (3733 infants).

4.4.1. Preterm infants

Among preterm deliveries, delayed cord clamping slightly increased hematocrit (6–10 weeks, SMD 1.09, 95% CI 0.72–1.47, $P<0.00001$, 2 trials, n = 128) and serum ferritin (6–10 weeks, SMD 0.38, 95% CI 0.01 to 0.74, $P = 0.004$, 2 trials, n = 118) (Fig. 2). C.A. Ultee et al. reported that hemoglobin was mildly a little higher in the late, compared with the early cord clamping group (10 weeks, WMD 1.10, 95% CI 0.35–1.85, $P = 0.008$, 1 trials, n = 34) (Ultee et al., 2008) (Appendix Table 2).

4.4.2. Low birth weight infants

For low birth weight infants, Sybrich Tiemersma et al. showed that delayed cord clamping was associated with lower mean corpuscular volume (2–3 months, WMD -2.00, 95% CI -3.86 to

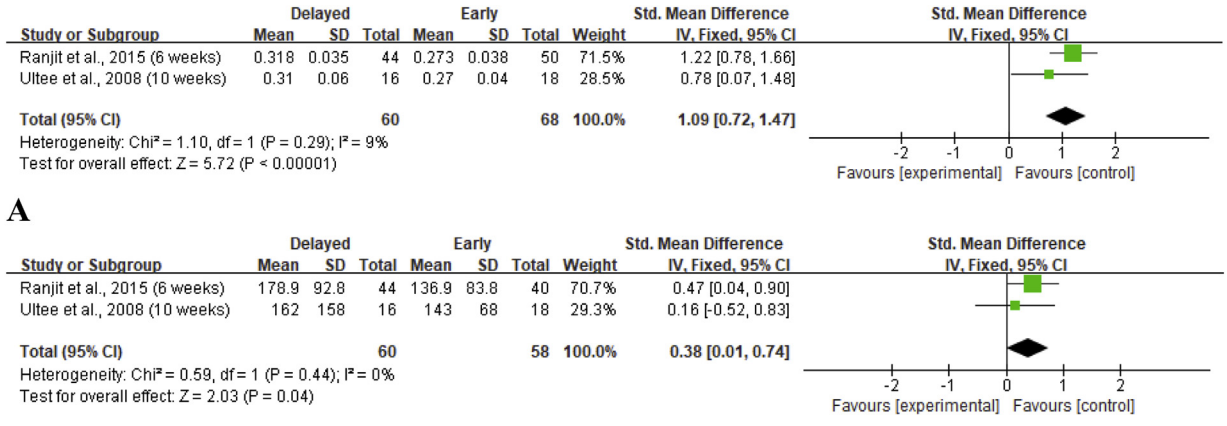
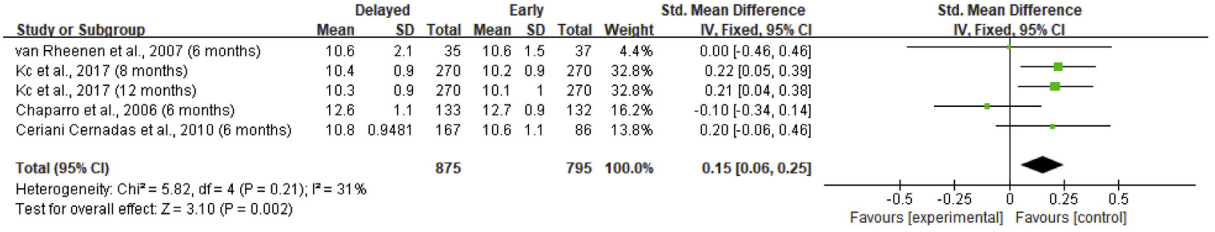


Fig. 2. Meta-analysis and forest plots for preterm infants. A. Hematocrit, 6–10 weeks. B. Serum ferritin (SF), 6–10 weeks.

-0.14, $P = 0.04$, 1 trials, n = 73) and higher weight gain (2–3 months, WMD 0.30, 95% CI 0.02 to 0.58, $P = 0.03$, 1 trials, n = 73) (Tiemersma et al., 2015) (Appendix Table 3).

4.4.3. Term infants

Results of meta analyses in term deliveries suggested that delayed cord clamping reduced the incidence of anemia after six months of age (≥6 months group: RR 0.92, 95% CI 0.87 to 0.99, $P = 0.02$, 5 trials, n = 1717), iron deficiency (< 6 months group: RR 0.13, 95% CI 0.04 to 0.44, $P = 0.0009$, 2 trials, n = 507; ≥6 months group: RR 0.55, 95% CI 0.43 to 0.72, $P<0.00001$, 3 trials, n = 1071) and iron deficiency anemia (4–12 months, RR 0.68, 95% CI 0.49 to 0.94, $P = 0.02$, 6 trials, n = 1799) (Figs. 3 and 5). Delayed cord clamping also increased the levels of mean corpuscular volume before six months of age (< 6 months group: SMD 0.33, 95% CI 0.15 to 0.51, $P = 0.0003$, 3 trials, n = 661), hemoglobin after six months of age (≥6 months group: SMD 0.15, 95% CI 0.06 to 0.25, $P = 0.002$, 5 trials, n = 1670), serum iron (2–4 months, SMD 0.23, 95% CI 0.06 to 0.40, $P = 0.007$, 3 trials, n = 570), total body iron (4–6 months, SMD 0.45, 95% CI 0.29 to 0.62, $P<0.00001$, 2 trials, n = 578), serum ferritin (< 6 months group: SMD 1.22, 95% CI 0.47–1.98, $P = 0.001$, 7 trials, n = 975; ≥6 months group: SMD 2.37, 95% CI 0.99–3.76, $P = 0.0008$, 5 trials, n = 1867) and transferrin saturation (2–12 months, SMD 1.05, 95% CI 0.53–1.57, $P<0.0001$, 4 trials, n = 874) (Figs. 3 and 4). Ola Andersson et al. found that reticulocyte hemoglobin (4 months, WMD 0.70, 95% CI 0.28–1.12, $P = 0.001$, 1 trials, n = 343) and reticulocyte count (4 months, WMD 3.00, 95% CI 0.67–5.33, $P = 0.01$, 1 trials, n = 343) were higher for those allocated to delayed cord clamping (Andersson et al., 2011). In addition, delayed cord clamping increased body iron (6 months, WMD 20.80, 95% CI 6.39–35.13, $P = 0.001$, 1 trials, n = 235), stored iron (6 months, WMD 19.90, 95% CI 7.67–32.13, $P = 0.0001$, 1 trials, n = 235) and serum bilirubin (3–5 months, WMD 2.02, 95% CI 1.59–2.45, $P<0.00001$, 1 trials, n = 160) (Al-Tawil et al., 2012; Chaparro et al., 2006). Data on



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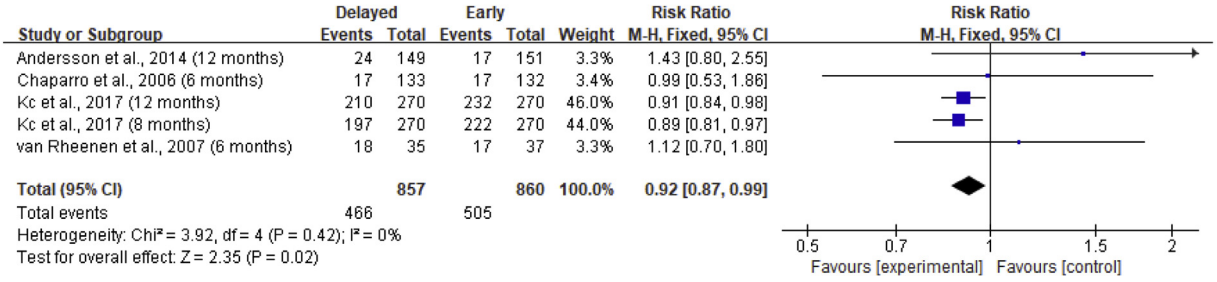

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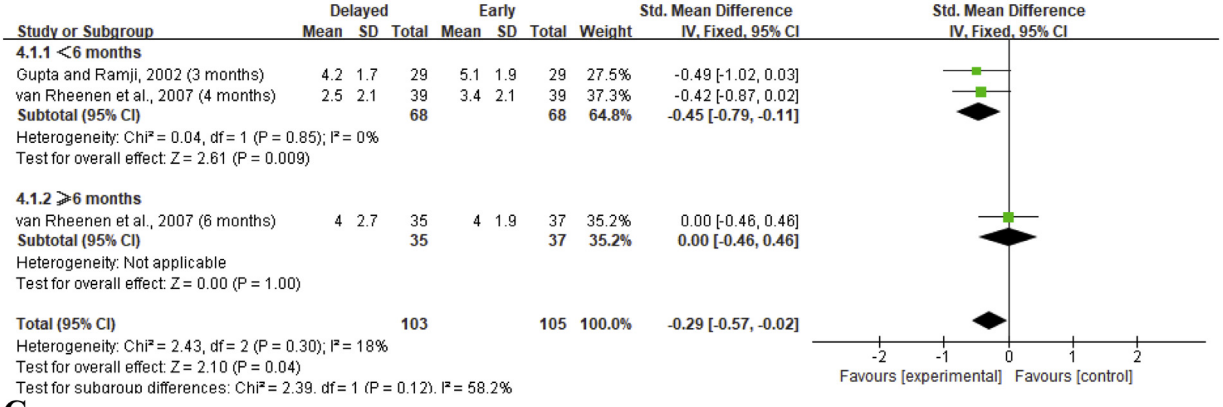
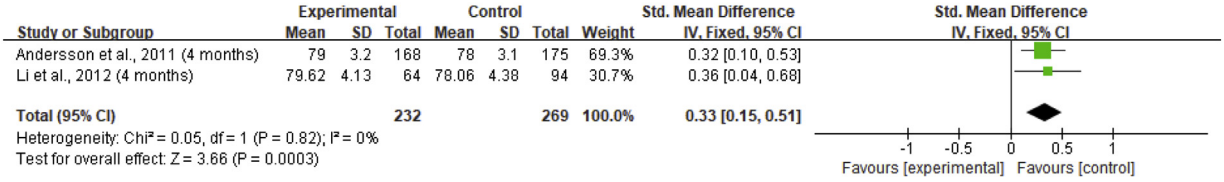
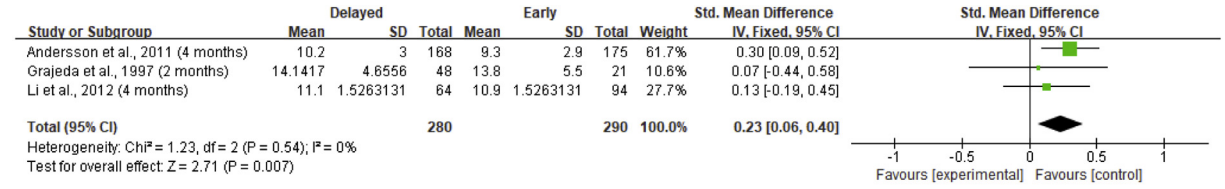


C

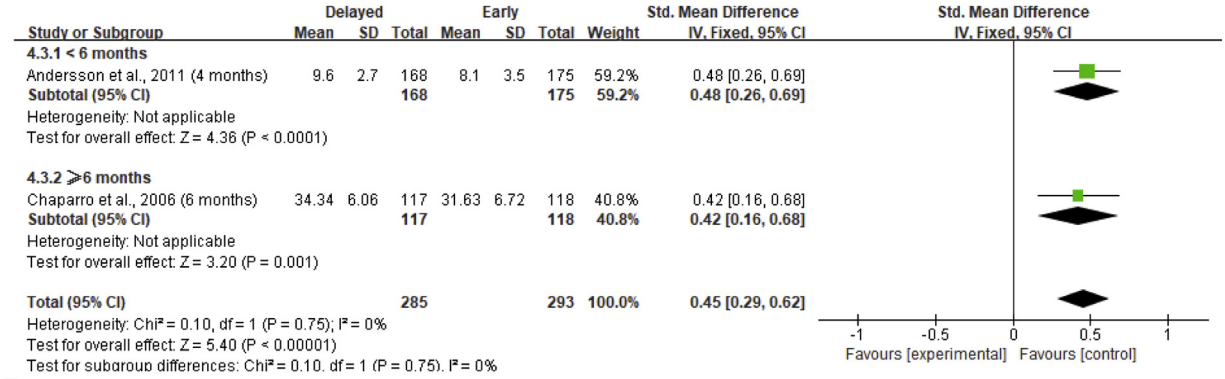


D

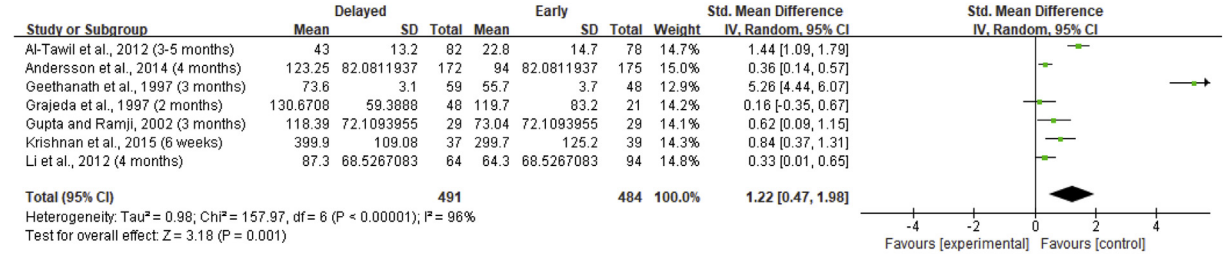
Fig. 3. Meta-analysis and forest plots for hematologic outcomes in term infants. A. Hemoglobin (Hb), ≥6 months. B. Anemia, ≥6 months. C. Hb change from baseline, 4–6 months. D. Mean corpuscular volume (MCV), <6 months.



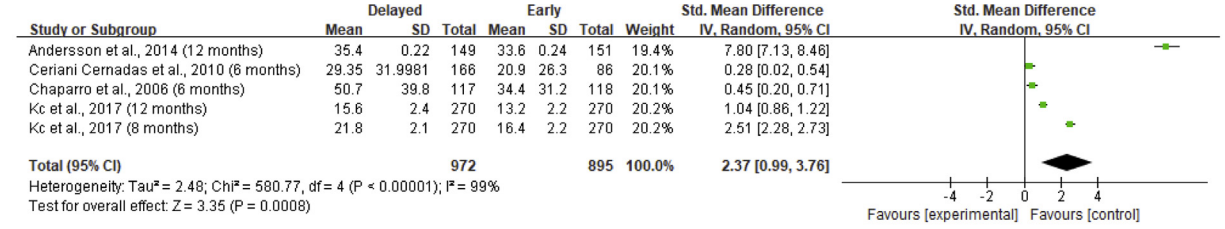
A



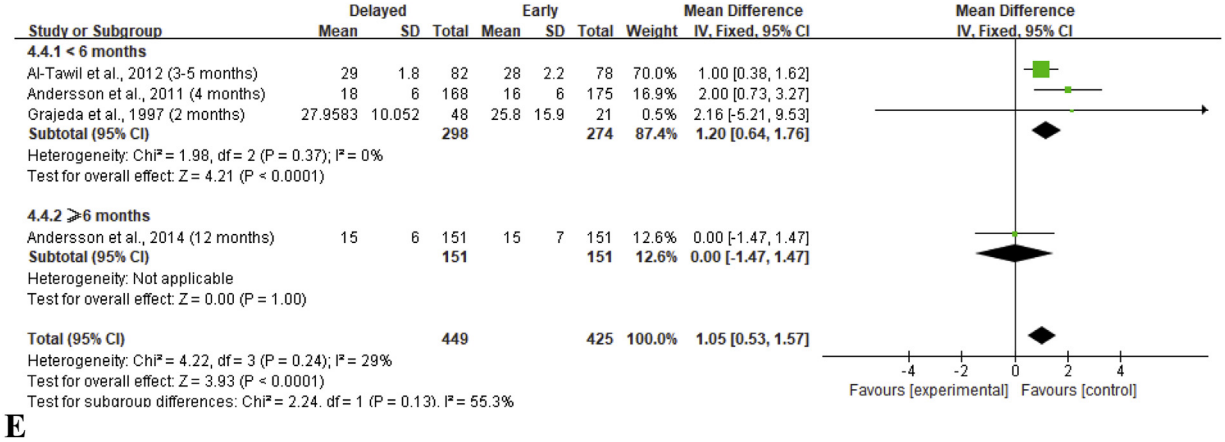
B



C



D



E

Fig. 4. Meta-analysis and forest plots for continuous iron outcomes in term infants. A. Serum iron, 2–4 months. B. Total body iron, 4–6 months. C. Serum ferritin, < 6 months. D. Serum ferritin, ≥ 6 months. E. Transferrin saturation (TS), 2–12 months.

the Meta-analysis of other variables did not show significant differences between delayed cord clamping and early cord clamping (Appendix Table 4. Appendix Figure 1–22).

After excluding Andersson et al.'s (2011) study from the analysis of delayed cord clamping on hemoglobin of term infants after 6 months of age, the heterogeneity (I^2) changed from 69% to 31% and

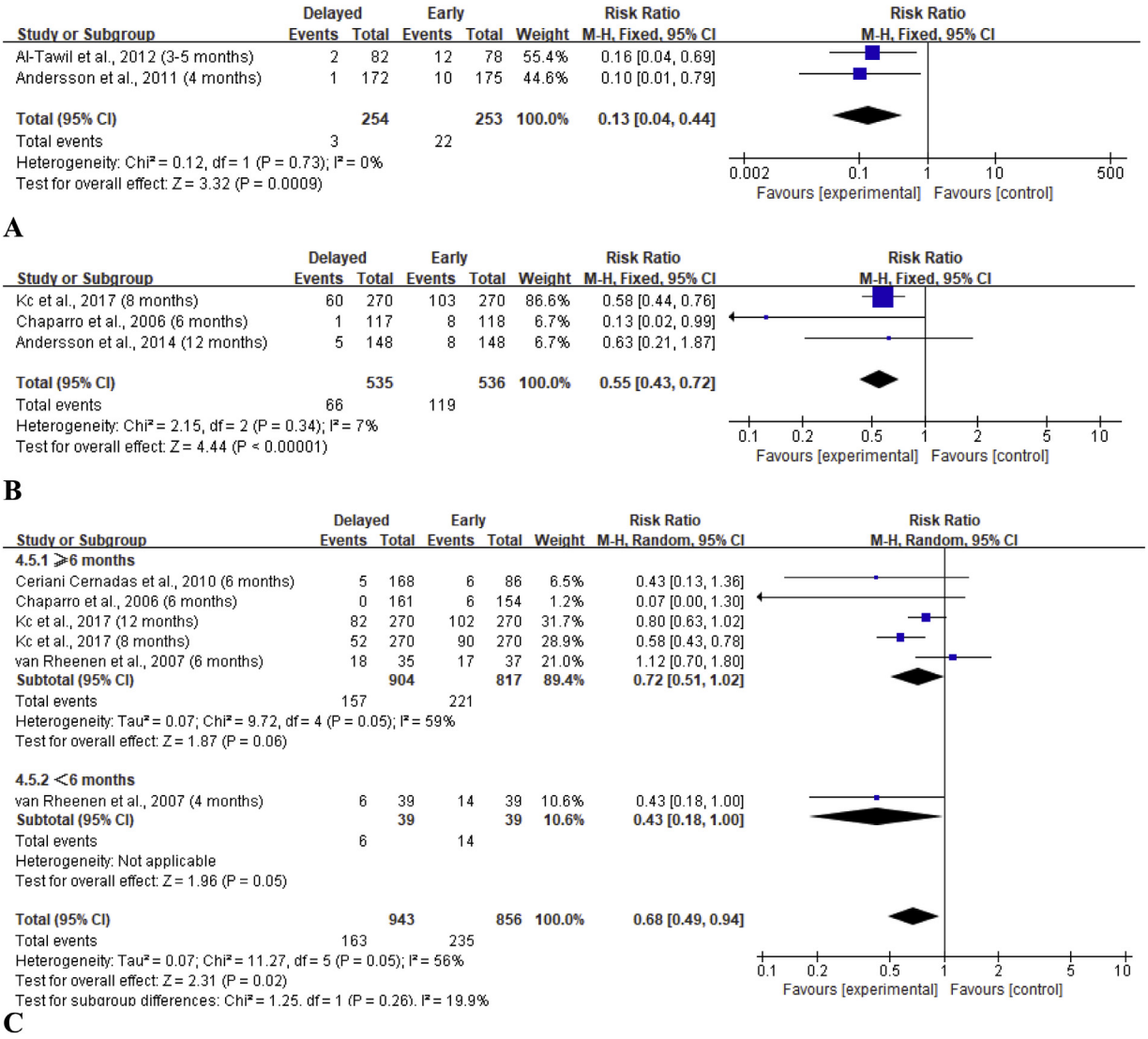


Fig. 5. Meta-analysis and forest plots for dichotomous iron outcomes in term infants. A. Iron deficiency, < 6 months. B. Iron deficiency, ≥ 6 months. C. Iron deficiency anemia, 4–12 months.

the pooled effect size favored the delayed cord clamping group. Besides, when removing Al-Tawil et al.'s (2012) and Kc et al.'s (2017) (data on 12 month) studies from analyses of delayed cord clamping on mean corpuscular volume (< 6 months) and iron deficiency (≥6 months) on term infants respectively, heterogeneity (I^2) reduced from level of above 50% to less than 10% and the effects observed in the primary analyses were not changed significantly. Whereas sensitivity analyses for other variables showed no substantial changes.

In theory, publication bias should be assessed by visual inspection of funnel plots when more than ten studies were pooled. However, no single outcome reaches this requirement, and thus no publication bias is presented.

5. Discussion

As for the long-term effects of delayed cord clamping on preterm infants, only two out of twenty RCTs were identified, with their results indicating that delayed cord clamping slightly increased hematocrit and serum ferritin between six and ten weeks old with no heterogeneity in the analysis of these results (128 and 118 infants respectively). In addition, no evidence of longer term effects of delayed cord clamping on preterm infants is identified. As described by Rabe et al., higher iron or ferritin status at 4–6 months of age in preterm infants has not been reported due to the high iatrogenic blood loss during the hospital stay after birth for this patient group (Rabe et al., 2009).

Among term deliveries, delayed cord clamping lowered the incidence of anemia (≥6 months), iron deficiency (<6 months, ≥6 months) and iron deficiency anemia (4–12 months) as well as raised the levels of hemoglobin (≥6 months), mean corpuscular volume (<6 months), serum iron (1–5 months), total body iron (4–6 months), serum ferritin (<6 months, ≥6 months) and transferrin saturation (2–12 months).

Consistent with previous results, this systematic review and meta-analysis shows a significant difference in ferritin levels of both preterm and term infants in favour of delayed cord clamping (Hutton and Hassan, 2007; Mathew, 2011; McDonald and Middleton, 2008; van Rheenen and Brabin, 2004). Furthermore, delayed clamping was associated with better iron status in infants, which is measured by indicators of iron status such as higher serum iron, total body iron and transferrin saturation, as well as reduced iron deficiency and iron deficiency anemia. This also

agrees with the results of previous studies which provides a paucity of evidence concerning long-term effects of delayed cord clamping (Hutton and Hassan, 2007; McDonald and Middleton, 2008; McDonald et al., 2013; van Rheenen and Brabin, 2004). Despite the fact that red cell mass increases significantly during mid-infancy, which slightly influences the levels of iron status indicators, the potential benefits of delayed cord clamping would be more apparent in older infants. The availability of follow-up data enhances clinical implications for improving iron status. This is of particular importance for countries and regions who suffered from relatively higher prevalence rate of iron deficiency during infancy and childhood, because the consequences of infant morbidity associated with iron deficiency extend to later neuro-developmental deficits and increased vulnerability to infection, which exerts a substantial economic burden (Al-Tawil et al., 2012; Andersson et al., 2015). A number of animal models have demonstrated that iron is essential for normal neurodevelopment, since iron deficiency affects neuronal energy metabolism, the metabolism of neurotransmitters, myelination, and memory function (Baker et al., 2010). Moreover, iron deficiency may increase susceptibility to infection as iron is required for normal immune function including bactericidal activity of macrophages of peroxide- and nitrous oxide-generating cellular enzymes1 and also for T-cell numbers and function (Jonker and Boele van Hensbroek, 2014).

Although diet such as iron-fortified formulas or milk plays a pivotal role in prevention of iron deficiency, from a pragmatic point of view, it would be much easier to implement the policy of delayed cord clamping than to improve dietary intakes in the general population. In addition, three studies suggested that breast feeding did not differ between delayed cord clamping and early cord clamping groups (Andersson et al., 2011, 2015; Grajeda et al., 1997). In Ola Andersson et al.'s study, no differences were found among the exclusively breastfed infants at 4 months old, who were supposed to be more likely to have iron deficiency (Andersson et al., 2011). Even though, the consumption of infant foods fortified with iron and iron supplements showed differences between delayed cord clamping and early cord clamping groups at different age stages in Camila M Chaparro et al.'s study, the mechanism of regulation on iron absorption might be mature after six months old, and thus iron status may not be significantly affected by diet (Chaparro et al., 2006). However, before this month of age, the high intake of dietary iron may mask differences of iron status between two groups.

According to previous studies, initial hematocrit at birth was reported to be higher in both preterm and term neonates in the delayed cord clamping group compared with early cord clamping (Backes et al., 2014; Fogarty et al., 2018; Hutton and Hassan, 2007; Mathew, 2011; Nesheli et al., 2014; van Rheenen and Brabin, 2004). Whereas delayed cord clamping can lead to improved follow-up hematocrit only in preterm infants but not term infants. This finding is consistent with results of Joseph L Mathew's systematic review of randomized controlled trials (Mathew, 2011). Perhaps preterm infants are more prone to be compromised and need additional resuscitative efforts, and delayed cord clamping may facilitate the process of physiological transition to extrauterine life (Bhatt et al., 2013). Our results illustrates that mean corpuscular volume increases only before six months of age, which is somewhat beyond our comprehension and further verification and exploration is still needed.

Small difference in hemoglobin level was found between two groups after 6 months of age, meanwhile delayed cord clamping reduced the risk of anemia in term infants after six months of age. These results were similar to previous studies, in spite of a few inconsistent findings (Ghavam et al., 2014; Hutton and Hassan, 2007; Mathew, 2011; McDonald et al., 2013; van Rheenen and Brabin, 2004). Probably, the improved iron stores before six months old are hypothesized to protect against anemia later in infancy (Kc et al., 2017). Besides, according to Chaparro et al.'s study, hemoglobin is normally not affected until iron stores are depleted (Chaparro et al., 2006). In addition, van Rheenen and Brabin (2004) pointed out that maintaining higher hemoglobin levels in the newborn period may improve neurodevelopmental outcome (Ghavam et al., 2014), which indicates that delayed cord clamping may have neurodevelopmental benefits. Whereas the limited data has not yet provided fully conclusive evidence on the effects of delayed cord clamping on neurodevelopment, especially long-term influences, and this in turn necessitates further research and exploration.

Although all long-term effects of delayed cord clamping on infants after neonatal period were included and analyzed in this study, the majority outcomes of statistical significance focus on hematological and iron status, which are of less clinical significance than infant mortality and morbidity. There was no RCTs mentioning and measuring infant mortality, while numerous medical and financial efforts to reduce infant mortality rate have been made at both national and international levels during the last few decades simple because it is not only an indicator of the health status and the socioeconomic condition of children and of a population as a whole but also a sensitive indicator of the quality of and access to health care services (Finkelstein et al., 2016). Besides, only three RCTs investigated and reported the long-term effects of delayed cord clamping on a few infants' diseases or their corresponding clinical symptoms (255–615 infants). Nonetheless, all of these outcomes failed to reach statistical significance between two groups, which could be partly attributed to the small sample sizes or the relatively low incidence rates.

This systematic review and meta-analysis provides the first comprehensive evaluation of the long-term effects of delayed cord clamping on infants after neonatal period. Our study includes trials of randomized design, so it controls for confounding factors which may influence infant hematological and iron status, including obstetric factors, maternal hematological and iron status, infant feeding practices and maternal or infant dietary supplement of iron. The findings suggest several hematological and iron benefits for infants in the long run and provide further verification of the practice of delayed cord clamping. However, the changes of hematological and iron indicators, even though statistically significant, are relatively small and not significant enough to cause clinically significant alteration. This is partly because of the small amount of study participants and insufficiency of evidence for long-term effects of delayed cord clamping on infants, and thus more large-scale randomized controlled trials are needed in the future, especially those on preterm and low birth weight infants, as well as long-term effects of neurodevelopment, immune function, host defense and repair (Committee on Obstetric Practice, 2017).

According to the results of this study, delayed cord clamping should be performed during the provision of essential neonatal care for all births, including preterm, term and low birthweight deliveries. Although the practice of delayed cord clamping is recommended by many international and national organizations and clinical practice guidelines, except for Japan Academy of Midwifery (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017; Chinese Maternal and Child Health Association, 2018; International Confederation of Midwives, 2017; Leduc et al., 2009; Mariko et al., 2018; National Institute for Health and Clinical Excellence, 2017; Queensland Government, 2017; Royal College of Midwives, 2016; Sri Lanka College of Obstetricians and Gynaecologists, 2013; WHO, 2014, 2018), the recommended times for umbilical cord clamping varies, ranging from 30 s to 5 min after birth. We suggest that umbilical cord should be clamped no earlier than 1 min after birth or after the cord stopped pulsating or after placental separation, which

provide further evidence for the optimal time of umbilical cord clamping, based on findings of our systematic review and meta-analysis. Among the three optional clamping times, delayed clamping the umbilical cord at least 1 min after birth necessitates midwives additionally estimating or calculating the time after fetal expulsion, with the latter to some extent elaborating their routine maternity and newborn care with trivial details. Nonetheless, clamping the umbilical cord after the cord stopped pulsating would be easier to operate precisely, since the signs of completed perfusion are simpler to identify. After delivery, the infant should be placed skin-to-skin on the mother's abdomen or in her arms, dried and covered with a warm blanket, and the umbilical cord should be leaved intact until it becomes pale or white, flat and look obviously emptied. Moreover, the guideline of intrapartum care for healthy women and babies developed by the National Institute for Health and Clinical Excellence in the United Kingdom suggests to clamp the cord before 5 min in order to perform controlled cord traction as part of active management, whereas the time for placenta delivery ranges from 5 to 30 min (National Institute for Health and Clinical Excellence, 2017). Thus clamping the umbilical cord after placental separation is controversial and further evidence is still needed.

This study has several limitations. First, despite several subgroups of interest, no analysis is performed on most of them owing to the lack of reported data or relatively few trials with reported data. This could also be attributed to previous findings that although gravity affects the amount of placental transfusion that an infant receives, positioning the infant above or below the placenta does not appear to influence infant outcome (Kluckow and Hooper, 2015; Mercer and Erickson-Owens, 2012). Besides, no effect of uterotonic drug administration during birth on the amount of placental transfusion has been found (Mercer and Erickson-Owens, 2012). Second, the optimal timing of umbilical cord clamping is still not yet determined, and we established the definition of delayed cord clamping and early cord clamping as well as the selection criteria of studies based on the guidelines developed by WHO and International Confederation of Midwives (International Confederation of Midwives, 2017; WHO, 2014, 2018). This may lead to the omission of many trials that investigated the long-term effects of delayed cord clamping on infants as well, and the inclusion of them may alter the final results. Third, the quality of some RCTs is relatively low, since risk of bias is unclear or unknown, especially those published more than thirty years ago. Fourth, we divided infants' data into two groups and set the six months of age as the cut-off point when synthesizing and analyzing follow-up data, instead of providing all results at every month, since there were not enough data available that would allow for more detailed and elaborate findings. Finally, data from different follow-up duration as well as from different umbilical cord clamping times in both experimental (delayed cord clamping) and control (early cord clamping) groups were combined and analyzed collectively, which in turn may make our findings of meta analyses less accurate and effective.

6. Conclusions

This study provides the first thorough evaluation of long-term effects of delayed cord clamping on infants after neonatal period and arrives at a conclusion that delayed cord clamping modestly improved hematological and iron status of both preterm and term infants after neonatal period. This affords cogent evidence on the implementation 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. In the future, more large-scale randomized controlled trials are needed to further validate other significant long-term effects.

Conflict of interests

The authors report no conflict of interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijnurstu.2019.01.012.

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