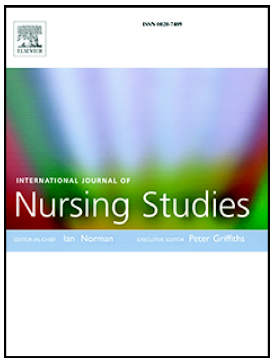

Deferred cord clamping to improve neonatal blood values. A systematic review and meta-analysis

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Title

Deferred cord clamping to improve neonatal blood values. A systematic review and meta-analysis

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Abstract

Background: Practices related to umbilical cord clamping at birth should be evidence-based. Deferred cord clamping, compared to immediate cord clamping, shows benefits for preterm neonates but this may also apply to healthy term neonates. Different blood sampling techniques are used to measure effect of deferred and immediate cord clamping.
Objective: To assess the statistical and effect size differences between blood biomarkers from umbilical cord and capillary blood samples of healthy term neonates following either immediate or deferred cord clamping.
Design: Systematic review and meta-analysis.
Methods: The databases PubMed, Medline, CENTRAL, CINAHL and EMBASE were systematically searched. We included studies with a randomised clinical trial design comparing deferred and immediate cord clamping among healthy term neonates born by a spontaneous vaginal birth, reporting on blood biomarkers. Studies including caesarean births and premature births/neonates were excluded. Study attributes, sampling technique, blood biomarkers, mean differences, and standard deviations were extracted. The standardised mean differences (SMD) and sampling errors were calculated for effect size estimation. Meta-analyses were performed if ≥2 studies reported the same outcome using RevMan 5. Subgroup analyses distinguished effects from umbilical cord and capillary blood samples. Moderator tests and publication bias analyses were performed using JASP.
Results: Thirteen studies were included for analysis. The biomarkers haematocrit, haemoglobin, and bilirubin were reported in ≥2 studies and thus eligible for pooling. No differences were found in haemoglobin (SMD 0.05, 95%CI -0.73 to 0.82) or bilirubin values (SMD 0.03, 95%CI -0.24 to 0.31) between umbilical cord blood samples collected after deferred or immediate cord clamping. Deferred cord clamping led to lower haematocrit values (SMD -0.3, 95%CI -0.53 to -0.07). Higher haematocrit (SMD 0.67, 95%CI 0.37 to 0.97) and haemoglobin values (SMD 0.75, 95%CI 0.42 to 1.09) from capillary blood samples, collected 2 to 72 hours postpartum, showed when cord clamping was deferred. No effect was found on bilirubin values (SMD 0.13, 95%CI -0.09 to 0.36) irrespective of the sampling technique.

Conclusions: Blood collected after deferred umbilical cord clamping showed increased haemoglobin and haematocrit values up to 72 hours after birth, opposed to bilirubin values. Clinical evaluation of blood biomarkers from the umbilical cord shows different values compared to capillary blood. Sampling time and technique therefore seem essential in estimating the effects of deferred cord clamping.

Tweetable abstract: This systematic review and meta-analysis show that sampling time and technique are essential in estimating the effects of deferred cord clamping

Keywords

Bilirubin; Haematocrit; Haemoglobin; Meta-analysis; Neonate; Obstetrics; Umbilical Cord Clamping; Systematic Review

Contribution of the Paper

What is already known

- The timing of umbilical cord clamping after birth influences neonatal blood supply and nutrient transfer.
- Deferred cord clamping is associated with health benefits for preterm neonates, including improved blood values.
- Concerns exist that deferred cord clamping increases the risk of jaundice.

What this paper adds

- Deferred cord clamping is associated with improved blood biomarkers of healthy neonates.
- There is no evidence of associations between deferred cord clamping and the increased risk of jaundice.
- The clinical evaluation of blood biomarkers from the umbilical cord differs from capillary blood, emphasising the importance of sampling time and technique in estimating the effects of cord clamping based on blood biomarkers.

Background

The first moments after birth are crucial for neonates because they must adapt from intra- to extra-uterine life. Immediately after birth, routine active management practices such as skin-to-skin contact, neonatal health assessments (e.g., Apgar), management of the third stage of labour, and umbilical cord clamping (UCC) are carried out. Because of the routine nature of these procedures, a critical reflection is pertinent to ensure the quality of intrapartum/early postpartum care.

UCC is categorised as deferred cord clamping (DCC) and immediate cord clamping (ICC). In terms of terminology, deferred and immediate are regarded as less normative and therefore more neutral, replacing ‘delayed’ and ‘early’ (1). Terminology, however, lacks a consistent definition of or guidance on the exact timing of immediate and/or deferred cord clamping and therefore varies (2): ICC involves cord clamping within the first 15 seconds after birth (3, 4) while DCC involves maintaining the connection between the neonate and the placenta for more than 30 seconds, one to two minutes, as recommended by the World Health Organization (WHO) (3), or until the cord ceases to pulse (3-5).

DCC is associated with clinically significant health benefits, particularly for preterm neonates (6). These benefits encompass enhancements in blood volume, cell count, and blood components such as ferritin and haemoglobin levels (7). DCC has shown promises in reducing the risks of necrotising enterocolitis and intraventricular haemorrhage in preterm neonates (5, 8). However, deferring UCC could potentially increase the risk of jaundice due to elevated bilirubin levels, providing a rationale for ICC practices (9). Numerous studies have highlighted the advantages of DCC in preterm neonates, demonstrating its potential to enhance health outcomes (10). This health benefit might also be applicable to healthy term neonates born after a low-risk pregnancy, the extended blood flow from the placenta could confer benefits to the term neonate (11).

Evaluating the timing of UCC seems crucial because of the different attitudes towards the timing of UCC that contribute to differences in practices, recommendations, and methods of evaluation (2, 12, 13). Considering the biomarkers from blood collected using different sampling techniques for rigorous analysis and data interpretation might be of value to evaluate neonatal health at birth and postpartum, in order to inform practice (14). Neonatal blood biomarkers collected at three to six months postpartum, respectively, did not show statistically significantly differences between immediate and deferred cord clamping (11). However, it can be anticipated that blood samples from the umbilical cord or from neonatal capillary blood may show different biomarker values due to their composition and physiological functions (15, 16). The difference in blood biomarker values from umbilical cord and from neonatal capillary blood samples after birth are yet unknown but might be critical factors for the clinical evaluation of the timing of UCC (14). The full extent or degree of the impact or benefits of DCC is not well understood or quantified. So far, one meta-analysis has been conducted to estimate the effect of DCC on healthy neonates being born at term (11). However, this review pooled data from cases born spontaneously and vaginally and from cases born by caesarean. Moreover, the sampling technique was not considered.

This review aimed to assess the impact of DCC and ICC on blood biomarkers from healthy neonates born at term by conducting a systematic review and meta-analysis. The objectives were to 1) compare the effect from DCC versus ICC on blood biomarkers in umbilical cord and neonatal capillary blood samples, 2) quantify the magnitude of the effect of DCC on neonates' blood profiles; 3) investigate if any differences of impact are due to confounding factors or potential publication bias. By addressing these objectives, this review will contribute to a deeper understanding of the implications of DCC for neonatal health and

inform evidence-based intrapartum and early postpartum care practices.

Methodology

A systematic review and meta-analysis were performed (17). The intervention of interest was the UCC timing, which were categorised into two groups: DCC and ICC. To address variations in UCC timing across studies, the timing as specified by the authors in their methods section for defining DCC and ICC was adopted.

The outcome of interest was neonatal blood biomarkers such as haematocrit, bilirubin, ferritin, transferrin, blood cell counts, and haemoglobin collected from the umbilical cord and from neonatal capillary blood. This systematic review was conducted as part of updating the Belgian low-risk intrapartum care guideline, not requiring PROSPERO registration.

Literature search and selection process

The literature search was conducted (August 2023) in the following databases: PubMed, Medline, CENTRAL, CINAHL and EMBASE, according to the search strategy described in supplemental file 1, without setting a date limit. The low-risk intrapartum care guideline format instructed not to include grey literature. Two authors, XX and XX, conducted the selection process independently. The authors screened the reference lists of the included studies to ensure relevant papers were included. When disagreement occurred, XX resolved this through discussing paper eligibility and a subsequent mutual thorough examination of the full text. The study screening and selection of retrieved titles was done according to PRISMA and the Cochrane Handbook for Systematic Reviews of Interventions guidelines, using the Rayyan application (17-19).

Eligibility criteria

Studies comparing DCC and ICC in randomised controlled trials (RCTs) and reporting neonatal blood biomarker values collected within the first week post-birth were included. If studies used different cut-off values for ICC and DCC, they were still included and extracted as such. Studies including neonates being born at term after a spontaneous vaginal birth (i.e., neonates born without instrumental/surgical procedures such as forceps, ventouse or caesarean section) to mothers classified by the authors of the respective studies as low-risk, and identified as healthy (e.g., no history of smoking, pre-eclampsia, gestational diabetes, ante/postpartum haemorrhage) were eligible. Studies that did not stratify their data according to method of birth were excluded, as were studies with a mixed cohort of high and low-risk maternal cases and/or births. No language restrictions were applied. Studies with incomplete data, those of which full-text versions were unavailable or not directly attainable from the authors were excluded.

Risk of bias assessment

The methodological quality of the included studies was assessed using the Risk of Bias-2 tool for RCTs from the Cochrane Handbook for Systematic Reviews of Interventions (20). The results were reported using the Cochrane Revman© 5 tools to produce an overview per study and summary graphs.

Data abstraction

Data were abstracted by XX and verified by XX and XX. The study characteristics, the

number of participants per arm, outcome measures, sampling time and method, mean estimates, standard deviations (SD) and moderators were extracted. Most of the studies used different scales at the various time points as continuous outcomes (levels of specific blood biomarkers). The authors decided to calculate the standardised mean difference (SMD) and sampling error (SE) from the extracted means and SDs rather than the absolute mean difference in blood units (such as g/dL). The rationale being that the SMD allows standardising the effect estimate between studies, which can be used for data pooling and calculating the effect size and magnitude between two interventions rather than focusing only on statistical differences in mean values (21). Additionally, an SMD allows for quantifying the difference between the groups and estimating the magnitude of the effect, e.g., the effect size. The effect size, reported as SMD, can be interpreted as a small, moderate or large effect using the following cut-off values: 0.20-0.50 for a small effect, 0.50-0.80 for a moderate effect, and ≥0.80 for a large effect (21, 22).

Statistical analysis

A meta-analysis was conducted when at least two papers ($K \geq 2$) reported the same outcome, i.e., biomarker. If a study reported the same biomarkers over multiple periods (e.g., after 24 hours, 48 hours, or one week postpartum), only the first time point was included in the meta-analysis to prevent data doubling. There was insufficient data to perform a time series analysis. We pooled the overall effect of DCC and ICC and produced subgroup analyses based on the sampling technique: umbilical cord blood and neonatal capillary blood sampling. The random effect models calculated the pooled SMD with a 95% confidence interval (95% CI). Heterogeneity was tested and reported using the following I^2 cut-off values: high = >75%; moderate = 50-74%; low = 25-49%; and none = <25%.

Instead of a sensitivity analysis, we tested for moderators that may influence the robustness of the data. Pooled analyses with an I^2 value >50% were subjected to a moderator test. We identified several moderators that may affect the heterogeneity and effect size. The neonatal birth weight was regarded as a moderator as the average birth weight varies across regions and countries (23). UCC timing was included as a moderator due to the differences between DCC and ICC timing in practice (3-5). Maternal age was deemed relevant for moderation, considering the regional fluctuations in maternal age at labour and birth (24). Furthermore, because of the suggested correlation between DCC and oxytocin administration, this was regarded as a potential moderator (25).

Publication bias

Publication bias was considered present if the funnel plot displayed an asymmetry and when the p-value was <0.05 according to either the Rank correlation test or Egger's test. An additional trim-and-fill analysis was conducted to assess the potential impact of publication bias on the pooled effect size. The trim-and-fill analysis was performed to inform on the assumption of missing studies, how they would impact the overall effect and in favour of either DCC or ICC. This analysis was performed regardless of the number of studies included due to its nonparametric nature (26).

All analyses were considered statistically significant at an alpha level of less than 5%. The meta-analyses and forest plots were conducted using Review Manager© Version 5.4. (RevMan 5.4 [Computer program]. The Cochrane Collaboration, 2020). For moderators' effect and publication bias analyses JASP© was used (JASP Team (2022) JASP (Version

0.16.3) [Computer software]).

Results

Study selection and characteristics

The literature search resulted in 1635 papers, of which 15 (27-41) met the eligibility criteria based on full text that were included for analysis. The screening and selection of studies are shown in the PRISMA flowchart (Figure 1) (42).

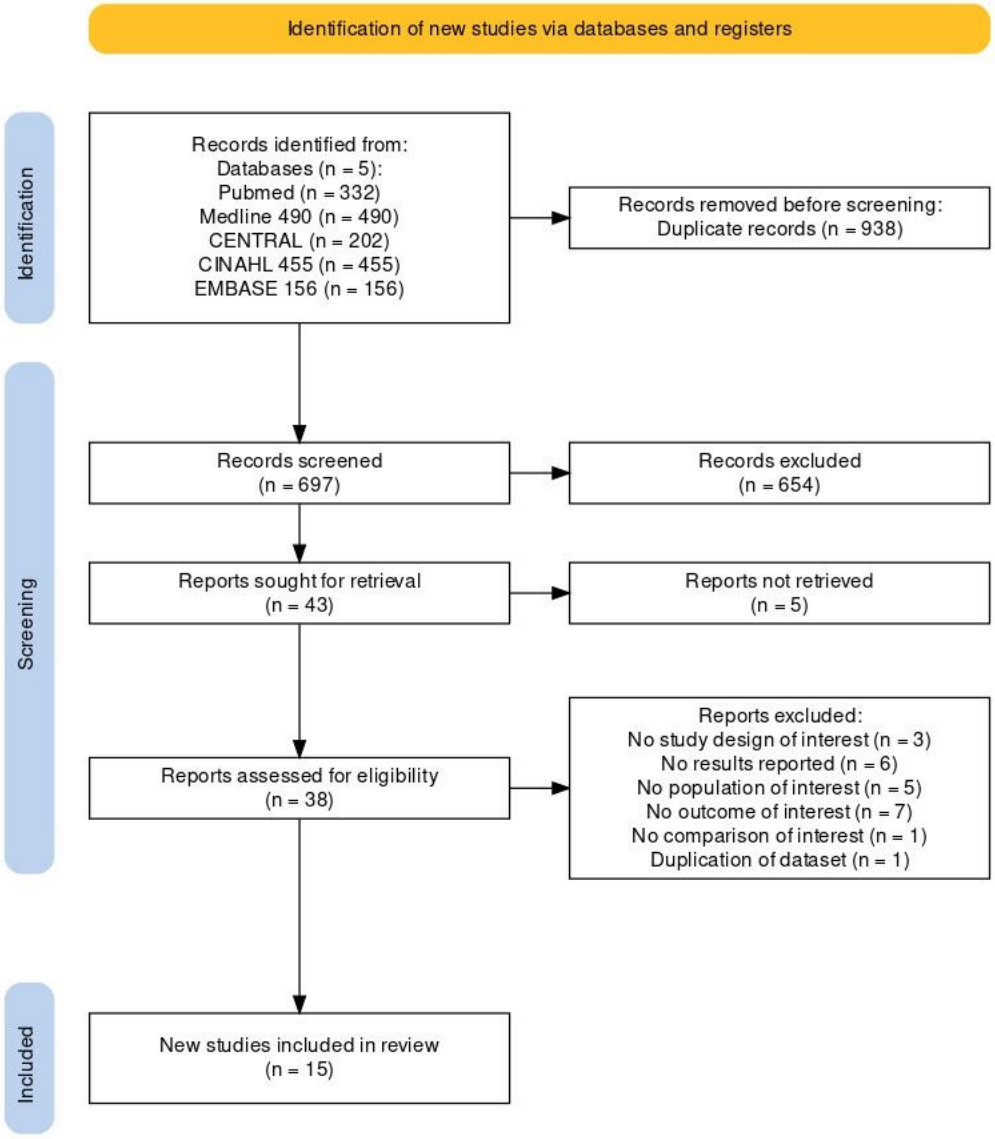


Figure 1: Prisma flowchart

Risk of bias of included studies

The overall risk of bias was evaluated as moderate. Because of the nature of the intervention, it was impossible to blind personnel but therefore evaluated as high risk. However, the laboratory staff who analysed the blood samples were blinded to the intervention, apart from the fact they knew whether it was a cord or capillary sample. No detection bias could have occurred due to the objective measure of biomarkers. There were no self-reported outcomes and therefore this field was left blank. A complete overview of the

risk of bias per study and the risk of bias summary are reported in Supplementary File 3. Risk of bias assessment, Figures 1 and 2.

Study characteristics

The studies included 1052 participants in the DCC and 1021 participants in the ICC arm. DCC timing varied from 60 to over 300 seconds (>5 minutes) or until the cord ceased pulsing. ICC timing varied from <10 seconds to 30 seconds. The umbilical cord blood samples were collected following the clamping and cutting of the cord. Capillary blood sampling timing varied between 2 and 48 hours after UCC. The overview of included studies, study and sample characteristics, outcomes, sampling time and technique and effect sizes are reported in Table 1. We pooled the following biomarkers based on $K \geq 2$: haemoglobin, haematocrit, and bilirubin, reported in the forest plots. Singular data on transferrin, ferritin, red blood cells, and blood values can be found in Table 1.

Table 1: Study characteristics and data overview.

Author, year, reference, country	Study characteristics	Sample characteristics	Outcome	Sampling time (h)	Sampling technique	Mean DCC	SD DCC	Mean ICC	SD ICC	SMD	SE
Al-Tawil, 2012 (27), Egypt	Total N = 180 N DCC = 90 N ICC = 90 Timing DCC (s) = 180 Timing ICC (s) = <15 Oxytocin use: no/not reported	DCC group: Mean age mother = 25 y Mean birth weight child (g) = 3348 ICC group: Mean age mother = 26 y Mean birth weight child (g) = 3110	Haemoglobin	24h	Capillary	19.6	3.8	16.8	2.9	0.82	0.15
			Haematocrit	24h	Capillary	55.8	5.1	51.4	3.8	0.97	0.15
			Ferritin	24h	Capillary	213	81	202	76	0.14	0.14
			Bilirubin	24h	Capillary	3.5	1	3.1	0.8	0.44	0.15
Andersson, 2011 (28), Sweden,	Total N = 328 N DCC = 168 N ICC = 160 Timing DCC (s) = >180 Timing ICC (s) = <10 Oxytocin use = yes	DCC group: Mean age mother = NR Mean birth weight child (g) = 3620 ICC group: Mean age mother = NR Mean birth weight child (g) = 3530	Haemoglobin	48h	Capillary	18.9	1.7	17.5	1.9	0.77	0.11
			Transferrin	48h	Capillary	1.76	0.22	1.76	0.26	0.0	0.11
Chaparro, 2006 (38), Mexico	Total N = 358 N DCC = 187 N ICC = 171 Timing DCC (s) = 120 Timing ICC (s) = <10 Oxytocin use = no/not reported	DCC group: Mean age mother = 25.8 y Mean birth weight child (g) = 3182 ICC group: Mean age mother = 25.9 y Mean birth weight child (g) = 3196	Haemoglobin	4h	Capillary	19.9	2.4	19.3	2.3	0.25	0.10
Chen, 2018 (29), China	Total N = 180 N DCC = 90 N ICC = 90 Timing DCC (s) = 30	DCC group: Mean age mother = 29 y Mean birth weight child	Haematocrit	24h	Capillary	58.8	5.9	56.5	6.4	0.37	0.15
			Bilirubin	24h	Capillary	9.7	3	9.5	2.3	0.07	0.14

	Timing ICC (s) = 15 Oxytocin use = no/not reported	(g) = 3333 ICC group: Mean age mother = 29 y Mean birth weight child (g) = 3387									
De Paco, 2016 (34), Spain	Total N = 95 N DCC = 45 N ICC = 45 Timing DCC (s) = 120 Timing ICC (s) = <10 Oxytocin use = no/not reported	DCC group: Mean age mother = 30.18 y Mean birth weight child (g) = 3293 ICC group: Mean age mother = 31.46 y Mean birth weight child (g) = 3181	Red blood cells	0h	Umbilical cord	3.6	0.4	3.8	0.5	-0.43	0.45
			Haematocrit	0h	Umbilical cord	31.8	4	33.1	3.8	-0.33	0.20
			Haemoglobin	0h	Umbilical cord	10.5	1.4	11	1.4	-0.35	0.20
Emhamed, 2004 (37), Libya	Total N = 104 N DCC = 58 N ICC = 46 Timing DCC (s) = stop pulsation Timing ICC (s) = <10 Oxytocin use = yes	DCC group: Mean age mother = 28.4 y Mean birth weight child (g) = 3390 ICC group: Mean age mother = 28.9 y Mean birth weight child (g) = 3428	Blood value	0h	Umbilical cord	87.3	6	88.3	5.1	-0.18	0.20
			Haemoglobin	0h	Umbilical cord	14.9	1.7	15.4	1.4	-0.31	0.19
			Haemoglobin	24h	Capillary	18.5	2.1	17.1	1.9	0.69	0.20
Fawzy, 2015 (39), Egypt	Total N = 100 N DCC = 50 N ICC = 50 Timing DCC (s)= stop pulsation Timing ICC (s) = <30 Oxytocin use = NR	DCC gourp: Range age mother = 20 – 35 Range birth weight child (g) = 3000 – 4500 ICC group: Range ange mother = 25 – 34 Range birth weight child (g) = 3300 - 4000	Haemoglobin	0h	Umbilical cord	14.82	1.98	14.99	1.87	-0.08	0.45
			Bilirubin	72h	Capillary	6.95	2.01	7.01	2.31	-0.02	0.45
Jahazi, 2008 (35), Iran	Total N = 64 N DCC = 30 N ICC = 34 Timing DCC (s) = 180 Timing ICC (s) = 30 Oxytocin use = yes	DCC group: Mean age mother = 23 y Mean birth weight child (g) = 3008 ICC group: Mean age mother = 21.3 y Mean birth weight child (g) = 3272	Haematocrit	0h	Umbilical cord	50	4.4	51.2	3.4	-0.30	0.25
			Haematocrit	2h	Capillary	61.6	4.5	61	4.9	0.12	0.25
			Haematocrit	18h	Capillary	56.2	3.9	56.9	4.1	-0.17	0.25
Krishnan, 2015 (40), India	Total N = 76 N DCC = 37 N ICC = 39 Timing DCC (s) = 180 Timing ICC (s)	DCC group: Mean age mother = 26.4 y Mean birth weight child	Haemoglobin	24h	Capillary	19.2	1.86	17.5	1.96	0.89	0.49
			Bilirubin	24h	Capillary	6.9	2.4	5.8	2.4	0.46	0.48

	= <10 Oxytocin use = yes	(g) = 2962 ICC group: Mean age mother = 25.15 y Mean age birth weight child (g) = 3072									
Mercer, 2022 (36), USA	Total N = 41 N DCC = 21 N ICC = 20 Timing DCC (s) = 300 Timing ICC (s) = <20 Oxytocin use = no/not reported	DCC group: Mean age mother = 30 y Mean birth weight child (g) = 3507 ICC group: Mean age mother = 30 y Mean birth weight child (g) = 3321	Haemoglobin	48h	Capillary	19.6	1.9	17.6	2	1.02	0.24
			Haematocrit	48h	Capillary	59	6	52	5	1.26	0.25
Mercer, 2017 (32), USA	Total N = 73 N DCC = 37 N ICC = 36 Timing DCC (s) = >300 Timing ICC (s) = <20 Oxytocin use = no/not reported	DCC group: Mean age mother = 28.3 y Mean birth weight child (g) = 3584 ICC group: Mean age mother = 27.2 y Mean birth weight child (g) = 3584	Haemoglobin	0h	Umbilical cord	14.8	2	15.2	2	-0.2	0.23
			Haemoglobin	24h-48h	Capillary	19.4	2	17.8	2	0.8	0.24
			Haematocrit	0h	Umbilical cord	44.2	6.3	45.9	4.7	-0.30	0.23
			Haematocrit	24h-48h	Capillary	58	6.2	53	5.4	0.85	0.24
			Ferritin	0h	Umbilical cord	154.3	115	143.6	81	0.10	0.23
Mohammed, 2019 (33), Jordan	Total N = 128 N DCC = 64 N ICC = 64 Timing DCC (s) = 90 Timing ICC (s) = 30 Oxytocin use = yes	DCC group: Mean age mother = 28.9 y Mean birth weight child (g) = NR ICC group: Mean age mother = 28.9 y Mean birth weight child (g) = NR	Bilirubin	12h	Capillary	3.48	1.23	3.73	2.05	-0.14	0.17
			Bilirubin	72h	Capillary	8.85	3.85	8.42	3.91	0.11	0.17
			Haemoglobin	12h	Capillary	18.57	1.8	16.7	1.68	1.07	0.18
Ofojebe, 2021 (30), Nigeria	Total N = 204 N DCC = 102 N ICC = 102 Timing DCC (s) = 60 Timing ICC (s) = <15 Oxytocin use = yes	DCC group: Mean age mother = 27.93 y Mean birth weight child (g) = 3210 ICC group: Mean age mother = 27.82 y Mean birth weight child (g) = 3240	Haemoglobin	0h	Umbilical cord	15.65	0.29	15.25	0.48	0.48	0.14
			Haemoglobin	24h	Capillary	16.51	1.71	15.16	2.27	0.67	0.14
			Bilirubin	0h	Umbilical cord	3.13	1.35	3.09	1.07	0.03	0.14
			Bilirubin	24h	Capillary	3.88	1.54	3.71	1.2	0.15	0.14
Salari, 2014 (31), Iran	Total N = 56 N DCC = 27 N ICC = 29 Timing DCC (s) = 180 Timing ICC (s) = 10	DCC group: Mean age mother = 27.1 y Mean birth weight child (g) = 3040	Haemoglobin	2h	Capillary	17.2	2	15.7	1.6	0.82	0.27
			Haematocrit	2h	Capillary	49.5	4.4	45.1	4	4.0	0.27
			Haemoglobin	18h	Capillary	18.7	1.7	16.7	2	1.07	0.28
			Haematocrit	18h	Capillary	52.9	4.3	47.7	5.5	1.05	0.28

	Oxytocin use = yes	ICC group: Mean age mother = 27.5 y Mean birth weight child (g) = 3029									
Van Rheenen, 2007 (41), Zambia	Total N = 91 N DCC = 46 N ICC = 45 Timing DCC (s) = stop pulsation Timing ICC (s) = 20 Oxytocin use = yes	DCC group: Median age mother = 20.5 Mean birth weight child (g) = 3142 ICC group: Median age mother = 22.9 Mean birth weight child (g) = 3119	Haemoglobin	0h	Umbilical cord	14.3	1.7	14.9	1.5	-0.37	0.46

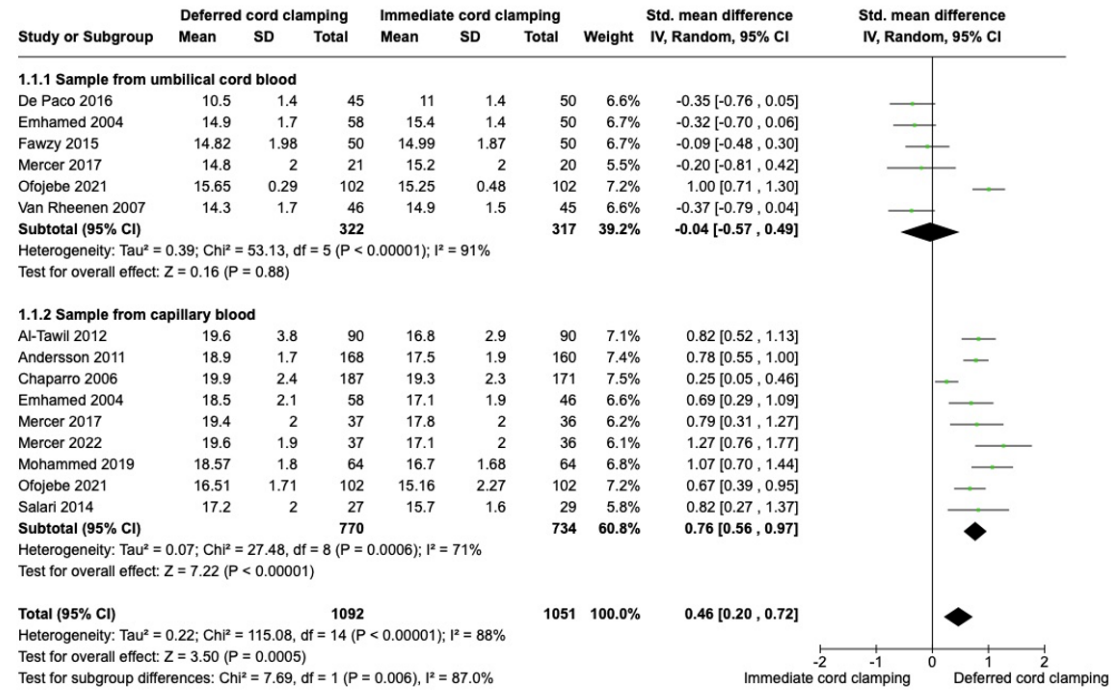
Abbreviations: DCC = deferred cord clamping; ICC = immediate cord clamping; g = grams; h = hours; s = seconds; y = years; N = sample size, NR = not reported; SD = standard deviation, SMD = standardised mean difference, SE = standard error.

Effect of DCC on haemoglobin

Thirteen studies were eligible for pooling the haemoglobin values (Figure 2). The overall pooled effect indicated statistically significantly higher haemoglobin levels in the DCC arm compared to the ICC arm, showing a moderate effect: SMD 0.46 (95%CI 0.20 to 0.72, p=0.0005). No difference of effect was found between DCC and ICC when blood samples were taken from the umbilical cord: SMD -0.04 (95%CI -0.57 to 0.49, p=0.88). The study of Ofojebe *et al.* (30) showed to be a considerable outlier (Figure 2). A sensitivity analysis, removing the data from Ofojebe *et al.* (30), resulted in statistically significantly higher umbilical cord haemoglobin levels in the ICC group: SMD -0,27 (95%CI -0.46 to -0.08, p=0.005) and no heterogeneity (I^2=0%).

Postpartum (between >2 and 48 hours) capillary haemoglobin levels were statistically significantly higher in the DCC group, showing a large effect: SMD 0.76 (95%CI 0.56 to 0.97, p=0.00001). High study heterogeneity was reported (I^2=71%), and none of the moderators statistically significantly influenced pooled effects for umbilical cord or capillary haemoglobin levels (Supplementary file, analysis 4.1 and 4.4).

Egger's test showed no statistically significant funnel plot asymmetry for the stratified data from the umbilical cord blood samples (z=-0.801, p=0.012) (Supplementary File, analysis 4.2). The subgroup analyses of capillary samples revealed a statistically significant asymmetric funnel plot suggesting potential publication bias (z=0.075, p=0.026) (Supplementary File, analysis 4.5). The trim-and-fill analysis revealed that four additional studies would be necessary to influence the effects of DCC concerning neonatal haemoglobin levels (Supplementary file analysis 4.6). However, these studies would not alter the differences between DCC and ICC.



Sensitivity analysis output without the outlier of Ofojebe *et al.*, 2021

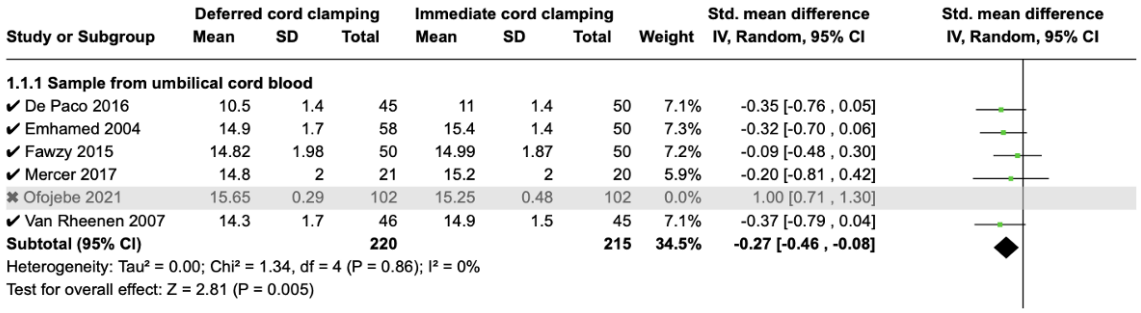


Figure 2. Forest plot of the pooled SMD on outcome haemoglobin, including sensitivity analysis output.

Effect of DCC on bilirubin

Six studies were pooled to estimate the effect of DCC on bilirubin levels (Figure 2). The meta-analysis showed no statistically significant differences between the DCC and ICC arm and a small effect: SMD 0.13 (95%CI -0.03 to 0.28, p=0.22). The pooled effect size was negligible for umbilical cord bilirubin values: SMD of 0.03 (95%CI -0.24 to 0.31, p=0.82) and small for neonatal capillary values: SMD 0.15 (95%CI -0.04 to 0.33, p=0.12). Low statistical heterogeneity ($I^2$46%) was reported among the included studies in the capillary blood sampling subgroup.

The Egger's test showed no statistically significant funnel plot asymmetry (z= 0.084, p= 0.933), not indicating potential bias. The trim-and-fill analysis suggested that there were no potential missing studies to adjust for publication bias (Supplementary file, analysis 5.1 and 5.2).

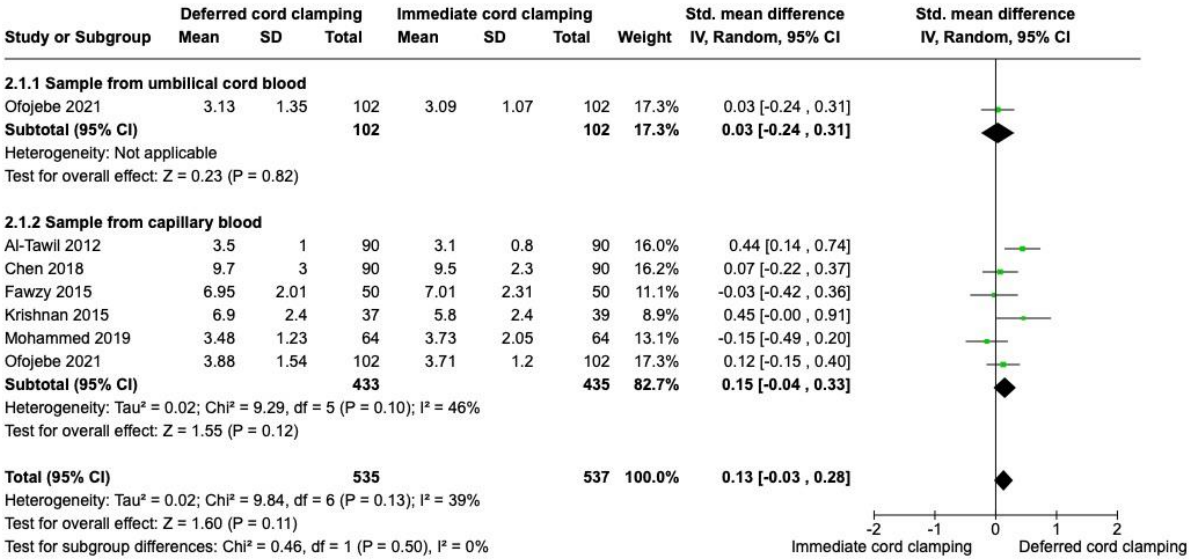


Figure 3. Forest plot of the pooled SMD on outcome bilirubin.

Effect of DCC on haematocrit

Eight studies were pooled to estimate the effect of DCC on haematocrit levels (Figure 4). The overall pooled effect size was small-to-moderate: SMD 0.4 (95%CI 0.00 to 0.80). The haematocrit levels were statistically significantly lower in the DCC arm than the ICC arm when collected from the umbilical cord, with a small effect size: SMD -0.3 (95% -0.53 to -0.07, p=0.01), showing no heterogeneity (I^2 0%). The haematocrit levels from the capillary blood samples were statistically significantly higher in the DCC arm, showing a large effect size: SMD 0.75 (95%CI 0.42 to 1.09, p <0.001) and high heterogeneity (I^2 74%).

The meta-analysis showed statistical significance for the moderator maternal mean age. The overall effect of mean birth weight was statistically insignificant (Supplementary file, analysis 5.1). The Egger's test showed no statistically significant funnel plot asymmetry (z=1.204, p=0.228), and the trim-and-fill analysis suggested that there were no potential missing studies to adjust for publication bias (Supplementary file, analysis 5.2 and 5.3).

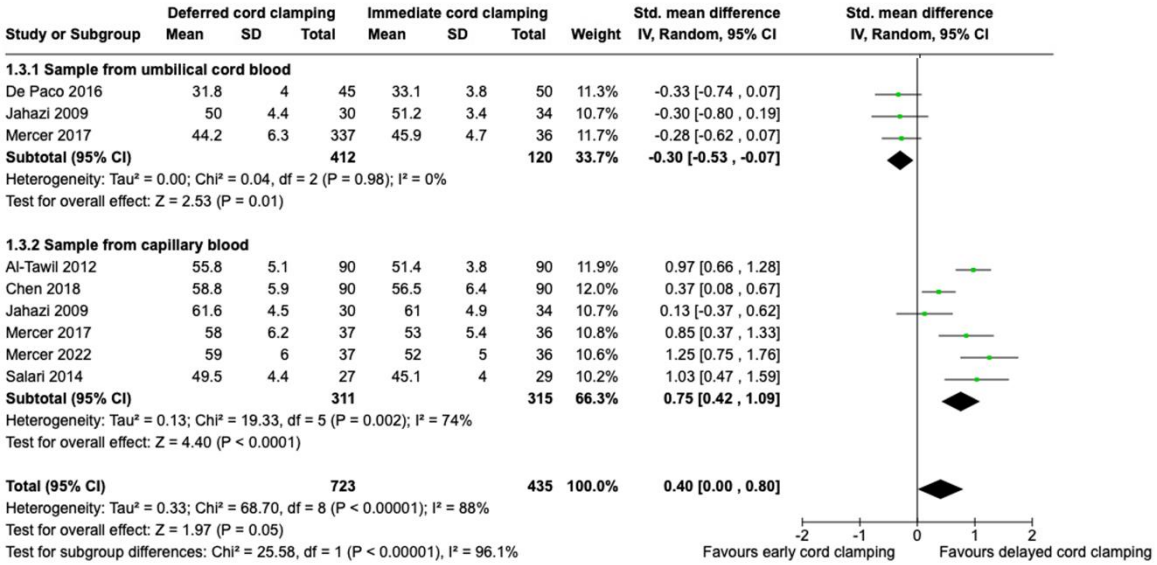


Figure 4. Forest plot of the pooled SMD on outcome haematocrit.

Discussion

This review examined the impact and effect size differences between blood biomarkers from umbilical cord and capillary blood samples of healthy term neonates collected after either immediate or deferred cord clamping. This is the first review to show that the blood sampling technique, umbilical cord blood sampling versus neonatal capillary blood sampling, is crucial for measuring biomarkers and, therefore, the effect of UCC. We found that capillary blood haematocrit and haemoglobin values improved in favour of DCC with a moderate-to-large intervention effect. There was no difference in effect between DCC and ICC on bilirubin values regardless of sampling technique. Our findings support the recommendation of the World Health Organization and of the American College of Obstetricians and Gynecologists to defer UCC to improve neonatal blood biomarkers (3, 5).

A major finding from the meta-analysis is that the timing and sampling technique of blood matter. When the blood values were evaluated from the cord blood, sampled early postpartum, no difference in effect between DCC and ICC was found. However, the neonatal blood values from capillary samples, sampled later postpartum (between 2 and 72 hours), showed a moderate-to-high effect in favour of DCC for haematocrit and haemoglobin levels. The differences in blood values and the sampling methods could be attributed to circulatory changes transitioning from oxygen and blood supply from the umbilical cord to pulmonary blood flow (43). Since UCC affects cardiopulmonary transition at birth, the cord clamping effect may only be accurately estimated from the neonatal capillary blood samples (44). This might explain why biomarkers at birth from the umbilical cord blood samples do not show a difference between DCC and ICC. Furthermore, DCC improves the shift to pulmonary blood flow, which could partially explain the enhanced blood values (43).

In this study no difference in bilirubin levels were found, either in cord blood or capillary blood samples. The liver and elimination processes regulate bilirubin. Neonates' bilirubin levels can vary due to red blood cell breakdown rate, liver function, and efficiency, with limited impact from cord clamping timing. Other factors, such as health status and intricate interactions, contribute to neonatal bilirubin levels and overall wellbeing beyond the cord clamping (45). Our findings align with previous studies, which indicate that DCC is unrelated to a rise in bilirubin levels or risk of jaundice, affirming its safety for practice (11, 46-48).

Deferred cord clamping increased the levels of haematocrit and haemoglobin, two crucial blood biomarkers. Both biomarkers inform on the blood quality and measure different aspects of the neonatal condition. Our findings support earlier evidence that neonates in the DCC group had statistically significant higher haematocrit and haemoglobin values within the clinically relevant thresholds, when compared with ICC (10, 11). Improved haematocrit levels can help reduce the need for blood transfusions by ten percent and do not affect polycythaemia (10, 11). Our findings are not comparable with those of preterm neonates or neonates being born via caesarean section, where the risk of polycythaemia is higher (10, 49). Therefore, the clinical relevance of the effect should be interpreted based on the gestational age of the neonate and method of birth.

Strengths and limitations

This meta-analysis yields relatively high power, with at least 700 participants per arm per analysis. The review's strength lies in the stratification of data based on the blood sampling technique, which seemed to determine if and when the health effects of DCC become notable. Furthermore, the current review included only cases born after a spontaneous vaginal birth instead of combining vaginal and caesarean births, as done in a previous meta-analysis (11). This review conducted extensive publication bias analysis to ensure the results were representative. Publication bias was established in one outcome although the trim-and-fill analysis showed that the potential missing studies would not have affected our overall effect.

There were discrepancies in the timing of UCC reported by the authors of the included studies; the exact timing, e.g. <20 seconds or after pulsation ceases, sometimes not specified at all. Even though the moderator analysis did not show any statistically significant impact on the point estimate, the interpretation of results relies on these cut-off periods. The chosen moderators are clinical maternal and neonatal core characteristics. However, we are aware we could have missed moderators that affect timing of cord clamping related to parental choices such as umbilical nonseverance and cord blood donation and storage, but also the management and philosophy of care and varying attitudes and practices have been identified between midwifery and medical professionals towards cord clamping, affecting patient involvement and decision-making (2, 50-52) and thus potentially affecting the outcomes of the meta-analyses. Considering these moderators in future meta-analyses is recommended.

The meta-analyses showed high heterogeneity but we were unable to determine if these factors had a clinical, methodological or statistical origin (53). There was variety in methodology and sampling time between the studies, which we tried to adjust by standardising the mean differences and applying a random-effect model. Although most of the included RCTs had low power (<100 participants per arm per study), pooling improved the power of our meta-analysis (54) albeit that the confidence intervals of the pooled estimates were broad, ranging from a small to a large effect size. Future studies should aim to generate high-powered RCTs or methodologically robust retrospective data. Our findings cannot be generalised to neonates from high-risk pregnancies, born preterm or born via a caesarean section. Also, we only pooled data on three biomarkers, while other biomarkers, such as ferritin of blood volume, could provide additional insights.

Implications

The main implication of this review is that the blood sampling technique, either the umbilical cord or neonatal capillary blood sampling, impacts on the effect of DCC. This emphasises that the moment of blood sampling and assessment is crucial in understanding the clinical status of the neonate. In the included studies, the postpartum capillary sampling times varied from two to 72 hours, identifying a gap in knowledge about the optimal time of capillary blood sampling. Since blood biomarkers' values differed between the sampling technique and timing (early or later postpartum), a discussion point may arise about which values are clinically relevant to assess neonatal health. For future studies, researchers should consider the sampling technique and timing when interpreting blood values. More importantly, this

also applies to maternity care professionals who use blood values to evaluate and monitor neonatal health. The discussion and decision about DCC versus ICC can thus be biased by selective use of evidence to underpin the debate and utilisation of clinical management. It is vital to critically reflect on the physiological explanation and meaning of the blood marker value differences between the blood sampling techniques and sampling times to benefit the neonate. In addition, practitioners need to reflect on standard procedure practices entailing the timing of UCC and the use of evidence resulting from sampling time and sampling technique to inform parents about the management of care, to actively engage parents and care professionals and or change management of care (53, 55, 56). DCC is a non-invasive, minimally time-consuming, low-cost intervention that can be applied to achieve positive neonatal health outcomes (57).

Conclusions

Deferring clamping of the umbilical cord is a form of neonatal healthcare management in intrapartum care to improve blood supply in healthy neonates who are born vaginally and spontaneously. According to our analyses, DCC has a moderate and statistically significant effect on neonatal capillary blood values. The sampling technique is a crucial factor for the clinical evaluation. Evaluation of the umbilical cord blood biomarker values show no immediate effect of UCC. However, when neonatal capillary blood is evaluated, DCC has a clinically significant and positive impact. More high-powered studies are required and comprehensive using standardised time frames to study the effects of DCC in healthy neonates who are spontaneously and vaginally born at term. Our findings cannot be generalised to preterm neonates or neonates born via caesarean section.

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Conflict of interest

None

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Author contribution statement

Charifa Zemouri: design; conceptualisation; investigation; search strategy; methodology development; data abstraction; data analyses; meta-analyses; data interpretation; writing – original draft.

Eveline Mestdagh: data interpretation; writing - editing; project administration.

Mieke Stiers: conceptualisation; literature screening; literature selection; data interpretation.

Kimberly Torfs: conceptualisation; literature screening; literature selection; data interpretation.

Yvonne Kuipers: conceptualisation; data interpretation; writing - editing; project administration; supervision.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: