Original Article

Comparison of Incidence of Neonatal Anemia in Different Timing of Delayed Cord Clamping; at 30 Seconds, 1 Minute and 2 Minutes in Term Vaginal Delivery: A Randomized Controlled Trial

Srisuda Songthamwat, MD[1], Patthamon Witsawapaisan, MD[1], Surapong Saenpoch, MD[1], Sopida Tanthawat, MD[2], Ueamporn Summart, PhD[1], Metha Songthamwat, MD, PhD[1]

[1] Department of Obstetrics and Gynecology, Udon Thani Hospital, Udon Thani, Thailand

[2] Department of Pediatrics, Udon Thani Hospital, Udon Thani, Thailand

Objective: To compare the effect of cord clamping time on the incidence of neonatal anemia, clinical outcomes, and maternal and neonatal complications in term vaginal delivered newborns.

Materials and Methods: A randomized controlled study was undertaken. Two hundred forty healthy full term vaginal delivered newborns were randomly allocated to either 30-seconds, 1-minute, or 2-minutes groups (group 1, 2, and 3) of umbilical cord clamping. During the interval between delivery and cord clamping, the attendant held the neonate supine at the level of the introitus. Neonatal venous hematocrit (Hct) was measured at 48 to 72 hours after birth.

Results: Two hundred thirty newborns completed the present study. Neonatal anemia (Hct less than 45%) was detected in six of 77 cases (7.8%) in group 1, five of 76 cases (6.6%) in group 2, and three of 77 case (3.9%) in group 3, and there were no significant differences among the groups. Mean venous hematocrit values at 48 to 72 hours of life ± standard deviations were 53.1±6.4% in group 1, 53.0±5.5% in group 2, and 53.0±5.7% in group 3. The incidence of polycythemia (hematocrit more than 65%) and neonatal jaundice were similar among all the groups. There were no significant differences in the estimated postpartum blood loss and other neonatal outcomes.

Conclusion: Neonatal hematocrit was not significantly different following delayed cord clamping (DCC) at 30-seconds, 1-minute, and 2-minutes, but the incidence of neonatal anemia decreased with the longer timing of DCC. The estimated blood loss and other complications were not different between the groups. Therefore, a minimum of a one minute DCC should be considered for neonatal anemic prevention when compared with the 30-seconds DCC.

Keywords: Delayed cord clamping, Timing, Hematocrit, Neonatal anemia

Received 30 April 2020 | Revised 22 July 2020 | Accepted 26 July 2020

J Med Assoc Thai 2020;103(12):1255-61
Website: http://www.jmatonline.com

Anemia is an important problem in many countries. The global prevalence of anemia is estimated to be 30.2% in non-pregnant women rising to 47.4% during pregnancy[1]. In newborns, the reported prevalence is 32.6%[2]. The anemic newborn is at increased risk of long-term complications such as impaired neurological, emotional, and behavioral development[3,4]. These complications can persist for more than 10 years after treatment[5]. Protection of anemia in newborns is crucial for the prevention of long-term problems.

Delayed cord clamping (DCC) can protect against anemia in newborns by transferring residual blood in the placenta. This practice is easy and effective without cost[6,7]. Many researchers have supported these advantages[7-10]. The proper time for DCC is different among health authorities, for example, the World Health Organization (WHO)

Correspondence to:

Songthamwat M.

Department of Obstetrics and Gynecology, Udon Thani Hospital, Udon Thani 41000, Thailand.

Phone: +66-81-5451499, **Fax**: +66-42-247251

Email: udonhome@yahoo.com

How to cite this article:

Songthamwat S, Witsawapaisan P, Saenpoch S, Tanthawat S, Summart U, Songthamwat M. Comparison of Incidence of Neonatal Anemia in Different Timing of Delayed Cord Clamping; at 30 Seconds, 1 Minute and 2 Minutes in Term Vaginal Delivery: A Randomized Controlled Trial. J Med Assoc Thai 2020;103:1255-61.

doi.org/10.35755/jmedassocthai.2020.12.11393

(2012) recommends one to three minutes DCC[11], the American College of Obstetricians and Gynecologists (ACOG) recommends 30 to 60 seconds DCC[6], and the National Institute for Health and Care Excellence (NICE) recommends 1 to 5 minutes DCC or more, if the mother desired[12]. There is no research study on the result of these different time approaches for DCC. The longer time for DCC may correlate with jaundice and polycythemia, while the shorter time may cause neonatal anemia[7]. The present research was aimed at studying the appropriate time between 30 seconds, 1 minute, and 2 minutes for the prevention of anemia in newborns.

Materials and Methods

The present study was a randomized controlled trial conducted in the Department of Obstetrics and Gynecology, Udon Thani Hospital, Udon Thani, Thailand. It was conducted according to the declaration of Helsinki, and the national laws and regulations about clinical studies. The present study's protocol was approved by the Udon Thani Hospital Research Ethics Committee (number 37/2561) and was registered in the Thailand Clinical Trial Registry (TCTR 20181007002). The study's participants were 240 pregnant women that underwent vaginal delivery between October 2018 and September 2019. They were counseled and invited to participate in the present study.

The inclusion criteria were singleton pregnancies, age 20 years or older, who delivered vaginally between 37 to 41 weeks gestation, which was defined by the last menstrual period and ultrasonographic result at first half of pregnancy from antenatal care record. The exclusion criteria were a pregnancy with severe medical complication, such as heart disease, chronic hypertension, or renal disease, fetal anomaly, fetal growth restriction, having signs of birth asphyxia or heavy bleeding immediately after birth, or unwilling to participate in the study.

The written informed consents were obtained after the explanation of the study to the participants. Then, all participants were randomly allocated into one of the three study groups. A simple randomization using a computer-generated number and sealed opaque envelope, was performed.

During the first and second stage of labor, the participants were attended to by the standard hospital protocol. After delivering the infant, the obstetrician placed the baby at level of the introitus and waited 30 seconds in group 1, one minute in group 2, and two minutes in group 3 before clamping the umbilical cord. Then the placenta was delivered, the episiotomy wound was sutured, and routine newborn and maternal postpartum care were done[10,13]. Blood loss during delivery was measured using a blood collecting bag.

Maternal complication, Apgar scores, and birth weight were recorded. The newborn Hct and microbilirubin (MB) were measured using venous blood at 48 to 72 hours after delivery. Complete blood count was analyzed by an automated hematology analyzer (Sysmex XN-3000, Meditop Company). MB was analyzed by an automated hematology analyzer (MB NEO-BIL Plus, Zenith Science Company). Newborn Hct was measured using a hematocrit centrifuge and a hematocrit reader.

Neonatal anemia was defined as when the neonatal Hct was less than 45%, neonatal polycythemia was when Hct was more than 65%[9,14]. Clinical neonatal jaundice was defined by pediatricians using MB level of more than standard curve value graph[15] and clinical judgement. Anemia in the mother was defined as when the maternal Hct was less than 33%.

The mean neonatal Hct and prevalence of neonatal anemia at 48 hours in groups 1, 2, and 3 were compared. Neonatal polycythemia, jaundice, and other neonatal complications were compared between groups. Estimated maternal blood loss at delivery and maternal complication between groups were also analyzed.

Statistical analysis

The sample size was calculated using the formula for randomized controlled trial for binary data[16]. The proportion of neonatal anemia was estimated to be 0.15 at 30-seconds DCC, 0.02 at 1-minute DCC and 0.02 at 2-minutes DCC with a 0.13 difference which was used for calculation[14]. A α was 0.05 and the power was 80%. The calculated sample size was 72 participants in each group. An estimated drop-out rate of 10% was added for a total sample size of 240 participants, with 80 per group, was used.

The participants' characteristics were presented in number, percentage, range, or mean ± standard deviation. The continuous variables were compared between groups using mean difference with 95% confidence interval and p-value using the one-way ANOVA test. The categorical variables were compared between groups by risk ratio with 95% confidence interval and the Pearson's chi-square. Data were analyzed as per-protocol method. Statistical analysis was performed using Stata, version 13 (StataCorp LP, College Station, TX, USA). A p-value of less than 0.05 was considered statistically significant.

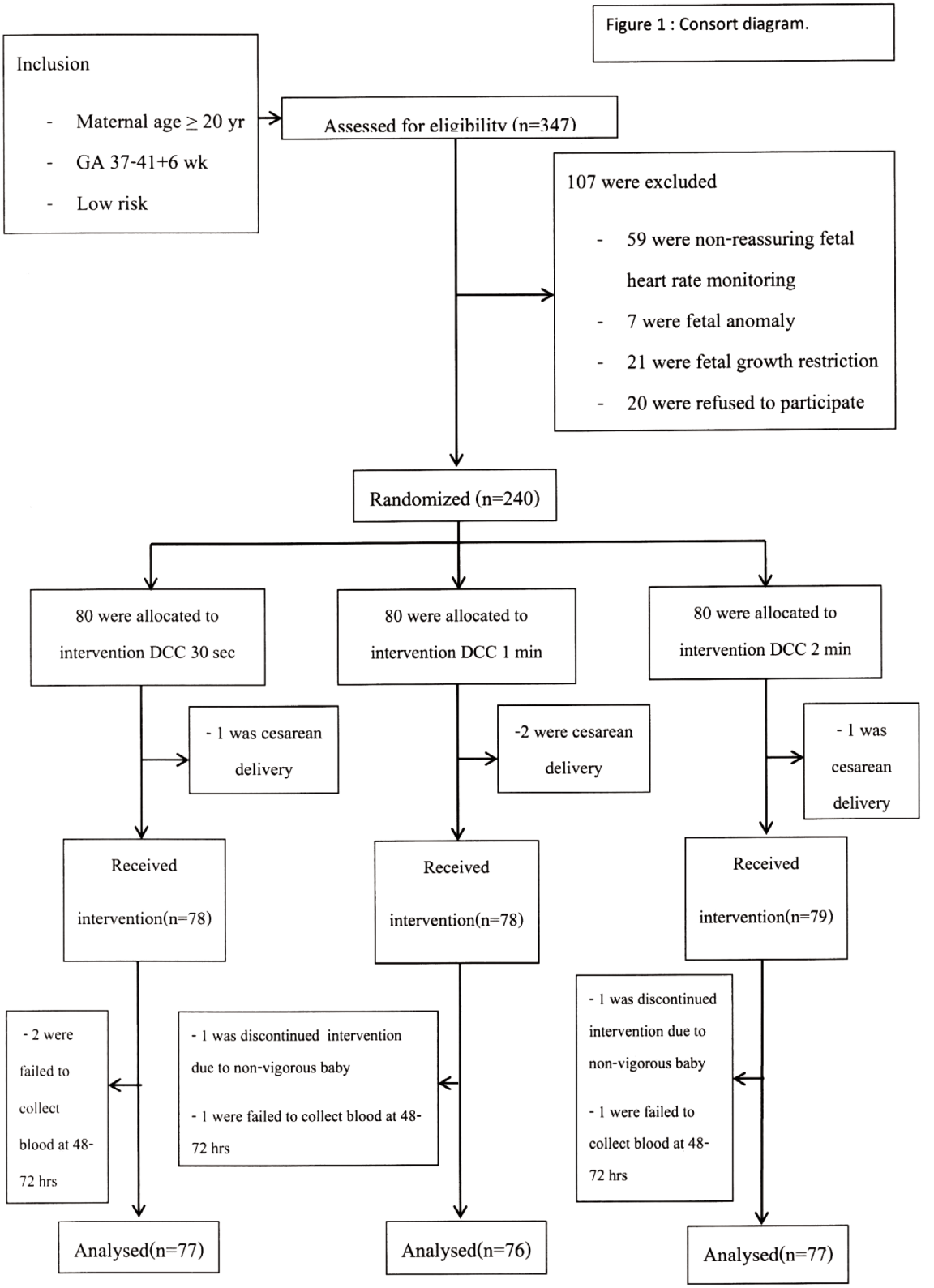

Figure 1. Consort diagram.

Table 1. Comparison of maternal characteristics between three study groups

Characteristics	DCC 30 seconds (n=77) Mean±SD	DCC 1 minute (n=76) Mean±SD	DCC 2 seconds (n=77) Mean±SD	p-value[β]
Maternal age (year)	27.3±4.9	27.9±4.9	25.8±4.8	0.028*
Gravida; mean±SD	2.0±1.0	2.0±1.0	2.0±1.0	0.944
Nulliparity; n (%)	32 (41.6)	27 (35.5)	31 (40.3)	0.724
Gestational age (week)	38.9±1.1	38.8±1.2	38.6±1.1	0.304
BMI (kg/m^2)	27.6±4.0	27.7±5.8	27.2±5.2	0.797
Maternal Hct	35.8±3.5	36.7±3.2	35.6±3.4	0.078
Anemia; n (%)	14 (18.2)	10 (13.2)	18 (23.4)	0.262
Third stage time (minute)	6.0±3.8	6.2±2.9	5.7±2.8	0.639
Cord length (cm)	48.9±8.8	50.1±9.5	50.1±8.9	0.617
Placental weight (g)	564.3±124.4	556.8±105.5	593.4±133.8	0.148

DCC=delay clamp cord; BMI=body mass index; Hct=hematocrit; SD=standard deviation

[β] p-value was calculated by the one-way ANOVA test for continuous outcome and by Pearson's chi square for categorical outcome, * Statistically significant difference (p<0.05)

Table 2. Comparison primary and secondary outcome measurement between three study groups

Characteristics	DCC 30 seconds (group 1, n=77) Mean±SD	DCC 1 minute (group 2, n=76) Mean±SD	DCC 2 minutes (group 3, n=77) Mean±SD	Mean difference or RR between group 2-1 (95% CI, p-value)	Mean difference or RR between group 3-2 (95% CI, p-value)	p-value*
Neonatal Hct at 48 to 72 hours (%)	53.1±6.4	53.0±5.5	53.0±5.7	−0.09 (−1.96 to 1.78, 1.000)	−0.08 (−1.79 to 1.95, 1.000)	0.995
Neonatal anemia; n (%)	6 (7.8)	5 (6.6)	3 (3.9)	0.65 (0.17 to 2.39, 0.516)	0.49 (0.08 to 2.73, 0.414)	0.349
Polycythemia; n (%)	1 (1.3)	0 (0.0)	1 (1.3)	N/A	N/A	N/A
MB at 48 to 72 hours	10.2±2.3	10.3±2.6	10.1±2.2	0.13 (−0.63 to 0.90, 1.000)	−0.28 (−1.05 to 0.48, 1.000)	0.760
Clinical jaundice; n (%)	29 (37.7)	25 (32.9)	32 (41.6)	0.80 (0.42 to 1.54, 0.504)	1.47 (0.77 to 2.81, 0.249)	0.511
Phototherapy; n (%)	21 (27.3)	21 (27.6)	22 (28.6)	1.00 (0.49 to 2.02, 1.000)	1.07 (0.53 to 2.14, 0.858)	0.979
Estimate blood loss (mL)	124.2±75.8	116.1±77.5	125.2±82.5	−8.11 (−33.2 to 16.9, 1.000)	9.09 (−16.0 to 34.2, 1.000)	0.676

DCC=delay clamp cord; RR=risk ratio; CI=confidence interval; SD=standard deviation; Hct=hematocrit; MB=microbilirubin; N/A=not available

* p-value was calculated by the one-way ANOVA and the Bonferroni multiple-comparison test for continuous outcome and by the logistic regression analysis and Pearson's chi-square for categorical outcome

Results

The present study included 240 participants who were randomly allocated to 80 participants per group, which were DCC at 30-seconds group (group 1), DCC at 1-minute group (group 2), and DCC at 2-minutes (group 3). After the study was completed, three participants in group 1, four participants in group 2, and three participants in group 3 were excluded due to non-vigorous baby (no breathing or crying) or failure to collect neonatal blood for Hct at 48 to 72 hours. There were four cases of caesarean delivery and no other operative delivery was performed. Consort diagram is presented in Figure 1. The maternal baseline characteristics of each group are shown in Table 1. All groups were comparable in terms of gravida, parity, gestational age, maternal body mass index, maternal Hct and anemia, third stage time, and estimated postpartum blood loss, except maternal age.

At 48 to 72 hours after birth, blood sampling was done on 77, 76, and 77 babies in group 1, 2, and 3, respectively. Mean venous Hct values were 53.1±6.4% in group 1 (range 39 to 68), 53.0±5.5% in group 2 (range 40 to 65), and 53.0±5.7% in group 3 (range 42 to 66) without any statistically significant difference. Neonatal anemia (Hct less than 45%) was detected in six of 77 cases (7.8%) in group 1, five of 76 cases (6.6%) in group 2, and one of 77 case (3.9%) in group 3, and there were no statistically significant differences among the three groups (Table 2). Neonatal polycythemia was found in one case (1.3%) in group 1 and group 3 at 48 to 72 hours, and in one case in group 2 that developed polycythemia after 72 hours (partial

Table 3. Comparison of neonatal outcome between three study groups

Characteristics	DCC 30 seconds (n=77) Mean±SD	DCC 1 minute (n=76) Mean±SD	DCC 2 minutes (n=77) Mean±SD	p- value*
Newborn birthweight (kg)	3,226.6±331.7	3,100.3±355.3	3,192.1±402.5	0.088
Newborn length (cm)	51.2±1.7	50.8±1.9	51.2±1.9	0.264
Newborn HC	32.7±1.4	32.4±1.4	32.6±1.3	0.331
Apgar 1 minute	8.9±0.5	9.0±0.5	9.0±0.5	0.197
Apgar 5 minute	9.9±0.4	9.9±0.3	9.9±0.3	0.789
Apgar 10 minute	9.9±0.4	9.9±0.3	9.9±0.3	0.893
Respiratory complication; n (%)	5 (6.5)	4 (5.3)	5 (6.5)	0.935
NICU admission; n (%)	0 (0.0)	1 (1.3)	0 (0.0)	N/A

SD=standard deviation; DCC=delay clamp cord; HC=head circumference; NICU=neonatal intensive care unit; N/A=not available

Respiratory complications included respiratory distress syndrome, pneumonia and transient tachynep of the newborn

* p-value was calculated by the one-way ANOVA test for continuous outcome and by Pearson's chi square for categorical outcome

blood exchange transfusion was done). Clinical neonatal jaundice was found in 29 cases (37.7%) in group 1, 25 cases (32.9%) in group 2, and 32 cases (41.6%) in group 3, which was not statistically significant different (range MB in all cases was 3.7 to 19.3). Phototherapy was done in 21 cases (27.3%) in group 1, 21 cases (27.6%) in group 2, and 22 cases (28.6%) in group 3, which was similar among groups. No neonatal hypothermia was found in all groups.

The mean third stage time of all participants was 6.0 minutes (range 1 to 25 minutes) and mean estimated blood loss after delivery was 121.8 ml (range 20 to 500 ml) without statistically significant difference among groups. There was no case with estimated blood loss greater than 500 ml. Placenta weight and cord length were also similar in all groups. The mean neonatal birthweight was 3,173.3 gram (range 2,220 to 4,260) with 10 (4.4%) low birthweight baby (less than 2,500 gram). The neonatal length and head circumference were also comparable among groups. Neonatal Apgar scores at 1, 5, and 10 minutes were not different among groups (Table 3). Other neonatal outcomes, such as pneumonia, respiratory distress syndrome, and transient tachypnea of the newborn, were similar among groups (Table 3).

Discussion

DCC has been recommended by the WHO, ACOG, and NICE guidelines[6,10,12] with many researchers supporting its advantage in reducing anemia in newborn[11,17-22]. The recommended DCC timing is different in each guideline ranging from 30 seconds to more than one minute or as long as the mother's request it. In the present study, three timings of DCC (30-second, 1- and 2-minutes) were studied to compare their effectiveness in reducing neonatal anemia and potential undesirable medical effect such as jaundice or polycythemia. The results demonstrate that no statistically significant difference exists in mean neonatal hematocrit and incidence of anemia among groups. The incidences of neonatal anemia trend to decrease in the longer timing of DCC (7.8%, 6.6%, and 3.9%, respectively).

The benefit of DCC can be explained by the increased transference time of residual blood in the placenta to the newborn. There are some disadvantages such as increased unnecessary blood to the newborn leading to polycythemia, and jaundice when compared with early cord clamping[9]. The DCC can also delay the process of newborn care including temperature care and increased waiting time before perineum wound care, which may increase blood loss. Therefore, a proper time of DCC should be defined. From the present study, the authors found no significant difference of adverse neonatal and maternal effects from one and two minutes DCC, so the authors' recommendation is prolonged DCC of at least one minute, which is compatible with some other recommendations[7,10].

The mean neonatal blood concentration after DCC in the present study was similar to a Thai report[23] but was lower than other reports, which the mean neonatal hemoglobin of DCC infants at 24 to 48 hours was 18.5 to 18.9 g/dL[20,24]. The incidence of neonatal anemia after DCC at 30-seconds in the present study (7.8%) was still lower than early cord clamping in a previous study, which reported 16.8% of neonatal anemia at 24 to 48 hours after

early cord clamping. The incidence of anemia in DCC at 2-minutes (3.9%) were closer to a previous DCC report, which was 2.8%[14]. Therefore, DCC at 30-seconds still has benefit for the baby however, longer DCC seems to be better for reducing neonatal anemia.

The incidence of neonatal jaundice in the present study was 32.9 to 41.6%, which is higher than a previous DCC study[9]. Observation for clinical neonatal jaundice is recommended in DCC babies. Most jaundice cases in the present study were mild and all responded to the phototherapy treatment. The incidence of polycythemia was close to a previous study, which reported polycythemia in 2.5% of DCC babies[9].

The strength of the present study is the prospective randomized controlled trial. The limitations of the present study are, first, a long-term study is still needed to determine the proper time of DCC effect in older children such as anemia or long term sequalae. Second, a larger sample size study is still needed to determine the difference between 30-seconds and 1-minute DCC.

Conclusion

Neonatal hematocrit was not significantly different following DCC at 30-seconds, 1-minute and 2-minutes, but the incidence of neonatal anemia decreased with the longer timing of DCC. The estimated blood loss and other complications were not different between the groups. Therefore, a minimum of one minute-DCC should be considered for neonatal anemic prevention when compared with the 30-seconds DCC.

What is already known on this topic?

Delayed umbilical cord clamping during vaginal delivery can reduce the incidence of neonatal anemia when compared with early umbilical cord clamping.

What this study adds?

The neonatal hematocrit and incidence of neonatal anemia was not significant different following 30-seconds, 1-minute and 2-minutes of delayed umbilical cord clamping. However, the incidence of neonatal anemia decreased with the longer time of delayed clamping without maternal and neonatal complications. Therefore, at least one minute of DCC should be considered for neonatal anemic prevention.

Acknowledgement

The authors gratefully acknowledge Dr. Narong Tadadet, Director of Udon Thani Hospital for permission and grant support. Thanks for Udon Thani Hospital staff and all pregnant ladies who participated in the present trial.

Funding disclosure

The study was supported by Udon Thani Hospital.

Disclosure statement

None of the authors has any conflict of interest relative to this work. The present study did not receive pharmaceutical support. All available anonymized data can be obtained by contacting the corresponding author until five years after publication.

Conflicts of interest

The authors declare no conflict of interest.

References

1. World Health Organization. Weekly iron-folic acid supplemention (WIFS) in women of reproductive age: its role in promoting optimal maternal and child health. Geneva: WHO; 2009.
2. de Sá SA, Willner E, Duraes Pereira TA, de Souza VR, Teles Boaventura G, Blondet de Azeredo V. Anemia in pregnancy: Impact on weight and in the development of anemia in newborn. Nutr Hosp 2015;32:2071-9.
3. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:649S-66S; discussion 66S-68S.
4. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol 2006;13:158-65.
5. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000;105:E51.
6. Committee on Obstetric Practice. Committee Opinion No. 684: Delayed umbilical cord clamping after birth. Obstet Gynecol 2017;129:e5-e10.
7. Funai EF, Norwitz ER. Management of normal labor and delivery. UpToDate 2019.
8. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA 2007;297:1241-52.
9. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2013;(7):CD004074.
10. Pan American Health Oragnization, World Health Organization. Beyond survival: Integrated delivery care practices for long-term maternal and infant nutrition, health and development. Washington DC:

PAHO; 2013.
11. World Health Organization. Delayed clamping of the umbilical cord to reduce infant anemia. Geneva: WHO; 2013.
12. National Institute for Health and Care Excellence. Intrapartum care for healthy women and babies [Internet]. 2014 [cited 2019 Oct 2]. Availble from: https://www.nice.org.uk/guidance/cg190.3.
13. Perinatal Services BC: Provincial perinatal guidelines standards for neonatal resuscitation [Internet]. 2017 [cited 2019 Oct 2]. Availble from: http://residents.pediatrics.med.ubc.ca/wp-content/uploads/2013/11/PSBC_Guideline_NewbornResuscitation.pdf.
14. Ceriani Cernadas JM, Carroli G, Pellegrini L, Otaño L, Ferreira M, Ricci C, et al. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics 2006;117:e779-86.
15. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14.
16. Rosner B. Hypothesis testing: Two-sample inference. In: Rosner B, editor. Fundamentals of biostatistics. 8th ed. Boston, MA: Cengage Learning; 2015. p. 279-337.
17. Garofalo M, Abenhaim HA. Early versus delayed cord clamping in term and preterm births: a review. J Obstet Gynaecol Can 2012;34:525-31.
18. Mercer JS, Erickson-Owens DA, Collins J, Barcelos MO, Parker AB, Padbury JF. Effects of delayed cord clamping on residual placental blood volume, hemoglobin and bilirubin levels in term infants: a randomized controlled trial. J Perinatol 2017;37:260-4.
19. Mathew JL. Timing of umbilical cord clamping in term and preterm deliveries and infant and maternal outcomes: a systematic review of randomized controlled trials. Indian Pediatr 2011;48:123-9.
20. Andersson O, Hellström-Westas L, Andersson D, Domellöf M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ 2011;343:d7157.
21. Chaparro CM, Neufeld LM, Tena Alavez G, Eguia-Líz Cedillo R, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. Lancet 2006;367:1997-2004.
22. Jahazi A, Kordi M, Mirbehbahani NB, Mazloom SR. The effect of early and late umbilical cord clamping on neonatal hematocrit. J Perinatol 2008;28:523-5.
23. Viprakasit V. Approach to childhood anemia. J Hematol Transfus Med 2014;24:395-405.
24. Emhamed MO, van Rheenen P, Brabin BJ. The early effects of delayed cord clamping in term infants born to Libyan mothers. Trop Doct 2004;34:218-22.