Original Article

Delayed Cord Clamping Effects, with or without Umbilical Cord Milking, on Premature Infant Hemodynamic Circulation: A Randomized Control Trial

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Abstract

Introduction: Delayed cord clamping (DCC) results in decreased incidence of intraventricular hemorrhage (IVH) by increasing the systemic blood flow which is assessed by measuring superior vena cava (SVC) flow, right ventricular (RV) output and left ventricular (LV) output. Umbilical cord milking (UCM) is an alternative placental transfusion method with higher levels of systemic blood flow. We intend to explore if UCM can augment DCC benefits.

Objectives: To compare placental transfusion hemodynamic effects between 3 techniques: DCC, DCC with UCM before clamping (DCM-B), and DCC with UCM after cord clamping (DCM-A).

Methods: Premature infants at 28-33 weeks GA born at Thammasat University Hospital were randomized by placental transfusion methods. Vital signs were recorded, and blinded echocardiography was performed to evaluate hemodynamic circulation within 24 hours of age.

Results: One hundred and twenty infants were divided into 3 groups. No significant differences in incidence of intraventricular hemorrhage (IVH) were observed between groups and no severe IVH had occurred. DCC group had higher SVC flow (150.9 ± 81.1 mL/kg/min), RV output (271.3 ± 110.4 mL/kg/min), and LV output (232.4 ± 81.6 mL/kg/min) in comparison to DCM-B and DCM-A group but were not statistically significant.

Conclusions: Our study showed DCC with or without UCM had no significant variations in hemodynamic effects and may benefit preterm infants. DCC combined with UCM appeared to be safe with none of the participants developing severe IVH.

Keywords: Delayed cord clamping, Placental transfusion, Preterm infants, Systemic blood flow, Umbilical cord milking

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Introduction

Delayed cord clamping (DCC) significantly decreases intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) incidences in preterm infants. Umbilical cord milking (UCM) presents a type of alternative placental transfusion, which does not delay neonatal resuscitation when compared to DCC. Preterm infants with UCM have higher blood pressure and less IVH versus immediate cord clamping (ICC).[1,2]

In preterm infants, fluctuations in cerebral blood flow (CBF) and systemic blood pressure are associated with IVH.[3-5] However, the correlation between blood pressure and systemic blood flow or cardiac output is weak.[6] Measurement of superior vena cava (SVC) blood flow is an indirect assessment of CBF and systemic blood flow: infants having low SVC flow are shown to have a higher chance of earlier and more severe IVH.[7]

Preterm infants born by cesarean delivery with UCM had higher systemic blood flow compared to 45-60 seconds of DCC.[8] The American College of Obstetricians and Gynecologists (ACOG) recommends that DCC 30-60 seconds after birth should be done in preterm infants.[9] Currently, there are a variety of placental transfusion techniques which may also benefit preterm infants. In this study, the objective is to compare the hemodynamic effects of DCC, DCC with UCM before cord clamping (DCM-B), and DCC with UCM after cord clamping (DCM-A).

Methods

Study Design

A randomized controlled trial was conducted on premature infants with $28^{0/7}$ weeks to $33^{6/7}$ weeks of gestational age (GA) born at Thammasat University Hospital between July 1st, 2016 and December 31st, 2019. Infants who were multiples, diagnosed with severe disabilities, having chromosomal abnormalities, hydrops fetalis, intrauterine growth retardation, or from mothers with placenta previa with hemorrhage, abruption of placenta, prolapsed cord, or having fetal distress before birth, delivered before or on arrival or unable to give consent were not eligible. This study was approved by the Human Research Ethics Committee No.1, Faculty of Medicine, Thammasat University.

Randomization

Participants were arranged into three groups via a block-of-three randomization. Sealed, opaque envelopes were used to conceal group allocation. These envelopes were opened by the delivery nurse team at the time, mothers began preterm labor and entered the 3rd stage of labor or when mothers had premature birth scheduled due to severe pre-eclampsia for either cesarean operation or vaginal birth.

Placental Transfusion Techniques

DCC is defined as umbilical cord clamping delayed for 45 seconds after birth. DCM-B is DCC done by the attending obstetrician who would perform UCM over the length of 25 cm of the umbilical cord toward the infant for 3 times with a speed of 5-10 cm/s before cutting it. DCM-A is DCC for 45 seconds with the umbilical cord cut to around 25 cm length; after this, the pediatrician milks the umbilical cord toward the infant 3 times before cutting the cord to the usual length.

During these interventions, infants born by cesarean section were placed on their maternal abdomen, and those born by vaginal delivery, the obstetrician held the baby at the level of the maternal vaginal level.

Outcomes

All outcomes were analyzed by blinded team researchers. Echocardiography (ECHO), using a Philips HD15 PureWave with a 12 Hz probe was performed within 24 hours of age to evaluate SVC flow, right ventricular output (RVO), and left ventricular output (LVO) as the primary outcomes by a pediatric cardiologist who was blinded to the study and using ECHO technique proposed by Kluckow et al.[10]

The secondary outcomes were vital signs and physiological parameters including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) at the first 6 hours after birth. These outcomes were monitored and recorded hourly for the first six hours of life.

Sample Sizes

Meyer PM, et al. show the median SVC flow was 91 mL/kg/min (IQR 81-101) in the preterm infants with DCC.[11] We predicted that infants in the DCM-A and DCM-B groups would have a 20% difference in the SVC flow with 80% power and a two tailed test of confidence value of 0.05, hence 40 preterm infants were required for each group.

Statistical Analysis

Demographic data were reported as mean, median, range, standard deviation (SD), inter-quartile range (IQR), and percentage. One-way analysis of variance (ANOVA) was used for comparison between groups. Repeated-measures were analyzed by repeated-measures ANOVA. Statistically significance was defined as *P*-value of less than .05.

Results

There were 192 preterm infants born in the study period. From those, 72 preterm infants were excluded due to twins (n = 18), triplets (n = 6), diagnosed with severe disabilities (n = 3), chromosomal abnormalities (n = 1), hydrops fetalis (n = 1), intrauterine growth retardation (n = 8), mother with placenta previa with hemorrhage or abruption of placenta (n = 3), prolapsed cord (n = 2), fetal distress before birth (n = 7), birth before or on arrival (n = 15), and absence of consent (n = 8) (Figure 1); a total of 120 infants were enrolled with 40 infants randomized and allocated into DCC, DCM-B, and DCM-A groups. Due to unforeseen circumstances; unavailability of pediatric cardiologist or ultrasound machine, only 43 infants had ECHO results.

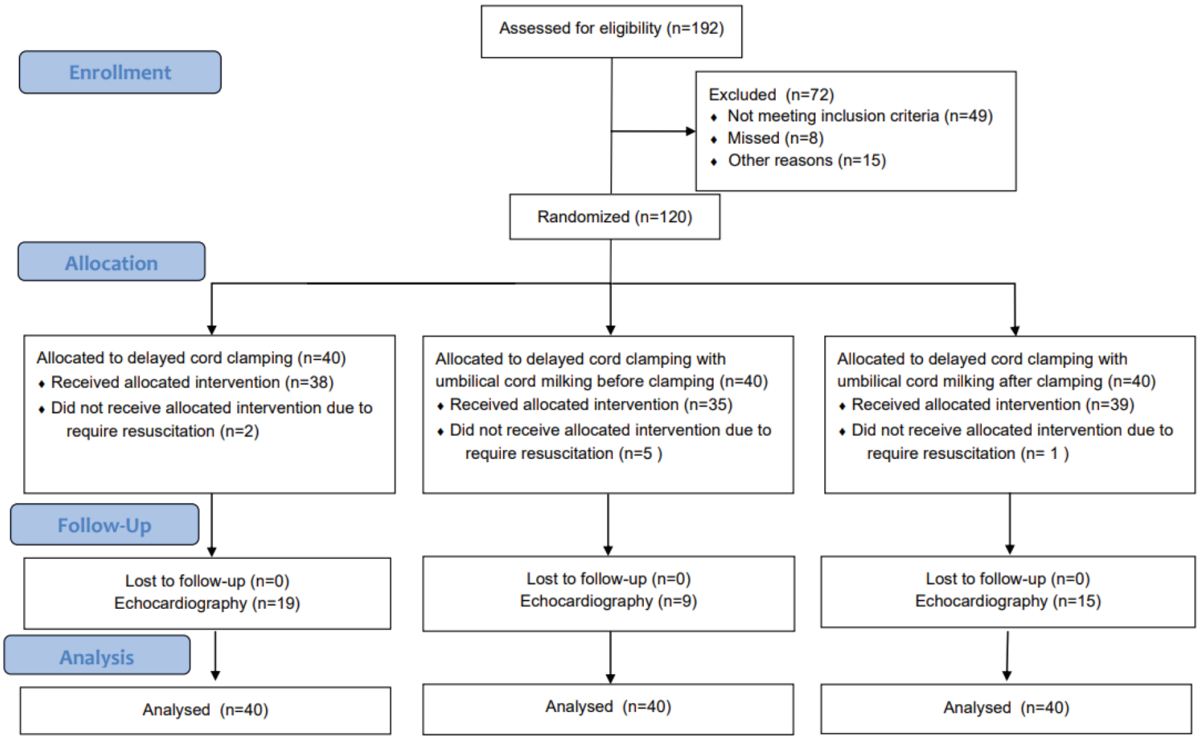

Figure 1 study flow.

Infants in the DCC group had significantly lower GA than those in DCM-B and DCM-A groups with mean GA of 31.5 ± 1.7 versus 32.1 ± 1.7 and 32.4 ± 1.1 weeks, respectively. There were no significant differences in maternal age, medical conditions, or prenatal steroid use. Among the infants, there were no significant differences in the number of male infants, birthweight, and infants with GA less than 32 weeks (Table 1). The incidence of grade I IVH was 30%, 15%, and 32.5% in DCC, DCM-B, and DCM-A, respectively, which was not statistically significant difference and there was no other grade of IVH nor severe IVH. One infant in the DCC group had shock which was caused by hypovolemia, which improved with a single dose of normal saline loading.

Table 1 Demographic data

Demographic data	**DCC (n = 40)**	**DCM-B (n = 40)**	**DCM-A (n = 40)**	***P***
Maternal age, y (mean ± SD)	29.5 ± 6.0	28.3 ± 6.2	29.2 ± 7.7	.24
Maternal diabetes (n, %)	3 (7.5)	5 (12.5)	5 (12.5)	.28
Pre-eclampsia (n, %)	7 (17.5)	9 (22.5)	5 (12.5)	.35
Full course antenatal steroids (n, %)	21 (52.5)	14 (35)	19 (47.5)	.95
Cesarean section (n, %)	24 (60)	17 (42.5)	17 (42.5)	1.00
Male (n, %)	21 (52.5)	20 (50)	21 (52.5)	1.00
Gestational age, weeks (mean ± SD)	31.5 ± 1.7	32.1 ± 1.7	32.4 ± 1.1	.01
Birthweight, g (mean ± SD)	1724.3 ± 413.2	1785.3 ± 397.2	1880.6 ± 355.9	.64
GA≤ 32 week (n, %)	29 (72.5)	23 (57.5)	24 (60)	.79
Apgar at 1 min (median, range)	9 (0-9)	9 (4-9)	9 (5-9)	< .01
Apgar at 5 min (median, range)	10 (3-10)	10 (5-10)	10 (7-10)	< .01
Intraventricular hemorrhage grade I* (n, %)	12 (30)	6 (15)	13 (32.5)	.22

**No other severity than grade I intraventricular hemorrhage*

Hemodynamic data in the first 6 hours of life demonstrated that infants in the DCM-A group had significantly higher SBP, DBP, and MAP than infants in DCC and DCM-B groups. However, there were no significant differences in heart rate, SBP, DBP, and MAP between the DCC and DCM-B groups (Figure 2). ECHO was performed on 19, 9, and 15 infants in DCC, DCM-B, and DCM-A groups respectively. Infants in DCC group had SVC flow of 150.9 ± 81.1 mL/kg/min, RVO of 271.3 ± 110.4 mL/kg/min, and LVO of 232.4 ± 81.6 mL/kg/min which were higher in comparison to infants in DCM-B and DCM-A groups, although not statistically significant (Table 2).

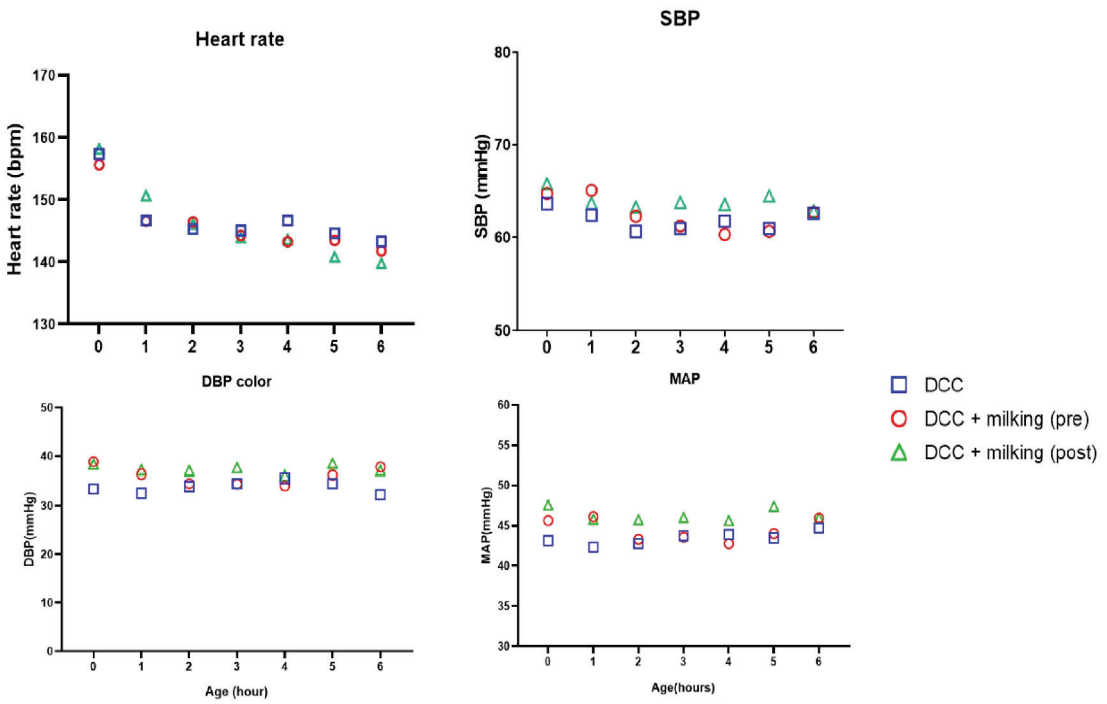

Figure 2 Changes in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) at the first 6 hours after birth.

Table 2 Hemodynamic outcomes

Outcomes	DCC (n = 19)	DCM-B (n = 9)	DCM-A (n = 15)	*P*
Time of ECHO, h:min (mean ± SD)	11:06 ± 7:24	11:42 ± 5:30	10:06 ± 5:18	.92
Superior vena cava flow, mL/kg/min (mean ± SD)	150.9 ± 81.1	136.4 ± 67.2	131.7 ± 47.4	.80
Right ventricular outflow, mL/kg/min (mean ± SD)	271.3 ± 110.4	262.0 ± 80.9	266.7 ± 66.7	.89
Diameter of atrial shunt, mm (mean ± SD)	3.23 ± 2.1	3.06 ± 1.5	3.59 ± 1.0	.03
Diameter of patent ductus arteriosus, mm (mean ± SD)	2.57 ± 1.1	1.47 ± 0.8	1.94 ± 0.9	.39
Left ventricular outflow, mL/kg/min (mean ± SD)	232.4 ± 81.6	194.7 ± 71.2	226.0 ± 48.8	.17
Patent ductus arteriosus necessitating treatment (n, %)	8 (42.1)	5 (55.6)	6 (40)	.99
Patent ductus arteriosus ligation (n, %)	2 (10.5)	0	1 (6.7)	.44

Discussion

The current ACOG recommendation is that all preterm infants should have DCC 30-60 seconds after delivery.[9] This practice is shown to reduce preterm complications such as IVH and NEC on the basis of providing better hemodynamic stability in preterm infants. The main objective of this study is to investigate potential hemodynamic changes in association with different techniques of DCC and UCM.

In terms of hemodynamics, several previous studies found differences, albeit not statistically significant, in hemodynamic parameters between infants who received UCM and DCC. A study conducted by Katheria et al. demonstrated that among infants delivered at GA less than 32 weeks by cesarean section, infants who received UCM (4 times) showed greater SVC flow and RVO with higher blood pressure in comparison to infants who received DCC. However, no differences were found among infants delivered vaginally in this study.[8] Alan et al. evaluated UCM using 3 times of milking on an intact cord over the length of 30 cm in comparison to immediate cord clamping (ICC) for preterm infants with birth weight less than 1,500 grams, the results showed that infants in the UCM group had higher MAP, although not statistically significant, in the first hour after birth when compared with infants receiving ICC.[12] The study also found that other hemodynamic parameters within the first 24 hours of life did not display any significant variations. Popat et al. also showed no significant differences in mean lowest SVC flow between infants receiving 60 seconds of DCC versus ICC within 10 seconds among infants with GA less than 30 weeks.[13] In contrast to the aforementioned studies, the studies from Hosono et al. in 2008 and 2009 found that UCM in preterm infants with GA less than 29 weeks had significantly higher mean systemic blood pressure and urine output in the first 72 hours.[2,14]

In this study, despite the fact that infants in DCM-A group had significantly higher SBP, DBP, and MAP than infants in DCC and DCM-B groups, there were no differences in SVC flow, RVO, and LVO which could explain the similarity of IVH incidences among infants in these groups. The hemodynamic results in this study were similar to studies conducted by Alan et al.[12] and Popat et al.[13] but differed from studies by Katheria et al.[8] and Hosono et al.[2,14] The differences in post-placental transfusion hemodynamics may be due to variations in actual practices of placental transfusion techniques among obstetricians and pediatricians, and also different characteristics of the studied populations.

As mentioned, our incidence of IVH was 25.8% with only IVH grade I. This was slightly more than stated by a previous report having IVH grade I-IV incidence at 15-20% for infants born < 32 weeks GA,[15] in which no placental transfusion was performed. Our study also had a higher rate of IVH than the previous study. Katheria AC, et al. which had UCM and DCC done on preterm infants born by cesarean section, IVH incidence was 10%.[8] Jasani B, et al. conducted a network meta-analysis showing the incidence of IVH in DCC group was 15.4% less than ICC group (17.8%). Of UCM group, 16.2% had IVH which also was less than ICC group (22.5%).[16] This variation may be explained in that only 50% of our infants received a complete course of antenatal steroids which was less than those studied by Katheria AC, et al.[8] (93.5%).

For severe IVH, Kluckow M, and Evans N.[7] demonstrated an association between low perfusion and the subsequent development of IVH. Jasani B, et al. had a study conclusion that DCC and UCM were associated with reductions in IVH.[16] Katheria A, et al. found a statistically significantly higher rate of severe IVH in the umbilical cord milking group, among infants born at 23 to 27 weeks' gestation, compared to delayed umbilical cord clamping (22% vs 6%, respectively).[17] Our results showed the incidences of IVH were not statistically significant difference between DCC (30%), DCM-B (15%), and DCM-A (32.5%) group, which was consistent with Krueger MS and colleagues study.[18] They demonstrated the infants less than 32 weeks had the rates of 12.5% in the 30-second DCC group and 14.3% in the 30 second DCC plus 4 times umbilical cord stripping which was not a statistically significant difference.[18] However, our study did not find any serious IVH. This could be explained by the participating infants in our study being more mature than those in other studies. Another reason was that all three methods can increase SVC flow, causing a decrease in serious IVH.

This study design was unique with the comparison among 3 different techniques of placental transfusion; DCC, DCM-B, and DCM-A, unlike previous studies which compared DCC or UCM with ICC or DCC with UCM. The small number of participants might not be sufficient to represent the general population. Our study had a statistically significant difference in GA which represented a discrepancy of internal validity. Therefore, the future study should be done using a stratified sampling method to achieve validity.

Despite the primary objective of this study being to compare the hemodynamic effects among infants received different placental transfusion techniques, only 35.8% of infants had received ECHO evaluation in contrast to 71.0% in the previous study.[8] This was caused by having only one pediatric cardiologist at the study site and further unforeseen unavailability of the echocardiogram machine which were the major obstacles for obtaining ECHO results in all of the infants. It is suggested that a further study should emphasize having a larger sample size by conducting a study in a multi-center setting and to ensure the availability of ECHO results.

In conclusion, the three methods of placental transfusion; DCC, DCM-B, and DCM-A, in premature infants have shown the similar hemodynamic effects without the increase in incidence of severe IVH. These techniques appeared to be safe and should be encouraged for the benefit of preterm infants.

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Conflict of interest: All authors report no conflicts of interest relevant to this article.

References

1. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. *JAMA Pediatr.* 2015;169:18-25.
2. Hosono S, Mugishima H, Fujita H, et al. Blood pressure and urine output during the first 120 h of life in infants born at less than 29 weeks' gestation related to umbilical cord milking. *Arch Dis Child Fetal Neonatal Ed.* 2009;94:328-331.
3. Goldberg RN, Chung D, Goldman SL, Bancalari E. The associations of rapid volume expansion and intraventricular hemorrhage in the preterm infant. *J Pediatr.* 1980;96; 1060-1063.

4. Hill A, Perlman JM, Volpe JJ. Relationship of pneumothorax to the occurrence of intraventricular hemorrhage in the premature newborn. *Pediatrics.* 1982;69:144-149.
5. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood flow velocity in respiratory distress syndrome. Relation to the development of intraventricular hemorrhage. *N Engl J Med.* 1983;309:204-209.
6. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr.* 1996;129:506-512.
7. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in the preterm infant. *Arch Dis Child Fetal Neonatal Ed.* 2000;82:188-194.
8. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm infants. *Pediatrics.* 2015;136:61-69.
9. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Delayed Umbilical Cord Clamping After Birth: ACOG Committee Opinion, Number 814. *Obstet Gynecol.* 2020;136:100-106.
10. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed.* 2000;82:182-187.
11. Meye MP, Midildenhall L. Delayed cord clamping and blood flow in the superior vena cava in preterm infants: an observational study. *Arch Dis Child Fetal Neonatal Ed.* 2012;97:484-486.
12. Alan S, Arsan S, Okulu E, et al. Effects of umbilical cord milking on the need for packed red cell transfusions and early neonatal hemodymamic adaptation in preterm infants born ≤1500 g: a prospective, randomized, controlled trial. *J Pediatr Hematol Oncol.* 2014;36:493-498.
13. Popat H, Robledo KP, Sebastian L, et al. Effect of delayed cord clamping on systemic blood flow: A randomized controlled trial. *J Pediatr.* 2016;178:81-86.
14. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2008;93:14-19.
15. Heuchan AM, Evans N, Henderson Smart DJ, Simpson JM. Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand Neonatal Network, 1995-1997. *Arch Dis Child Fetal Neonatal Ed.* 2002;86:86-90.
16. Jasani B, Torgalkar R, Ye XY, Syed S, Shah PS. Association of umbilical cord management strategies with outcomes of preterm Infants: A systematic review and network meta-analysis. *JAMA Pediatr*. 2021;175:e210102.
17. Katheria A, Reister F, Essers J, et al. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping with death or severe Intraventricular Hemorrhage Among Preterm Infants. *JAMA.* 2019;322:1877-1886.
18. Krueger MS, Eyal FG, Peevy KJ, Hamm CR, Whitehurst RM, Lewis DF. Delayed cord clamping with and without cord stripping: a prospective randomized trial of preterm neonates. *Am J Obstet Gynecol.* 2015;212(3):394.