SMJ Singapore Medical Journal

The haemodynamic effects of umbilical cord milking in term infants: a randomised controlled trial

Mehmet Tekin[1], MD, Mahmut Gokdemir[2], MD, Erzat Toprak[3], MD, Musa Silahli[4], MD, Hasan Energin[3], MD, Zeynel Gokmen[4], MD

[1]Department of Pediatrics, [2]Department of Pediatric Cardiology, Baskent University Konya Training and Research Hospital, [3]Department of Obstetric and Gynecology, Meram Medicine Faculty, Necmettin Erbakan University, [4]Neonatal Intensive Care Unit, Baskent University Konya Training and Research Hospital, Konya, Turkey

Correspondence: Dr Mehmet Tekin, Consultant, Department of Pediatrics, Baskent University Konya Training and Research Hospital, Saray Street, 42080 Selcuklu, Konya, Turkey. dr.mehmettekin@gmail.com

Singapore Med J 2021, 1–13
https://doi.org/10.11622/smedj.2022041
Published ahead of print: 3 April 2022

ABSTRACT

INTRODUCTION Umbilical cord milking (UCM) is a method which allows for postnatal placental transfusion. Several benefits of this method have been demonstrated in studies. However, our knowledge about the haemodynamic effects of this method is limited among term infants. The aim of this study was to evaluate the haemodynamic effects of UCM in term infants.

METHOD In this prospective randomised controlled study, 149 healthy term infants with a birth week of 37 weeks or more were randomised to either the UCM or immediate cord clamping (ICC) groups. Blinded echocardiographic evaluations were performed in all the neonates in the first 2 to 6 hours.

RESULTS Superior vena cava (SVC) flow measurements were higher in the UCM group compared to the ICC group (132.47 ± 37.0 mL/kg/min vs. 126.62 ± 34.3 mL/kg/min), but this difference was not statistically significant. Left atrial diameter (12.23 ± 1.99 mm vs. 11.43 ± 1.78 mm) and left atrium-to-aorta diastolic diameter ratio (1.62 ± 0.24 vs. 1.51 ± 0.22) were significantly higher in the UCM group. There were no significant differences in other echocardiographic parameters between the UCM and ICC groups.

CONCLUSION We found that no difference in the SVC flow measurements in term infants undergoing UCM. The lack of any significant difference in SVC flow may be explained by a mature cerebral autoregulation mechanism in term neonates.

Keywords: echocardiography, infant, perinatal care, superior vena cava, umbilical cord

INTRODUCTION

The optimal time for postnatal umbilical cord clamping is still a matter of debate. Immediate cord clamping (ICC) is used more frequently during the third stage of labor in modern clinical practice, nevertheless has no physiological basis. Alternative methods are available to increase the amount of 'placental transfusion' which is defined as the blood volume that passes to the baby during the time period between birth and cord clamping. Many studies have demonstrated the beneficial effects of alternative methods such as delayed cord clamping (DCC) and umbilical cord milking (UCM) on term and preterm infants.[1] In 2015, the World Health Organization (WHO) recommended DCC in term or preterm newly born infants not requiring positive-pressure ventilation for the prevention of iron deficiency anemia.[2] UCM is a method that has similar benefits to DCC and a low risk of delayed resuscitation and hypothermia due to its short duration.[3]

Doppler ultrasound is a well-defined and reliable method when performed by experienced clinicians for cardiac output and vascular flow measurements in newborns.[4-6] Doppler echocardiography enables assessment of right ventricular output (RVO) and left ventricular output (LVO).[5-7] However, none of these two parameters are able to represent the exact systemic blood flow, due to the occurrence of remnant shunts in the early stages of the postnatal adaptation period.[8,9] To overcome this problem, Kluckow and Evans have introduced measuring superior vena cava (SVC) flow in preterm infants.[10] The SVC provides venous drainage of the head, upper extremities, and brain. It is affected by neither ductal nor atrial shunts. Therefore, SVC flow measurement has been accepted as a reliable indicator of cerebral perfusion and intravascular volume status.[10]

In this study, we aimed to evaluate the effect of UCM on SVC flow measurement, using Doppler echocardiography in term infants. Our hypothesis was that the SVC flow, which is an indicator of intravascular volume, is raised with UCM.

METHODS

This single-center, randomized controlled trial was undertaken between April 2016 and August 2016. 149 healthy term infants with a birth week of 37 weeks or more were included in the study. Local Ethics Committee approval was obtained before the study (KA16/09). Informed consent was obtained from all families before delivery. The exclusion criteria were as follows: Premature (< 37 weeks) and postmature (> 42 weeks) infants; monochorionic twins; infants with placenta previa and ablatio placenta, Rh sensitization, meconium aspiration syndrome, hydrops fetalis, intrauterine growth restriction (IUGR), maternal anemia (Hct < 29%), syndromic lethal anomalies, congenital complicated structural heart diseases, persistent left SVC and short umbilical cord (< 20 cm). In addition, cases in which the obstetrician rejected performing the intervention (ie, unaware of the study protocol) or optimal data acquisition could not be achieved, were not included in the study.

Infants were randomly assigned to the UCM or the ICC group. For randomization, we used computer created random numbers in blocks of 4. Multiple-birth infants, once eligible for inclusion, were assigned to the same group. Due to the structure of the interventions, blinding of the clinicians was not feasible. The laboratory investigator and pediatric cardiologist performing the echocardiographic examinations were blinded to the interventions.

In the UCM group, infants were located at or below the placental level during vaginally delivery or at the same placental level during cesarean section delivery. Afterwards, the umbilical cord was milked 5 times at approximately 20 cm towards the umbilicus. The milking speed was about 10 cm per second. The cord was clamped within 10 seconds after delivery in the ICC group. Then umbilical cord cut immediately. 1 ml cord blood was collected in a heparin-containing vial for blood gas analysis in all groups. These samples were analyzed using Radiometer ABL 700 blood gas analyzer (Radiometer Medical APS, Bronshoj, Denmark). Prenatal, natal and postnatal data were recorded, along with the sociodemographic data. Blinded

echocardiographic evaluations were performed in all neonates in the first 2 to 6 hours by an experienced pediatric cardiologist. Echocardiography was not performed within the first 2 hours not to interfere with the first contact between the infant and the mother and to protect the baby from hypothermia. During the hospitalization period, the newborns were followed for polycythemia, neonatal jaundice, and respiratory distress. Secondary outcomes included Apgar scores, umbilical cord pH, hemoglobin (Hb) and hematocrit (Hct) levels, respiratory distress, peak bilirubin level of infants with clinical jaundice and need for phototherapy.

Echocardiographic examination was applied using the Vivid S6 cardiovascular ultrasound system with a 6S phased-array transducer (GE Vingmed Ultrasound AS, Horten, Norway) while the infants were asleep or in a quite awake state. The same probe was used for color Doppler, pulsed wave Doppler and M-mode measurements. The images were analyzed offline. For each measurement, at least three consecutive waveforms were recorded for analysis of SVC diameter and SVC flow according to the method described by Kluckow and Evans.[10]

The SVC flow was detected from a low subcostal view and the pulsed Doppler recording was made at the intersection of the SVC and the right atrium. The SVC flow formula is as follows: cross-sectional area x velocity-time integral x heart rate/body weight (kg) where VTI = velocity time integral (in centimeters), π = 3.14 and the flow is stated as milliliters per kilogram per minute.[10,11]

The SVC VTI was determined from the Doppler velocity tracings and found the middle value of from 10 consecutive cardiac cycles. The forward flow was positively integrated, while any retrograde flow was disregarded due to its little volume and inconsistent appearance. The heart rate calculated using cardiac cycles.

High parasternal long-axis view was used for SVC diameter measurement. The transducer was placed as near to the midline as possible to acquire directly anteroposterior views of the SVC. The maximum and minimum internal diameters were then measured at the

point where the SVC begins to open up into the right atrium. These measurements were made offline. A mean of the greatest and least diameter was used for the flow calculation due to the variation in vessel diameter through the cardiac cycle. Ten cardiac cycles were examined for measuring the diameters, and these measurements were averaged.

M-mode images were obtained at the level of the mitral valve and through the aortic valve from the parasternal long-axis view. In assessing left ventricular size and function we use the excursion of the left ventricular posterior wall (LVPW) to indicate the site of measurement. The maximum posterior excursion of the LVPW defines end-diastole and the maximal anterior excursion of the LVPW defines end-systole. Using the same parasternal long-axis view, the cursor was aligned with the root of the aortic valve. The aortic root diameter was the distance between parallel echoes of the anterior and posterior wall of the ascending aorta. The left atrium dimension was measured at the end of systole and was compared with the aortic root at the same time to create a ratio. In the suprasternal view, the duct was imaged with cross-sectional and color Doppler echocardiography to determine its size. The ductal internal diameter was measured at the narrowest point of the color Doppler in the duct.

The sample size was calculated by using Katheria et al's study.[12] Sample size calculation determined at least 48 neonates in each group were required to demonstrate at least a 20% difference in SVC between UCM and ICC groups with type one error to 0.05 and 90% power. (R 3.0.1. open-source program). Intra-observer variability was determined by the repetition of analysis by a single observer 6 months later. Bland–Altman plots were used to illustrate intra-observer variability for the measurement of SVC VTI and SVC diameters.

We performed statistical analyses using SPSS for Windows 11.5 (International Business Machines Corp., New York, USA). Normally distributed continuous variables were compared using the unpaired Student's t-test. Not normally distributed variables were applied to logarithmic transformation. Non-parametric continuous variables were compared using the

Mann-Whitney U test. Categorical data were compared using chi-square or Fisher's exact test, as applicable. A p-value of less than 0.05 was considered significant.

RESULTS

Between 1 April 2016 and 31 August 2016, 149 infants were enrolled in the study (Fig. 1). The baseline characteristics of the study population are shown in Table I. There were no significant differences in Apgar scores at 1 and 5 minutes, cord blood pH, Hb and Hct between ICC and UCM groups. Only one infant randomized to UCM group had respiratory distress and respiratory distress prevalence did not differ significantly between two groups (p = 0.500). There were no significant differences in the peak bilirubin levels between UCM and ICC groups. Need for phototherapy was also similar in both groups (Table II).

Left atrial diameter and the left atrium-to-aorta diastolic diameter ratio were significantly higher in the UCM group (p = 0.013 and p = 0.005, respectively). There were no significant differences regarding other echocardiographic parameters between UCM and ICC groups. SVC VTI, SVC diameter, and SVC flow measurements were higher in the UCM group, but these differences did not reach statistical significance (Table II).

The UCM procedure has been performed by four obstetricians. No statistically significant difference was found between UCM and ICC groups when all the babies are divided into groups according to obstetricians. Bland–Altman plots were used to illustrate intra-observer variability. A mean difference (bias) for maximum SVC diameter was -0.01 mm (95%Cl -0.07 to 0.05 mm) and for minimum SVC diameter was 0.04 mm (95%Cl -0.04 to 0.11 mm). There was no evidence of a difference between the repetitive measurements of SVC maximum and minimum diameters (p = 0.51 and 0.35, respectively). A mean difference (bias) for SVC VTI was 0.13 cm (95%Cl -0.27 to 0.54 cm, p = 0.51)

DISCUSSION

This is the first study in the literature to examine the effects of UCM on the SVC flow in term newborns. SVC flow volume was higher in the UCM group; however, this difference did not reach statistical significance.

Katheria et al have demonstrated that premature infants less than 32 weeks undergoing UCM had greater SVC flow in the first 6 and 18 hours.[12] Similarly, Takami et al have found increased SVC flow at 3, 6 and 12 hours of life in 50 premature infants under 29 weeks gestational age.[13] Contrary to this, in a study that investigated the UCM on the effect of SVC flow in less than 31 weeks gestational age premature infants, they found no significant difference between the groups in term of SVC flow.[14] Herein, we showed that left atrial diameter and left atrium-to-aorta diastolic diameter ratio are significantly higher in infants undergoing UCM, which represents the increased blood volume in these infants. On the other hand, we did not find a significant increase in SVC flow volume in the UCM group. Ilves et al. showed that blood pressure and mean blood flow velocity in cerebral arteries have no correlation and healthy neonates can autoregulate their cerebral blood flow during the first day of life.[15] More mature autoregulation mechanisms in term babies may explain the fact that the difference in SVC flow measurements does not occur despite the increase in volume load.

The greatest concerns about UCM are symptomatic polycythemia, jaundice, and respiratory distress. Although we did not evaluate polycythemia in our study, previous studies have not reported an increased risk of polycythemia in term infants.[16,17] In a randomized controlled study performed in 200 healthy term and near-term infants, there was no difference regarding jaundice prevalence and peak bilirubin levels.[16] Bora et al have performed UCM on a 40 cm cord segment in term babies and have not detected any differences concerning jaundice prevalence.[17] There was also no increase in jaundice prevalence or need for phototherapy in studies performed in preterm infants.[12,18] Our results were in accordance with these findings.

Studies investigating the effects of placental transfusion in term and preterm infants have not reported any adverse effect on the respiratory system that could lead to respiratory distress.[19] It has been shown that placental transfusion methods reduce the duration of oxygen therapy, ventilation, and oxygen requirement frequency at 36 weeks PMA in preterm infants.[12,20]

We did not evaluate the hemoglobin and hematocrit values at birth among the groups. There were different results in previous studies. Silahli et al found no significant differences in the hemoglobin or hematocrit levels between the UCM and ICC groups among premature infants less than 32 weeks gestational age.[21] In another study on extremely premature infants, they found a statistically significant difference as a birth hemoglobin level between the ICC and UCM groups.[18] This may be related to the different methodological approaches of the UCM procedure. There is a need for standardization studies about UCM procedure.

The strengths of our study include the larger study population compared to prior studies and the presence of a single investigator who made the SVC flow measurements which avoided interobserver variability. In order to evaluate the intraobserver variability, the measurements of diameters and VTI were performed by the same pediatric cardiologist for the second time 6 months later. There was no significant mean bias between the first and second measurements.

The limitation of our study is that UCM procedure has been performed by multiple obstetricians who had varying levels of experience. But we could not find the difference in the SVC flow between groups when we evaluate obstetricians one by one. In addition, we performed echocardiographic measurements in the first 2 to 6 hours for once and did not perform recurrent measurements. A randomized controlled study of preterm infants has shown a significant increase in SVC measurements at 6 and 30 hours, but there was no difference in the measurement at 18 hours. The authors have attributed this lack of difference to a period of

adaptation.[12] In our study, there could have been a significant difference in the SVC flow if recurrent measurements were made.

In conclusion, we found that there is no difference in the SVC flow measurements in term infants undergoing UCM. The lack of significant difference in the SVC flow may be explained by mature cerebral autoregulation mechanism in term neonates.

Table I. Maternal and neonatal baseline characterics.

	UCM (n =74)	ICC (n=75)	P
Gestational age, wk, mean±SD	38.36±0.90	38.15±0.75	0.115
Birth weight, gr, mean±SD	3360.13±448.94	3325.47±423.80	0.627
Sex, Male(n)/Female(n)	34/40	39/36	0.514
Maternal age, year, mean±SD	31.43±4.39	30.55±4.85	0.246
Gravida, median, (range)	2.0 (1-8)	2.0 (1-6)	0.288
Parity, median, (range)	2 (1-5)	2(1-4)	0.257
Pregnancy-induced hypertension, n (%)	0 (0.0)	0(0.0)	---
Gestational DM, n (%)	7(9.5)	8(10.7)	0.785
Anesthesia (spinal), n (%)	69(93.0)	72(96.0)	0.247
Vaginal delivery, n (%)	6(7.0)	3(4.0)	0.247
Maternal Hb, g/dl, mean±SD	12.26±1.30	12.25±1.19	0.951
Maternal Hct, %, mean±SD	37.081±3.62	37.25±3.30	0.767

DM: diabetes mellitus; ICC: immediate cord clamping; UCM: umbilical cord milking

Table II. Echocardiographic parameters and secondary outcomes.

	UCM (n=74)	ICC (n=75)	P
D. arteriosus diameter, mm, mean±SD	2.47±0.69	2.40±0.73	0.588
F. ovale diameter, mm, mean±SD	2.98±1.18	2.81±0.88	0.343
L. atrium diameter, mm, mean±SD	12.23±1.99	11.43±1.78	***0.013***
Aorta diameter, mm, mean±SD	7.54 ± 0.66	7.55 ± 0.84	0.891
Left atrium-to-aorta diastolic diameter ratio, mean±SD	1.62±0.24	1.51±0.22	***0.005***
LVEDD, mm, mean±SD	17.02 ± 1.61	16.89 ±2.02	0.670
LVESD, mm, mean±SD	10.89 ± 1.55	10.74 ±1.57	0.574
EF, %, mean±SD	69.56 ± 6.35	69.39 ± 6.27	0.826
FS, %, mean±SD	36.53 ± 5.39	36.32 ± 5.07	0.803
Heart rate, bpm, mean±SD	130.83±14.83	128.21±13.86	0.267
Cord blood gas sample pH,mean±SD	7.38±0.05	7.36±0.05	0.330
Cord blood gas sample Hb, g/dl, mean±SD	15.80±1.50	15.91±1.58	0.670
Cord blood gas sample Hct, %, mean±SD	48.36±4.57	48.70±4.76	0.661
Peak total bilirubin, mg/dl, mean±SD	15.16±2.85	15.28±3.65	0.898
Peak direct bilirubin, mg/dl, mean±SD	0.44±0.08	0.46±0.08	0.372
Respiratory distress, n (%)	1(1.3)	0(0.0)	0.500
Phototherapy, n (%)	8(10.8)	8(10.7)	1.000
Apgar score 1 min, median, (range)	9(8-9)	9(8-9)	1.000
Apgar score 5 min, median, (range)	10(9-10)	10(9-10)	1.000
SVC VTI, cm/sec, mean±SD	14.62±3.21	14.68±3.15	0.912
SVC diameter, mm, mean±SD	5.43±0.57	5.33±0.63	0.314
SVC flow, ml/kg/min, mean±SD	132.47±37.0	126.62±34.3	0.318

EF: ejection fraction; FS: fractional shortening; ICC: immediate cord clamping; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; SVC: superior vena cava; UCM: umbilical cord milking; VTI: velocity time integral

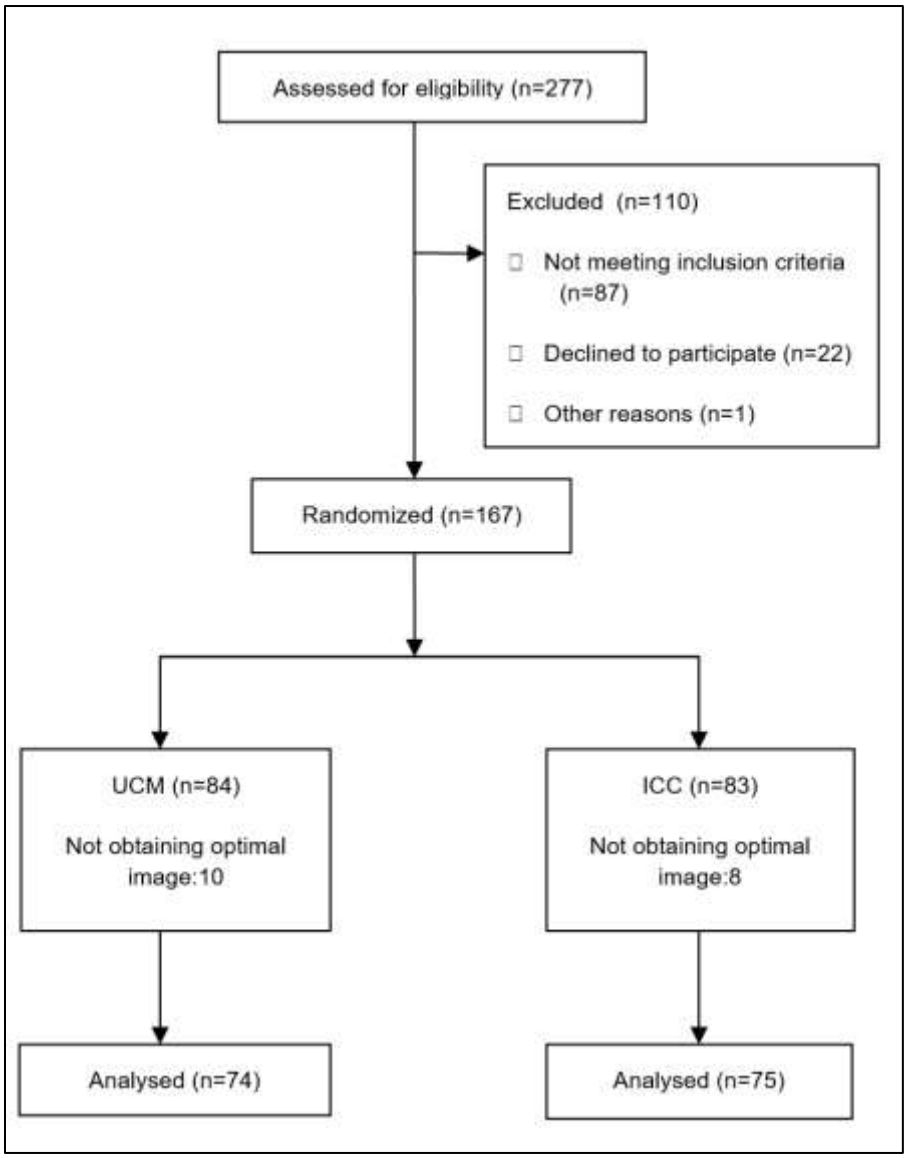

Fig. 1 Flow diagram.

REFERENCES

1. Raju TN. Timing of umbilical cord clamping after birth for optimizing placental transfusion. Curr Opin Pediatr 2013, 25:180-7.
2. World Health Organization. Delayed clamping of the umbilical cord to reduce infant anaemia. Available at: http://apps.who.int/iris/bitstream/handle/10665/120074/WHO_RHR_14.19_eng.pdf?sequence=1. Accessed March 21, 2022.
3. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm ınfants. Pediatrics 2015; 136:61-9.
4. Mellander M, Sabel KG, Caidahl K, Solymar L, Eriksson B. Doppler determination of cardiac output in infants and children: comparison with simultaneous thermodilution. Pediatr Cardiol. 1987; 8:241-6.
5. Alverson DC, Eldridge M, Dillon T, Yabek SM, Berman W Jr. Noninvasive pulsed Doppler determination of cardiac output in neonates and children. J Pediatr 1982; 101:46-50.
6. Alverson DC, Eldridge MW, Johnson JD, et al. Noninvasive measurement of cardiac output in healthy preterm and term newborn infants. Am J Perinatol 1984; 1:148-51.
7. Tsai-Goodman B, Martin RP, Marlow N, Skinner JR. The repeatability of echocardiographic determination of right ventricular output in the newborn. Cardiol Young 2001; 11:188-94.
8. Evans N. Current controversies in the diagnosis and treatment of patent ductusarteriosus in preterm infants. Adv Neonatal Care 2003; 3:168–77.
9. Evans N, Iyer P. Incompetence of the foramen ovale in preterm infants supported by mechanical ventilation. J Pediatr 1994;125(5 Pt 1):786-92.
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:F182-7.
11. Lee A, Liestøl K, Nestaas E, et al. Superior vena cava flow: feasibility and reliability of the off-line analyses. Arch Dis Child Fetal Neonatal Ed 2010; 95:F121-5.

12. Katheria AC, Leone TA, Woelkers D, et al. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. J Pediatr 2014; 164:1045-50.
13. Takami T, Suganami Y, Sunohara D, et al. Umbilical cord milking stabilizes cerebral oxygenation and perfusion in infants born before 29 weeks of gestation. J Pediatr 2012; 161:742-7.
14. El-Naggar W, Simpson D, Hussain A, et al. Cord milking versus immediate clamping in preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2019; 104:F145-50.
15. Ilves P, Mare L. Development changes in cerebral and visceral blood flow velocity in healthy neonates and infants. J Ultrasound Med 2008; 27:199-207.
16. Upadhyay A, Gothwal S, Parihar R, et al. Effect of umbilical cord milking in term and near term infants: randomized control trial. J Obstet Gynecol 2013; 208:120.e1-6.
17. Bora R, Akhtar SS, Venkatasubramaniam A, Wolfson J, Rao R. Effect of 40-cm segment umbilical cord milking on hemoglobin and serum ferritin at 6 months of age in full-term infants of anemic and non-anemic mothers. J Perinatol 2015; 35:832-6.
18. March MI, Hacker MR, Parson AW, Modest AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. J Perinatol 2013; 33:763-7.
19. Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. J Midwifery Womens Health 2001; 46:402-14.
20. 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:F14-9.
21. Silahli M, Duman E, Gokmen Z, et al. The relationship between placental transfusion, and thymic size and neonatal morbidities in premature infants - a randomized control Trial. J Pak Med Assoc 2018; 68:1560-5.