Journal of Perinatology (2013) 33, 763–767

www.nature.com/jp

ORIGINAL ARTICLE

The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial

MI March[1,2,3], MR Hacker[2,3], AW Parson[4], AM Modest[2] and M de Veciana[5]

OBJECTIVE: Delayed cord clamping has been shown to decrease the need for transfusion in preterm neonates, but may delay resuscitation. The aim of this study was to determine whether umbilical cord milking compared with immediate cord clamping in extremely preterm deliveries reduces the need for neonatal red blood cell transfusion.

STUDY DESIGN: Women admitted to a tertiary care center and expected to deliver between 24 to 28 completed weeks of gestation were randomized to cord milking before clamping or immediate cord clamping. The primary outcome was the risk of neonatal transfusion, reported as risk ratio (RR) and 95% confidence interval (CI).

RESULT: Of 113 women who were enrolled and randomized, 56 were assigned to cord milking with 36 remaining eligible and completing the study and 57 were assigned to the control group with 39 remaining eligible and completing the study. Albeit not statistically significant, neonates in the cord milking group were less likely to require transfusion compared with those in the control group (RR: 0.86; 95% CI: 0.73 to 1.0). Neonates whose cords were milked had higher hematocrits at birth ($P = 0.004$) and were less likely to develop an intraventricular hemorrhage ($P = 0.0195$).

CONCLUSION: Milking the umbilical cord of a preterm neonate is an easy intervention with the potential to improve perinatal outcomes. Our results suggest that milking of the cord increases the neonate's initial hematocrit and may lessen the need for transfusion in the neonatal period. The observed reduction in the incidence of intraventricular hemorrhage may have important long-term implications that warrant further study.

Journal of Perinatology (2013) **33,** 763–767; doi:10.1038/jp.2013.70; published online 18 July 2013

Keywords: umbilical cord milking; preterm delivery; anemia of prematurity

INTRODUCTION

Despite recent advances in perinatal and neonatal medicine that have improved the survival of very low birth weight infants (less than 1500 g), anemia of prematurity continues to complicate the care of these infants who often require red blood cell transfusions within the first three weeks of life.[1] Although transfusion remains the mainstay of management for anemia of prematurity, it is a temporary and imperfect treatment. Its use inhibits erythropoiesis and comes with risks such as infection, graft-versus-host disease and transfusion-related lung and gut injuries. Current strategies to reduce the number of transfusions include the administration of recombinant human erythropoietin and supplementation with iron, folate and vitamin B12. However, these treatments have unclear benefits and accompanying risks.[2–5]

After birth, the timing of cord clamping may have a substantial impact on the amount of blood transfused to the newborn from the placenta. During the first 5 to 15 s after delivery, blood volume increases by 5 to 15 ml kg^{-1} as a result of uterine contractions. This early placental transfusion does not occur if the cord is clamped immediately after birth or if uterine contractions do not occur.[6] In preterm neonates, randomized trials and meta-analyses have shown that delaying cord clamping for at least 30 s compared with immediate cord clamping results in increased circulating blood volume in the first 24 h of life, and a lower incidence of red blood cell transfusion, necrotizing enterocolitis and intraventricular hemorrhage.[7–16]

Despite these advantages, a delay in cord clamping of 30 s or more may theoretically interfere with neonatal resuscitation and potentially increase the risk of neonatal hyperbilirubinemia.[9] An alternative method, active placental transfusion (milking the umbilical cord toward the baby before clamping), should take less than 5 s and therefore should not interfere with neonatal resuscitation. One published randomized controlled trial has compared delaying cord clamping for 30 s to cord milking in preterm infants and found that the two interventions resulted in a similar amount of placento-fetal blood transfusion.[17] A recent study of cord milking compared with immediate clamping in term infants delivered by cesarean section showed an increase in hematocrit at 36 to 48 h of age.[18] Although some practitioners have adopted this practice of active milking of the umbilical cord in preterm deliveries, there is a paucity of data to support this practice.[19]

[1]Division of Maternal-Fetal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Harvard Medical School, Boston, MA, USA; [4]Hampton Roads Ob/Gyn Center, Norfolk, VA, USA and [5]Eastern Virginia Medical School, Norfolk, VA, USA. Correspondence: Dr MI March, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KS Third Floor, Boston 02215, MA, USA.
E-mail: melissamarch@gmail.com

This study was previously presented at the Society for Maternal Fetal Medicine's 31st Annual Meeting, held in San Francisco, CA ('The Efficacy of Umbilical Cord Milking on the Reduction of Red Blood Cell Transfusion Rates in Infants Born Between 24 and 28 6/7 Weeks Gestation - A Randomized Controlled Trial,' Abstract ID: 221362) on 7–12 February 2011.
Received 16 January 2013; revised 27 March 2013; accepted 23 May 2013; published online 18 July 2013

Only one published randomized controlled trial has compared umbilical cord milking with immediate cord clamping in extremely preterm deliveries (less than 28 weeks). This study was performed in Japan and reported that umbilical cord milking reduced the need for red blood cell transfusions in the neonatal period.[20] The same study also reported that milking the cord in extremely preterm infants increased infant blood pressure in the first 12 h of life and urine output in the first 72 h of life.[21] A recent retrospective study confirmed these results and demonstrated that umbilical cord milking as compared with immediate cord clamping also improved neonatal left ventricular diastolic function and stabilized neonatal cerebral oxygenation.[22]

The objective of our pilot randomized controlled trial was to investigate the influence of active umbilical cord milking before cord clamping, compared with immediate cord clamping, on the red blood cell transfusion requirements in neonates born between 24 and 28 completed weeks of gestation in a US population.

METHODS

This randomized controlled trial was conducted at a single tertiary care center and was approved by the Institutional Review Board at Eastern Virginia Medical School. Pregnant women (aged 18 years or older) admitted to our institution at risk for delivering a singleton preterm infant between 24 and 28 completed weeks of gestation were eligible to participate if there were adequate time before anticipated delivery to obtain written informed consent. Exclusion criteria included antenatally diagnosed major fetal congenital anomaly, known Rh sensitization, hydrops fetalis, known recent maternal exposure to Parvovirus, elevated peak systolic velocity of the fetal middle cerebral artery or clinical suspicion of placental abruption at delivery due to excessive maternal bleeding or uterine hypertonicity. All participants were given antenatal corticosteroids on admission.

Women who gave written informed consent were randomized before delivery to one of two groups using random permuted blocks of 10; an independent statistician provided the randomization sequence. Serially numbered opaque envelopes contained arm bands identifying whether a patient was assigned to the cord milking or control group. These arm bands were secured on the patient's wrist after randomization to alert the obstetrical staff that the patient was a study participant.

In order to ensure standardization of the cord milking technique, all delivering physicians were shown a video on how to perform the cord milking before study initiation (Supplementary Movie 1). An extended hand's width length of cord (from the tip of the thumb to the tip of the pinky finger, 20 ± 2 cm) was used as the standard. Infants in the cord milking group were placed at or below the level of the placenta if delivered vaginally or at the same level as the placenta if delivered by cesarean section, and ~ 20 cm of the umbilical cord was actively milked towards the umbilicus three times before clamping the cord. Infants in the control group had the cord clamped and cut immediately after delivery.

The neonatologists and pediatric support staff were not blinded to treatment assignment given that they were required to be present for the delivery. However, they were not alerted for study participation or treatment assignment and no notation of study participation was made in the neonate's chart in order to minimize the possibility that postnatal treatment decisions would be influenced by study participation. Demographic and outcome data were obtained from the electronic medical records of the women and their neonates. The primary outcome was the need for red blood cell transfusion in the first 28 days of life. Secondary outcomes included Apgar scores, umbilical cord pH, type of resuscitation, initial neonatal hemoglobin and hematocrit, initial neonatal blood pressure, time (in days) from birth to transfusion, total volume of red blood cells transfused in the first 28 days of life, need for phototherapy, number of days of phototherapy and known complications of prematurity such as respiratory distress syndrome, intraventricular hemorrhage (including stage), periventricular leukomalacia, chronic lung disease, retinopathy of prematurity, hyperkalemia, sepsis, necrotizing enterocolitis (defined by Bell's criteria) and death. All neonatal diagnoses were obtained from pediatric discharge summaries or death summaries.

The sample size was calculated based on the expected incidence of red blood cell transfusion in extremely preterm neonates. With immediate cord clamping, $\sim 70\%$ of neonates were expected to require transfusion in the first 28 days of life; this was estimated from data provided by the neonatologists at our institution. We hypothesized that cord milking would result in a 30% reduction in the incidence of blood transfusion, which would yield an incidence of 49% in the treatment group. Assuming a one-sided α level of 0.05, 67 evaluable infants were needed in each group to achieve 80% power. We aimed to enroll 80 women in each group to account for loss due to patient withdrawal and the expectation that some participants would become ineligible due to continuation of pregnancy beyond 28 completed weeks of gestation or the development of bleeding suspicious for placental abruption.

All data analysis was performed using SAS 9.3 (SAS institute, Cary, NC, USA). All tests were two sided and an intent-to-treat approach was used. Data are presented as median (interquartile range) or proportion. Comparisons were made using a χ^2 or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. We used Poisson regression with the robust error variance to calculate risk ratios and 95% confidence intervals. One planned interim analysis and one unplanned interim analysis were conducted. An adjusted *P*-value that would account for the interim analyses was not specified *a priori*. We considered the methods of adjustment typically used in trial design and chose the most conservative option given that the choice was being made after conclusion of the trial. To account for the two interim analyses and the final analysis, we have used Pocock's method to adjust the *P*-values and preserve the Type 1 error. On the basis of these considerations, a *P*-value <0.0221 was considered statistically significant[23]. The study was discontinued after the second interim analysis with 113 enrolled patients.

RESULTS

From September 2009 through June 2011, 113 women consented to participate and were enrolled and randomized; 57 women were assigned to the control group (immediate cord clamping) and 56 were assigned to the cord milking group. Of these women, 75 (66.4%) were included in the final analysis and the remaining 38 were excluded. Of the participants who were excluded from the final analysis, 16 in each group remained pregnant past 28 completed weeks of gestation. In the control group, an additional 2 women were excluded after enrollment when they were noted to be ineligible—one who did not meet the maternal age criteria and another who had known Rh sensitization. In the cord milking group, 4 women were excluded because they developed vaginal bleeding that was concerning for placental abruption before or during delivery. Included in the final analysis were 39 women in the control group and 36 in the cord milking group. During the delivery of one woman in the cord milking group, the cord was inadvertently clamped and cut immediately.

The median gestational age at admission and randomization was 25.9 (24.9 to 27.1) weeks in the cord milking group and 25.0 (24.3 to 26.4) weeks in the control group. The most common diagnoses at admission were preterm labor, preterm premature rupture of membranes, preeclampsia and intrauterine growth restriction. The hemoglobin and hematocrit at admission were within normal limits in both groups. Baseline participate characteristics are shown in Table 1.

The median gestational age at delivery was 27.0 (25.5 to 28.1) weeks in the cord milking group and 26.3 (25.1 to 27.1) weeks in the control group. The most common intrapartum complication in each group was non-reassuring fetal heart tracing (22.2% in the cord milking group and 20.5% in the control group). In the cord milking group, three participants (8.3%) had chorioamnionitis, whereas in the control group eight participants had chorioamnionitis (20.5%). In each group, the majority of women had a cesarean delivery (55.6% in the cord milking group and 66.7% in the control group). Intrapartum and neonatal characteristics are displayed in Table 2.

In the cord milking group, 83.3% of neonates required transfusion of packed red blood cells in the first 28 days of life compared with 97.4% in the control group ($P = 0.05$), yielding a RR of 0.86 (95% confidence interval: 0.73 to 1.0). Although not an *a priori*-specified analysis, we evaluated the need for transfusion in the more immediate postnatal period (the first 14 days of life).

Table 1. Baseline participant characteristics

Characteristic	*Milked* (n = *36*)	*Control* (n = *39*)
Maternal age (years)	26.9 (22.6–30.7)	29.5 (23.7–33.5)
Gravidity		
1	8 (22.2)	6 (15.4)
⩾2	28 (77.8)	33 (84.6)
Parity		
0	17 (47.2)	19 (48.7)
1	11 (30.6)	11 (28.2)
⩾2	8 (22.2)	9 (23.1)
Gestational age at randomization (weeks)	25.9 (24.9–27.1)	25.0 (24.3–26.4)
Diagnosis at admission[a]		
Preterm premature rupture of membranes	12 (33.3)	19 (48.7)
Preterm labor	10 (27.8)	21 (53.9)
Preeclampsia	13 (36.1)	11 (28.2)
Maternal disease	2 (5.6)	1 (2.6)
Intrauterine growth restriction	7 (19.4)	5 (12.8)
Maternal hemoglobin at admission (%)	11.4 (10.5–12.5)	11.2 (10.4–12.3)
Maternal hematocrit at admission ($g\,l^{-1}$)	33.1 (30.3–35.6)	32.3 (30.4–35.3)

Data are presented as n (%) or median (interquartile range).
[a]Percentages do not add up to 100% because women may have had multiple diagnoses.

Table 2. Intrapartum and neonatal characteristics

Characteristic	*Milking* (n = *36*)	*Control* (n = *39*)
Intrapartum complications		
Chorioamnionitis	3 (8.3)	8 (20.5)
Non-reassuring fetal heart tones	8 (22.2)	8 (20.5)
Type of anesthesia		
None	8 (22.2)	8 (20.5)
Epidural	9 (25.0)	6 (15.4)
Spinal	15 (41.7)	23 (59.0)
General endotracheal	4 (11.1)	2 (5.1)
Type of delivery		
Vaginal	16 (44.4)	13 (33.3)
Cesarean Section	20 (55.6)	26 (66.7)
Gestational age at delivery (weeks)	27.0 (25.5–28.1)	26.3 (25.1–27.1)
Sex		
Male	19 (52.8)	27 (69.2)
Female	17 (47.2)	12 (30.8)
Birthweight (g)	755.0 (687.5–980.0)	770.0 (650.0–940.0)

Data are presented as n (%) or median (interquartile range).

In the cord milking group, 19 (52.8%) neonates had a transfusion before 14 days of life versus 30 neonates (76.9%) in the control group (risk ratio: 0.67; 95% confidence interval: 0.48 to 0.98; $P = 0.04$).

In addition, the incidence of intraventricular hemorrhage was significantly lower in the cord milking group (25.0%) compared with the control group (51.3%; $P = 0.0195$), such that neonates in the cord milking group were 51% less likely to develop an intraventricular hemorrhage (risk ratio: 0.49; 95% confidence interval: 0.26 to 0.93). Among neonates who developed intraventricular hemorrhage, there was no difference between the groups in the median grade of the intraventricular hemorrhage ($P = 0.79$). The incidence of a grade 3 or 4 intraventricular hemorrhage was similar in the cord milking group (33.3%) compared with the control group (30.0%; $P = 1.0$).

The neonates in the cord milking group had significantly higher initial hemoglobin ($P = 0.005$) and hematocrit ($P = 0.004$) levels than the neonates in the control group. There was not a significant increase in the need for phototherapy to treat hyperbilirubinemia in the cord milking group (91.7%) compared with the control group (97.4%; $P = 0.35$). There also were no significant differences between the groups with respect to median Apgar scores at 1, 5 and 10 min and median cord pH (all $P > 0.44$). Every neonate in both groups was intubated at delivery and given surfactant in the delivery room. There were no statistically significant differences between the groups concerning other diagnoses or complications of prematurity, including neonatal death (all $P > 0.09$). Neonatal outcomes are shown in Table 3.

DISCUSSION

Although the difference in the incidence of neonatal transfusion did not reach statistical significance in our study, the 14.1% absolute decrease observed in the cord milking group may indeed be clinically significant. Despite the theoretical concern that active milking of the umbilical cord before cord clamping may increase the risk of hyperbilirubinemia and the need for phototherapy in the neonatal period, our data did not support this.

Neonates in the cord milking group were significantly less likely to develop an intraventricular hemorrhage, which is consistent with results of previous studies of delayed cord clamping in preterm deliveries.[7,8,14] This finding may in fact be more clinically meaningful than the potential reduction in the need for red blood cell transfusion, as an intraventricular hemorrhage in the neonatal period may have lifelong implications. Given that intraventricular hemorrhage is an important contributor to mortality and serious long-term neurodevelopmental disability, if this finding is replicated in other studies, active milking of the umbilical cord could substantially improve neonatal outcomes. Long-term data are needed to further investigate these findings.

Despite randomization, compared with the cord milking group a larger proportion of participants in the control group had an intrapartum diagnosis of chorioamnionitis (Table 1) and a larger proportion of neonates had sepsis (Table 2). The diagnoses of chorioamnionitis during labor and sepsis in the neonatal period are associated with aggressive management and multiple venipunctures, which may increase the likelihood of requiring neonatal red blood cell transfusion. All of the neonates with either intrapartum chorioamnionitis or neonatal sepsis were transfused in the neonatal period. It is of course difficult to know whether anemia in the postnatal period of neonates who did not undergo cord milking may have predisposed them to an increased risk of neonatal sepsis.

The generalizability of our conclusions may be limited due to the fact that the study was conducted in a tertiary care facility with state of the art neonatal resuscitation available for all deliveries. Although to our knowledge this is the largest randomized controlled trial comparing cord milking with immediate cord clamping, our relatively small sample size limited our ability to assess secondary outcomes, such as necrotizing enterocolitis and other neonatal complications. One reason for our limited sample size was the post-randomization exclusion of participants, mainly for delivery after 28 completed weeks of gestation. Although this was primarily due to the fact that we recruited participants at the time of admission for pregnancy complications indicative of delivery in the short term, we were concerned that we would face similarly limiting challenges if we delayed the recruitment

Table 3. Neonatal outcomes

Characteristic	*Milking* (n = *36*)	*Control* (n = *39*)	P-*value*
Apgar score			
1 min	4.0 (1.0–5.5)	4.0 (2.0–5.0)	0.75
5 min	6.5 (5.0–7.0)	7.0 (5.0–7.0)	0.74
10 min[a]	7.0 (6.0–7.0)	7.0 (7.0–7.0)	0.44
Umbilical cord pH ($n = 26$)	7.3 (7.3–7.3)	7.3 (7.3–7.4)	0.44
Neonatal resuscitation			
Intubation	36 (100.0)	39 (100.0)	1.0
Surfactant	36 (100.0)	39 (100.0)	1.0
Stimulation	6 (16.7)	6 (15.4)	0.88
Epinephrine	0 (0.0)	1 (2.6)	1.0
Initial neonatal clinical values			
Hemoglobin ($g\,l^{-1}$)	14.9 (13.3–18.1)	13.6 (12.6–15.0)	0.005
Hematocrit (%)	43.3 (39.9–53.6)	40.8 (37.1–44.0)	0.004
Systolic blood pressure (mm Hg)	43.0 (37.0–51.0)	40.5 (36.0–46.5)	0.32
Diastolic blood pressure (mm Hg)	22.0 (18.0–29.0)	21.0 (15.0–28.5)	0.68
Transfusion			
Age (days)	7.0 (2.0–16.0)	5.0 (2.0–11.0)	0.47
Volume (ml)	32.0 (16.0–57.0)	38.0 (29.0–55.0)	0.33
<14 days of life	19 (52.8)	30 (76.9)	0.04
<28 days of life	30 (83.3)	38 (97.4)	0.05
Phototherapy	33 (91.7)	38 (97.4)	0.35
Days	5.0 (3.0–7.0)	5.0 (4.0–7.0)	0.67
Peak bilirubin ($mg\,dl^{-1}$)	5.2 (4.6–5.7)	5.5 (4.7–6.6)	0.59
Days of ventilation	9.0 (2.0–28.0)	16.0 (2.0–28.0)	0.40
Neonatal death	2 (5.6)	4 (10.3)	0.68
Age (days)	4.0 (2.0–6.0)	7.0 (6.0–15.0)	0.27
Neonatal complications			
Respiratory distress syndrome	36 (100.0)	39 (100.0)	1.0
Intraventricular hemorrhage	9 (25.0)	20 (51.3)	0.0195
Grade—median (IQR)[b]	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.79
Periventricular leukomalacia	1 (2.8)	3 (7.7)	0.62
Chronic lung disease	9 (25.0)	4 (10.3)	0.09
Retinopathy of prematurity	28 (77.8)	31 (79.5)	0.86
Hyperkalemia	1 (2.8)	1 (2.6)	1.0
Sepsis	10 (27.8)	18 (46.2)	0.10
Necrotizing enterocolitis	6 (16.7)	10 (25.6)	0.34

Data are presented as n (%) or median (IQR, interquartile range).
[a]10-min Apgar scores were only given for 19 neonates with 5-min Apgar scores <7. [b]Only among those with intraventricular hemorrhage.

until just before the anticipated time of delivery. In addition, the unplanned interim analysis and the conservative Type 1 error adjustment yielded a lower cutoff for statistical significance than would have been utilized if the interim analyses had been accounted for in the study design. With one exception, each participant received the correct assigned intervention. The one participant in the cord milking group whose cord was immediately clamped also received a red blood cell transfusion. If this participant was analyzed in the control group, the difference observed between the two groups would have been even larger.

We believe that the results of our preliminary trial justify the need for a larger multicenter study to further evaluate the potential benefits of active umbilical cord milking in preterm deliveries. In particular, the observed reduction in the incidence of intraventricular hemorrhage may have important long-term clinical implications that warrant further study. Hastening the passive transfusion that has been demonstrated in delayed cord clamping by instead actively milking the cord should be clinically beneficial due to the need for resuscitation of preterm neonates. If future studies find similar benefits from active cord milking, then routinely implementing this simple practice could potentially have a dramatic benefit on outcomes for preterm infants. In developing countries, where medical facilities often are not equipped with the resources of a tertiary care facility and the risk of transmitting infection through transfusion may be greater, the potential benefit of cord milking may be even more dramatic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was conducted with support from Harvard Catalyst. The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from the Harvard University and its affiliated academic health-care centers.

REFERENCES

1 Hosono S, Ohno T, Kimoto H, Shimizu M, Harada K. Morbidity and mortality of infants born at the threshold of viability: ten year's experience in a single neonatal intensive care unit, 1991-2000. *Pediatr Int* 2006; **48**: 33–39.
2 Stockman JA, Graeber JE, Clark DA, McClellan K, Garcia JF, Kavey RE. Anemia of prematurity: determinants of the erythropoietin response. *J Pediatr*. 1984; **105**: 786–792.
3 Ohls RK. The use of erythropoietin in neonates. *Clin Perinatol*. 2000; **27**: 681–696.
4 Haiden N, Schwindt J, Cardona F, Berger A, Klebermass K, Wald M *et al*. Effects of a combined therapy of erythropoietin, iron, folate, and vitamin B12 on the transfusion requirements of extremely low birth weight infants. *Pediatrics* 2006; **118**: 2004–2013.
5 Ross MP, Christensen RD, Rothstein G, Koenig JM, Simmons MA, Noble NA *et al*. A randomized trial to develop criteria for administering erythrocyte transfusions to anemic preterm infants 1 to 3 months of age. *J Perinatol* 1989; **9**: 246–253.
6 Padbury JF. Placental Transfusion. In *Rudolph's Pediatrics*. McGraw Hill Medical: New York, NY, USA, (2003) pp 163–164.
7 Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonatology* 2008; **93**: 138–144.
8 Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012(8).
9 Aladagandy N, McHugh S, Aitchison TC, Wardrop CA, Holland B. Infant's blood volume in a controlled trial of placental transfusion at preterm delivery. *Pediatrics* 2006; **117**: 93–98.
10 Strauss RG, Mock DM, Johnson KJ, Cress GA, Burmeister LF, Zimmerman MB *et al*. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. *Transfusion* 2008; **48**: 658–665.
11 Oh W, Fanaroff AA, Carlo WA, Donovan EF, McDonald SA, Poole WK *et al*. Effects of delayed cord clamping in very-low-birth-weight infants. *J Perinatol* 2011; **31**(Suppl 1): S68–S71.
12 Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CA. Umbilical cord clamping and preterm infants: a randomized trial. *BMJ* 1993; **306**: 172–175.
13 Kugelman A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R *et al*. Immediate versus delayed umbilical cord clamping in premature neonates born <35 weeks: a prospective, randomized, controlled study. *Am J Perinatol* 2007; **24**(5): 307–315.
14 Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. *Pediatrics* 2006; **117**: 1235–1242.
15 Rabe H, Wacker A, Hulskamp G, Hornig-Franz I, Schulze-Everding A, Harms E *et al*. A randomized controlled trial of delayed cord clamping in very low birth weight preterm infants. *Eur J Pediatr* 2000; **159**: 775–777.
16 Utlee CA, Van der Deure J, Swart J, Lasham C, van Baar AL. Delayed cord clamping in preterm infants delivered at 34-36 weeks' gestation: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F20–F23.
17 Rabe H, Jewison A, Alvarez RF, Crook D, Stilton D, Bradley R *et al*. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates. *Obstet Gynecol* 2011; **117**: 205–211.

18 Erickson-Owens DA, Mercer JS, Oh W. Umbilical cord milking in term infants delivered by cesarean section: a randomized controlled trial. *J Perinatol* 2012; **32**: 580–584.
19 American College of Obstetricians and Gynecologists. Committee Opinion No. 543:Timing of umbilical cord clamping after birth. *Obstet Gynecol* 2012; **120**: 1522–1526.
20 Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T *et al*. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born less than 29 weeks' gestation: a randomized control trial. *Arch Dis Child Fetal Neonatal Ed* 2007; **10**: 1136.
21 Hosono S, Mugishima H, Fujita H, Hosono A, Okada T, Takahashi S *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**: F328–F331.
22 Takami T, Suganami Y, Sunohara D, Kondo A, Mizukaki N, Fujioka T *et al*. Umbilical cord milking stabilizes cerebral oxygenation and perfusion in infants born before 29 weeks gestation. *J Pediatr*. 2012; **161**(4): 742–747.
23 Pocock S. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977; **62**: 191–199.

Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)