EDITORIAL

Placental Transfusion Improves Iron Stores at 6 Weeks of Age in Late Preterm Infants

*JUDITH S MERCER AND DEBRA A ERICKSON-OWENS

*From the University of Rhode Island, Alpert Medical School, Brown University, and Women & Infants Hospital of Rhode Island, Kingston, Rhode Island; USA. *jsmercer@uri.edu*

At any point in fetal life, approximately 30% of the fetus' blood volume is circulating through the placenta where all respiratory and many metabolic functions occur. At birth, allowing this blood to be redistributed to the infant provides up to 50% more iron-rich red blood cells in the circulation [1]. These red blood cells contribute to higher iron stores in infancy [2]. Placental transfusion which facilitates this blood transfer is accomplished in one of three ways: delayed cord clamping (DCC); milking the umbilical cord (UCM) before separating it from the placenta; or clamping and cutting the umbilical cord and milking after cutting (C-UCM). Most studies contrast these methods to immediate cord clamping (ICC), the dominant world-wide practice. In term infants, placental transfusion can result in increased iron stores during the first 6 months of life [2]. To date, ferritin, a marker of iron stores, has not been measured in early or late preterm infants in studies of placental transfusion.

Measuring ferritin is important because adequate iron is essential for normal brain development, especially during the critical first year when the most rapid brain growth occurs. A recent study of 400 Swedish term infants demonstrated that DCC increased ferritin levels by 48% at 4 months of age. At 4 years of age, those children who had a placental transfusion had higher fine motor and social-emotional scores [3].

In this issue of *Indian Pediatrics*, Kumar, *et al.* [4] are the first to report ferritin levels in late preterm infants born between 32 and 36 weeks gestational age [4]. Using C-UCM with three milkings, they found ferritin levels almost double at 6 weeks of age in infants who received C-UCM (n=91) when compared to infants (n=86) who received ICC. They also report significantly higher bilirubin levels and an increased need for phototherapy in the C-UCM group. This is in direct contrast to most recent studies on placental transfusion. These important findings suggest the need for further follow-up of these children to determine long-term developmental effects and weigh risks versus benefits.

There is no meta-analysis for late preterm infants with placental transfusion. Only two other studies specifically address this age group. The first examined infants between 34-36 weeks (n=41) and compared a 3-minute delay *versus* ICC [5]. They found higher hemoglobin levels at 1 day and 10 weeks without any difference in jaundice [5]. Ranjit, *et al*. [6] randomized 94 infants between 30 and $36^{6/7}$ weeks to either DCC (at least 2 minutes) or ICC. They found higher hematocrit and ferritin levels at 6 weeks of age. The DCC group had longer duration of phototherapy but no difference in the incidence of significant jaundice.

Comparisons across studies of late preterm infants are difficult because age groupings are inconsistent. Many available studies draw conclusions from samples containing both early preterm and late preterm infants. Yet, health differences between infants at 32 weeks *versus* 36 weeks are striking. Infants at 32 to 34 weeks have double the mortality of those at 35 to 36 weeks (18.5 *versus* 6.9/1000, US statistics) [7]. This suggests that it maybe informative to separately report the findings and adverse events on infants grouped as $32\text{-}33^{6/7}$ *versus* $34\text{-}36^{6/7}$ weeks rather than combining these two groups in reporting morbidities such as hyperbilirubinemia.

Provider fear of hyperbilirubinemia has hindered the adoption of placental transfusion (DCC/UCM/C-UCM) throughout the world. Nevertheless, Zahir, *et al.* [8] suggested that bilirubin levels that are elevated but still within a normal range may provide a unique protective antioxidant effect, especially in the brain. We propose that more specific criteria for recognizing risk factors for hyperbilirubinemia be reported, including gestational age, G6PD, ABO incompatibility, and cephalhematoma. Use of the Bilitool (bilitool.org) may allow for quantification of risk. Although the Bilitool only includes infants 35 weeks and up, it could potentially be modified for research purposes to include infants 32 weeks through 34 weeks.

Another important issue from the study by Kumar,

et al. [4] is the use of "the cut by the obstetrician and milk by the neonatologist" technique. More research is needed to establish the benefits and/or potential harm of using C-UCM *versus* UCM or DCC. Recent animal studies suggest a smoother and better cardiorespiratory transition with DCC [9]. Yet, in some clinical situations DCC is not feasible. Combining DCC and UCM just prior to clamping may be beneficial in increasing ferritin levels over either method alone [10].

Kumar, *et al.* [4] confirm the importance of placental transfusion and its role in increasing ferritin levels in late preterm infants. However, the best method to accomplish this without increasing jaundice in late preterm infants is still unclear. Further long-term developmental follow-up in such studies may assist in deciphering the benefits from the risks.

Funding: None; *Competing interests*: The authors are principal investigators on an NIH funded trial "Effects of Placental Transfusion on Early Brain Development."

REFERENCES

1. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet. 1969;2:871-3.
2. 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.
3. Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of delayed cord clamping on neurodevelopment at 4 years of age: A randomized clinical trial. JAMA Pediatr. 2015;169:631-8.
4. Kumar B, Upadhyay A, Gothwal S, Jaiswal V, Joshi P, Dubey K. Umbilical cord milking and hematological parameters in moderate to late preterm neonates: A randomized control trial. Indian Pediatr. 2015;52:753-7.
5. Ultee 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 randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2008;93:F20-3.
6. Ranjit T, Nesargi S, Rao PN, Sahoo JP, Ashok C, Chandrakala BS, *et al.* Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. Indian J Pediatr. 2015;82:29-34.
7. Matthews TJ, MacDorman MF. Infant mortality statistics from the 2010 period linked birth/infant death data set. Natl Vital Stat Rep. 2013;62:1-26.
8. Zahir F, Rabbani G, Khan RH, Rizvi SJ, Jamal MS, Abuzenadah AM. The pharmacological features of bilirubin: The question of the century. Cell Mol Biol Lett. 2015;20:418-47.
9. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, *et al.* Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol. 2013;591:2113-26.
10. Yadav AK, Upadhyay A, Gothwal S, Dubey K, Mandal U, Yadav CP. Comparison of three types of intervention to enhance placental redistribution in term newborns: randomized control trial. J Perinatol. 2015 Jun 18. doi: 10.1038/jp.2015.65. [Epub ahead of print].

EDITORIAL

Delayed Cord Clamping and Umbilical Cord Milking at Birth

SIDDARTH RAMJI

From the Department of Neonatology, Maulana Azad Medical College, New Delhi, India. siddarthramji@gmail.com

Early cord clamping could deprive the neonate of about a quarter of its blood volume and iron (upto 50 mg/kg). World Health Oganization recommends delaying cord clamping (defined variably as till pulsations cease or upto 120-180 s) as the standard of care in the delivery room for newborns not needing resuscitation. The benefits of delayed cord clamping include improved iron status and hemoglobin, reduced need for blood transfusion, and improved hemodynamic stability after birth. Yet, there appears to be concerns about practicing delayed cord clamping, especially in neonates needing resuscitation. In such situations, an alternative that could provide the newborn with the desired additional blood is Umbilical Cord Milking (UCM). In this issue of *Indian Pediatrics*, Kumar, *et al.* [1] report the hematological effects of UCM compared to early cord clamping in preterm (32-36 wk) neonates. While they reported higher ferritin and hemoglobin in the UCM group at 6 weeks postnatal age, they also noted with concern the higher rates of jaundice needing phototherapy with UCM. Upadhyay, et *al*. [2] from the same center have previously reported similar results in neonates >35 weeks, but did not note increased jaundice or the need for phototherapy in UCM group.

A systematic review of UCM in preterm neonates (<33 weeks) reported significantly higher hematocrit, and reduced risk of oxygen need at 36 weeks and intraventricular hemorrhage (IVH) [3]. Another systematic review of delayed cord clamping in neonates between 24-36 weeks (738 infants) reported similar hematological benefits of higher hematocrit and decreased blood transfusion, better hemodynamic stability, decreased risk of IVH and necrotizing enterocolitis (NEC) [4]. However, this analysis also noted higher peak bilirubin concentrations in those with delayed cord clamping (which did not apparently translate to increased phototherapy need). It appears that provision of additional placental blood at birth in preterm neonates is associated with higher bilirubin levels, but may not be a matter of concern as it does not translate to increased interventions for hyperbilirubinemia. Patel, *et al*. [5] demonstrated the benefits of UCM even in neonates <30 weeks. In their study amongst preterm neonates (<32 weeks) delivered by cesarean section, UCM resulted in better systemic blood flow than those with delayed cord clamping.

There is considerable body of evidence to support the practice of providing additional blood volume to term and preterm neonates not needing resuscitation at birth by delaying cord clamping. Similar results have been observed even amongst neonates where umbilical cord milking was done. In neonates delivered by cesarean section or amongst those needing resuscitation, umbilical cord milking may be a more practical option for providing the additional blood volume to the neonate resulting in better hematologic parameters and hemodynamic stability. In under-resourced countries where maternal anemia is highly prevalent, delayed cord clamping or UCM could decrease anemia in early infancy, and also possibly improve survival in preterm infants by decreasing morbidities such as IVH and NEC. There should be a concerted effort at implementing such low cost but potentially useful strategy in the delivery room settings globally, but more so in regions where there is high neonatal mortality.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. Kumar B, Upadhyay A, Gothwal S, Jaiwal V, Joshi P, Dubey K. Umbilical cord milking and hematological parameters in moderate to late preterm neonates: A randomized control trial. Indian Pediatr. 2015;52:753-7.
2. Upadhyay A, Gothwa S, Parihar R, Garg A, Gupta A, Chawla D, *et al.* Effect of umbilical cord milking in term and near term infants: Randomized control trial. Am J Obstet Gynecol. 2013;208:120.e1-6.
3. 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.
4. 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:CD003248.
5. Patel S, Clark EAS, Rodriguez CE, Metz TD, Abbaszadeh M, Yoder BA. Effect of umbilical cord milking on morbidity and survival in extremely low gestational age neonates. Am J Obstet Gynecol. 2014,211:519.e1-7.

EDITORIAL

Shift From PMTCT Program to ART Program

SUNIL GOMBER AND *POOJA DEWAN

Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India.

*poojadewan@hotmail.com

Mother-to-child transmission (MTCT) accounts for 90% of HIV infections in children under the age of 15 years [1]. Without any intervention, the infant born to an HIV-infected pregnant woman has 25-45% risk of HIV infection during pregnancy, delivery, and breastfeeding [2]. In the absence of breastfeeding, intrauterine (transplacental) infection and peripartum infection account for 25-40% and 60-75%, respectively, of vertical infection. Breastfeeding carries an 8-25% risk of vertical transmission in the developing countries [3,4].

In 2000, there was a global surge in the new cases of HIV infections, and the world was staring at an HIV epidemic [5]. The alarm bells were enough to arouse the United Nations and its member states, and they became a signatory to the Millennium Declaration in September 2000 wherein they resolved to take terse measures to combat HIV by 2015 (Millennium Development Goal-6). The United Nations General Assembly Special Session on HIV/AIDS, held in June 2001, set the goal of reducing the proportion of infants infected with HIV by 20% by 2005, and by 50% by 2010 [6]. Scaling up of Prevention of Mother-to-Child Transmission (PMTCT) of HIV services and increased access to anti-retroviral therapy were the major armamentaria to attain this goal. Over the next fifteen years, much was achieved due to sustained efforts of all member states, and HIV-infection rates and AIDS-related deaths decreased by 40% [5].

PMTCT of HIV has been at the helm of all research in HIV. Ever since the Pediatric AIDS Clinical Trials Group demonstrated that administration of zidovudine (AZT) to pregnant women and their infants could reduce risk of perinatal transmission by nearly 70% [7], several clinical trials have used single, dual, or triple Anti Retroviral Therapy (ART) with or without breastfeeding, with different modes of delivery to reduce the risk of transmission from mother to child. Clinical trials initially focused on shortened zidovudine-alone prophylaxis regimens and moved to evaluating whether combination ARV regimens, such as short-course zidovudine combined with lamivudine, might have improved efficacy over zidovudine alone. Studies also evaluated whether even simpler, less expensive, single-drug regimens, such as single-dose intrapartum/neonatal nevirapine (NVP), would be effective, and whether combining such regimens with other short-course regimens might result in improved efficacy. The HIVNET 012 regimen advocated administration of single dose oral nevirapine (200 mg) to the mother during labour and also to the neonate (2 mg/kg) soon after birth [8]. The mothers were advised to exclusively breastfeed their babies till 6 months unless replacement feeding was acceptable, feasible, affordable, sustainable and safe. This regimen resulted in lesser chances of infant deaths and lesser HIV transmission during labour, and was well accepted in resource-poor countries as it was quite economical and convenient. However, it totally neglected the maternal health, and was not shown to be useful in preventing risk of HIV transmission antenatally or during the breastfeeding period. The rates of vertical transmission using this regimen were reported upto 10% [9,10]. Avoidance of breastfeeding was not a feasible option in several developing countries. In conditions where the mothers chose to breastfeed, it was not clear whether this option was made due to compulsion or by choice. In addition, there was a problem of acquisition of viral resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs [11].

In 2010, the WHO laid down new PMTCT ARV guidance [12] wherein countries had the option to choose between two prophylaxis regimens for pregnant women living with HIV with CD4 greater than 350 cells/mm3: Option A and Option B. Under Option A, women received antenatal (AZT starting at 14th week of gestation) and intrapartum (single dose NVP at onset of labour with first dose of AZT/3TC) antiretroviral prophylaxis along with an antiretroviral postpartum tail regimen (AZT/3TC for 7 days postpartum) to reduce risk of drug resistance, while infants receive daily nevirapine starting from birth until 1 week after cessation of all breastfeeding; or, if not

breastfeeding or if mother is on treatment, through age 4-6 weeks. Under Option B, all pregnant and lactating women with HIV initially are offered triple ART – beginning in the antenatal period and continued throughout the duration of breastfeeding. At the end of breastfeeding, women who do not yet require ART for their own health would discontinue the prophylaxis and continue to monitor their CD4 count, eventually re-starting ART when the CD4 falls below 350 cells/mm^3. Infants would be offered daily NVP or AZT from birth through age 4-6 weeks regardless of infant feeding method.

In 2011, a systematic review published clearly advocated that triple ART for all expectant and breastfeeding mothers along with NVP prophylaxis to the baby for 6 weeks duration is the best approach to mitigate MTCT of HIV [13]. In 2013, a third more efficacious approach was recommended by WHO i.e., Option B+, in which all pregnant women living with HIV are offered life-long triple-drug ART, regardless of their CD4 count or clinical staging and all HIV-exposed infants are offered 4-6 weeks of NVP/AZT regardless of feeding method [14]. This new regimen was shown to be associated with less than 2% risk of HIV transmission by vertical route. The WHO emphasized that whereever possible Option B+ be adopted as it was shown to reduce HIV-related mortality and also ensure better maternal health. Based on the new guidelines from WHO (June 2013), the National AIDS Control Organization (NACO) decided to provide life-long ART (triple drug regimen) for all pregnant and breastfeeding women living with HIV, in which all pregnant women living with HIV receive a triple drug ART regimen regardless of CD4 count or WHO clinical stage, with effect from January 1, 2014 [15]. This would not only ensure better maternal health, but also prevent stopping and starting ARV drugs with repeat pregnancies, reduce vertical transmission in future pregnancies and avoid drug resistance. In addition, infants would be administered 6 weeks of daily oral nevirapine therapy.

The study by Seenivasan, *et al*. [16] published in the current issue of *Indian Pediatrics* shows a vertical transmission rate of 6.7% amongst breastfed groups despite use of ARV prophylactic regimen using single dose NVP for mother-infant pairs. There was no HIV transmission detected amongst neonates born to mothers receiving triple ART. This study comes at a time when there is sufficient evidence to prove the superiority of triple ART for pregnant and breastfeeding mothers over the regimens using shorter regimens using fewer ARVs. All the same, it does add weight to the current recommendations of NACO on lifelong use of triple ARV in all pregnant women living with HIV and ARV prophylaxis with NVP in infants. However, it remains to be seen whether triple/dual ARV will replace nevirapine monotherapy for ARV prophylaxis in neonates exposed to HIV in the times to come. Till then the PMTCT centers should work in close conjunction with the ART centers to monitor both mothers and infants receiving anti-retroviral therapy/prophylaxis.

We must accept that changing guidelines is not a piece of cake and the entire health system needs to be refurbished. More healthcare workers, drugs, costs, laboratory set-ups, and better monitoring will be needed to enforce the revised guidelines. Only time will tell if resource-poor countries will be able to cope with the increased demands of these new guidelines and show positive results.

Funding: None; *Competing interests*: None stated.

REFERENCES

1. Kourtis AP, Bulterys M. Mother-to-child transmission of HIV: Pathogenesis, mechanisms and pathways. Clin Perinatol. 2010;37:721-37.
2. Kourtis AP, Lee FK, Ebrams EJ, Jamieson DJ, Buttery M. Mother to child transmission of HIV: Timing and implications for prevention. Lancet Infect Dis. 2006; 6:726-32.
3. Watts DH. Drug therapy: Management of human immunodeficiency virus infection in pregnancy. N Eng J Med. 2002;346:1879-91.
4. Mor Z, Chemtob D, Pessach N, Nitzan-Kaluski D. Human immunodeficiency virus in new born of infected mothers: Pregnancy, breastfeeding and prevention. Harefua. 2006;145:682-6.
5. UNAIDS. UNAIDS announces that the goal of 15 million people on life-saving HIV treatment by 2015 has been met nine months ahead of schedule. Available from: *http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2015/july/20150714_PR_MDG6report.* Accessed August 5, 2015.
6. United Nations General Assembly. Declaration of commitment on HIV/AIDS: Five years later. Follow-up to the outcome of the twenty-sixth special session: Implementation of the declaration of commitment on HIV/AIDS. Report of the Secretary General. Agenda 45. 2006. Available from: *http://www.unaids.org/sites/default/files/sub_landing/files/20060324_sgreport_ga_a60737_en.pdf*. Accessed August 12, 2015.
7. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, *et al*. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331:1173-80.
8. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, *et al*. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012

randomised trial. Lancet. 2003;362:859-68.
9. Arora D, Gupta RM, Kochar SP. Efficacy of single dose nevirapine in reducing viral load in HIV positive mother in labour and transmission of HIV infection to new born babies as part of prevention of parent to child transmission. Med J Armed Forces India. 2014;70:309-14.
10. Kesho Bora Study Group, de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11:171-80.
11. Flys T, Nissley DV, Claasen CW, Jones D, Shi C, Guay LA, *et al.* Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012. J Infect Dis. 2005;192:24-9.
12. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Recommendations for a public health approach 2010 version. Available from: *http://apps.who.int/iris/bitstream/10665/75236/1/9789241599818_eng.pdf*. Accessed August 12, 2015.
13. Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev. 2011;7:CD003510.
14. Global Network of People living with HIV. Understanding the perspectives and/ or experiences of women living with HIV regarding Option B+ in Uganda and Malawi. Available from: *www.gnpplus.net/assets/wbb_file_updown/2793/Option-B+%20Understanding%20perspectives %20experiences%20of%20women% 20living%20with% 20HIV.pdf*. Accessed August 12, 2015.
15. National AIDS Control Organization. Updated Guidelines for Prevention of Parent to Child Transmission (PPTCT) of HIV using Multi Drug Anti-retroviral Regimen in India. December, 2013. Available from: *http://naco.gov.in/upload/NACP%20-%20IV/18022014%20BSD/National_Guidelines_for_PPTCT.pdf*. Accessed August 12, 2015.
16. Seenivasan S, Vaitheeswaran N, Seetha V, Anbalagan S, Karunaianantham R, Swaminathan S. Outcome of prevention of parent to child transmission of HIV in an urban population in Southern India. Indian Pediatr. 2015;52:759-62