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

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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 neonate's 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 (LPT) 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 and colleagues are the first to report ferritin levels in LPT 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 (p <0.001). 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 LPT infants with placental transfusion. Only two other studies specifically address this age group. The first, a study by Ultee, 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.* randomized infants between 30 and 36^{6/7} weeks (n=94) to either DCC (at least 2 minutes) or ICC (6). 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 LPT infants are difficult because age groupings are inconsistent. Many available studies draw conclusions from samples containing both early preterm and LPT 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 may be informative to separately report the findings and adverse events on infants grouped as 32-33^{6/7} versus 34-36^{6/7} weeks rather than combining these 2 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 and colleagues (8) suggest 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 cephalohematoma. 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 Kumar's article is the use of "the cut by the obstetrician and milk by the neonatologist" technique (4). 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. Yadav reports that combining DCC and UCM just prior to clamping is beneficial in increasing ferritin levels over either method alone (10).

Kumar, *et al.* confirm the importance of placental transfusion and its role in increasing ferritin levels in LPT infants (4). However, questions are raised about the

best method to accomplish this without increasing jaundice in LPT infants. Further long-term developmental follow up in such studies may assist in deciphering the benefits from the risks.

Competing interests: The authors are principal investigators on an NIH funded trial "Effects of Placental Transfusion on Early Brain Development."

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