Review

Placental Transfusion Strategies in Very Preterm Neonates

A Systematic Review and Meta-analysis

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OBJECTIVE: To investigate the effects of interventions promoting placental transfusion at delivery (delayed cord clamping or umbilical cord milking) compared with early cord clamping on outcomes among premature neonates of less than 32 weeks of gestation.

DATA SOURCES: A systematic search was conducted of PubMed, Embase, and ClinicalTrials.gov databases (January 1965 to December 2013) for articles relating to placental transfusion strategies in very preterm neonates.

METHODS OF STUDY SELECTION: Literature searches returned 369 articles with 82 considered in full. We only included data from studies with an average gestational age of less than 32 weeks of gestation enrolled in randomized trials of enhanced placental–fetal transfusion interventions (delayed cord clamping or umbilical cord milking) compared with early cord clamping.

TABULATION, INTEGRATION, AND RESULTS: We identified 12 eligible studies describing a total of 531 neonates with an average gestation of 28 weeks. Benefits of greater placental transfusion were decreased mortality (eight studies, risk ratio 0.42, 95% confidence interval [CI] 0.19–0.95, 3.4% compared with 9.3%, P = .04), lower incidence of blood transfusions (six studies, risk ratio 0.75, 95% CI 0.63–0.92, 49.3% compared with 66%, P < .01), and lower incidence of intraventricular hemorrhage (nine studies, risk ratio 0.62, 95% CI 0.43–0.91, 16.7% compared with 27.3%, P = .01). There was a weighted mean difference of −1.14 blood transfusions (six studies, 95% CI −2.01 to −0.27, P < .01) and a 3.24-mmHg increase in blood pressure at 4 hours of life (four studies, 95% CI 1.76 to 4.72, P < .01). No differences were observed between the groups across all available safety measures (5-minute Apgar scores, admission temperature, incidence of delivery room intubation, peak serum bilirubin levels).

CONCLUSIONS: Results of this meta-analysis suggest that enhanced placental transfusion (delayed umbilical cord clamping or umbilical cord milking) at birth provides better neonatal outcomes than does early cord clamping, most notably reductions in overall mortality, lower risk of intraventricular hemorrhage, and decreased blood transfusion incidence. The optimal umbilical cord clamping practice among neonates requiring immediate resuscitation remains uncertain.

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In contemporary medical settings, clamping and cutting of the umbilical cord usually occur within seconds after delivery.1,2 This immediate separation has long been considered medically advantageous to the neonate, in part as a result of the perceived need for prompt resuscitation and as active management of the third stage of labor.3,4 However, evidence is growing that early cord clamping and resultant lower circulating blood volumes may, in fact, increase the risk of hemodynamic compromise, impair physiologic transition, and worsen clinical outcomes.5–7

These observations have led to interest in alternative strategies that promote a more gradual physiologic transition at birth and optimize placental–fetal transfusion, including delayed umbilical cord clamping and umbilical cord milking. Evidence is growing on the benefits of enhanced placental transfusion in improving
neonatal outcomes, including higher hematocrits, improved hemodynamic stability, less need for blood transfusions, and lower prevalence of necrotizing enterocolitis and sepsis. Perhaps the most important advantage is an almost 50% reduction in the incidence of intraventricular hemorrhage. However, the majority of evidence supporting placental transfusion strategies comes from term and late-preterm neonates.

Recently, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the World Health Organization issued statements supporting the practice of enhanced placental transfusion at birth, but cited the need for a better understanding of the risks and benefits among very preterm neonates, those born at 28 weeks of gestation or less. Previous clinical trials have excluded very preterm neonates based on concerns that enhanced placental transfusion strategies lead to critical delays in resuscitation. In contrast, other studies have shown that optimizing placental transfusion at birth decreases the need for resuscitation by promoting a more physiologic transition to extrauterine life. This controversy has provided clinicians with little evidence to guide their clinical management. In fact, a recent survey of obstetricians in the United States showed that although a majority of respondents believe the timing of cord clamping is "very or moderately important" on neonatal outcomes, most are unaware of the optimal timing of the intervention and are concerned that the practice may worsen clinical outcomes and delay resuscitation, particularly among neonates born very preterm.

Although previous reviews on placental transfusion have broadly defined prematurity as less than 37 weeks of gestation, the purpose of the present review and meta-analysis is to perform a systematic appraisal of the literature among neonates born very preterm (average gestational age less than 32 weeks of gestation), the neonates at the crux of the medical debate. Neonates born very preterm are more complex and medically fragile than their more mature counterparts. Thus, a separate consideration of the potential risks and benefits of placental transfusion strategies in this unique subgroup is needed. We conducted a study to investigate the effects of interventions promoting placental transfusion at delivery (delayed cord clamping or umbilical cord milking) compared with early cord clamping on outcomes among premature neonates of less than 32 weeks of gestation.

STUDY SELECTION
The a priori inclusion criteria of our meta-analysis were randomized trials of placental transfusion strategies compared with early cord clamping, trials with a reported average gestational age of neonates less than 32 weeks, and studies that were published in peer-reviewed journals. Randomized controlled trials were considered if the investigator defined them as such in the Methods section of the article. “Early cord clamping” was defined as clamping the cord at no later than 15 seconds after delivery. The minimum time considered to be “delayed cord clamping” was 20 seconds. “Umbilical cord milking” was defined as squeezing and pulling the umbilical cord blood toward the newborn at least three times after delivery.

Two authors independently assessed the eligibility of included studies and extracted data from included trials or published outcomes using standardized forms. Authors of included studies were contacted for additional data, when necessary. Differences in data between the two analyses of forms were resolved by reviewing the corresponding article with a third author, and the final determination was agreed on by consensus. The methodologic quality of each trial was also independently assessed using a modified version of the Jadad scale. Trials rated 10 or higher are considered high quality. No disagreements existed between reviewers that affected categorization of trials as being of low quality or high quality.

Meta-analysis was conducted using Review Manager 5.2. Heterogeneity was assessed visually from the forest plot of weighted mean differences and relative risks of individual studies. Statistical estimates of heterogeneity also were assessed using the I² statistic in Review Manager. Fixed-effects analysis was used if no evidence of significant heterogeneity was observed ($p > 0.05$, $I^2 < 30\%$), and a random-effects analysis was used when heterogeneity was significant.
(I²≥30%). Publication bias was assessed by plotting the treatment effect against study size for each meta-analysis (see funnel plots in Appendix 2 [I–III], available online at http://links.lww.com/AOG/A517). “Leave-out-one” analyses were conducted by iteratively deleting each study and calculating the resulting effect size.36

In cases when reviewed manuscripts reported mean±standard error of the mean, the standard deviation was calculated by multiplying the reported standard error of the mean by the square root of the reported number of participants (N). In cases in which reviewed manuscripts reported median and data range, the means and standard deviations were estimated using the method recommended by Hozo et al.37 Outcomes are reported as risk ratios (RRs) or weighted mean differences with 95% confidence intervals (CIs). A P value <.05 was considered significant for overall effect. Four general categories for analyses were defined before the study: 1) maternal and obstetric considerations; 2) safety variables; 3) hematologic status; and 4) neonatal outcomes. Maternal and obstetric outcomes assessed included mode of delivery (vaginal or cesarean delivery), uterine treatment(s), position of the neonate during the maneuver, and neonate stimulation (drying, suctioning) during the intervention. Outcomes categorized as safety outcomes included Apgar scores at 5 minutes, temperature on admission, incidence of intubation in the delivery room, and mean blood pressure at 4 hours of life. Hematologic status assessed included initial reported hematocrit, peak serum bilirubin, rates of transfusion, mean number of transfusions, need for phototherapy, and incidence of polycythemia (venous hematocrit greater than 65). Neonatal outcomes assessed included incidence of all grades of intraventricular hemorrhage, severe intraventricular hemorrhage (defined as grade 3 or 4), sepsis, necrotizing enterocolitis (defined as Bell’s stage 2 or greater), and mortality before discharge. All outcomes were considered throughout the neonate’s initial hospitalization.

RESULTS
Searching PubMed, Embase, and ClinicalTrials.gov returned a total of 369 articles with 268 articles remaining after removal of duplicates. Of the 82 articles considered in full, 18 potential studies met the gestational age criterion. Six manuscripts were excluded as a result of lack of randomization9,11,38,39 or no early cord clamping comparison group.40,41 Figure 1 outlines the selection process that left 12 studies describing a total of 531 very premature neonates.10,12,13,16,42–49 Characteristics of these studies are presented in Appendix 3, available online at http://links.lww.com/AOG/A518. The average gestational ages in the early cord clamping and enhanced placental transfusion cohorts were 28.0 and 28.2 weeks, respectively.

Modest heterogeneity was suggested in two comparisons, incidence of delivery room intubation (four studies, χ²=4.95, df=3 [P=.18]; I²=39%) and incidence of sepsis (five studies, χ²=6.22, df=4 [P=.18]; I²=36%), but these comparisons were not different statistically. Tests of heterogeneity were significant for number of blood transfusions (six studies, χ²=13.72, df=5 [P=.02]; I²=64%) and initial hematocrit (10 studies, χ²=25.01, df=9 [P=.003]; I²=64%), respectively. In those instances, using a random-effects model, as opposed to a fixed-effects model, did not appreciably affect the meta-analysis results. In five of 12 primary outcomes for this review, only four or fewer studies provided data for meta-analysis. Therefore, power to detect heterogeneity was low because of the relatively small number of available trials. Sensitivity analyses using the leave-one-out method (influence analysis) were performed across all measured outcomes. We found that the 95% CI included the value of 1 when the Mercer et al16 (RR 0.7, 95% CI 0.46–1.06) and March et al45 (RR 0.7, 95% CI 0.44–1.11) studies were removed from the total intraventricular hemorrhage risk analyses. Funnel plots suggested no presence of publication bias in these data [Appendix 2 I–III], available online at http://links.lww.com/AOG/A517, thereby indicating that the loss of statistical significance with study deletion is more likely attributable to lower statistical power from smaller sample sizes.

No differences in Apgar scores at 5 minutes, temperature on admission, or incidence of delivery room intubation were indicated (Fig. 2). There was a weighted mean difference of −1.14 blood transfusions (six studies, 95% CI −2.01 to 0.27, P<.01) and a 3.24-mmHg increase in blood pressure at 4 hours of life (four studies, 95% CI 1.76–4.72, P<.01). None of the trials documented umbilical cord gases. Three of the four hematologic outcomes (Fig. 3) indicate beneficial effects of enhanced placental transfusion compared with early cord clamping, including higher initial reported hematocrits (10 studies, weighted mean difference 4.49, 95% CI 2.48–6.50, P<.01), lower transfusion incidence (six studies, RR 0.75, 95% CI 0.63–0.90, P<.01), and lower mean number of transfusions (six studies, weighted mean difference −1.14 transfusions, 95% CI −2.01 to −0.27, P=.01). No difference in mean peak serum bilirubin levels was observed (eight studies, weighted mean difference 0.53 mg/dL, 95% CI −0.01 to 1.07, P=.05).
Mortality before initial discharge was lower in the enhanced placental transfusion group than in the early cord clamping group (eight studies, RR 0.42, 95% CI 0.19–0.95, P = .04; Fig. 4). An additional positive benefit of greater placental transfusion at delivery was a lower incidence of total intraventricular hemorrhage (nine studies, RR 0.62, 95% CI 0.43–0.91, P = .01). As part of the leave-one-out sensitivity analysis, statistical significance was lost after exclusion of either the Mercer et al or March et al studies.16,45 These studies had the highest weights (24.1% and 35.6%) in the total intraventricular hemorrhage model. The loss of statistical significance on removal of studies with the highest weights may reflect a loss of precision and higher standard errors resulting from their exclusion. No differences were observed in the incidence of severe intraventricular hemorrhage (six studies, RR 0.64, 95% CI 0.34–1.21, P = .17), sepsis, or necrotizing enterocolitis.

Only one study reported maternal hematocrits before delivery. No studies reported on incidence of maternal complications, including postpartum hemorrhage. As a result of lack of data provided in the reports, subgroup analysis of potential antenatal confounders (treatment with antibiotics, exposure to indomethacin or ibuprofen) was not possible. Additionally, of the 12 included studies, eight excluded multiple gestation pregnancies, and none provided a separate analysis of singleton compared with twin gestations.

CONCLUSION

This meta-analysis demonstrates that enhanced placental transfusion (delayed cord clamping or umbilical cord milking) at birth in very premature neonates provided better neonatal outcomes than did early cord clamping, most notably reductions in overall mortality, blood transfusion incidence, and the risk of intraventricular hemorrhage. These observations are consistent with previous work showing that enhanced placental–fetal transfusion at delivery improves neonatal outcomes in larger, more developmentally mature neonates.14,30,44,50

Lower neonate mortality before discharge among neonates receiving enhanced placental transfusion, compared with early cord clamping, differs from previous systematic reviews and meta-analyses that included more mature neonates.14,31 In contrast with previous reviews of studies based on neonates born at less than 37 weeks of gestation, our review is based on neonates born, on average, before 32 weeks of
gestation (average gestational age of 28 weeks). Our working premise was that the more immature neonates would represent a separate question and address concerns on the optimal cord clamping practice among very preterm neonates.17

The lower risk of total, but not severe, forms of intraventricular hemorrhage in neonates receiving enhanced placental transfusion is consistent with previous studies14,16,31 and may reflect differences in pathogenic mechanisms for brain injury among very preterm neonates.51–54 Additional studies will be needed to determine whether reduction in the incidence of total intraventricular hemorrhage after enhanced placental–fetal transfusion translates to long-term neurodevelopmental benefits.

The higher initial hematocrits, lower autologous blood transfusion exposures, and lower numbers of blood transfusions associated with enhanced placental transfusion are noteworthy in view of the risks and adverse effects of blood product exposures.55–58 Factors that may influence the volume of placental–fetal transfusion, including route of delivery, uterine contractions, onset of respirations, and relative position of the neonate and placenta,6,59,60 were reported inconsistently, thereby precluding any determination of possible contributions of these variables in the present analysis.

Previous investigators have shown that enhanced placental transfusion strategies are associated with higher peak bilirubin concentrations.14 Although we found no statistically significant difference in peak serum bilirubin concentration between the two groups, this observation was limited by the relatively small number of included neonates in the analysis. Consistent with previous reports, we found no evidence that enhanced
Fig. 3. Meta-analysis and forest plots for hematologic outcomes. A. Transfusion incidence. B. Number of transfusions. C. Initial hematocrits. D. Peak serum bilirubin. MH, Mantel-Haenszel test; CI, confidence interval; SD, standard deviation; IV, inverse variance.

placental transfusion was associated with the incidence of polycythemia or the need for phototherapy.

Some investigators have argued that promoting placental transfusion will result in critical delays in resuscitation and may worsen neonatal outcomes.\textsuperscript{61-63} We found no differences between the two groups across a number of safety outcomes, including Apgar scores at 5 minutes, admission temperature, or incidence of delivery room intubation. However, resuscitation events were not reported consistently, and the optimal cord clamping practice among neonates requiring immediate resuscitation remains unknown. Compared with delayed cord clamping, umbilical cord “milking” may facilitate more rapid resuscitation of the newborn and expedite obstetric interventions while still providing the benefits of enhanced placental transfusion. The physiologic consequences of “milking,” in particular its effects on fragile germinal matrix vessels, warrant consideration in future studies.

Strengths of this analysis are the systematic identification of all relevant published randomized studies and their meta-analysis. Most outcomes were reported by subsets of trials and had wide CIs. The trials included in this meta-analysis were, collectively, of good quality. However, safeguards to ensure concealment of allocation were not reported consistently, some trials did not account properly for dropout, and others did not provide clear justification for sample size. Although the average gestational ages of neonates included in the analysis were 28 weeks, neonates born beyond 32 weeks of gestation were included. None of the studies enrolled neonates before 24 weeks of gestation; therefore, determining the optimal cord clamping practice for this subgroup of extremely preterm neonates was precluded.

In conclusion, our systematic review and meta-analysis suggests that enhanced placental transfusion at birth in very preterm neonates provides better neonatal outcomes than does early cord clamping, including reductions in overall mortality, lower risk of intraventricular hemorrhage, and decreased blood transfusion incidence. However, resuscitation events are not reported consistently, precluding determination of the optimal cord clamping practice among neonates born severely depressed or requiring immediate resuscitation. Large-scale, randomized clinical trials of enhanced placental transfusion strategies with sufficient power to assess clinically important outcomes including long-term neurodevelopmental and neurologic sequelae are needed to confirm these findings.

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