OBSTETRICS

Timing of cord clamping in very preterm infants: more evidence is needed

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In December 2012, the American College of Obstetricians and Gynecologists published a Committee Opinion entitled "Timing of umbilical cord clamping after birth." It stated that "evidence exists to support delayed cord clamping in preterm infants, when feasible. The single most important benefit for preterm infants is the possibility for a nearly 50% reduction in IVH." However, the Committee Opinion added that the ideal timing of umbilical cord clamping has yet to be determined and recommended that large clinical trials be conducted in the most preterm infants. Published randomized controlled trials include <200 infants of <30 weeks' gestation, with assessments of neurodevelopmental outcome in less than one-half of the children. This is a major gap in the evidence. Without reliable data from randomized controlled trials that optimally include childhood follow-up evaluations, we will not know whether delayed cord clamping may do more overall harm than good. Ongoing trials of delayed cord clamping plan to report childhood outcomes in >2000 additional very preterm infants. Current recommendations may need to change when these results become available. Greater international collaboration could accelerate resolution of whether this promising intervention will improve disability-free survival in about 1 million infants who will be born very preterm globally each year.

Key words: delayed cord clamping, placental transfusion, umbilical cord, very preterm infant

In December 2012, the American College of Obstetricians and Gynecologists (ACOG) published a Committee opinion entitled "Timing of umbilical cord clamping after birth." It stated that "Several systematic reviews have suggested that clamping the umbilical cord...should be delayed for at least 30-60 seconds...because of the associated neonatal benefits, including increased blood volume, reduced need for blood transfusion, (and) decreased incidence of intracranial hemorrhage in preterm infants...Evidence exists to support delayed cord clamping in preterm infants, when feasible. The single most important benefit for preterm infants is the possibility for a nearly 50% reduction in IVH."[1]

Consistent with this opinion, delayed cord clamping (DCC) is increasingly being advocated for the routine care of preterm infants.[2,3] It has been claimed that failure to implement this procedure may represent an unnecessary harm for vulnerable neonates.[4]

In light of the evidence reviewed by the ACOG Committee, which has been summarized in 2 systematic reviews, can clinicians and institutional review boards continue to support trials of DCC in very preterm infants?[5,6] The answer is clearly "yes" (Video clip). The ACOG Committee Opinion added the disclaimer that it "should not be construed as dictating an exclusive course of treatment or procedure to be followed."[1] Further, the effects on severe intracranial hemorrhage and

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neurodevelopmental outcome in very preterm infants remain unclear. The Committee Opinion continued "the ideal timing for umbilical cord clamping has yet to be established" and "large clinical trials are needed to investigate the effect of delayed cord clamping on infants delivered at less than 28 weeks gestation."[1]

European consensus guidelines for preterm infants

The recent European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants[7] reviewed the same evidence that was available to the ACOG Committee.[5,6] In contrast to the ACOG Committee Opinion, the European guidelines made a formal recommendation: "If possible delay clamping of the umbilical cord for at least 60 s with the baby held below the mother to promote placentofetal transfusion."[7] The guidelines noted that a large multicenter trial is underway to determine whether this practice genuinely improves short- and long-term outcome.[8] However, the guidelines did not mention the current lack of evidence as to whether DCC improves or worsens survival or neurosensory disability. Despite these major gaps in the evidence, the advice to delay clamping of the cord in preterm infants was graded A, which suggests the highest level of evidence to support the recommendation.[9]

Potential mechanisms, benefits and risks

Enhancing placental transfusion by DCC might benefit the very preterm infant by increasing neonatal blood volume,[5,10] thereby potentially improving perfusion and reducing organ injury.[11-14] DCC may also allow more time for spontaneous breathing to begin before the umbilical cord is clamped, achieving a smoother transition of the cardiopulmonary and cerebral circulation[15] and reducing the risk of invasive and potentially injurious resuscitation.[16] DCC may also increase iron stores,[5,10] reduce childhood anaemia,[17] and increase the transfer of stem cells, which may have anti-inflammatory, neurotrophic and neuroprotective effects.[18,19] However, DCC may increase the incidence and severity of jaundice and hypothermia and its long-term effects are unknown. Also, if DCC delays urgently needed resuscitation, it may cause net long-term harm.[5,10,20]

How have others interpreted current evidence?

Authors of systematic reviews and consensus statements have drawn varying conclusions from the available evidence.[5,7,10,21] Importantly, few have noted that conclusions may need to change in the light of results from ongoing randomized controlled trials (RCTs),[8,22] which could enroll >10 times as many very preterm infants as those on which current advice is based.

Trials in infants at <37 weeks' gestation

The most recent Cochrane Review synthesized evidence from 15 RCTs in 738 infants who were born at <37 weeks' gestation, an average of only 49 infants per trial, or about 25 infants per study arm in each trial.[5] The number born at <30 weeks' gestation could not be ascertained. Also, several studies were at risk of bias, with missing data for several outcomes. The trials compared early cord clamping, in <20 seconds, with strategies to enhance placental transfusion. These were DCCs for 30-120 seconds or, in 1 RCT,[23] cord milking. The 4 primary outcomes were death, severe (grade 3 or 4) intraventricular hemorrhage (IVH), periventricular leukomalacia, and neurodevelopment in early childhood. Increased placental transfusion appeared to protect against the secondary outcome of IVH (all grades). Among 534 infants, the risk ratio (RR) was 0.59 (95% confidence interval [CI], 0.41−0.85; $P = .0048$). However, the clinical significance of this was unclear because there were too few data about the primary outcomes of severe (grades 3 or 4) IVH (n = 305; RR, 0.68; 95% CI, 0.23−1.96; $P = .20$) and neurodevelopment at age 2-3 years (n = 0). There were no differences in development in 58 children 7 months after discharge from hospital. The authors concluded that "there were insufficient data for reliable conclusions about the comparative effects on any of the primary outcomes for this review."[5]

DCC also improved other short-term outcomes, including necrotizing enterocolitis, transfusions for anemia, use of inotropes, late onset sepsis, and increased peak bilirubin. However, the Cochrane authors concluded that "larger multicentre studies are essential and demand international collaboration …. Future studies should include more data … on long term neurodevelopmental outcome at two years of age. …"[5]

Trials in infants at <30 weeks' gestation

In a systematic review, Ghavam et al[10] evaluated neurodevelopmental outcome at 18-24 months in RCTs of very low birthweight (<1000 g) preterm infants of <30 weeks' gestation. Infants were assigned randomly either to early clamping or to enhanced placental transfusion by DCC or milking. Trial authors were contacted for additional information. In 10 eligible RCTs, 199 infants were enrolled, which was an average of 20 per trial or approximately 10 per study arm in each trial. Information on the primary outcome of neurodevelopment at 18-24 months could be obtained for just 96 infants, from just 3 of the 10 trials.[23-25] No difference was found in rates of disability or death between early clamping and enhanced placental transfusion in these 3 trials.

Two RCTs followed 42 children at 18-24 months but used different developmental scales and were inconclusive.[23,25] Short-term benefits in all 10 trials included improved blood pressure and hemoglobin concentration, fewer blood transfusions, late-onset sepsis, and a trend ($P = .08$) to reduced IVH of all grades.[10] The authors concluded that, for very low birthweight infants of <30 weeks' gestation, "paucity of data on neurodevelopmental outcomes and safety concerns tempers enthusiasm for these interventions. Appropriately designed RCTs to assess short-term and long-term outcomes are needed."

Need for adequate power and follow up

Adequate sample size and power are critical in perinatal trials.[26,27] Recent neonatal oxygen-targeting trials underline the need