

Optimizing Placental Transfusion for Preterm Infants

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There are many potential benefits of delayed or deferred cord clamping (DCC) compared with immediate cord clamping (ICC).¹ Increasing placental transfusion by DCC increases neonatal blood volume and improves transitional hemodynamics. DCC may also increase iron stores, reducing childhood anemia and increasing the transfer of stem cells, which may have antiinflammatory neurotropic and neuroprotective effects.

The American College of Obstetricians and Gynecologists (ACOG) gives conditional support for a 30- to 60-second delay in umbilical cord clamping (DCC) for all preterm infants.² To a great degree, the ACOG opinion piece was informed by the meta-analysis of Rabe et al,³ which analyzed the results from 15 eligible studies that enrolled 738 premature infants born between 24 and 36 weeks' gestation. DCC was associated with fewer infants needing transfusion for anemia or low blood pressure and less intraventricular hemorrhage (IVH). However, no differences were noted in severe IVH, periventricular leukomalacia, mortality, or neurodevelopmental follow-up.

The ACOG opinion qualifies its support by noting that many aspects of DCC need additional study.² Little is known about the effects of timing, mode of delivery, and technique on longer-term outcomes. Despite promising short-term evidence, we cannot yet exclude the possibility that DCC may do more long-term harm than good.⁴

One alternative to DCC is umbilical cord milking (UCM) or stripping, in which blood is pushed or "milked" toward the infant several times before the cord is clamped. Theoretical benefits exist for this approach, especially in the preterm infant. A meta-analysis of 7 randomized controlled trials of UCM compared with ICC in 501 infants born at <33 weeks' gestation demonstrates similar benefits as for DCC with, in addition, less need for supplemental oxygen at 36 weeks' gestation.⁵

Fewer studies have directly compared techniques of improving placental transfusion for extremely preterm infants, and none have addressed the unique problems posed by cesarean delivery, their most common mode of delivery.⁶ In this issue of *Pediatrics*, Katheria et al⁷ report on "Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants." Mothers at risk for delivering before 32 weeks' gestation were stratified by mode of delivery and randomly assigned to either DCC or UCM. The investigators used "delayed consent," in which parents were notified of the already randomized intervention by the obstetric and research team and were approached immediately after birth to provide written consent to enroll their newborns for continued data collection.

Although the investigators planned to recruit 600 patients, the study was stopped after 197 patients because of the "futility" of demonstrating a difference in IVH. Improved cardiovascular status was seen in cesarean delivery infants randomly

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assigned to UCM. Katheria et al⁷ state that “umbilical cord milking should no longer be considered experimental and rather is a proven intervention that ensures premature infants receive an adequate placental transfusion at birth.” However, in the next paragraph the authors suggest that larger trials are needed.

The second statement seems much closer to the truth. There is broad consensus about the need for large-scale, randomized clinical trials of enhanced placental transfusion strategies with sufficient power to assess clinically important outcomes, including survival and long-term neurodevelopment.^{1–5,8–11} Although ICC lacks a physiologic basis,¹ our other choices for cord management are myriad, and their effects on survival and disability remain unknown. Concluding that UCM should be standard care could, paradoxically, inhibit additional trials.

To elucidate the risks and benefits of different approaches to cord management, we must enroll more patients, more rapidly and at lower cost, with better representation of infants at highest risk. We suggest 3 ways forward to help achieve these aims. First, innovative approaches to obtaining consent, as used by Katheria et al,⁷ can ensure that infants delivered under emergency conditions are not denied participation in future trials. Second, differences in outcome may vary according to adherence to study protocol between patients, sites, or time periods.^{12,13} Sensitivity analyses weighted by difference achieved between randomized groups in hemoglobin, as a measure of increased placental transfusion, can provide valuable insights into whether treatment effects are increased by greater adherence to protocol. Third, if individual units within networks are willing to be randomly assigned to UCM or DCC for,

say, a year and then switch to the alternative policy for a similar period, cluster crossover trials could rapidly and reliably compare these techniques in large, representative samples of patients,^{14–16} helping to integrate randomized research into routine care.¹⁷

More than 25 000 extremely low birth weight infants will be born in the United States in 2015.¹⁸ Are we really going to rely, for this most basic management of their initial care, on evidence of improved surrogate outcomes in <500 infants of <30 weeks’ gestation^{3,4,10} without reliable data on survival or disability?

ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists

DCC: delayed umbilical cord clamping

ICC: immediate cord clamping

IVH: intraventricular hemorrhage

UCM: umbilical cord milking

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YOU ARE WHAT YOU ORDER: *My wife and I do not dine at restaurants particularly often. When we do, however, we spend a long time perusing the menu and discussing what we should order. Some patterns have emerged over the years; I am far more interested in appetizers, and game for the main entrée, and less interested in dessert than she. I had not thought our food preferences fell along gender lines, but according to The Wall Street Journal (Life: March 24, 2015), they do. Evidently restaurateurs and menu consultants report that men and women frequently order along gender-based lines, and restaurants need to take gender preference into account when designing individual dishes and the overall menu. Broadly, men order heavier entrees that include meat and a starch. Women tend to order more vegetable-based dinners and splurge on dessert – and are less likely to find dishes made from named animal parts appetizing.*

Interestingly, the words used to describe the dishes may have enormous impact. Items described as “delicate” are more attractive to women, while those described as “hearty” are more appealing to men. Recognizing that gender-based differences exist, some restaurants have been expanding the selection of simply-prepared proteins (such as fish) that have few sauces and do not include starches and other offerings. The rationale is that such dishes appeal more to calorie-counting customers (more often women than men) and do not make the diners feel that they are “high maintenance” asking for special items or modifying items already on the menu. It is all a bit strange to me as I have had many meals with women who have ordered all sorts of items off the menu.

As for my wife and me, we like to share. We usually wind up sharing an exotic appetizer that we cannot make at home and compromise by ordering two entrees that we both like (and then make a solemn pledge to split the entrees in half). It seems to work for us.

Noted by WVR, MD

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